Risk Factors Comparison 2024-03-06 to 2023-03-06 Form: 10-K

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Investing in our common stock involves a high degree of risk because our business is subject to numerous risks and uncertainties, as fully described below. The principal factors and uncertainties that make investing in our common stock risky include, among others: ● We are substantially dependent on the success of **oral difelikefalin for the treatment of NP, which is** our **only current** product ~~and product candidates~~ **candidate**. If we are unable to successfully complete clinical development, obtain regulatory approvals and successfully commercialize **oral difelikefalin** ~~our products and product candidates~~, or experience significant delays in doing so, our business will be materially harmed. ● We **recently engaged in a strategic prioritization of our pipeline. We may be unable to successfully execute our strategic prioritization plans, including efforts to reduce our costs. ● We** rely, and expect to continue to rely, on third parties to conduct our preclinical and clinical studies, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials. ● If the manufacturers upon whom we rely fail to produce our ~~products or~~ product ~~candidates~~ **candidate or any potential future product** in the volumes that we require on a timely basis, or to comply with stringent regulations applicable to pharmaceutical drug manufacturers, we may face delays in the development ~~and commercialization~~ of ~~, or~~ **our** ~~be unable to meet demand for, our products~~ **product candidate** ~~and may lose potential revenues~~. ● Even if we obtain additional regulatory approvals for our product ~~candidates~~ **candidate or any potential future product candidate**, they may never be successfully launched or become profitable, in which case our business, prospects, operating results and financial condition may be materially harmed. ● If we or our collaborators are unable to establish sufficient and effective marketing and sales capabilities, or if we are unable to enter into or maintain agreements with third parties to market and sell our products and product ~~candidates~~ **candidate**, if ~~they are~~ **it is** approved, we may be unable to generate product revenues. ● Any collaboration arrangements that we ~~are a party to, such as our collaboration with CSL Vifor, or may~~ enter into in the future may not be successful, which could adversely affect our ability to develop and commercialize our product ~~candidates~~ **candidate**. ● We face significant competition from other pharmaceutical and biotechnology companies, academic institutions, government agencies and other research and development organizations. Our operating results will suffer if we fail to compete effectively. ● **If we experience continuous delays** ~~To the extent that KORSUVA injection, or Kapruvia, or our~~ **or difficulties in** ~~product candidates, if approved, do not achieve broad market acceptance, the revenues that we generate from their~~ **the** ~~respective sales will~~ **enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could** be **delayed or prevented** ~~limited. ● Our business, operations and clinical development and regulatory timelines and plans have been, and could continue to be, adversely affected by the effects of health epidemics, including the COVID- 19 pandemic~~. ● The regulatory approval processes of the U. S. Food and Drug Administration, or FDA, and comparable foreign authorities are lengthy, time consuming and inherently unpredictable. If we are not able to obtain, or if there are delays in obtaining, required additional regulatory approvals, we will not be able to commercialize our product ~~candidates~~ **candidate** as expected, and our ability to generate revenue will be materially impaired. ● **Our** ~~For our approved products, KORSUVA injection and Kapruvia, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expenses. Additionally, our~~ product ~~candidates~~ **candidate** ~~, if approved, could be subject to labeling and other restrictions or market withdrawal, and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products. ● Our approved products, including KORSUVA injection and Kapruvia,~~ may have **serious adverse events or** undesirable side effects that may ~~require them to be taken off the market, require them to include safety warnings or otherwise limit their sales. Further, our product candidates may have serious adverse events or undesirable side effects that may~~ limit dosing during development, or delay or prevent regulatory or marketing approval ~~. ● If we experience continuous delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented~~. ● We have incurred significant losses since inception, and we anticipate that we may incur losses in the foreseeable future. **We** ~~Our first commercial product was only recently approved, and we~~ may never achieve profitability. ● **Failure** ~~We are dependent on third parties to decide to utilize KORSUVA injection and Kapruvia and to make them readily available at the point of care throughout their dialysis centers or hospitals. ● We rely on third parties to perform many essential services for~~ **or perceived failure** ~~KORSUVA injection and Kapruvia and may do so in the future for any products that we commercialize, including services related to warehousing and inventory control, distribution, customer service, accounts receivable management, cash collection and adverse event reporting. If these third parties fail to perform as expected or~~ to comply with ~~legal and~~ **laws,** ~~regulatory~~ **regulations** ~~requirements~~, **contracts** ~~our ability to successfully commercialize KORSUVA injection~~, ~~Kapruvia~~ **notices**, **and** ~~or any~~ other ~~product candidate, will be significantly impacted and we may be subject to regulatory sanctions. ● We are dependent on our collaboration agreements for certain revenues, and if our commercial partners do not perform their~~ obligations ~~under~~ **related to data privacy and security (including security incidents) could harm our business. Compliance or the actual or perceived failure to comply with** such **obligations** ~~agreements, we~~ could **increase** ~~lose revenues. ● If the government or~~ **our business costs** ~~other third- party payers fail to provide coverage and adequate reimbursement and payment rates for KORSUVA injection~~, ~~Kapruvia,~~ **limit adoption of** ~~or~~ **our** ~~any of our other current or future product~~ **products** ~~candidates~~, ~~if any,~~ **and otherwise negatively affect** ~~or~~ **our operating results** ~~if providers choose to use therapies that are less expensive, our revenue~~ and **business** ~~prospects for profitability will be limited~~. ● We may need to license certain intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms. ~~4Industry and Market DataWe obtained the industry and market data in this Annual Report on~~

~~Form 10- K from our own research as well as from industry and general publications, surveys and studies conducted by third parties. Industry and general publications, studies and surveys generally state that the information contained therein has been obtained from sources believed to be reliable. These third parties may, in the future, alter the manner in which they conduct surveys and studies regarding the markets in which we operate our business. As a result, you should carefully consider the inherent risks and uncertainties associated with the industry and market data contained in this Annual Report on Form 10- K, including those discussed in Part I Item~~ **3Item** ~~1A. " Risk Factors. " Item~~ 1. Business. OverviewWe are a ~~commercial~~ **development** - stage biopharmaceutical company **driving innovation in sizable, yet underserved diseases and conditions. Specifically, we are focused on** leading a new treatment paradigm to improve the lives of patients suffering from **chronic** pruritus ~~. Our KORSUVA injection is the first and only FDA- approved treatment for moderate- to- severe pruritus associated with chronic kidney disease, or CKD, in adults undergoing hemodialysis~~. We are developing an oral formulation of difelikefalin ~~and have initiated Phase 3 programs~~ **, a selective, predominantly peripherally acting, non- scheduled Kappa opioid receptor agonist,** for the treatment of **chronic neuropathic** pruritus **associated** ~~in patients~~ with **Notalgia Paresthetica** ~~NDD- CKD~~, **a common** ~~and atopic dermatitis~~, ~~or AD~~ **underdiagnosed neuropathy affecting the upper back**. We **are conducting** ~~have also initiated~~ a Phase 2 / 3 program **with topline results** of ~~oral difelikefalin~~ **the dose- finding portion expected in the third quarter of 2024. We also developed an IV formulation of the same molecule, which is approved** for the treatment of moderate- to- severe pruritus **associated** ~~in patients~~ with ~~NP~~ **advanced chronic kidney disease in adults undergoing hemodialysis in the United States, EU and multiple other countries. The IV formulation is out- licensed worldwide**. Chronic Pruritus – Overview ~~of the Unmet Need~~ Pruritus, or itch, is defined as an unpleasant sensation that provokes the desire to scratch, which can range from a mild annoyance to an intractable, disabling condition. Chronic pruritus ~~is~~ **, defined as an itch lasting longer than 6 weeks, has a variety of etiologies including inflammatory, metabolic and neuropathic, the latter being caused by direct damage to the nerve itself. Chronic pruritus represents** a significant unmet need with few if any robustly efficacious or pruritus- specific treatment options. **Because chronic pruritus is often not amenable to currently available treatments, it can result in a debilitating course, including the development of symptoms of depression, global distress, and impairment of sleep. Multiple studies have demonstrated this significant impact of chronic pruritus on health- related quality of life, some suggesting an impact similar to chronic pain. In contrast to pain, chronic pruritus is often under- reported by patients and therefore under- treated by providers.** Overall, **it is estimated that** about one in every eight people globally suffer from chronic pruritus. ~~The condition~~ **Chronic Neuropathic Pruritus- OverviewChronic neuropathic pruritus is a common subcategory of chronic pruritus representing approximately 8 % of all chronic pruritus cases. Chronic neuropathic pruritus can be caused by local nerve fiber compression (e. g., notalgia paresthetica, brachioradial pruritus) or localized or generalized nerve fiber degeneration (e. g., small fiber neuropathy) affecting different neuronal structures in the peripheral or central nervous system. Chronic neuropathic pruritus can be divided into localized and generalized forms with localized forms occurring on almost any area of the body (e. g., notalgia paresthetica affecting the upper back). Chronic neuropathic pruritus** is often ~~under~~ **accompanied by sensory damage experienced as pain, allodynia, paresthesia, allokinesis, hyperesthesia, or hypothesia. There are no approved treatments for chronic neuropathic pruritus and off** ~~- reported by patients and therefore under- treated by providers~~ **label use of other therapies, frequently treatments indicated for neuropathic pain, are mostly ineffective or associated with significant side effects**. ~~The result~~ **Hence, there** is a significant ~~and sometimes disabling impact on patients' quality of life. Chronic pruritus occurs in primarily three broad disease categories: systemic diseases, dermatologic diseases, and neurologic diseases. Numerous diseases fall into each of these categories, with each of them having pruritus as a key symptomatic feature. Systemic diseases with associated pruritus include endocrine and metabolic diseases such as CKD and chronic liver disease like PBC, infectious diseases, hematologic and lymphoproliferative diseases, visceral neoplasms, and drug- induced pruritus. Dermatologic diseases with associated pruritus include inflammatory dermatoses – such as AD, infectious dermatoses, autoimmune dermatoses, neoplasms, genodermatoses, and dermatoses of pregnancy. Neurologic diseases associated with pruritus include NP, brachioradial pruritus and post- herpetic neuralgia. Each one of these disease categories has potential as an area of exploration for our lead compound, difelikefalin. The unaddressed~~ unmet need ~~remains substantial. According to a study we conducted with IQVIA utilizing medical claims data from 2019, or the IQVIA study, approximately 23 million patients were diagnosed with diseases associated with chronic pruritus and received a prescription~~ for an **effective** ~~anti- pruritic agent such as corticosteroids~~, ~~antihistamines~~ **safe**, ~~select antidepressants, counterirritants, bile acid sequestrants, rifampin, narcotic antagonists,~~ and **well tolerated treatment** ~~partial agonists, topical immunomodulators or~~ **for** ~~gabapentin~~ **chronic neuropathic pruritus**. Role of Difelikefalin in Chronic PruritusRecent advancements in the understanding of the biology of pruritus have led to the discovery of novel targets in the central nervous system, or CNS, and a unique pathway central to chronic pruritus. Pruritus, commonly referred to as itch, originates in the epidermis and dermal – epidermal junction and is transmitted by itch- selective sensory neuron C ~~5fibers~~ **fibers**, or pruriceptors. Some of these fibers are sensitive to histamine while others are not, and there is evidence for histamine- insensitive C fibers that are activated by numerous itch- inducing substances or pruritogens, many of which initiate signals through interaction with specific G- protein- coupled receptors. In addition, there is increasing evidence for the differential involvement of these systems in various forms of itch which may involve disease- specific pruritogens. ~~As an example, chronic pruritus associated with kidney failure is thought to involve complex interactions among peripheral cells (T cells, mast cells, neutrophils, eosinophils, and keratinocytes) and histamine- insensitive nerve fibers, involving increased release of cytokines, proteases, and neuropeptides, interacting with multiple receptors that lead to exacerbation of itch. These different~~ **Different** peripheral cell types express kappa opioid receptors, or KORs, which can regulate the release of these pruritogenic substances, while the KORs on C fibers are thought to regulate their response to these pruritogens. Because KORs are expressed in peripheral tissues, there is a potential to modulate itch signals peripherally without impacting the central KORs. The itch- sensitive sensory nerve fibers transmit signals to the cell bodies in the dorsal root ganglia (that ~~also~~ **4also** have KORs), which

send fibers to enter the spinal cord. Itch signals then ascend via the spinothalamic tract to multiple brain areas for sensory processing and interactions with cognitive and other systems. Additionally, the activation of kappa receptors via an agonist is thought to reduce itching by functionally counteracting increased mu opioid receptor activity which is suggested to be associated with some chronic forms of pruritus. Activation of the mu opioid receptor in the brain and in the peripheral nerve endings results in itching while non- selective mu opioid antagonists can inhibit itching. KOR stimulation inhibits the effects of mu receptor activation both centrally and peripherally. Our novel compound, difelikefalin, is a highly selective, predominantly peripherally acting KOR agonist. Its design includes specific characteristics that limit entry into the CNS. As a KOR agonist, difelikefalin' s mechanism of action turns off the itch sensation by acting on the peripheral neurons responsible for sensing pruritus. In other words, difelikefalin disrupts the itch sensation of chronic pruritus at the nerve level. In addition, difelikefalin acts on KORs expressed on a range of activated immune cells to subsequently block the release of pruritogenic cytokines. A central hypothesis driving our development work is that by acting on peripheral nerves that sense pruritus, difelikefalin may be able to address pruritus regardless of the underlying disease. Our ~~StrategyOur~~ **StrategyCara Therapeutics is a development stage biotechnology company with the** mission ~~is~~ to **drive innovation** ~~become the leader~~ in ~~the treatment of~~ **sizable, yet underserved diseases and conditions. We are focused on** chronic pruritus **, a** ~~and transform the way pruritus is treated to improve the quality of life for millions of people who suffer from this~~ condition **associated with many diseases across multiple therapeutic areas** . ~~Our goal~~ **Due to** ~~is~~ **its mechanism** ~~to maximize the potential and utility~~ of **action,** our unique compound ~~,~~ difelikefalin, a selective ~~KOR~~ **, predominantly peripherally acting, non- scheduled Kappa opioid receptor** agonist **, has broad applicability** for the treatment **of** chronic pruritus ~~, across our two core franchises, nephrology and medical dermatology~~ . We ~~believe this will drive both near and long- term growth and create significant value for all our stakeholders. To achieve our goal, we~~ are ~~pursuing the following strategies: ● Expanding our Nephrology Franchise by optimizing the commercial potential of KORSUVA injection and~~ developing **an** oral **formulation of** difelikefalin for ~~the treatment of pruritus in earlier stages of chronic kidney disease: Our Nephrology Franchise is anchored in our lead product, KORSUVA injection, the first and only FDA approved treatment for moderate- to- severe~~ pruritus associated with ~~chronic kidney disease in adults undergoing hemodialysis. We estimate the addressable patient population to be around 200, 000 patients in the United States alone with similar size patient pools in other regions around the world. KORSUVA injection is a global brand with additional approvals in the EU, UK, Switzerland, Canada, Australia, Singapore, and the United Arab Emirates, or UAE, using the trade name Kapruvia in some of these countries. Our partner CSL Vifor is leading the commercialization of KORSUVA injection in all countries except Japan and South Korea with the goal to educate providers and patients on the unmet medical need and drive utilization of KORSUVA injection thereby maximizing its commercial potential. Our intent is to build upon our existing KORSUVA injection approval and expand the utility of difelikefalin by moving to earlier stage CKD patients with the oral formulation. In 2022, we initiated a Phase 3 program in 6advanced CKD stages IV- V for patients who are not on dialysis. Like in the dialysis setting, there are no approved therapies and expanding to this population will roughly double our addressable market if oral difelikefalin is approved for this indication. ● Building a Medical Dermatology Franchise by executing our late stage clinical programs in Atopic Dermatitis and~~ Notalgia Paresthetica **(** ~~: Our Dermatology Franchise is focused on developing oral difelikefalin in pruritus associated with AD and~~ NP **)** ~~, two complementary indications with the same medical dermatology call point. AD is the most common of the inflammatory dermatologic conditions and pruritus is the primary symptom. The vast majority of patients have mild- to- moderate disease and many of them suffer from moderate- to- severe pruritus. We estimate this itch- dominant population to represent roughly 3 million patients. Most of these patients receive topical steroids to address the inflammation but there are no approved systemic therapies to target pruritus. In 2022, we initiated a Phase 3 program in this population with the goal to develop the first systemic, symptomatic therapy focused on pruritus in AD~~ . NP is a **common but under- recognized and consequently undertreated** neuropathic disorder ~~that is~~ characterized by ~~significant~~ **chronic** pruritus ~~in~~ **affecting** the upper back. ~~We~~ **NP is challenging to manage and there are currently no FDA- approved therapies or therapies in development. NP represents a sizable patient population with an** ~~estimate~~ **estimated** ~~that approximately~~ **addressable market of** 650, 000 patients ~~with NP~~ **in the United States who** are **under** ~~currently in~~ the care of a **healthcare** provider ~~. Like~~ **, not accounting for** ~~the~~ **those who** ~~other indications we~~ are **undiagnosed. We** ~~pursuing, there is a significant unmet need as there~~ are **conducting** ~~no approved therapies to treat NP. We recently initiated~~ a Phase 2 / 3 program with the intent to develop the first treatment indicated for pruritus associated **NP** ~~with this underdiagnosed and undertreated condition~~ . We believe our strategy **to focus on NP** , which is anchored in the **favorable preclinical and** clinical profile and benefit of difelikefalin ~~seen in our trials to date~~ , will ~~maximize the potential of our difelikefalin and~~ lead to sustainable, long- term growth for our company. ~~7Our~~ **5Our** Product ~~PortfolioProgram~~ **PortfolioProduct** ~~Product~~ Candidate ~~Primary~~ Indication Status **Next Milestone** Commercialization ~~RightsPruritus~~ **RightsOral difelikefalin Pruritus NP Phase 2 / 3 KOURAGE 1 ongoingPhase 3 KOURAGE 2 planned Phase 2 KOURAGE 1Topline 3Q2024 Cara (Worldwide excl. South Korea)** KORSUVA (difelikefalin) injection **/ Kapruvia** Pruritus CKD- Hemodialysis ~~• FDA approved~~ **Approved** in ~~August~~ **the U. S. (08 /** 2021 **) Approved** ~~• TDAPA designation granted~~ in ~~December 2021 by CMS, effective April~~ **EU incl. UK (04 /** 2022 **)** ~~• EMA MAA approved~~ **Approved** in **Japan** ~~April 2022~~ (~~Kapruvia~~ **09 / 2023**) **Other approvals:** ~~• UK MAA approved in April 2022 (Kapruvia) •~~ Switzerland ~~(Kapruvia)~~ , Canada **,** ~~(KORSUVA) and~~ Singapore **,** ~~(KORSUVA) MAAs approved in August 2022 •~~ Australia **, Kuwait, Israel, UAE, Saudi Arabia** ~~(KORSUVA) approved in November 2022 • Japan New Drug Application filed in September 2022 • U. S. commercial launch commenced in April 2022 • EU commercial launch commenced in third quarter of 2022~~ CSL Vifor (Worldwide **excl.** ~~, other than~~ Japan and South Korea) ***** ; Maruishi (Japan); CKDP (South Korea) *** We are party to two collaborations for** ~~Oral difelikefalin Pruritus AD- aP • Phase 3 program initiated in first quarter of 2022 Cara (Worldwide, other~~ -- **the commercialization** ~~than South Korea); CKDP (South Korea) Oral difelikefalin Pruritus NDD- CKD • Phase 3 program initiated in first quarter~~ of **KORSUVA** ~~2022 Cara (Worldwide, other than Japan and South Korea); Maruishi (Japan); CKDP (South Korea) Oral difelikefalin Pruritus NP • Phase 2 trial reported in second quarter of 2022 • Phase 2 / 3~~

program initiated in first quarter of 2023 Cara (Worldwide, other than South Korea); CKDP (South Korea) Our Nephrology FranchiseKORSUVA (difelikefalin) injection **/ Kapruvia** – Our Commercial ProductOverviewOn August 23, 2021, our lead product, KORSUVA injection, was approved by the FDA for the treatment of moderate- to- severe pruritus associated with CKD in adults undergoing hemodialysis. In December 2021, CMS granted Transition Drug Add- on Payment Adjustment, or TDAPA, to KORSUVA injection in the anti- pruritic functional category. TDAPA went into effect on April 1, 2022, for a **joint venture between** minimum of two years. The commercial launch of KORSUVA injection commenced in April 2022 and we began recording the associated profit- sharing revenues in the second quarter of 2022. We are partnering with CSL Vifor to commercialize KORSUVA injection in dialysis patients with CKD- aP worldwide, excluding Japan (Maruishi / sub- licensee Kissei), and South Korea (CKDP). For the year ended December 31, 2022, CSL Vifor recorded net sales of KORSUVA injection in the United States of approximately $ 35. 0 million and we recorded associated collaborative revenue of $ 16. 6 million which represented our share of the profit from these sales. In April 2022, the European Commission granted marketing authorization to difelikefalin injection under the brand name Kapruvia for the treatment of moderate- to- severe pruritus associated with chronic kidney disease in adult 8hemodialysis patients. The marketing authorization approves Kapruvia for use in all member states of the EU, as well as Iceland, Liechtenstein, and Norway. Kapruvia was also approved in the UK in April 2022. Commercial launches in Austria, Germany, Sweden, and Denmark have commenced and we expect the remaining EU countries to launch in 2023. In August 2022, as part of the Access Consortium, difelikefalin injection was approved in Switzerland under the brand name Kapruvia, as well as in Singapore and Canada under the brand name KORSUVA. In November 2022, difelikefalin injection was approved in the last Access Consortium country, Australia, under the brand name KORSUVA. For the year ended December 31, 2022, we recorded royalty revenue of approximately $ 72, 000 which represented our royalties on net sales of Kapruvia in Europe. In addition, our partner in Japan, Maruishi, announced positive Phase 3 top- line data in January 2022. Maruishi and its sublicensee Kissei confirmed the primary endpoint was achieved in a Japanese Phase 3 clinical study (double- blind, placebo- controlled period) of difelikefalin injection for the treatment of pruritus in hemodialysis patients. In the Phase 3 study, 178 patients were administered difelikefalin or placebo for 6 weeks followed by an **and** open- label extension period of difelikefalin administration for 52 weeks. The primary endpoint, change in itch numerical rating scale, or NRS, and the secondary endpoint, change in itch scores of Shiratori severity criteria, were significantly improved from baseline compared to the placebo group. Difelikefalin was well- tolerated. In September 2022, Maruishi submitted a New Drug Application in Japan for the approval of difelikefalin injection for the treatment of pruritus in hemodialysis patients. A final decision on the application is expected in the second half of 2023. In January 2023, Vifor Fresenius Medical Care Renal Pharma Ltd. and Winhealth Pharma signed a long- term exclusive licensing agreement **In this Annual Report, unless the context otherwise requires, " CSL** for **Vifor " refers to CSL Vifor and its affiliated entities, including, where applicable,** the co- **joint venture. Oral Difelikefalin, Our** development **Development Stage Product CandidateNotalgia Paresthetica** and **Associated PruritusNotalgia paresthetica (NP)** commercialization of KORSUVA injection for the treatment of moderate- to- severe pruritus in adult patients undergoing hemodialysis in China. Pruritus in CKD in Adults on Dialysis: CKD is a clinical condition wherein progressive kidney damage leads to **common chronic cutaneous neuropathy primarily characterized by localized pruritus in the upper back** an **and associated dysesthesias,** impairment of kidney function over time. Primary risk factors culminating into CKD include **including** diabetes **sensations of pain** , hypertension **numbness** , **and tingling** cardiovascular disease, or hereditary renal disease. Early- stage disease **While the exact pathophysiology remains unknown, the sensory neuropathy characteristic of NP** is generally **thought to result from spinal nerve entrapment possibly caused by degenerative changes in the spine or musculoskeletal compression. The symptomatic area may be** associated with few mild clinical manifestations; however, CKD can progress to kidney failure or ESRD which is fatal without dialysis or transplantation. According to the National Kidney Foundation, ESRD is estimated to affect approximately 750, 000 individuals per year in the United States, of which approximately 500, 000 patients undergo regular dialysis. Chronic pruritus is one of the many comorbidities of CKD in patients undergoing dialysis, characterized by a **hyperpigmented patch** highly unpleasant and irritating sensation that triggers an urge to scratch the skin. CKD- aP adversely affects patient quality of life and can result in infections , **most often** sleep- deprivation, depression, and even increased risk of mortality. CKD- aP' s intractable systemic itch has a high prevalence. According to Fresenius Medical Care, a world leading provider of products and medical care for dialysis patients, there were approximately 3. 2 million patients globally undergoing dialysis in 2017. According to the Dialysis Outcomes and Practice Patterns Study published in December 2017 in the Clinical Journal of the American Society of Nephrologists, it is estimated that nearly 70 % of these patients suffer from some form of CKD- aP with approximately 40 % of these patients experiencing moderate to severe pruritus. Summary of the Clinical Results for KORSUVA injection / Kapruvia: KORSUVA injection was approved by the FDA on August 23, 2021 and is the first and only product approved for the treatment of moderate- to- severe pruritus associated with CKD in adult patients undergoing hemodialysis in the United States. It was approved based on the NDA filing that was supported by positive data from two pivotal Phase 3 trials – KALMTM- 1, conducted in the United States, and KALM- 2 conducted globally, as well as supportive data from an additional 32 clinical studies. KORSUVA injection was found to be generally well tolerated in the pivotal studies highlighted below. 9In April 2020, we announced positive top- line results from the double blinded KALM- 2 pivotal Phase 3 trial of KORSUVA injection in hemodialysis patients with moderate- to- severe CKD- aP. The study met the primary efficacy endpoint with 54 % of the patients receiving 0. 5 mcg / kg of KORSUVA injection vs. 42 % of patients receiving placebo achieving at least a three- point improvement from baseline with respect to the weekly mean of the daily 24- hour worst itch intensity NRS at week 12 ($p = 0.$ 02). The study also met the key secondary endpoint with 41 % of patients receiving KORSUVA injection achieving a four- point or greater improvement from baseline in the weekly mean of the daily 24- hour worst itch NRS score at week 12 vs. 28 % for patients receiving placebo ($p = 0.$ 01). In this trial, KORSUVA injection was generally well- tolerated with a safety profile consistent with that seen in KALM- 1 and the KORSUVA clinical program in patients with CKD- aP. Overall, the incidence of

adverse effects, or AEs, and serious AEs were similar across both KORSUVA injection and placebo groups. The most common treatment emergent AEs reported in greater than 5 % of patients were diarrhea (8. 1 % KORSUVA vs. 5. 5 % placebo), falls (6. 8 % KORSUVA vs. 5. 1 % placebo), vomiting (6. 4 % KORSUVA vs. 5. 9 % placebo), nausea (6. 4 % KORSUVA vs. 4. 2 % placebo) and dizziness (5. 5 % KORSUVA vs. 5. 1 % placebo). In May 2019, we announced positive results from the double blinded phase of our KALM- 1 pivotal Phase 3 trial of KORSUVA injection in hemodialysis patients with moderate- to - severe CKD- aP. The..... in Non- Dialysis- Dependent Chronic **chronic scratching** Kidney Disease (NDD- CKD) Associated PruritusCKD- aP is a frequent and **rubbing to relieve** wearisome symptom in patients with NDD- CKD. We initiated a Phase 3 program with oral difelikefalin for the treatment of pruritus in NDD- CKD, specifically in patients diagnosed with Stage IV and V advanced CKD. There are approximately 1. 2 million patients diagnosed with Stage IV and V CKD in the United States and approximately 300, 000 of these -- **the discomfort** patients suffer from moderate- to- severe pruritus . There are no FDA- approved treatment **treatments** options specifically for this indication in the United States or Europe. Patients are generally managed with a multitude of products including corticosteroids, gabapentin, antihistamines, antidepressants, and other -- **the management** therapies with varying degrees of **NP** success. There is **challenging** one product, nalfurafine (Remitch ®) marketed by Toray Industries, approved to treat CKD- aP in Japan, but it is not approved in either the United States or Europe. In December 2019, we announced top- line data from our Phase 2 trial of oral difelikefalin for the treatment of pruritus in NDD – CKD patients diagnosed with Stage III – V CKD. The Phase 2, multicenter, randomized, double- blind, placebo- controlled 12- week trial was designed to evaluate the safety and efficacy of three dosage strengths (0. 25 mg, 0. 5 mg and 1 mg, once daily administration) of oral difelikefalin vs. placebo in approximately 240 stage III- V (moderate- to- severe) CKD patients with moderate- to- severe pruritus. The primary efficacy endpoint was the change from baseline in the weekly mean of the daily 24- hour worst itch NRS score at week 12 of the treatment period. Secondary endpoints included change from baseline in itch- related quality of life scores at the end of week 12, as **conventional** assessed by the total Skindex- 10 and 5- D itch scores, as well as the proportion of patients achieving an improvement from baseline ≥ 3 points with respect to the weekly mean of the daily 24- hour worst itch NRS score at week 12. Patients treated with the 1 mg dosage strength of oral difelikefalin achieved the primary endpoint of statistically significant reduction in weekly mean of the daily worst itch NRS scores vs. placebo after the 12- week treatment **treatments** period (- 4. 4 difelikefalin vs.- 3. 3 placebo, p = 0. 018). The treatment was statistically significant after two weeks of treatment with sustained benefit through the 12- week treatment period. Regarding secondary endpoints, the proportion of patients on 1 mg tablet strength achieving a 3 point or greater improvement from baseline in the weekly mean of the daily worst itch NRS score at week 12 was 72 % vs. 58 % for placebo but did not achieve statistical significance. Furthermore, 11patients on 1 mg dosage strength showed positive improvements vs. placebo in itch quality of life endpoints as measured by the self- assessment Skindex- 10 and 5- D Itch scales but this did not achieve statistical significance. Oral difelikefalin was generally well- tolerated with a safety profile consistent with that seen in earlier KORSUVA clinical trials. Overall, the incidence of treatment AEs were similar across difelikefalin and placebo groups. The most common AEs reported in > 5 % of patients in the 1 mg difelikefalin group vs. placebo were dizziness (7. 5 % difelikefalin vs. 0 % placebo), fall (6 % difelikefalin vs. 0 % placebo), diarrhea (6 % difelikefalin vs. 1. 5 % placebo) and constipation (6 % difelikefalin vs. 3 % placebo). In April 2021, we held an End of Phase 2 Meeting with the FDA to discuss the results of the Phase 2 trial of oral difelikefalin in NDD- CKD and the potential Phase 3 program. The FDA indicated the acceptability of Stage V pre- dialysis CKD patients as a viable patient population for a program. In November 2021, the FDA provided written guidance indicating the patient population can be expanded to include the group of Stage IV pre- dialysis patients with advanced CKD in a registration program consisting of two pivotal Phase 3 clinical trials. In the first quarter of 2022, we initiated the Phase 3 NDD- CKD program. The Phase 3 program consists of two identical trials (U. S. and global), KICK 1 and KICK 2. Each trial is expected to enroll approximately 400 patients, who will be randomized 1: 1 to either oral difelikefalin 1 mg once daily or matching placebo. The study population will include adult patients suffering from moderate- to- severe pruritus with advanced CKD in Stages IV or V, not on dialysis. The primary endpoint will be the proportion of patients with a ≥ 4- point improvement at Week 12 from baseline in the worst- itch NRS after which patients will be re- randomized to either oral difelikefalin or placebo for 52- weeks. We expect to report top- line results from this program in the second half of 2024. Our Dermatology FranchiseAtopic Dermatitis and Associated PruritusAD is a chronic, pruritic inflammatory dermatosis that affects up to 25 % of children and 2 % to 5 % of adults. Chronic pruritus is one of the defining features of AD. The itch is so common in AD that AD is often described as the itch that rashes. The point prevalence of chronic pruritus ranges between 87 % to 100 % in AD. According to a study published in Allergy in 2018, the point prevalence in adults in the United States is 4. 9 %, or approximately 12 million adults. Both quality of life and psychosocial well- being are known to negatively correlate with itch severity. The associated psychosocial morbidity of this distressing symptom includes sleep disruption, depression, agitation, anxiety, altered eating habits, reduced self- esteem and difficulty concentrating. AD patients can be segmented into groups based on the severity of their skin lesions as well as the severity of their itch. In a study published in Annals of Allergy, Asthma Immunology in 2021, it was found that nearly 25 % of AD patients had mild- to- moderate lesions but still had severe pruritus. This " itch dominant " AD phenotype has a significant unmet medical need as their skin lesions have been controlled, but their severe itch has persisted. Most times, these patients have tried available agents (i. e., topical therapies, including corticosteroids, antihistamines) to control pruritus related to their AD unsuccessfully resulting in a significant patient population that needs a systemic agent for pruritus relief. Oral difelikefalin for the Treatment of Moderate- to- Severe Pruritus Associated with Atopic Dermatitis (AD) In April 2021 , **such** we announced top- line data from our Phase 2 KARE clinical trial. The KARE Phase 2 trial was a randomized, double- blind, placebo- controlled study designed to evaluate the efficacy and safety of oral difelikefalin for moderate- to- severe pruritus in 401 adult subjects with AD- aP. KARE enrolled 64 % of patients characterized as **antihistamines** mild- to- moderate AD (Body Surface Area, or BSA, < 10 %) and 36 % as moderate- to- severe AD (BSA > 10 %). Subjects were randomized to three dosage strengths of oral difelikefalin: 0. 25 mg, 0. 5 mg and 1 mg taken twice daily

~~(BID) vs. matching placebo for 12 weeks followed by 4 weeks of an~~ **and** ~~open- label active extension phase. A prespecified interim conditional power assessment was conducted after approximately 50 % of the originally targeted patient number completed the 12- week treatment period. Based on the Independent Data Monitoring Committee' s recommendation, the sample size for each of the 0. 5 mg dose and placebo groups were increased, taking the total trial size up by 28 %. 12KARE' s primary efficacy endpoint was change from baseline in the weekly mean of the daily 24- hour Itch NRS score at week 12 of the treatment period for the intent to treat, or ITT, population. Although no dose group met this endpoint, a statistically significant improvement from baseline was evident as early as week 1 for the 1 mg dose group, which was sustained through 75 % of the treatment period. In a prespecified analysis, a statistically significant change in the primary efficacy endpoint was observed in the mild- to- moderate (BSA < 10 %) AD patient population (p = 0. 036, All doses vs. placebo), which was evident at week 1 and sustained through the 12- week treatment period. The key secondary endpoint for KARE was the assessment of the proportion of patients achieving an improvement from baseline of ≥ 4 points with respect to the weekly mean of the daily 24- hour Itch NRS score at week 12 (4- point Responder Analysis). No dose group met this endpoint for the ITT population. A prespecified analysis by disease severity indicated a statistically significant improvement in the 4- point Responder Analysis in the mild- to- moderate (BSA < 10 %) AD patient population with 33 % of difelikefalin- treated patients achieving a ≥ 4- point reduction in NRS at Week 12 vs. 19 % in the placebo group for the 0. 5 mg dose (p = 0. 046). All doses performed similarly (0. 25 mg, 0. 5 mg, and 1 mg) vs. placebo. Oral difelikefalin was generally well- tolerated across all doses. In the first quarter of 2022, we initiated a Phase 3 program for the treatment of moderate- to- severe pruritus in AD patients. The pivotal Phase 3 program for difelikefalin in AD comprises two studies: KIND 1 and KIND 2 and will investigate the use of oral difelikefalin as adjunctive treatment to~~ topical **steroids** ~~corticosteroids. The KIND 1 study will be composed of two parts: Part A and Part B. KIND 1 and KIND 2 will be double- blind~~ . **are largely ineffective** ~~controlled, 12- week studies with patients allowed to roll- over into open label 52- week extensions. Part A of KIND 1, the dose finding portion of the trial, is expected to include 280 patients who will be randomized equally to four arms (0. 25 mg BID TCS, 0. 5 mg BID TCS, placebo BID TCS, placebo BID vehicle). At the end of the 12- week treatment period in Part A of KIND 1, we expect to have an internal data read out targeted for the second half of 2023. This readout will provide key information, specifically the dose and the sample size to initiate Part B of KIND 1 and KIND 2. Part B and KIND 2 will be identical in design. They will be double- blind, controlled, 12- week studies with patients randomized 1: 1 to either difelikefalin or matching placebo as adjunct treatment to topical corticosteroids. The difelikefalin dose is expected to be based on the results from Part A of KIND 1. The primary endpoint will be the proportion of patients with a ≥ 4- point improvement at Week 12 from baseline in the worst itch NRS. The studies will include adult patients with AD whose chronic pruritus has not been adequately controlled by topical therapy alone and who have had chronic pruritus of moderate- to- severe intensity for ≥ 6 weeks (worst itch NRS of ≥ 5). Patients must have an Investigator Global Assessment ≥ 2 and a BSA ≤ 20 %. We will stratify patients to a BSA < 10 % or ≥ 10 % with the aim to enroll 85 % of patients with a BSA < 10 %. We expect to release top- line results for both KIND 1 Part B and KIND 2 in the first half of 2025. Notalgia Paresthetica and Associated PruritusNP is a common, neurosensory condition caused by alteration and damage to thoracic spinal nerves and is characterized by chronic pruritus in the upper back~~ . It is estimated that chronic pruritus affects up to 13 % of the U. S. population. NP falls within the subcategory of chronic neuropathic pruritus which comprises approximately 8 % of all cases of chronic pruritus. We estimate that approximately 650, 000 adult patients with NP associated pruritus are in the care of a healthcare provider **,** ~~. There are no~~ **not** ~~FDA~~ **accounting for mis** ~~approved treatments for~~ **or** ~~NP~~ **undiagnosed patients** . ~~The management of NP is challenging and conventional treatments for pruritus, such as antihistamines and topical steroids, are largely ineffective. 13Oral~~ -- **Oral** Difelikefalin for Treatment of Moderate- to- Severe Pruritus Associated with Notalgia Paresthetica (NP) In June 2022, we announced positive top- line results from the proof- of- concept Phase 2 KOMFORT trial of oral difelikefalin for the treatment of pruritus in patients with NP. KOMFORT was a Phase 2 randomized, double- blind, placebo- controlled trial designed to evaluate the efficacy and safety of oral difelikefalin for moderate- to- severe pruritus in 125 adult patients with NP and moderate- to- severe pruritus. Patients were randomized to receive oral difelikefalin 2 mg twice daily (BID) vs. matching placebo for eight weeks followed by a 4- week open- label active extension period and follow- up visit approximately 14 days after the last dose of the study drug. ~~KOMFORT~~ **6KOMFORT** ' s primary efficacy endpoint was the change from baseline in the weekly mean of the daily 24- hour worst itch NRS score at week 8 of the treatment period. Patients treated with oral difelikefalin achieved the primary endpoint (- 4. 0 difelikefalin vs.- 2. 4 placebo, p = 0. 001) with statistically significant improvement observed as early as ~~Week~~ **Day** 1 and sustained through Week 8. Other endpoints included a ≥ 4- point improvement in worst itch NRS, complete response in worst itch NRS, and safety assessments. A statistically significantly greater proportion of patients treated with oral difelikefalin achieved a ≥ 4- point improvement in worst itch NRS score at Week 8 vs. placebo (41 % difelikefalin vs. 18 % placebo, p = 0. 007). In addition, oral difelikefalin met the complete response endpoint, defined as a worst itch NRS score of 0 or 1 for 70 % of the daily non- missing worst itch NRS scores for the week. At Week 8, a significantly greater proportion of patients receiving oral difelikefalin vs. placebo achieved a complete response (22 % difelikefalin vs. 5 % placebo, p < 0. 01). Oral difelikefalin was generally well tolerated, with all **adverse events, or** AEs **,** in difelikefalin- treated patients reported as mild or moderate in severity. Nausea, headache, dizziness, constipation, and increased urine output were more commonly reported in patients on difelikefalin. In November 2022, we had a positive interaction with the FDA leading to the initiation of a Phase 2 / 3 program for the treatment of chronic pruritus associated with NP. In February 2023, the results of our KOMFORT Phase 2 trial were published in the New England Journal of Medicine. In the first quarter of 2023, we initiated a Phase 2 / 3 program for the treatment of moderate- to- severe pruritus in NP ~~patients~~ . The Phase 2 / 3 program for difelikefalin in NP will comprise two studies: KOURAGE 1 and KOURAGE 2. The KOURAGE 1 study will be composed of two parts: Part A and Part B. **Part A of** KOURAGE 1 **, the dose finding portion of the study, is a double- blind, placebo- controlled, 8- week study. In the first quarter of 2024, we completed enrollment with 214 patients who were randomized equally to four arms (0. 25 mg BID, 1. 0 mg BID, 2. 0 mg BID, placebo BID).**

Part A is not powered for statistical significance. We expect to have topline efficacy and **safety results from KOURAGE 1 Part A in the third quarter of 2024. This readout will provide key information, specifically the dose and the sample size, to initiate the pivotal Phase 3 portions of the program- Part B of KOURAGE 1 and the second study** KOURAGE 2 **. Part B of KOURAGE 1 and KOURAGE 2, the pivotal studies,** will **be identical in design. They will likely** be double- blind, placebo- controlled, 8- week studies with patients allowed to roll ~~-~~over into open label 52- week extensions. ~~Part A of KOURAGE 1, the dose finding portion of the trial, is expected to include 200 patients~~ **Patients** ~~who~~ will be ~~randomized equally to four arms (0. 25 mg BID, 1. 0 mg BID, 2. 0 mg BID, placebo BID). At the end of the 8- week treatment period in Part A of KOURAGE 1, we expect to have an internal data read out targeted for the second half of 2024. This readout will provide key information, specifically the dose and the sample size to initiate Part B of KOURAGE 1 and KOURAGE 2. Part B and KOURAGE 2 will be identical in design. They will be double- blind, placebo- controlled, 8- week studies with patients~~ randomized 1: 1 to either difelikefalin or matching placebo. The ~~difelikefalin dose is expected to be based on the results from Part A of KOURAGE 1. The~~ primary endpoint will **likely** be the proportion of patients with a ≥ 4- point improvement at Week 8 from baseline in the worst itch NRS. ~~The studies~~ **KOURAGE 1 and KOURAGE 2** will include adult patients with NP who have had chronic pruritus of moderate- to- severe intensity for ≥ 6 months (worst itch NRS of ≥ 5). We expect to release **final topline** ~~top- line~~ results ~~for both~~ **from the first pivotal study** KOURAGE 1 Part B ~~and~~ **by the end of 2025 with the second pivotal study** KOURAGE 2 **results** in **early** ~~the first half of~~ 2026. ~~Other Program (s) 14Oral Difelikefalin for the Treatment of Chronic Liver Disease- Associated Pruritus (CLD- aP), Including PBCWe had been evaluating oral difelikefalin in PBC to establish a proof- of- concept in CLD- aP. In June 2019, we announced the initiation of a proof- of- concept Phase 2 trial of oral difelikefalin for the treatment of pruritus in patients with hepatic impairment due to PBC. The Phase 2 multicenter, randomized, double- blind, placebo- controlled 16- week trial was designed to evaluate the safety and efficacy of 1 mg of oral difelikefalin taken twice daily (BID) vs. placebo in approximately 60 patients with PBC and moderate- to- severe pruritus. The primary efficacy endpoint was the change from baseline in the weekly mean of the daily 24- hour worst itch NRS score at week 16 of the treatment period. Secondary endpoints include change from baseline in itch- related quality of life scores at the end of week 16 as assessed by the Skindex- 10 and 5- D itch scales, as well as the assessment of proportion of patients achieving an improvement from baseline of ≥ 3 points with respect to the weekly mean of the daily 24- hour worst itch NRS score at week 16. Based on slow enrollment due primarily to COVID- 19, we made a strategic decision to discontinue and unblind the proof- of- concept Phase 2 clinical trial of oral difelikefalin for the treatment of pruritus in patients with PBC. The unblinded data showed no unexpected AEs. However, the low number of patients (N = 14) limits the ability to draw a meaningful conclusion regarding the efficacy (worst itch NRS change from baseline at 16 weeks:- 3. 8 difelikefalin vs.- 3. 0 placebo) of difelikefalin in this patient population. At this time, we plan to focus our resources on our nephrology and dermatology franchises. Collaboration and License AgreementsVifor (International) Ltd., or Vifor InternationalIn October 2020, we entered into a license agreement with Vifor International, or Vifor Agreement No. 1, under which we granted Vifor International an exclusive license solely in the United States to use, distribute, offer for sale, promote, sell and otherwise commercialize~~ KORSUVA (difelikefalin) injection **– Our Commercial Stage ProductOverviewWe have out- licensed to CSL Vifor the commercialization of KORSUVA injection / Kapruvia in dialysis patients with advanced CKD- aP worldwide, excluding Japan (licensed to Maruishi / sub- licensee Kissei), and South Korea (licensed to CKDP). On August 23, 2021, KORSUVA injection was approved by the FDA** for ~~all therapeutic uses relating to~~ the ~~inhibition, prevention or~~ treatment of ~~itch~~ **moderate- to- severe pruritus** associated with ~~pruritus~~ **advanced CKD** in **adults undergoing** hemodialysis **. In December 2021, CMS granted Transition Drug Add- on Payment Adjustment, or TDAPA, to KORSUVA injection in the anti- pruritic functional category. TDAPA went into effect on April 1, 2022 for a minimum of two years. The commercial launch of KORSUVA injection 7commenced in April 2022** and ~~peritoneal~~ **we began recording the associated profit- sharing revenues in the second quarter of 2022. On October 27, 2023, CMS published the final CY 2024 rule, which finalized the post- TDAPA add- on payment as proposed in the draft CY 2024 rule. Under the final rule, TDAPA drugs in existing functional categories will receive a post- TDAPA add- on payment set at 65 percent of the total trailing 12- months expenditure levels for the given renal** dialysis **drug or biological product. The post- TDAPA add- on payment will be applied to all ESRD PPS** ~~patients~~ **payments and paid for 3 years, adjusted annually. The add- on payments for KORSUVA injection will commence on April 1, 2024. The anticipated unfavorable CMS reimbursement codified in the final CY2024 rule resulted in a lack of sequential revenues growth for KORSUVA injection since its launch. For the years ended December 31, 2023 and 2022, CSL Vifor recorded net sales of KORSUVA injection** in the United States **of approximately $ 26 . 5 million and $ 35. 0 million, respectively, and we recorded associated collaborative revenue of $ 12. 4 million and $ 16. 6 million, respectively, which represented our share of the profit from these sales. We expect no meaningful revenue contribution from KORSUVA injection post its TDAPA expiration. In April 2022, the European Commission granted a marketing authorization to difelikefalin injection** ~~Under~~ **under the brand name Kapruvia for the treatment of moderate- to- severe pruritus associated with advanced CKD in adult hemodialysis patients. The marketing authorization approves Kapruvia for use in all member states of the European Union, or EU, as well as Iceland, Liechtenstein, and Norway. Difelikefalin injection was also approved in the United Kingdom, or UK, (04 / 2022) and Switzerland (08 / 2022) under the brand name Kapruvia as well as Singapore (08 / 2022), Canada (08 / 2022), Australia (11 / 2022), UAE (01 / 2023), Kuwait (05 / 2023), Israel (06 / 2023) and Saudi Arabia (01 / 2024) under the brand name KORSUVA injection. For the years ended December 31, 2023 and 2022, we recorded royalty revenue of approximately $ 415, 000 and $ 72, 000 respectively, which represented our royalties on net sales of Kapruvia and KORSUVA injection. During the fourth quarter of 2023, we entered into a Purchase and Sale Agreement with HCRX Investments Holdco, L. P. and Healthcare Royalty Partners IV, L. P., or collectively HCR, where we sold our future royalties and milestones for Kapruvia and KORSUVA injection to HCR. For the period of October 1, 2023 through December 31, 2023, we recorded**

other revenue of $ 699, 000, of which approximately $ 284, 000 related to royalties to be paid to HCR under this agreement (see " Royalty Purchase and Sale Agreement " below). We have out- licensed to Maruishi and its sub- licensee Kissei the commercialization of KORSUVA injection in Japan. In September 2023, Maruishi received manufacturing and marketing approval from Japan' s Ministry of Health, Labour and Welfare for KORSUVA IV Injection Syringe for the treatment of pruritus in hemodialysis patients. In conjunction with the approval, we earned a $ 1. 4 million milestone payment per the terms of the licensing agreement during the year ended December 31, 2023. During the fourth quarter of 2023, we entered into the Purchase and Sale Agreement with HCR where we sold our future royalties and milestones for KORSUVA in Japan to HCR. For the period of October 1, 2023 through December 31, 2023, we recorded other revenue of $ 699, 000, of which approximately $ 415, 000 related to royalties and milestones to be paid to HCR under this agreement (see " Royalty Purchase and Sale Agreement " below). KORSUVA Injection U. S. CommercializationIn April 2022, our partner CSL Vifor **initiated** ~~Agreement No. 1, we retain all rights with respect to~~ the **commercialization** ~~clinical development~~ of ~~, and activities to gain regulatory approvals of,~~ KORSUVA ~~(difelikefalin)~~ injection in the United States. ~~Under~~ **The launch was initially driven by independent and mid- size dialysis organizations coupled with product stocking at** the **wholesaler level** ~~terms of Vifor Agreement No~~ . ~~1~~ **In the third quarter of 2022** , ~~we received~~ **large dialysis organizations, or LDOs, came on- line driving a significant quarter- to- quarter increase in order volume** from ~~Vifor International~~ **the wholesaler. This stocking at the clinic level, particularly from Fresenius Medical Care (FMC), resulted in significant subsequent quarterly revenue fluctuations. In the third quarter of 2023, FMC decided to reallocate all remaining clinic level inventory within its network of clinics resulting in limited revenues in the fourth quarter of 2023. During the years ended December 31, 2023** ~~an~~ **and** ~~upfront payment~~ **2022, KORSUVA injection generated net sales** of **approximately** $ ~~100~~ **26. 5 million and $ 35** . 0 million ~~and~~ **, respectively,** ~~an~~ **and** ~~additional payment~~ **we recorded collaborative revenue** of $ ~~50~~ ~~on- line driving a significant quarter- to- quarter increase in order volume~~ **12.4 million and $ 16.6 million,respectively,which represented our share of the profit** from **sales** ~~the wholesaler.Specifically,Fresenius placed large orders to drive the trial and adoption~~ of **KORSUVA injection.** ~~KORSUVA~~ **8KORSUVA** ~~injection across its entire network of clinics.In the third quarter of 2022,CSL Vifor also contracted the sales force of Fresenius Renal Pharmaceuticals,a division of Fresenius Medical Care North America,to complement CSL Vifor' s sales force in selling into Fresenius clinics in the United States.After the initial inventory building at both the wholesaler and certain clinics (primarily,Fresenius),we have started to see shipments to dialysis organizations reflect true end- user demand versus the stocking activity seen in prior quarters.KORSUVA~~ Injection and Kapruvia Revenue and Other MetricsWe generate revenue from our lead products KORSUVA injection and Kapruvia primarily through our collaboration agreements with CSL Vifor:● Collaborative revenue from our share of the profit generated by KORSUVA injection sales in the United States.For the ~~year~~ **years** ended December 31, **2023 and** 2022,we recorded collaborative revenue of ~~approximately~~ **$ 12.4 million and** $ 16.6 million **,respectively** ~~related to our share of the profit~~ . ~~10~~ ● Commercial supply revenue from our sales of commercial product to CSL Vifor,which is subsequently sold to wholesalers.For the ~~year~~ **years** ended December 31, **2023 and** 2022,we recorded commercial supply revenue of ~~approximately~~ **$ 5.8 million and** $ 10.2 million **,respectively** . ~~●~~ Royalty revenue in conjunction with the launch of Kapruvia ~~in Europe~~ .For the ~~year~~ **years** ended December 31, **2023 and** 2022,we recorded **approximately $ 415,000 and $ 72,000,respectively,which represented** royalty ~~revenue~~ **payments earned by us.During the fourth quarter** of **2023,we entered into the Purchase and Sale Agreement with HCR where we sold our royalties for Kapruvia and KORSUVA injection to HCR.For the period of October 1,2023 through December 31,2023,we recorded other revenue of $ 699,000,of which** approximately $ ~~72~~ **284** ,000 **related to CSL Vifor royalties and approximately $ 415,000 related to Maruishi royalties to be paid to HCR under this agreement (see " Royalty Purchase and Sale Agreement " below)** .● Sales- based **or regulatory** milestone payments,which could be earned in the future in accordance with certain licensing agreements.For the year ended December 31, ~~2022~~ **2023** , **we earned regulatory milestone revenue of $ 1.4 million related to the manufacturing and marketing approval in Japan under the Maruishi Agreement,but** we did not record any sales- based milestone revenue. **Additional** ~~There are~~ metrics that we have reported in the past ~~and intend to continue to report in the future,including~~ :● Net sales of KORSUVA injection in the United States.This amount is the net sales amount recorded by CSL Vifor to reflect shipments of KORSUVA injection vials from CSL Vifor to wholesalers.For the ~~year~~ **years** ended December 31, **2023 and** 2022,CSL Vifor recorded net sales of KORSUVA injection in the United States of approximately $ **26.5 million and $** 35 ~~.0 million.● Our share of profit from KORSUVA injection that we record as collaborative revenue.For the year ended December 31,2022,we recorded collaborative revenue of approximately $ 16.6~~ . 0 million **, respectively. ● Shipments of KORSUVA injection vials from wholesalers in the United States to the dialysis clinics. 314, 100 and 207, 096 KORSUVA injection vials were shipped from wholesalers to the dialysis clinics** for the **years ended December 31, 2023 and 2022, respectively. Of the vials shipped to the FMC dialysis centers for the year ended December 31, 2023, a significant portion was reallocated product by FMC within its network of clinics. Royalty** ~~purchase~~ **Purchase and Sale AgreementDuring the fourth quarter** of **2023, we, through our wholly- owned subsidiary Cara Royalty Sub LLC, or Cara Royalty Sub, entered into the Purchase and Sale Agreement with HCR, or the HCR Agreement, pursuant to which Cara Royalty Sub sold to HCR certain of its rights to receive future royalties and milestone payments, or the Royalties, due and payable to Cara Royalty Sub (as our assignee) under our agreements with Maruishi and CSL Vifor, collectively the Covered License Agreements, in exchange for up to $ 40. 0 million. We have retained all of our right, title and interest in, to and under the Covered License Agreements that relate to any non- intravenous formulation of difelikefalin. Under the terms of the HCR Agreement, Cara received** an **initial payment** ~~aggregate of 2, 939, 552 shares of our common stock at a price~~ of $ 17. **5 million less certain transaction costs** ~~0094 per share, which represents a premium over a pre- determined average closing price of our common stock. The purchase of our common stock was governed by a separate stock purchase agreement, or the Vifor Stock Purchase Agreement. After U. S. regulatory approval of KORSUVA injection~~ in ~~August~~ **November** ~~2021~~ **2023 . In December 2023** , we received an additional $

~~50~~ **20** , 0 million ~~in October 2021~~ **less certain advisory fees, upon satisfying the milestone event** for **pricing** ~~the purchase~~ of **Kapruvia ®** ~~an aggregate of 3, 282, 391 shares of our common stock at a price of $ 15. 23 per share, which represents a 20 % premium to the 30- day trailing average price of our common stock. The purchase of our common stock was governed by the Vifor Stock Purchase Agreement. The excess of the stock purchase price over the cost of the purchased shares at the closing price of our common stock on the date of the achievement of the milestone of $ 5. 0 million was included as license and milestone fees revenue for accounting purposes for the year ended December 31, 2021. In addition, pursuant to Vifor Agreement No. 1, we are eligible to receive payments of up to $ 240. 0 million upon the achievement of certain sales- based milestones. In connection with Vifor Agreement No. 1, we also have a related supply agreement with Vifor International, or Vifor International Supply Agreement, pursuant to which we retain the right to make and have made KORSUVA injection, on a non- exclusive basis, worldwide for commercial sale of KORSUVA injection for use in all therapeutic uses to prevent, inhibit or treat itch associated with pruritus in hemodialysis and peritoneal- dialysis patients and for supply of difelikefalin injection, or Licensed Product, to Vifor International. The supply price is our cost of goods sold, 15or COGS, as calculated under GAAP, plus an agreed upon margin. The Vifor International Supply Agreement will co- terminate with Vifor Agreement No. 1. Vifor Agreement No. 1 provides full commercialization rights in dialysis clinics to Vifor International in the United States under a profit- sharing arrangement. Pursuant to the profit- sharing arrangement, we are generally entitled to 60 % of the net profits (as defined in Vifor Agreement No. 1) from sales of KORSUVA injection in the United States and Vifor International is entitled to 40 % of such net profits (excluding sales to Fresenius Medical Center dialysis clinics, compensation for which is governed by Vifor Agreement No. 2, as defined below), subject to potential temporary adjustment in future years based on certain conditions. Under Vifor Agreement No. 1, in consideration of Vifor International' s conduct of the marketing, promotion, selling and distribution of KORSUVA injection in the United States, we pay a marketing and distribution fee to Vifor International based on the level of annual net sales. This fee as well as Vifor International' s COGS are deducted from net sales in calculating the net profits that are subject to the profit- sharing arrangement under Vifor Agreement No. 1. Vifor Agreement No. 1 will continue in effect until its expiration upon the cessation of commercial sale of KORSUVA injection in the United States by Vifor International and its affiliates and sublicensees, or until the earlier termination of the Vifor Agreement No. 1. In connection with Vifor Agreement No. 1, the parties entered into the Vifor Stock Purchase Agreement governing the issuance of our common stock to Vifor International. Pursuant to the Vifor Stock Purchase Agreement, Vifor International was subject to certain restrictions on transacting in our common stock which restrictions expired on October 15, 2022. In May 2022, Vifor International assigned its rights and obligations under the license agreement and a supply agreement, as permitted under the agreements, to Vifor Fresenius Medical Care Renal Pharma Ltd. Our rights and obligations under these agreements were unaffected by this assignment, and the assignment did not affect our economic rights under the agreements with Vifor International. In August 2022, Vifor Pharma Group (which includes Vifor International) was acquired by CSL Limited and subsequently renamed CSL Vifor as part of the acquisition. The acquisition of Vifor Pharma Group did not affect any of the Company' s rights and obligations pursuant to these agreements. Vifor Fresenius Medical Care Renal Pharma Ltd. In May 2018, we entered into a license agreement, or Vifor Agreement No. 2, with Vifor Fresenius Medical Care Renal Pharma Ltd. under which we have granted Vifor Fresenius Medical Care Renal Pharma Ltd. a license to seek regulatory approval to commercialize, import, export, use, distribute, offer for sale, promote, sell and otherwise commercialize KORSUVA~~ (difelikefalin) ~~injection~~ **in Germany being approved above a certain threshold amount per dose. The terms of the HCR Agreement also provide** for **an additional $ 2. 5 million milestone payment to Cara Royalty Sub upon achievement of a 2024 sales milestone of KORSUVA in Japan. 9The HCR Agreement will automatically expire, and the payment of Royalties to HCR will cease, when HCR has received payments of Royalties equal to two times the aggregate amount of payments made by HCR under the HCR Agreement if achieved on or prior to December 31, 2029, or 2. 8 times the aggregate amount of payments made by HCR under the HCR Agreement, if not achieved on or prior to December 31, 2029. In the event of a change of control, Cara Royalty Sub will pay to HCR an amount equal to 2. 8 times the aggregate amount of payments made by HCR less the total net amounts paid by Cara Royalty Sub to HCR as of the effective date of control. In certain situations, Cara Royalty Sub would not be obligated to pay the change of control payment to HCR. After the HCR Agreement expires,** all **rights** ~~therapeutic uses~~ to ~~prevent~~ **receive the Royalties return to Cara Royalty Sub. Difelikafilin Development in Pruritus Difelkefalin** , ~~inhibit or~~ **our** ~~treat~~ **selective, predominantly peripherally acting, non- scheduled Kappa opioid receptor agonist, acts on the peripheral neurons responsible for sensing pruritus. Given this unique mechanism of action, difelikfelin is thought to work broadly independent of the origin of** itch **. To date, we have studied difelikefalin for pruritus** associated with ~~pruritus in hemodialysis~~ **systemic, inflammatory,** and ~~peritoneal- dialysis patients worldwide (excluding~~ **neuropathic diseases. The IV formulation is approved in** the United States, ~~Japan~~ **EU** and **other countries around the world** ~~South Korea). We retained full development and commercialization rights~~ for ~~KORSUVA injection for~~ the treatment of **moderate- to- severe pruritus associated with chronic kidney disease (** CKD- aP **)** in **adults undergoing** ~~dialysis~~ **hemodialysis (HD)** ~~patients in the United States except in the dialysis clinics of Fresenius Medical Care North America, or FMCNA, where Vifor Fresenius Medical Care Renal Pharma Ltd~~ . **We have studied** ~~will promote KORSUVA injection under a profit- sharing arrangement. Upon entry into Vifor Agreement No. 2, we received a non- refundable, non- creditable $ 50. 0 million upfront payment for~~ the **oral formulation** ~~purchase of an aggregate of 1, 174, 827 shares of our common stock~~ at **multiple dosage strengths** ~~a price of $ 17. 024 per share, which represented a premium over a pre- determined average closing price of our common stock. The purchase of our common stock was governed by the Vifor Stock Purchase Agreement. 16As a result of the European Commission' s regulatory approval of Kapruvia~~ in ~~April 2022, we received a $ 15. 0 million regulatory milestone payment from Vifor Fresenius Medical Care Renal Pharma Ltd. under Vifor Agreement No. 2, which was recorded as license and milestone fees revenue for the year ended December 31, 2022. After U. S. regulatory approval of KORSUVA injection in August 2021, we received a $ 15. 0 million regulatory milestone payment which was~~

~~recorded as license and milestone fees revenue for the year ended December 31, 2021. We are eligible to receive from CSL Vifor commercial milestone payments in the aggregate of up to $ 440. 0 million, all of which milestones are sales related. We are also eligible to receive tiered double- digit royalty payments based on annual net sales, as defined, of KORSUVA (difelikefalin) injection in the licensed territories. In the United States, CSL Vifor will promote KORSUVA (difelikefalin) injection in the dialysis clinics of FMCNA under a profit- sharing arrangement (subject to the terms and conditions of the Vifor Agreement No. 2) based on net FMCNA clinic sales (as defined in Vifor Agreement No. 2) and Vifor Fresenius Medical Care Renal Pharma Ltd. is entitled to 50 % of such net profits, subject to potential adjustments in a calendar year based on certain conditions. In connection with Vifor Agreement No. 2, we also have a related supply agreement with Vifor Fresenius Medical Care Renal Pharma Ltd., or the Vifor Fresenius Medical Care Renal Pharma Ltd. Supply Agreement, pursuant to which we retain the right to make and have made KORSUVA (difelikefalin) injection worldwide (excluding the United States, Japan and South Korea), or the Territory, for commercial sale by Vifor Fresenius Medical Care Renal Pharma Ltd. in or outside the Territory, and for supply of KORSUVA (difelikefalin) injection to Vifor Fresenius Medical Care Renal Pharma Ltd. The supply price is our COGS, as calculated under GAAP, plus an agreed upon margin. The Vifor Fresenius Medical Care Renal Pharma Ltd. Supply Agreement will co- terminate with Vifor Agreement No. 2. In January 2023, Vifor Fresenius Medical Care Renal Pharma Ltd. and Winhealth Pharma signed a long- term exclusive licensing agreement for the co- development and commercialization of KORSUVA injection for the treatment of~~ moderate- to- severe pruritus ~~in adult~~ **associated with advanced kidney disease (5 trials / over 430** patients **on DFK)** ~~undergoing hemodialysis in China. Maruishi Pharmaceutical Co.~~ , ~~Ltd.~~ **atopic dermatitis (2 trials / over 590 patients on DFK)** , **and notalgia paresthetica (2 trials / over 270 patients on DFK, 1 trial ongoing) with positive efficacy signals across all completed mono therapy studies. In these studies, oral difelikefalin was generally well tolerated with all AEs in difelikefalin- treated patients reported as mild** or ~~MaruishiIn April~~ **moderate in severity. In December** ~~2013~~ **2023** , we ~~entered into~~ **announced the outcome from the dose- finding Part A of the KIND 1 study evaluating the efficacy and safety of oral difelikefalin in moderate- to- severe pruritus associated with atopic dermatitis as an adjunct to topical corticosteroids. In the study, oral difelikefalin did not demonstrate** a ~~license agreement with Maruishi~~ **meaningful clinical benefit.** , ~~or the Maruishi Agreement, under~~ which **resulted** ~~we granted Maruishi an exclusive license to develop, manufacture and commercialize drug products containing difelikefalin~~ in **our decision to discontinue** ~~Japan in the acute pain and uremic pruritus fields. Maruishi has a right of first negotiation for any other~~ -- **the clinical program** ~~indications for which we develop difelikefalin and, under certain conditions, Maruishi may substitute another pruritus indication for the uremic pruritus indication originally included~~ in **atopic dermatitis** ~~its license from us. Maruishi is required to use commercially reasonable efforts, at its expense, to develop, obtain regulatory approval for and commercialize difelikefalin in Japan. We are required to use commercially reasonable efforts, at our expense, to develop, obtain regulatory approval for and commercialize difelikefalin in the United States~~ . In January ~~2022~~ **2024** , **following** ~~Maruishi and its sublicensee Kissei confirmed the primary endpoint was achieved in~~ a ~~Japanese~~ **review of our strategic priorities, we announced a strategic prioritization to focus our resources on our late- stage clinical program evaluating oral difelikefalin in chronic pruritus associated with NP, which we believe is the therapeutic indication with the greatest commercial potential for oral difelikefalin. As part of this strategic focus, we made the decision to terminate our** Phase 3 clinical **program evaluating oral** ~~study (double- blind, placebo- controlled period) of~~ difelikefalin **in** ~~injection for the treatment of~~ pruritus ~~in hemodialysis patients. In~~ **associated with advanced chronic kidney disease, including** the **ongoing KICK 1 and KICK 2** Phase 3 ~~study, 178 patients were administered difelikefalin or placebo for 6 weeks followed by an open- label extension period of difelikefalin administration for 52 weeks. The primary endpoint, change in itch NRS score, and the secondary endpoint, change in itching scores of Shiratori severity criteria, were significantly improved from baseline compared to the placebo group. Difelikefalin was well- tolerated. In September 2022, Maruishi submitted a New Drug Application in Japan for approval of difelikefalin injection for the treatment of pruritus in hemodialysis patients. A final decision on the application is expected in the second half of 2023. Under the terms of the Maruishi Agreement, we received a non- refundable and non- creditable upfront license fee of $ 15. 0 million and are eligible to receive up to an aggregate of $ 10. 5 million in~~ clinical ~~development and regulatory milestones (before contractual foreign currency exchange adjustments). In January 2021, we met the milestone criteria, as set forth in the Maruishi Agreement, for Maruishi' s first initiation of a Phase 3 trial~~ **trials** ~~for uremic pruritus in Japan. As a result, we received the $ 2. 0 million milestone payment ($ 1. 9 million after contractual foreign currency exchange 17adjustments) in May 2021. As of the date of this filing, we have received $ 4. 5 million (before contractual foreign currency exchange adjustments) of clinical development and regulatory milestones from Maruishi. We are also eligible to receive a one- time sales milestone of one billion Yen when a certain sales level is attained. We also receive a mid- double- digit percentage of all non- royalty payments received by Maruishi from its sublicensees, if any, and tiered royalties based on net sales, if any, with minimum royalty rates in the low double digits and maximum royalty rates in the low twenties. Maruishi' s obligation to pay us royalties continues, on a product- by- product basis, until the expiration of the last- to- expire licensed patent covering such product or the later expiration of any market exclusivity period. The Maruishi Agreement continues until terminated. Either we or Maruishi may terminate the Maruishi Agreement for the other party' s breach of the agreement or bankruptcy. Maruishi may terminate the agreement at any time at will. We may terminate the agreement as a whole if Maruishi challenges the licensed patent rights, and we may terminate the agreement with respect to any indication if Maruishi discontinues its development activities. In addition, in connection with the Maruishi Agreement, Maruishi made an $ 8. 0 million equity investment in our company. Chong Kun Dang Pharmaceutical Corporation, or CKDPIn April 2012, we entered into a license agreement with CKDP, or the CKDP Agreement, under which we granted CKDP an exclusive license to develop, manufacture and commercialize drug products containing difelikefalin in South Korea. CKDP is required to use commercially reasonable efforts, at its expense, to develop, obtain regulatory approval for and commercialize difelikefalin in South Korea. We are required to use commercially reasonable efforts, at our expense, to develop, obtain regulatory approval for and~~

commercialize difelikefalin in the United States. Under the terms of the CKDP Agreement, we received a non- refundable and non- creditable $ 0. 6 million upfront payment and are eligible to receive up to an aggregate of $ 3. 8 million in development and regulatory milestones (before South Korean withholding taxes). During the year ended December 31, 2020, we received a milestone payment of $ 0. 6 million (net of South Korean withholding tax) from CKDP, as set forth in the CKDP Agreement, for completion of a Phase 3 trial for uremic pruritus in the United States. As of the date of this filing, we have received $ 2. 3 million (before South Korean withholding tax) of development and regulatory milestones. We are also eligible to receive a mid- double- digit percentage of all non- royalty payments received by CKDP from its sublicensees, if any, and tiered royalties ranging from the high single digits to the high teens based on net sales, if any. CKDP' s obligation to pay us royalties continues, on a product- by- product basis, until the expiration of the last- to- expire licensed patent covering such product or the later expiration of any market exclusivity period. The CKDP Agreement continues until CKDP no longer has any obligation to pay us royalties on any product. Either we or CKDP may terminate the CKDP Agreement for the other party' s breach of the CKDP Agreement or bankruptcy. CKDP may terminate the CKDP Agreement if any of the licensed patent rights is invalid, unenforceable, is narrowed in scope or is deemed unpatentable, except as a result of a challenge by CKDP, or a third party commercializes a product containing a compound identical to difelikefalin without infringing any of the licensed patent rights in South Korea. We may terminate the CKDP Agreement if CKDP challenges the licensed patent rights or if a third party in South Korea owns an issued patent that claims difelikefalin and CKDP' s sale of products would infringe that patent. In addition, in connection with the CKDP Agreement, CKDP made a $ 0. 4 million equity investment in our company. Manufacturing and License AgreementsPolypeptide Laboratories S. A., or PPLIn July 2021, we entered into an Active Pharmaceutical Ingredient, or API, Commercial Supply Agreement with Polypeptide Laboratories S. A., or PPL, that defines each party' s responsibilities with respect to PPL' s manufacture and supply of API for the difelikefalin injection product candidate. Under the API Commercial Supply Agreement, PPL shall manufacture API at its facility for sale and supply to us, in the amounts as set forth in purchase orders to be provided by us. We will be required to purchase our requirements of API for each year of the term of the agreement, based on internal forecasts. 18The API Commercial Supply Agreement will continue until the fifth anniversary of the approval by the FDA of the NDA for KORSUVA injection, unless the API Commercial Supply Agreement is earlier terminated, and will automatically be extended for successive five- year periods unless either party gives notice to the other party of its intention to terminate. Enteris Biopharma, Inc., or EnterisIn August 2019, we entered into a Non- Exclusive License Agreement, or the Enteris License Agreement, with Enteris. Pursuant to the Enteris License Agreement, Enteris granted to us a non- exclusive, royalty- bearing license, including the right to grant sublicenses, under certain proprietary technology and patent rights related to or covering formulations for oral delivery of peptide active pharmaceutical ingredients with functional excipients to enhance permeability and / or solubility, known as Enteris' s Peptelligence ® technology, to develop, manufacture and commercialize products using such technology worldwide, excluding Japan and South Korea. As consideration for the licensed rights under the Enteris License Agreement, we paid an upfront fee equal to $ 8. 0 million, consisting of $ 4. 0 million in cash and $ 4. 0 million in shares of our common stock pursuant to the Enteris Purchase Agreement described below. We are also obligated, pursuant to the Enteris License Agreement, to pay Enteris (1) milestone payments upon the achievement of certain development, regulatory and commercial milestones and (2) low- single digit royalty percentages on net sales of licensed products, subject to reductions in specified circumstances. Until the second anniversary of the entry into the Enteris License Agreement, we had the right, but not the obligation, to terminate our obligation to pay any royalties under the Enteris License Agreement in exchange for a lump sum payment in cash, or the Royalty Buyout. We did not exercise our Royalty Buyout right and such right expired in August 2021. During the years ended December 31, 2022, 2021 and 2020, we paid $ 5. 0 million, $ 15. 0 million, and $ 5. 0 million, respectively, to Enteris for milestones earned in relation to the Enteris License Agreement, which were recorded in R & D expense for the respective periods. The Enteris License Agreement will expire on a country- by- country, licensed product- by- licensed product basis upon the later of (1) the expiration (or invalidation) of all valid claims in licensed patent rights that cover such product in such country, (2) the end of the calendar quarter in which generic competition (as defined in the Enteris License Agreement) occurs for such product in such country and (3) ten years from the first commercial sale of such product. Either party may terminate the Enteris License Agreement upon written notice if the other party has failed to remedy a material breach within 60 days (or 30 days in the case of a material breach of a payment obligation). Enteris may terminate the Enteris License Agreement upon 30 days' written notice to us if we or any of our affiliates formally challenge the validity of any licensed patent rights or assists a third party in doing so. We may terminate the Enteris License Agreement for any reason or no reason (a) prior to receipt of first regulatory approval for a licensed product in the United States for any indication upon 30 days' prior written notice to Enteris or (b) on or after receipt of first regulatory approval for a licensed product in the United States for any indication upon 60 days' prior written notice to Enteris. In August 2019, in connection with the Enteris License Agreement, we entered into the Enteris Purchase Agreement with Enteris and its affiliate, EBP Holdco LLC, collectively referred to as Purchaser, pursuant to which we issued and sold to Purchaser 170, 793 shares of our common stock in a private placement. Such shares were issued in satisfaction of the $ 4. 0 million portion of the upfront fee payable in shares of our common stock pursuant to the Enteris License Agreement and for no additional consideration, based on a purchase price of $ 23. 42 per share, which was equal to the 30- day volume weighted average price of our common stock on August 20, 2019. Pursuant to the Enteris Purchase Agreement, we effected the registration and sale of the shares issued and sold to Purchaser thereunder in accordance with the applicable requirements of the Securities Act of 1933, as amended, or the Securities Act, which included the filing of a registration statement with the SEC on September 9, 2019. In addition, the Purchase Agreement includes customary representations, warranties and covenants by us. 19Patheon UK Limited, or PatheonIn July 2019, we entered into a Master Services Agreement, or MSA, with Patheon UK Limited, or Patheon. The MSA governs the general terms under which Patheon, or one of its affiliates, will provide non- exclusive manufacturing services to us for the drug products specified by us from time to time. Pursuant to the MSA, we have agreed to order from Patheon at least a certain

~~percentage of our commercial requirements for a product under a related Product Agreement. Each Product Agreement that we may enter into from time to time will be governed by the terms of the MSA, unless expressly modified in such Product Agreement. The MSA has an initial term ending December 31, 2024, and will automatically renew after the initial term for successive terms of two years each if there is a Product Agreement in effect, unless either party gives notice of its intention to terminate the MSA at least 18 months prior to the end of the then current term. Either party may terminate the MSA or a Product Agreement upon written notice if the other party (1) has failed to remedy a material breach within a specified time or (2) is declared insolvent or bankrupt, voluntarily files a petition of bankruptcy or assigns such agreement for the benefit of creditors. We may terminate a Product Agreement (a) upon 90 days' prior written notice if any governmental agency takes any action that prevents us from selling the relevant product in the relevant territory, (b) upon six months' prior written notice if we do not intend to order manufacturing services due to a product's discontinuance in the market, or (c) upon 90 days' prior written notice if we determine that the manufacture or supply of a product likely infringes third- party rights. Patheon may terminate the MSA or a Product Agreement (i) upon six months' prior written notice if we assign such agreement to an assignee that is unacceptable to Patheon for certain reasons, or (ii) upon 30 days' prior written notice if, after the first year of commercial sales, we forecast zero volume for 12 months. The MSA contains, among other provisions, customary representations and warranties by the parties, a grant to Patheon of certain limited license rights to our intellectual property in connection with Patheon's performance of the services under the MSA, certain indemnification rights in favor of both parties, limitations of liability and customary confidentiality provisions. Also in July 2019, we entered into two related Product Agreements under the MSA, one with each of Patheon and Patheon Manufacturing Services LLC, or Patheon Greenville, to govern the terms and conditions of the manufacture of commercial supplies of difelikefalin injection, our lead product candidate. Pursuant to the Product Agreements, Patheon and Patheon Greenville will manufacture commercial supplies of difelikefalin injection at the Monza, Italy and Greenville, North Carolina manufacturing sites, respectively, from API supplied by us. Patheon and Patheon Greenville will be responsible for supplying the other required raw materials and packaging components, and will also provide supportive manufacturing services such as quality control testing for raw materials, packaging components and finished product .~~ Sales and MarketingIn executing our strategy, our goal is **to continue** to commercialize KORSUVA injection and Kapruvia in the dialysis setting by ~~partnering with~~ out- licensing ~~agreements~~, and to maintain significant control over the development process and commercial execution for the oral formulation of difelikefalin, if approved. We have executed out- licensing agreements on KORSUVA injection and Kapruvia in the dialysis setting in the United States and the rest of the world. Per the terms of the associated licensing agreements, CSL Vifor will commercialize KORSUVA injection and Kapruvia **in the United States and worldwide (excluding Japan and South Korea), Maruishi will commercialize KORSUVA in Japan** , and we will not be incurring costs for commercializing in the United States or outside of the United States as we will be relying on sales and marketing infrastructure support from our ~~partner~~ **partners** . For oral difelikefalin, we plan to develop and commercialize our drug candidate in **chronic** pruritus **associated with** ~~indications, such as NDD- CKD, AD, and~~ NP ~~,~~ on our own in the United States, while exploring partnerships for development and commercialization in geographical territories outside the United States. ~~20Intellectual -~~ **Intellectual** PropertyWe strive to protect the proprietary technologies that we believe are important to our business, including seeking and maintaining patent protection intended to cover the composition of matter of our product ~~candidates~~ **candidate** , ~~their~~ **its** methods of ~~use~~ **10use** , related technology and other inventions that are important to our business. As more fully described below, patent applications have been filed covering compositions and novel formulations of these compositions, as well as methods of using difelikefalin **and related compounds** . We own the patent portfolio of eighteen issued U. S. patents covering KOR agonists, sixteen of which cover composition of matter of difelikefalin and its uses; six of these include composition of matter claims directed to difelikefalin, and ten patents include claims to its uses. All of these U. S. patents covering difelikefalin and its uses are expected to expire no earlier than November 12, 2027. Additionally, three U. S. patents have been granted with claims to difelikefalin- like dimer compounds and their uses. We have filed patent applications in the United States and internationally claiming novel oral formulations of difelikefalin. ~~One~~ **Two** U. S. ~~patent~~ **patents** with claims to oral formulations of difelikefalin ~~has~~ **that are not currently under development have** been granted and ~~is~~ **are** expected to expire no earlier than September 13, 2039. Related U. S. and foreign applications, if granted, would also be expected to expire no earlier than September 13, 2039 ~~. We have also filed U. S. and foreign patent applications for additional formulations of difelikefalin, which if granted, would be expected to expire no earlier than March 18, 2040~~ . We also rely on trade secrets and careful monitoring of our proprietary information to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know- how related to our business, defend and enforce our patents, maintain our licenses to use intellectual property owned by third parties, preserve the confidentiality of our trade secrets and operate without infringing valid and enforceable patents and other proprietary rights of third parties. We also rely on know- how, and continuing technological innovation to develop, strengthen, and maintain our proprietary position in the field of **chronic** ~~peripheral analgesia and treatment of~~ pruritus. A third party may hold intellectual property, including patent rights, which are important or necessary to the development of our products. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially. If we were not able to obtain a license or were not able to obtain a license on commercially reasonable terms, our business could be harmed, possibly materially. We plan to continue to expand our intellectual property estate by filing patent applications directed to novel formulations and novel uses of our proprietary compounds. We anticipate seeking patent protection in the United States and internationally for the chemistries and processes for manufacturing these novel formulations and uses of these compounds in a variety of therapies. The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application

can be significantly reduced before the patent is issued, and the patent' s scope can be modified after issuance by later judicial decisions. Consequently, we do not know whether ~~any of~~ our product candidates will be adequately protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties. Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for up to 18 months, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of our entitlement to the inventions covered by pending patent applications. Moreover, although unlikely, we may have to participate in interference proceedings declared by the United States Patent and Trademark Office, or USPTO, to determine priority of invention, or in post- grant challenge proceedings in the USPTO, or a foreign patent office such as oppositions, inter- partes review, post grant review, or a derivation proceeding, that challenge our entitlement to an invention or the patentability of one or more claims in our patent applications or issued patents. Such proceedings could result in substantial cost, even if the eventual outcome is favorable to us. ~~21The~~ -- **The** patent portfolios for our most advanced programs are summarized below. ~~DifelikefalinOur~~ **11DifelikefalinOur** synthetic peptide amide kappa opioid agonist patent portfolio is wholly owned by us. The portfolio includes eighteen issued U. S. patents (U. S. Patent Nos. 7, 402, 564; 7, 713, 937; 7, 727, 963; 7, 842, 662; 8, 217, 007; 8, 236, 766; 8, 486, 894; 8, 536, 131; 8, 906, 859; 8, 951, 970; 9, 321, 810; 9, 334, 305; 9, 359, 399; 10, 017, 536; 10, 138, 270; 10, 793, 596; 10, 913, 769 and 11, 033, 629) with claims to compositions of a wide range of synthetic peptide amide kappa opioid agonists, including difelikefalin and related molecules, as well as formulations containing and methods of using these compounds. These patents claiming difelikefalin compositions are due to expire November 12, 2027. U. S. Patent No. 11, 033, 629 with claims to oral formulations of difelikefalin **that are not currently under development** is due to expire September 13, 2039. We have listed twelve of the patents claiming difelikefalin acetate and / or its uses in the Orange Book, a listing of patents relating to approved drug products maintained by the FDA. Difelikefalin acetate has been awarded a five- year data exclusivity from the approval date, i. e. until August 23, 2026, prohibiting the FDA from accepting an application for approval of a difelikefalin product from a generic manufacturer until after the exclusivity period expires. In addition, we have also submitted an application for a patent term extension of one of our difelikefalin U. S. patents, which if granted for the additional full five- year extension requested, would extend the patent term to November 12, 2032. Foreign applications relating to difelikefalin and related molecules, as well as formulations containing and methods of using these compounds, were filed in more than 40 foreign countries. National patents have been granted in 27 European countries, as well as in Australia, Brazil, Canada, China, Hong Kong, India, Israel, Japan, Malaysia, Mexico, New Zealand, Russian Federation, Singapore, South Africa and South Korea. These granted foreign patents with claims to difelikefalin are due expire no earlier than November 12, 2027. We **have applied for supplementary patent certificates (" SPCs ") for the basic product patent in Europe, including the five major European markets (France, Spain, Italy, Germany, and the UK). In the five major European markets, the SPC has been granted in France and Italy, (extending the patent term to November 12, 2032) and is pending in Germany, Spain, and the UK. We have also applied for a patent term extension in Japan, which is pending. We** also own pending U. S. continuation and foreign patent applications with claims to oral formulations containing difelikefalin and medium chain fatty acid glycerides as absorption enhancers **that are not currently under development** in Australia, Brazil, Canada, China, Europe, Japan, Hong Kong, Israel, India, South Korea, Malaysia, Mexico, New Zealand, Philippines, Russian Federation, Saudi Arabi, UAE, and South Africa. If granted, these patents would expire no earlier than September 13, ~~2029~~ **2039** . In addition, we own pending U. S. and foreign patent applications with claims to oral formulations containing difelikefalin and oligosaccharides **not currently under development** in Australia, Brazil, Canada, China, Europe, Japan, Hong Kong, Israel, India, South Korea, Malaysia, Mexico, New Zealand, Philippines, Russian Federation, Saudi Arabi, UAE, and South Africa. If granted, these patents would expire no earlier than March 18, 2041. Other Cara Patents and Patent ~~ApplicationsWe~~ **ApplicationsThe** ~~also own several other U. S. patents including U. S. Patent Nos. 7, 741, 350; 7, 960, 376; 7, 960, 377; and 8, 211, 926 with claims to other cannabinoid compounds and U. S. Patent No. 8, 217, 000 with claims to regulation of prolactin in mammals including humans. The~~ term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a PCT application or a non- provisional patent application. The term of a patent in the United States can be adjusted and extended due to the failure of the USPTO following certain statutory and regulation deadlines for progressing prosecution and issuing a patent. In the United States, the patent term of a patent that covers an FDA- approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for a portion of the patent term lost during the FDA regulatory review process. The Hatch- Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are ~~22available~~ -- **available** in Europe and other non- United States jurisdictions to extend the term of a patent that covers an approved drug. ~~In~~ **12In** the future, if and when our pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. Although we intend to seek patent term extensions to any of our issued patents in any jurisdiction where these are available there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions. Cara Trademark Applications and ~~registrationsWe~~ **RegistrationsWe** rely on our U. S. and foreign trademarks for authentication of our current and future products and for protection against counterfeits. In the United States, trademarks may be reserved under an " Intent to Use " designation but may only be registered upon a showing of actual use in the stream of commerce. Many countries permit registration without such a showing of actual use. However, such registrations become vulnerable to cancellation after a designated period of non- use. For example, a

trademark registered in EU States may be cancelled for non- use after five years from the date of registration. Trademark registrations can in principle last for as long as the owner uses the trademark and pays the maintenance fees due at regular intervals (every ten years in most jurisdictions after complying with filing requirements for confirmations of use and paying the designated fees during the first ten years from the registration date). We own the registered trademark " KORSUVA " in the United States and in ~~twelve~~ **fourteen** foreign countries (Australia, Brazil, Canada, **China, India,** Israel, Japan, Kuwait, Mexico, New Zealand, Norway, South Korea, Switzerland, and the UK). In addition, we own three **registered** Japanese ~~trademark~~ **trademarks** ~~applications~~ for Katakana versions of " KORSUVA " as may be pronounced in the Japanese language: " KORSUVA " Katakana version 1: " ko- ru- su- ba " コルスバ; Katakana version 2: " ko- ru- su- o- ba " コルスーバ; and Katakana version 3 " ko- o- su- ba " コースバ. ~~Our trademark applications for " KORSUVA " are pending in China and India.~~ Additionally, we own the U. S. trademark application for " KAPRUVIA " currently pending under an " Intent to Use " designation, as well as the " KAPRUVIA " trademark registered in all twenty- seven EU States (Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, ~~Singapore,~~ Slovakia, Slovenia, Spain and Sweden) and fourteen additional countries: Albania, Australia, China, Iceland, Israel, Monaco, New Zealand, North Macedonia, Norway, Russian Federation, Serbia, Switzerland, Turkey and the UK ~~. We have applied for registration of the trademark " OPRUITY " in the United States (which is currently pending under an Intent to Use designation) and in twenty other countries and regions: Australia, Brazil, Canada, China, EU, India, Israel, Japan, Malaysia, Mexico, New Zealand, Norway, Russian Federation, Saudi Arabia, Singapore, South Korea, South Africa, Switzerland, UAE and the UK. We also own the U. S. trademark application for " XAYLIANT " currently pending under an " Intent to Use " designation for use in future product (s) yet to be developed~~ . We rely on trade secret protection for our confidential and proprietary information. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Thus, we may not be able to adequately protect our trade secrets to prevent harm to our business. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning our business or financial affairs developed or made known to the individual during the course of the individual' s relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual, and which are related to our current or planned business or research and development, or R & D, or made during normal working hours, on our premises or using our equipment or proprietary information, are our exclusive property. ~~23CompetitionThe~~ -- **CompetitionThe** biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technology, knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many different sources, including large pharmaceutical and biotechnology companies, specialty pharmaceutical and generic drug companies, and medical technology companies. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. ~~There~~ **13There are no FDA- approved treatments for chronic pruritus associated with NP. The management of NP is challenging and conventional treatments for pruritus, such as antihistamines and topical steroids, are largely ineffective. However, there** are a ~~large~~ number of companies developing or marketing therapies for **different pruritic** ~~some of the~~ indications **. We believe** that ~~we are pursuing. Many of our competitors, including many of the organizations named below, have substantially greater financial, technical and human resources than we do and significantly greater experience in the development of product candidates, obtaining FDA and other~~ -- **the late** ~~regulatory approvals of products and the commercialization of those products. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of competitors. Small or early~~ - stage **nature of our oral difelikefalin clinical program, along with our substantial safety database developed over years of testing difelikefalin in different clinical settings, would give us an advantage over any competitor seeking to develop a competitive product candidate for neuropathic pruritus associated with NP. Accordingly, it is possible that one or more** companies **could elect** ~~may also prove~~ to ~~be significant competitors, particularly through collaboration arrangements~~ **develop a product candidate for chronic pruritus associated** with ~~large and established companies~~ **NP that could compete with oral difelikefalin** . We also compete with these companies in recruiting and retaining qualified scientific personnel and establishing clinical trial sites and patient ~~registration~~ **recruitment** for clinical trials. We believe the key competitive factors that will affect the development and commercial success of our product ~~candidates~~ - **candidate** , if approved for marketing, are likely to be ~~their~~ **its** safety, efficacy and tolerability profile, reliability, convenience of dosing, price and reimbursement from government and third- party payers. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third- party payers seeking to encourage the use of generic products. Generic products currently on the market are often tried off- label for the ~~indications~~ - **indication** that we are pursuing, and additional products are expected to become available on a generic basis over the coming years. If our product ~~candidates~~ - **candidate** ~~achieve~~ **achieves** marketing approval, we expect that ~~they~~ **it** will be priced at a significant premium over generic products. ~~If our product candidates are approved for the indications for which we are currently undertaking clinical trials, they will compete with the therapies and currently marketed drugs discussed below: KORSUVA~~

~~injection- CKD- aP. Currently, there are no approved products for management of CKD- aP in the United States and Europe. However, there are many products that are used to help manage CKD- aP. The most common of these agents are anti- itch creams and emollients as well as oral or injectable antihistamines. All of these products have limited degrees of efficacy and are available generically. Additionally, patients may try several other agents such as gabapentin or naltrexone, generally with limited success or therapies such as UVB light therapy with limited availability. Because of the substantial unmet need for products that are safe and effective in CKD- aP, there are other companies that either were in the past or are currently involved in the discovery, development, and / or marketing of such products for CKD- aP or related conditions. Some of such product candidates or products include nemolizumab from Galderma, nalbuphine from Trevi Therapeutics and Remitch ® or nalfurafine from Toray Industries. Oral difelikefalin – NDD- CKD. There are no FDA- approved treatment options specifically for this indication in the United States and worldwide. Patients are generally managed with a multitude of products including corticosteroids, gabapentin, antihistamines, antidepressants, and other therapies with varying degrees of success. There is one product, nalfurafine (Remitch ®) marketed by Toray Industries, approved to treat CKD- aP in Japan, but only in dialysis patients. It is not approved in either the United States or Europe for any indication. Oral difelikefalin – AD Associated Pruritus. We are developing oral difelikefalin for the management of moderate- to- severe chronic pruritus associated with AD. There are currently several products specifically approved in 24the United States to treat AD and the itching associated with it: Dupixent (dupilumab), Eucrisa (crisaborole), Opzelura (ruxolitinib), Adbry (tralokinumab- ldrm), Rinvoq (upadacitinib) and Cibinqo (abrocitinib). Additionally, the market for the management of mild- to- moderate and moderate- to- severe AD includes numerous generic products, including topical and oral formulations of corticosteroids and antihistamines. Because of the size and untapped potential of the AD market, there are other companies involved in the discovery, development, and / or marketing of new products for pruritus. Multiple companies are studying IL- 13 inhibitors (e. g. lebrikizumab), IL- 31 inhibitors (e. g. nemolizumab), JAK inhibitors (e. g. baricitinib) and OX40 inhibitors for treatment of AD. Oral difelikefalin – NP Associated Pruritus. There are no FDA- approved treatments for pruritus associated with NP. The management of NP is challenging and conventional treatments for pruritus, such as antihistamines and topical steroids, are largely ineffective.~~ ManufacturingWe do not have any manufacturing facilities. We currently rely, and expect to continue to rely, on third parties for the manufacture of our product ~~candidates~~ **candidate** for preclinical and clinical testing, as well as for commercial manufacture for KORSUVA injection and if our product ~~candidates~~ **candidate** ~~receive~~ **receives** marketing approval. We have negotiated long- term commitments with at least one primary supplier for our primary manufacturing and distribution functions. We have entered into a commercial manufacturing agreement with Patheon for KORSUVA injection, a commercial supply agreement with PPL to produce API, and a commercial packaging agreement with PCI Pharma Services. ~~All of~~ **During 2023, we negotiated to reduce** our **commitment based on much lower- than- expected demand going forward for KORSUVA injection in the United States. Our** product ~~candidates~~ **candidate** ~~are either~~ **is a** small ~~peptides~~ **peptide** ~~or organic small molecules~~ and ~~are~~ **is** manufactured in reliable and reproducible synthetic processes from ~~readily~~ available starting materials. The chemistry is amenable to scale up and does not require any special equipment or technology in the manufacturing process. We expect to continue to develop **our** product ~~candidates~~ **candidate** that can be produced cost- effectively at contract manufacturing facilities. Government Regulation and Product ApprovalGovernment authorities in the United States, at the federal, state and local level, and in other countries extensively regulate, among other things, the research, development, testing, manufacture, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, import and export of pharmaceutical products ~~such as KORSUVA injection~~. The processes for obtaining regulatory approvals in the United States and in foreign countries, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources. FDA RegulationIn the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or ~~judicial~~ **14judicial** sanctions, such as the FDA' s refusal to approve pending NDAs, withdrawal of an approval, imposition of a clinical hold, issuance of warning or untitled 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. The process required by the FDA before a drug may be marketed in the United States generally involves the following: ● completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA' s good laboratory practice, or GLP, regulations; ● submission to the FDA of an IND which must become effective before human clinical trials may begin; ~~25~~ ● approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated; ● performance of human clinical trials, including adequate and well- controlled clinical trials, in accordance with good clinical practices, or cGCP, to establish the safety and efficacy of the proposed drug product for each indication; ● submission to the FDA of an NDA; ● satisfactory completion of an FDA advisory committee review, if applicable; ● satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practices, or cGMP, and to assure that the facilities, methods and controls are adequate to preserve the drug' s identity, strength, quality and purity, as well as satisfactory completion of an FDA inspection of selected clinical sites to determine cGCP compliance; and ● FDA review and approval of the NDA. Preclinical Studies. Preclinical studies include laboratory evaluation of drug substance chemistry, toxicity and drug product formulation, as well as animal studies to assess potential safety and efficacy. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Manufacture of drug substance, drug product and the labeling and distribution of clinical supplies must all comply with cGMP standards. Some preclinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30

days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence. Clinical Trials. Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with cGCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must continue to oversee the clinical trial while it is being conducted. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their ClinicalTrials. gov website. ~~Human~~ **15Human** clinical trials are typically conducted in three sequential phases, which may overlap or be combined. In Phase 1, the drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an initial indication of its effectiveness. In Phase 2, the drug typically is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage. In Phase 3, the drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well- controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk- benefit profile of the product and to provide adequate information for the labeling of the product. Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully ~~26within --~~ **within** any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects 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 patients. Marketing Approval. Assuming successful completion of the required clinical testing, the results of the preclinical and clinical studies, together with detailed information relating to the product' s chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee. Under the ~~Prescription Drug User Fee Act, or PDUFA, guidelines that are currently in effect, the FDA has agreed to certain performance goals regarding the timing of its review of an application. In addition, under the~~ Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements ~~. The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, to mitigate any identified or suspected serious risks and ensure safe use of the drug. The REMS plan could include medication guides, physician communication plans, assessment plans, and elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools~~ . 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 application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in- depth substantive review. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product' s continued safety, quality and purity. The FDA may refer an application for a novel drug to an external advisory committee. 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 the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions **. The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, to mitigate any identified or suspected serious risks and ensure safe use of the drug. The REMS plan could include medication guides, physician communication plans, assessment plans, and elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools** . Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured, referred to as a Pre- Approval Inspection. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure ~~consistent~~ **16consistent** production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical trial sites to assure compliance with cGCP. The testing and approval process for an NDA requires substantial time, effort and financial resources, and each may take several years to complete. Data obtained from preclinical and clinical testing are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval of an NDA on a timely basis, or at all. After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete

response letter generally contains a statement of specific ~~27conditions~~ -- **conditions** that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing in order for FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA' s satisfaction, the FDA may issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, including a boxed warning, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug' s safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms under a REMS which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post- marketing studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes, and additional labeling claims, are subject to further testing requirements and FDA review and approval ~~. Breakthrough Therapy Designation. The FDA may expedite the review of a product candidate designated as a breakthrough therapy, which is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. A sponsor may request the FDA to designate a drug as a breakthrough therapy at the time of, or any time after, the submission of an IND application for the drug. If the FDA designates a drug as a breakthrough therapy, it must take actions appropriate to expedite the development and review of the application, which may include holding meetings with the sponsor and the review team throughout the development of the drug; providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable; involving senior managers and experienced review staff, as appropriate, in a collaborative, cross- disciplinary review; assigning a cross- disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor; and taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment. The FDA may rescind a Breakthrough Therapy designation in the future if further clinical development later shows that the criteria for designation are no longer met. Breakthrough Therapy designation does not change the standards for approval, but may expedite the development or review process~~ . Post- Approval Requirements. Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion, reporting of adverse experiences with the product, and compliance with any post- approval requirements imposed as a condition of approval, such as Phase 4 clinical trials and surveillance to assess safety and effectiveness after commercialization. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior FDA review and approval. There also are continuing, annual program user fee requirements for any marketed products, as well as new application fees for supplemental applications with clinical data. In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies and are subject to periodic announced and unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third- party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance. Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. ~~28Later~~ -- **Later** discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in mandatory revisions to the approved labeling to add new safety information; imposition of post- market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things: ● restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls; **17** ● fines, warning letters or holds on post- approval clinical trials; ● refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals; ● product seizure or detention, or refusal to permit the import or export of products; or ● injunctions or the imposition of civil or criminal penalties. The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Although physicians, in the practice of medicine, may prescribe approved drugs for unapproved indications, pharmaceutical companies are required to promote their drug products only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off- label uses, and a company that is found to have improperly promoted off- label uses may be subject to significant liability. However, physicians may, in their independent medical judgment, prescribe legally available products for off- label uses. The FDA does not regulate the behavior of physicians in their choice of treatments but the FDA does restrict manufacturer' s communications on the subject of off- label use of their products. In addition, the distribution of prescription pharmaceutical products is subject to the ~~Prescription~~ Drug ~~Marketing~~ **Supply Chain Security** Act ~~, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of~~

~~drug distributors by the states. Both the PDMA~~ and state laws **that** limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution. Fraud and Abuse, Data Privacy and Security and Transparency Laws and RegulationsIn addition to FDA restrictions on marketing of pharmaceutical products, federal and state health care regulatory laws restrict business practices in the biopharmaceutical industry. These laws include, among other things, anti- kickback and false claims laws and regulations, physician payment transparency laws and regulations, as well as data privacy and security laws and regulations. The federal Anti- Kickback Statute prohibits, among other things, any person or entity, from knowingly and willfully offering, paying, soliciting or receiving any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for purchasing, leasing, ordering, or arranging for or recommending the purchase, lease, or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term " remuneration " has been interpreted broadly to include anything of value. The Anti- Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti- Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case- by- case basis based on a cumulative review of all of its facts and circumstances. ~~29Additionally~~ -- **Additionally** , the intent standard under the federal Anti- Kickback Statute was amended by the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act (collectively, the " Health Care Reform Law "), to a stricter standard such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the Health Care Reform Law provided that the government may assert that a claim including items or services resulting from a violation of the federal Anti- Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. Federal false claims laws, including the federal civil False Claims Act prohibit, among other things, any person or entity from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment to, or approval by, the federal government or knowingly making, using, or causing to be made or used a false record or statement material ~~to~~ **18to** a false or fraudulent claim to the federal government. A claim includes " any request or demand " for money or property presented to the U. S. government. The federal civil False Claims Act has been used to assert liability on the basis of kickbacks and other improper referrals, improperly reported government pricing metrics such as Best Price or Average Manufacturer Price, improper use of Medicare provider or supplier numbers when detailing a provider of services, improper promotion of off- label uses not expressly approved by FDA in a drug' s label, and allegations as to misrepresentations with respect to the services rendered. Additionally, the civil monetary penalties statute, which, among other things, imposes fines against any person or entity who is determined to have presented, or caused to be presented, claims to a federal healthcare program that the person knows, or should know, is for an item or service that was not provided as claimed or is false or fraudulent. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, including private third- party payers and knowingly and willfully falsifying, concealing or covering up by trick, scheme or device 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 relating to healthcare matters. Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer. In addition, we may be subject to data privacy and security regulation by both the **U. S.** federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, including the Final HIPAA Omnibus Rule published on January 25, 2013, imposes specified requirements on certain types of individuals and entities subject to the law, known as covered entities, such as certain healthcare providers, health plans, and healthcare clearinghouses, as well as their business associates that process individually identifiable health information on their behalf, relating to the privacy, security and transmission of individually identifiable health information as well as their covered subcontractors. Among other things, HITECH makes security standards and certain privacy standards directly applicable to the business associates of covered entities that perform services for them that involve the creation, use, maintenance or disclosure of, individually identifiable health information. 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 attorney' s fees and costs associated with pursuing federal civil actions. In addition, **we are or may become subject to U. S.** state laws ~~may~~ **(such as the California Consumer Privacy Act of 2018 (" CCPA ") and foreign laws (such as the EU' s General Data Protection Regulation 2016 / 679 (" EU GDPR "), the EU GDPR as it forms part of UK law by virtue of section 3 of the European Union (Withdrawal) Act 2018 (" UK GDPR ") that** govern ~~the~~ **data** privacy ~~and~~ **,** security **and protection. These and other similar laws govern the privacy and security** of **personal data.** ~~health information in certain circumstances, many~~ **Many** of ~~which~~ **these laws** differ from each other in significant ways and may not have the same effect, ~~thus~~ **both of which** ~~complicating~~ **complicate** compliance efforts **to the extent we are or may become subject to these laws** . Additionally, federal transparency laws, including the federal Physician Payments Sunshine Act created under Section 6002 of the Health Care Reform Law and its implementing regulations, require that manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children' s Health Insurance Program (with certain exceptions) report annually to the Centers for Medicare & Medicaid Services, or CMS,

information related to payments or other transfers of value made or distributed to physicians (defined to include doctors of medicine, dentists, optometrists, podiatrists and chiropractors), other healthcare professionals (such as physician assistants and nurse practitioners), and teaching hospitals, or to entities or individuals at their request or designation. Additionally, applicable manufacturers and applicable group purchasing organizations are required to report annually to CMS certain ownership and investment interests held by physicians (as defined above) and their immediate family members. ~~30There~~ -- **There** are also an increasing number of analogous state laws that require manufacturers to file reports with states on pricing and marketing information, such as tracking and reporting of gifts, compensations, other remuneration and items of value provided to healthcare professionals and healthcare entities. For example, several states have enacted legislation requiring pharmaceutical companies to, among other things, establish and implement commercial compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials ~~and~~ **19and** other activities and / or register their sales representatives. Certain state laws also regulate manufacturers' use of prescriber- identifiable data. These laws may affect our sales, marketing and other promotional activities by imposing administrative and compliance burdens. In addition, given the lack of clarity with respect to these laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent state and federal authorities. If our operations are found to be in violation of any of the health regulatory laws described above or any other laws that apply to us, we may be subject to penalties, including significant criminal, civil and administrative penalties, damages, fines, imprisonment, exclusion from participation in government healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and / or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non- compliance with these laws, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post- marketing requirements, including safety surveillance, anti- fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals. Coverage and Reimbursement GenerallyThe commercial success of KORSUVA injection and our ability to commercialize any approved product ~~candidates~~ - **candidate** successfully will depend in part on the extent to which governmental payer programs at the federal and state levels, including Medicare and Medicaid, private health insurers and other third- party payers provide coverage for and establish adequate reimbursement levels. In the United States, private health insurers and other third- party payers often provide reimbursement for products and services based on the level at which the government provides reimbursement through the Medicare or Medicaid programs for such products and services. Patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third- party payers to reimburse all or part of the associated healthcare costs. Sales of KORSUVA injection and our product ~~candidates~~ - **candidate** to the extent approved will therefore depend substantially, both domestically and abroad, on the extent to which the costs of our products will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, such as Medicare and Medicaid, private health insurers and other third- party payers. Further, assuming coverage is approved, the resulting reimbursement payment rates might not be adequate. KORSUVA injection is expected to be designated as a component of the government' s bundled reimbursement for ESRD treatment. Our U. S. commercial partner, CSL Vifor, submitted the payment reimbursement application for TDAPA and HCPCS to CMS in September 2021. In December 2021, CMS granted TDAPA to KORSUVA injection in the anti- pruritic functional category. TDAPA will apply to KORSUVA injection beginning April 1, 2022 for two years **. On October 27, 2023, CMS published the final CY 2024 rule, which finalized the post- TDAPA add- on payment as proposed in the draft CY 2024 rule. Under the final rule, TDAPA drugs in existing functional categories will receive a post- TDAPA add- on payment set at 65 percent of the total trailing 12- months expenditure levels for the given renal dialysis drug or biological product. The post- TDAPA add- on payment will be applied to all ESRD PPS payments and paid for 3 years, adjusted annually. The add- on payments for KORSUVA injection will commence on April 1, 2024** . Third- party payers are increasingly imposing additional requirements and restrictions on coverage and limiting reimbursement levels for medical products, including pharmaceuticals. For example, federal and state governments reimburse covered prescription drugs at varying rates generally below average wholesale price. These restrictions and limitations influence the purchase of healthcare services and products. Third- party payers may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA- approved drug products for a particular indication. Additionally, third- party payers are increasingly challenging the price and examining the medical necessity and cost- effectiveness of medical products and services, in addition to their safety and efficacy. Therefore, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost- effectiveness of our products, in addition to the costs required to obtain the FDA approvals. KORSUVA injection and ~~31any of our~~ **20our** product ~~candidates~~ - **candidate** , to the extent ~~they~~ **it** ~~receive~~ **receives** approval, may not be considered medically necessary or cost- effective. Moreover, a payer' s decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved, and one payer' s determination to provide coverage for a product does not assure that other payers will also provide coverage. Adequate third- party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development. Legislative proposals to reform healthcare or reduce costs under government insurance programs may result in lower reimbursement for our products and product candidates or exclusion of our products and product candidates from coverage. The cost containment measures that healthcare payers and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of KORSUVA injection and any approved product ~~candidates~~ - **candidate** . Healthcare Regulatory DevelopmentsIn the United States and some foreign jurisdictions, the legislative landscape with respect to healthcare continues to evolve. There have been a number of legislative and regulatory changes to the healthcare system that

could affect our ability to sell our products profitably. Among policy makers and payers in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. For example, the Health Care Reform Law was passed in March 2010 and includes provisions that have substantially changed healthcare financing by both governmental and private insurers. Among other provisions that could have an impact on our business, the Health Care Reform Law revised the methodology by which rebates owed by manufacturers to the state and federal government for covered outpatient drugs under the Medicaid Drug Rebate Program are calculated, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program, extended the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations, subjected manufacturers to new annual fees and taxes for certain branded prescription drugs, and provided incentives to programs that increase the federal government' s comparative effectiveness research. Additionally, the Health Care Reform Law implemented a new Medicare Part D coverage gap discount program in which manufacturers must now agree to offer 70 % point- of- sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the outpatient drugs being covered under Medicare Part D. There have been executive, judicial and Congressional challenges to certain aspects of the Health Care Reform Law. For example, the Tax Cuts and Jobs Act of 2017, or TCJA, included a provision that repealed, effective January 1, 2019, the tax- based shared responsibility payment imposed by the Health Care Reform Law on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the " individual mandate ". On June 17, 2021, the U. S. Supreme Court dismissed a challenge on procedural grounds that argued the Health Care Reform Law is unconstitutional in its entirety because the " individual mandate " was repealed by Congress. Thus, the Health Care Reform Law will remain in effect in its current form. Prior to the U. S. Supreme Court ruling, on January 28, 2021, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the Health Care Reform Law marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the Health Care Reform Law. In addition, on August 16, 2022, President Biden signed the Inflation Reduction Act of 2022, or IRA, into law, which among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in Health Care Reform Law marketplaces through plan year 2025. The IRA also eliminates the " donut hole " under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out- of- pocket cost and creating a new manufacturer discount program. It is possible that the Health Care Reform Law will be subject to judicial or Congressional challenges in the future. It is unclear how such challenges and the healthcare reform measures of the Biden administration will impact the Health Care Reform Law and our business. ~~32In~~ **21In** addition, other legislative changes have been proposed and adopted since the Health Care Reform Law was enacted. In August 2011, President Obama signed into law the Budget Control Act of 2011, as amended, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee on Deficit Reduction did not achieve its targeted deficit reduction of at least $ 1. 2 trillion for the years 2013 through 2021, triggering the legislation' s automatic reductions to several government programs. These reductions include aggregate reductions to Medicare payments to providers of up to 2 % per fiscal year starting in 2013 and, due to subsequent legislative amendments, will remain in effect until ~~2031~~ **2032** ~~, except for a temporary suspension from May 1, 2020 through March 31, 2022 due to the COVID- 19 pandemic~~ , unless additional Congressional action is taken ~~. Under current legislation, the actual reduction in Medicare payments will vary from 1 % in 2022 to up to 4 % in the final fiscal year of this sequester. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years~~ . Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates 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. Congress is considering additional health reform measures. In the United States, the EU, and other potentially significant markets for our product candidates, government authorities and third- party payers are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which often has resulted in average selling prices lower than they would otherwise be. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU will put additional pressure on product pricing, reimbursement and utilization, which may adversely affect our future product sales and results of operations. For example, there have been several recent U. S. Presidential executive orders, Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform government program reimbursement methodologies for drugs. At the federal level, in July 2021, the Biden administration released an executive order, " Promoting Competition in the American Economy, " with multiple provisions aimed at prescription drugs. In response to Biden' s executive order, on September 9, 2021, the U. S. Department of Health and Human Services, or HHS, released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. No legislation or administrative actions have been finalized to implement these principles. It is unclear whether these or similar policy initiatives will be implemented in the future. In addition, the IRA, among other things, (1) directs HHS to negotiate the price of certain single- source drugs and biologics covered under

Medicare and (2) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions ~~will~~ take effect progressively starting in fiscal year 2023 **. On August 29** , ~~although~~ **2023, HHS announced** ~~they~~ -- **the** ~~may~~ **list of the first ten drugs that will** be subject to **price negotiations, although the Medicare drug price negotiation program is currently subject to** legal challenges. It is ~~currently~~ unclear how the IRA will be implemented but is likely to have a significant impact on the pharmaceutical industry. ~~Further,~~ **In response to** the Biden administration ~~released an additional~~ **' s October 2022** executive order **,** on ~~October~~ **February** 14, ~~2022~~ **2023** , ~~directing~~ HHS **released** ~~to submit~~ a report **outlining** ~~on how the~~ **three** ~~Center for Medicare and Medicaid Innovation can be further leveraged to test~~ new models for **testing by the CMS Innovation Center which will be evaluated on their ability to** ~~lowering~~ --- **lower** ~~drug~~ **the** ~~costs~~ -- **cost** ~~for Medicare~~ **of drugs, promote accessibility,** and ~~Medicaid beneficiaries~~ **improve quality of care** . It is unclear whether ~~these~~ -- **the models** ~~this executive order or similar policy initiatives~~ will be ~~implemented~~ **utilized in any health reform measures** in the future **. Further, on December 7, 2023, the Biden administration announced an initiative to control the price of prescription drugs through the use of march- in rights under the Bayh- Dole Act. On December 8, 2023, the National Institute of Standards and Technology published for comment a Draft Interagency Guidance Framework for Considering the Exercise of March- In Rights which for the first time includes the price of a product as one factor an agency can use when deciding to exercise march- in rights. While march- in rights have not previously been exercised, it is uncertain if that will continue under the new framework** . 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, and, in some cases, to encourage importation from other countries and bulk purchasing **. For example, on January 5, 2024, the FDA approved Florida' s Section 804 Importation Program (SIP) proposal to import certain drugs from Canada for specific state healthcare programs. It is unclear how this program will be implemented, including which drugs will be chosen, and whether it will be subject to legal challenges in the United States or Canada. Other states have also submitted SIP proposals that are pending review by the FDA. Any such approved importation plans, when implemented, may result in lower drug prices for products covered by those programs** . These pressures can arise from rules and practices of managed care groups, judicial decisions and laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical coverage and reimbursement policies and pricing in general. ~~These~~ **22These** and other healthcare reform initiatives may result in additional reductions in Medicare payments and other healthcare funding, which could have a material adverse effect on our financial operations. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could further limit the prices we are able to charge, or the amounts of reimbursement available, for KORSUVA injection and our product ~~candidates~~ - **candidate** once ~~33they~~ -- **they** are approved ~~. Further, it is possible that additional governmental action is taken in response to the COVID- 19 pandemic~~ . Foreign RegulationIn order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy ~~and~~ **. Individual countries** ~~governing~~ --- **govern** , among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. For example, in the EU, we must obtain authorization of a clinical trial application, or CTA, **through the Clinical Trials Registration process** in each member state in which we intend to conduct a clinical trial. Whether or not we obtain FDA **marketing** approval for a product, we would need to obtain the necessary approvals 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 can involve additional product testing and ~~additional~~ **varying** administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory ~~process~~ **outcome** in others. Employees and Human ~~CapitalAs~~ **CapitalOn January 22, 2024, we announced a planned workforce reduction of up to 50 % of our employees in order to reduce our operating expenses and focus our efforts on development of oral difelikefalin in chronic pruritus associated with NP. As** of March ~~2~~ **1** , ~~2023~~ **2024** , we had ~~106~~ **55** employees, of whom ~~32~~ **15** hold PharmD, PhD or MD degrees or the foreign equivalent. All of these employees are located in the United States. None of our employees are represented by a labor union or covered by a collective bargaining agreement. We consider our relationship with our employees to be good. Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing, and integrating our existing and new employees, advisors, and consultants. The principal purposes of our equity and cash incentive plans are to attract, retain and reward personnel through the granting of stock- based and cash- based compensation awards, in order to increase stockholder value and the success of our company by motivating such individuals to perform to the best of their abilities and achieve our objectives. Website Access to ReportsOur website is www. caratherapeutics. com. We are subject to the informational requirements of the Exchange Act and file or furnish reports, including our Annual Report on Form 10- K, Quarterly Reports on Form 10- Q, Current Reports on Form 8- K, and amendments to reports filed pursuant to Sections 13 (a) and 15 (d) of the Exchange Act, proxy statements and other information with the SEC. We make copies of these reports and other information available free of charge through our website (under the heading " SEC Filings ") as soon as reasonably practicable after we file or furnish them with the SEC. The SEC maintains a website that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC at www. sec. gov. The information contained on the websites referenced in this Annual Report on Form 10- K is not incorporated by reference into this filing, and the website addresses are provided only as inactive textual references. Item 1A. Risk FactorsIn addition to other information contained in this Annual Report on Form 10- K, the following risks should be considered in evaluating our business and future prospects and an investment in our common stock. The risks and uncertainties described below are not the only ones we face. If any of the following risks and uncertainties develops into

actual events, our business, financial condition, results of operations and cash flows could be materially adversely affected. In that case, the price of our common stock could decline and you may lose all or part of your investment. ~~34Risks~~ **23Risks** Related to Our Business and the Development and Commercialization of Our Product and Product ~~CandidatesWe~~ **CandidateWe** are substantially dependent on the success of **oral difelikefalin for the treatment of NP, which is** our **only current** product ~~and product candidates~~ **candidate** . If we are unable to successfully complete clinical development, obtain ~~additional~~ regulatory approvals and commercialize **oral difelikefalin** ~~our product and product candidates~~ , or experience significant delays in doing so, our business will be materially harmed. Our business depends on the successful development, regulatory approval **,** and commercialization of our ~~products, KORSUVA injection and Kapruvia, and other~~ product ~~candidates~~ **candidate** . In ~~August~~ **January** ~~2021~~ **2024** , **we announced a prioritization** ~~the FDA approved KORSUVA injection for the treatment~~ of ~~moderate~~ **our pipeline to focus our resources on our late** ~~to- severe CKD- aP~~ **stage clinical program evaluating oral difelikefalin** in **chronic** ~~adults undergoing hemodialysis. Our partner, CSL Vifor, submitted an MAA to the EMA in March 2021. On April 27, 2022, the European Commission granted marketing authorization to Kapruvia for the treatment of moderate- to- severe pruritis~~ **pruritus** associated with **NP** ~~CKD in adult hemodialysis patients. The marketing authorization approves Kapruvia for use in all member states of the EU, as well as in Iceland, Liechtenstein,~~ and **terminate our Phase 3 clinical program evaluating oral** ~~Norway. On April 28, 2022, Kapruvia was also approved in the U. K. Commercial launches in Austria, Germany, Sweden, and Denmark have commenced and we expect the remaining EU countries to launch in 2023. In August 2022, as part of the Access Consortium,~~ difelikefalin ~~injection was approved~~ in **pruritus associated** ~~Switzerland under the brand name Kapruvia, as well as in Singapore and Canada under the brand name KORSUVA. In November 2022, difelikefalin injection was approved in the last Access Consortium country, Australia, under the brand name KORSUVA. Our ability to generate product revenues in the near term is dependent on our and our commercial partners' ability to successfully commercialize KORSUVA injection. Although during the year ended December 31, 2022 we recognized collaborative revenue of $ 16. 6 million from the profit sharing agreement~~ with ~~CSL Vifor~~ **advanced chronic kidney disease** , **including our KICK 1** and **KICK** ~~commercial supply revenue of $ 10.~~ 2 **Phase 3 clinical trials** ~~million from the sale of KORSUVA injection to CSL Vifor, KORSUVA injection may never achieve significant commercial success~~ . **After this prioritization** ~~The successful commercialization of KORSUVA injection in the United States will require significant marketing efforts by our commercial partners. For example~~ , we ~~submitted required documents to CMS to ensure timely reimbursement and patient access to KORSUVA injection. CSL Vifor submitted the application for a HCPCS reimbursement code and the payment reimbursement application for a TDAPA to CMS in September 2021. In December 2021, CMS granted TDAPA to KORSUVA injection in the anti- pruritic functional category. TDAPA became effective for KORSUVA injection on April 1, 2022 for a minimum of two years. CMS expressed in its written communication to us and CSL Vifor, a continuing interest in engaging with the companies regarding potential post- TDAPA support to ensure all beneficiaries with ESRD have access to innovative products such as KORSUVA injection. However, there is no assurance that KORSUVA injection will be able to maintain its price established in the TDAPA period in the post- TDAPA timeframe. If we and our commercial partners do not successfully commercialize KORSUVA injection, we will not be able to generate revenue from sales of any products in the United States in the foreseeable future, or at all. Any significant delays in commercializing KORSUVA injection will~~ have a **single product candidate in clinical development** ~~substantial adverse impact on our business and financial condition. Further~~ , **oral difelikefalin for the treatment of chronic pruritus associated with NP, which** we **are currently evaluating in a Phase 2 / 3 clinical trial. We** cannot be certain that oral difelikefalin or any future product candidates will be successful in clinical trials or receive regulatory approval. Regulatory authorities may interpret our data differently than we have. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA or comparable foreign regulatory authorities, and we may never receive such regulatory approval for **oral difelikefalin or** any **future** ~~of our~~ product candidates. The success of our ~~products and~~ product ~~candidates~~ **candidate will** ~~depends~~ **depend** on many factors, including but not limited to: ● successful enrollment in, and completion of, clinical trials, as well as completion of preclinical studies ; ● ~~safety and~~ favorable efficacy and acceptable safety data from our clinical trials and other studies ; ● receipt of additional regulatory approvals ; ● managing our reliance on sole- source third parties such as our third- party **vendors,** suppliers **,** and manufacturers ; ~~35~~ ● the performance by CROs or other third parties **and consultants** we may retain of their duties to us in a manner that complies with our protocols and applicable laws and that protects the integrity of the resulting data ; ● obtaining and maintaining patent, trade secret and other intellectual property protection and regulatory exclusivity ; ● ensuring we do not infringe, misappropriate or otherwise violate the valid patent, trade secret or other intellectual property rights of third parties ; ● successfully launching **, either alone** ~~our~~ **or with a commercial partner, any** product ~~, such as KORSUVA injection, with our commercial partners, including market acceptance, and our other product candidates~~ **candidate for which regulatory** ~~, if and when approved~~ **approval is received** ; ● obtaining and maintaining favorable reimbursement from third- party payers **and governments** for products and product ~~candidates~~ **candidate** ; ● competition with other products ; ● post- marketing commitments, if any, to regulatory agencies following regulatory approval of our product ~~candidates~~ **candidate** ; ● continued acceptable safety profile following regulatory approval ; ~~and~~ **and24** ● manufacturing or obtaining sufficient supplies of our products and product ~~candidates~~ **candidate** that may be necessary for use in clinical trials for evaluation of our product ~~candidates~~ **candidate** and commercialization of ~~our~~ **any approved** ~~products~~ **product** . If we do not achieve and maintain one or more of these factors in a timely manner or at all, we could experience significant delays in our ability to, or be unable to obtain ~~additional~~ regulatory approvals for, and / or to successfully commercialize our products and product ~~candidates~~ **candidate** , which would materially harm our business and we may not be able to generate sufficient revenues and cash flows to continue our operations ~~and may occur for~~ **Any of these occurrences** ~~many~~ **may** ~~reasons~~ **harm our business,financial condition and prospects significantly.Additionally,our products** ,including **KORSUVA injection and Kapruvia** , ~~but~~ **are subject to continuing regulatory oversight.Drugs are more widely used by patients once approval has been obtained and**

therefore side effects and other problems may be observed after approval that were not ~~limited to~~ **seen or anticipated,or were not as prevalent or severe,during pre- approval clinical trials or nonclinical studies.The subsequent delivery of previously unknown problems with a product,or public speculation about adverse safety events,could face a number of potentially significant negative consequences could result,including** : **● regulatory authorities** ~~clinical sites and investigators~~ may **suspend** ~~deviate from clinical trial protocols,whether due to lack of training~~ or ~~otherwise,and~~ **withdraw approvals of such product;● regulatory authorities may require additional warnings on the label;●** we may ~~fail~~ **be required** to ~~detect any~~ **create a medication guide outlining the risks of** such **side effects** ~~deviations in a timely manner;patients may fail to adhere to any required clinical trial procedures,including any requirements for post- treatment follow- up;our product candidates may fail to demonstrate safety,potency (or~~ **for distribution to** ~~efficacy) in certain patient~~ **patients** ~~subpopulations,which has not been observed in earlier~~ **;● issue warning letters;● mandate modifications to promotional** ~~trials~~ **materials** ~~due to limited sample size,lack of analysis or otherwise;or our~~ - **or** ~~clinical trials may not adequately represent the patient populations we intend to treat,whether due to limitations in our trial designs or otherwise,such as where one patient subgroup is overrepresented in the clinical trial.There can be no assurance that we will not suffer similar setbacks despite the data we observed in earlier or ongoing studies.Based upon negative or inconclusive results,we or any current or any future collaborator may decide,or regulators may~~ require us ~~,~~ to ~~conduct additional preclinical studies~~ **provide corrective information to healthcare practitioners;● require us or** ~~or~~ **our** ~~clinical trials~~ **collaborators to enter into a consent decree** ,which **can include imposition of various fines,reimbursements for inspection costs,required due dates for specific actions and penalties for noncompliance;● impose other civil or criminal penalties;● impose restrictions on operations,including costly new manufacturing requirements;● seize or detain products or require a product recall;● we** ~~would~~ **could be sued and held liable for harm** ~~cause~~ **caused to patients;● the sales of the product may decrease significantly;and ● our reputation may suffer.Any of these events could prevent** us **from achieving** ~~to incur additional operating expenses and delays and may not be sufficient to support regulatory approval on a timely basis or at all.As a result,we cannot be certain that our~~ - **or maintaining market acceptance** ~~ongoing and planned clinical trials or preclinical studies will be successful.Any safety concerns observed in any one~~ of ~~our clinical trials in chronic pruritus associated with NP~~ **KORSUVA injection and the particular product candidate,if approved,and** could **significantly harm** ~~limit the prospects for regulatory approval of oral difelikefalin in NP or other indications,which could have a material adverse effect on~~ our business ~~,financial condition~~ ,results of operations and prospects.If we experience **continuous** delays or difficulties in the enrollment of patients in clinical trials,our receipt of necessary regulatory approvals could be delayed or prevented.We may not be able to initiate or continue conducting clinical trials for our product ~~candidate~~ **candidates** if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar ~~regulatory~~ **50regulatory** authorities outside the United States.Some of our competitors have ongoing clinical trials for product candidates that treat the same indications as our product ~~candidate~~ **candidates** ,and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates.Patient enrollment is affected by other factors including: ~~-~~● the size and nature of the patient population; ~~-~~● the severity of the disease under investigation; ~~-~~● the eligibility criteria for,and design of,the trial in question; ~~-~~● the perceived risks and benefits of the product candidate under study; ~~-~~● competition in recruiting and enrolling patients in clinical trials; ~~-~~● the efforts to facilitate timely enrollment in clinical trials; ~~-~~● the patient referral practices of physicians; ~~-~~● the ability to monitor patients adequately during and after treatment; ~~-~~● the proximity and availability of clinical trial sites for prospective patients;and ~~-~~● delays or difficulties due to **the COVID- 19** ~~public health crises,such as pandemics~~ **pandemic** ~~or other similar outbreaks~~ .For example,we experienced a delay in patient enrollment for our Phase 2 clinical trial of oral difelikefalin for the treatment of pruritus in patients with hepatic impairment due to PBC that led to our decision to **ultimately** discontinue and unblind ~~26this~~ -- **this** trial.We could in the future experience similar delays in our ongoing oral difelikefalin ~~program~~ **programs** ~~in chronic pruritus associated with NP or potential future product candidates~~ .Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays and could require us to abandon one or more clinical trials altogether.We may encounter difficulties and / or delays in completing our planned enrollments.Enrollment delays in our clinical trials may result in increased development costs for our product ~~candidate~~ **candidates** ,or the inability to complete development of our product ~~candidate~~ **candidates** ,which would cause the value of our company to decline,limit our ability to obtain additional financing,and materially impair our ability **to generate revenues.Risks** . We rely, and expect to continue to rely, on third parties to conduct our preclinical studies and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials. We rely on third-party CROs to conduct our ~~preclinical and~~ clinical trials for **oral difelikefalin** ~~all of our product candidates~~ , and do not plan to independently conduct **preclinical studies or** clinical trials of any other potential product candidates. We expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our preclinical studies and clinical trials. These agreements might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, that would delay our product development activities and adversely affect our business. Our reliance on these third parties for development activities will reduce our control over these activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards and our reliance on the CROs does not relieve us of our regulatory responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial and for ensuring that our preclinical trials are conducted in accordance with FDA' s good laboratory practice, or GLP, as appropriate. Moreover, the FDA and comparable foreign regulatory authorities require us to comply with standards, commonly referred to as good clinical practices, or GCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Regulatory authorities enforce these

requirements through periodic inspections of trial sponsors, clinical investigators and trial sites. If we or any of our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a ~~36given~~ -- **given** regulatory authority, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our clinical trials must be conducted with product produced, under current good manufacturing practices, or cGMP, regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We also are required to register certain clinical trials and post the results of certain completed clinical trials on a government- sponsored database, ClinicalTrials. gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions. Our CROs may also have relationships with other entities, some of which may be our competitors. In addition, our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our on- going clinical, non- clinical and preclinical programs ~~. In addition, the operations of our CROs may be constrained or disrupted by the ongoing COVID- 19 pandemic~~. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our preclinical studies or clinical trials in accordance with regulatory requirements or our stated protocols, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product ~~candidates~~ -- **candidate** and will not be able to, or may be delayed in our efforts to, successfully commercialize our products and product ~~candidates~~ -- **candidate** . As a result, our results of operations and the commercial prospects for our products and product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed. If any of our relationships with these third- party CROs terminate, we may not be able to enter into arrangements with alternative CROs or to do so on commercially reasonable terms. Switching or adding additional CROs involves ~~additional~~ **27additional** cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays could occur, which could compromise our ability to meet our desired development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects. If the manufacturers upon whom we rely fail to produce our ~~products or~~ product ~~candidates~~ -- **candidate or any potential future product candidate** in the volumes that we require on a timely basis, or to comply with stringent regulations applicable to pharmaceutical drug manufacturers, we may face delays in the development ~~and commercialization~~ of ~~, or our be unable to meet demand for, our products~~ -- **product candidate** ~~and may lose potential revenues~~ . We do not manufacture **oral difelikefalin** ~~KORSUVA injection or any of our product candidates~~ , and we do not currently plan to develop any capacity to do so. We currently rely, and expect to continue to rely, on third parties for the manufacture of ~~our~~ **oral difelikefalin and any potential future** ~~products~~ -- **product candidate** for ~~commercialization~~ **preclinical and clinical testing. If we were to experience** ~~and~~ -- **an unexpected loss of supply of our product candidate or any of our future** product candidates for ~~preclinical and~~ **any reason, whether as a result of manufacturing, supply or storage issues or otherwise, we could experience delays, disruptions, suspensions or terminations of, or be required to restart or repeat, any pending or ongoing** clinical ~~testing~~ **studies** . It is our intention that **,** by the time of ~~additional~~ **any** regulatory approvals for commercialization **of oral difelikefalin** , we will have negotiated long- term commitments with at least one primary supplier for each manufacturing and distribution function. ~~In July 2019, we entered into a non- exclusive commercial manufacturing agreement with Patheon for KORSUVA (difelikefalin) injection and in July 2021, we entered into a commercial supply agreement with PPL for the KORSUVA (difelikefalin) injection.~~ Any problems or delays we experience in preparing for commercial- scale manufacturing of a product or product candidate may result in a delay in FDA approval of the product **or product** candidate or may impair our ability to manufacture commercial quantities, which would adversely affect our business. For example, our manufacturers will need to produce specific batches of our ~~products and~~ product **or product** ~~candidates~~ -- **candidate** to demonstrate acceptable stability under various conditions and for commercially viable lengths of time. We and our contract manufacturers will need to demonstrate to the FDA and other regulatory authorities this acceptable stability data for our ~~products and~~ product **or product** ~~candidates~~ -- **candidate** , as well as validate methods and manufacturing processes, in order to receive and maintain regulatory approval to commercialize ~~KORSUVA injection or~~ any ~~other~~ **approved** product candidates. Furthermore, if our commercial manufacturers fail to deliver the required commercial quantities of bulk drug substance or finished product on a timely basis and at commercially reasonable prices, we would likely be unable to meet demand for our ~~products~~ -- **product** and we would lose potential revenues. The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling up initial production. These problems include ~~37difficulties~~ -- **difficulties** with production costs and yields, quality control, including stability of the products and product candidate and quality assurance testing, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. Our manufacturers may not perform as agreed. If our manufacturers were to encounter any of these difficulties, our ability to provide products for commercialization and product candidates to patients in our clinical trials would be jeopardized. This could, among other things, lead to increased costs, lost revenue, damage to customer relationships, time and expense spent investigating the cause and, depending on the cause, similar losses with respect to other batches or products. If problems are not discovered before the product is released to the market, recall and product liability costs may also be incurred. Further, we may rely on proprietary technology developed by our contract manufacturers for purposes of manufacturing certain of our products and product ~~candidates~~ -- **candidate** and our failure to negotiate or maintain the long- term use of any such proprietary technology or the inability for our contract manufacturers to

produce our products and product ~~candidates~~ **candidate** or components of our products and product ~~candidates~~ **candidate** in the volumes that we require on a timely basis, may lead to delays or interruptions in the regulatory approval or commercialization process, as well as increased costs. For example, in August 2019, we entered into the Enteris License Agreement and intend to use Enteris' s Peptelligence ® technology to develop, manufacture and commercialize oral difelikefalin. If we experience any interruptions in the manufacture, delivery or scale- up of the Enteris formulation technology, we may experience delays in the development and commercialization of oral difelikefalin. Further, if we are unable to maintain our relationship with Enteris, we may be forced to reformulate oral difelikefalin which could result in significantly delaying commercializing oral difelikefalin and require us to incur additional costs in connection with such reformulation and potentially needed to seek additional approvals from the FDA. The operations of our third- party manufacturers have been and may in the future be ~~constrained~~ **28constrained** or disrupted and their operating capacity may be reduced by ~~the COVID- 19~~ **public health crises, such as** ~~pandemic~~ **pandemics or other similar outbreaks**, which could negatively impact our clinical development and commercialization timelines. In addition, all manufacturers of our products and product ~~candidates~~ **candidate** must comply with cGMP requirements enforced by the FDA through its facilities inspection program. These requirements include quality control, quality assurance and the maintenance of records and documentation. Manufacturers of our products and product ~~candidates~~ **candidate** may be unable to comply with these cGMP requirements and with other FDA, state and foreign regulatory requirements. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, they will not be able to secure and / or maintain regulatory approval for their manufacturing facilities. In addition, regulatory agencies subject an approved product, its manufacturer and the manufacturer' s facilities to continual review and inspections, including periodic unannounced inspections. The subsequent discovery of previously unknown problems with our current or any future approved products, including adverse events of unanticipated severity or frequency, or problems with the facilities where our current or any future approved products are manufactured, may result in restrictions on the marketing of our current or any such future approved products, up to and including withdrawal of the affected product from the market. We have little control over our manufacturers' compliance with these regulations and standards. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our products and product ~~candidates~~ **candidate** or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our products and product ~~candidates~~ **candidate**, if approved. A failure to comply with these requirements may result in fines and civil penalties, suspension of production, suspension, delay or denial of product approval, product seizure or recall, or withdrawal of product approval. If the safety of any quantities supplied is compromised due to our manufacturers' failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for or successfully commercialize our products and product ~~candidates~~ **candidate**. ~~38Even~~ -- **Even** if we obtain ~~additional~~ regulatory approvals for our product ~~candidates~~ **candidate or any potential future product candidate**, they may never be successfully launched or become profitable, in which case our business, prospects, operating results and financial condition may be materially harmed. In order to successfully launch **a** ~~our products and~~ product ~~candidates~~ and have ~~them~~ **it** become profitable, we anticipate that we will have to dedicate substantial time and resources. Our ability to generate revenues from our commercialized products will depend on a number of factors, including, but not limited to: ● achievement of broad market acceptance and coverage by **government and** third- party payers for our ~~products~~ **product**; ● **our or** our partners' effectiveness in marketing and selling our ~~products~~ **product**; ● our ability to have manufactured commercial quantities of our ~~products~~ **product** at acceptable cost levels and in compliance with regulatory requirements; ● our ability to maintain a cost-efficient organization and, to the extent we seek to do so, to collaborate successfully with additional third parties; ● our ability to expand and maintain intellectual property protection for our ~~products~~ **product** successfully; ● the efficacy and safety of our ~~products~~ **product**; and / or ● our ability to comply with regulatory requirements, which are subject to change. Because of the numerous risks and uncertainties associated with our commercialization efforts, we may not be able to achieve profitability. **For example, we previously successfully developed KORSUVA injection through regulatory approval, for the treatment of moderate- to- severe pruritus associated with chronic kidney disease in adults undergoing hemodialysis. However, this product failed to achieve meaningful commercial success.** ~~Even~~ **29Even** if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. A failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment. If we or our collaborators are unable to establish effective marketing and sales capabilities, or if we are unable to enter into or maintain agreements with third parties to market and sell our ~~products and~~ product **and product** ~~candidates~~ **candidate**, if they are approved, we may be unable to generate product revenues. We currently do not have an internal commercial infrastructure for the marketing, sale **,** and distribution of pharmaceutical products **, but we intend to develop this infrastructure if oral difelikefalin or any future product candidate is approved for marketing in the United States**. In order to commercialize **oral difelikefalin** ~~our~~ **or any potential future** product ~~and product candidates~~ **candidate** (if approved) **in the United States**, we ~~must~~ **will need to** build our marketing, sales and distribution capabilities **. We have no prior experience in the marketing, sale and distribution of pharmaceutical products, and there are significant risks involved in the building and managing of a commercial infrastructure to the extent we choose to do so in the future. The establishment and development of** ~~or~~ **our own sales force and related plans to market any products in the United States we may develop will be expensive and time- consuming and could delay any product launch, and we may not be able to successfully develop this capability. If oral difelikefalin or any future product candidate is approved for marketing outside of the United States, we intend to** make and maintain arrangements with third parties to perform these services. We ~~have no prior experience in the marketing, sale and distribution of pharmaceutical products, and there are significant risks involved in the building and managing of a~~

~~commercial infrastructure to the extent we choose to do so in the future. The establishment and development of our own sales force and related plans to market any products we may develop will be expensive and time consuming and could delay any product launch, and we may not be able to successfully develop this capability. In August 2021, the FDA approved KORSUVA injection for the treatment of moderate- to- severe CKD- AP in adults undergoing hemodialysis in the United States. We have entered into agreements with CSL Vifor to commercialize KORSUVA injection in the United States. We are dependent on CSL Vifor to successfully commercialize KORSUVA injection in the United States with their own, or their collaborators', sales force. We have partnered with CSL Vifor to commercialize KORSUVA injection (known as Kapruvia in certain markets) worldwide, excluding Japan (Maruishi / sub- licensee Kissei), and South Korea (CKDP). We and CSL Vifor began commercializing KORSUVA injection in the United States in April 2022 and we began recording associated profit- sharing revenues in the second quarter of 2022. CSL Vifor began commercializing Kapruvia in select European markets in 2022 and we began receiving royalties based on these sales. 39We~~ , or our partners or collaborators, will have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train, manage and retain marketing and sales personnel. In the event that we or our partners or our collaborators are unable to develop a marketing and sales infrastructure, we may not be able to commercialize ~~KORSUVA injection~~ **oral difelikefalin** or any **potential** ~~of our other current or~~ future product ~~candidates~~ **candidate** , which would limit our ability to generate product revenues. Factors that may inhibit our or our partners' or collaborators' efforts to commercialize ~~KORSUVA injection or~~ **oral difelikefalin, if approved,** ~~our~~ **or any potential** ~~other current or~~ future product ~~candidates~~ **candidate** include: ● inability to recruit, train, manage and retain adequate numbers of effective sales and marketing personnel; ● inability of sales personnel to obtain access to physicians **and other providers** or educate adequate numbers of physicians **and other providers** on the benefits of prescribing ~~KORSUVA injection or our other~~ **the** ~~current or future~~ product ~~candidates~~ ; ● inability to effectively oversee a geographically dispersed sales and marketing team; ● the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and ● unforeseen costs and expenses associated with creating an independent sales and marketing organization. Our or our partners' or our collaborators' sales force and marketing teams may not be successful in commercializing **any approved product candidate that may receive regulatory approval. For example, we previously partnered with CSL Vifor for the commercialization of** KORSUVA injection **, but that** ~~or any of our other current or future~~ product ~~candidates~~ **has not achieved meaningful commercial success** . In the event that we are unable to successfully collaborate with a third- party marketing and sales organization to commercialize any approved product ~~candidates~~ **candidate** outside the United States, our ability to generate product revenues may be limited. To the extent that we rely on third parties to commercialize products for which we obtain regulatory approval, we may receive less revenues than if we commercialized these products ourselves. In addition, we would have less control over the sales efforts of any other third parties involved in our commercialization efforts. ~~We~~ **30We** face significant competition from other pharmaceutical and biotechnology companies, academic institutions, government agencies and other research organizations. Our operating results will suffer if we fail to compete effectively. The development and commercialization of new drug products is highly competitive. We face competition with respect to our current ~~products and~~ product **, KORSUVA injection, and our product** ~~candidates~~ **candidate,** and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of ~~pain and~~ pruritus. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization. Among the companies that currently market or are developing therapies in the pruritus space that, if approved, our **oral difelikefalin** ~~products and product candidates~~ may potentially compete with include: Pfizer, AbbVie, Eli Lilly, Amgen, Regeneron, Leo Pharma, Galderma, Chugai ~~, Trevi~~ , Incyte and others. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than our products or our current or future product candidates. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third- party payers seeking to encourage the use of generic products. Generic products are ~~currently on the~~ **approved or used in clinical practice in some** ~~market~~ **markets** for ~~some of~~ the ~~indications~~ **indication** that **our** ~~we are pursuing, and additional products~~ **product** ~~are 40expected~~ **candidate is intended** to **treat** ~~become available on a generic basis over the coming years~~ . We expect that **oral difelikefalin** ~~KORSUVA injection,~~ and ~~our~~ **any potential future** product candidates ~~(~~ **,** if approved ~~)~~ , ~~will~~ **would** be priced at a significant premium over competitive generic products **, if any** . Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in R & D, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Early- stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient ~~registration~~ **recruitment** for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs ~~. To the extent that KORSUVA injection or our product candidates, if approved, do not achieve broad market acceptance, the revenues that we generate from sales will be limited. We have never successfully commercialized a product or product candidate for any indication. KORSUVA injection and our other current or future product candidates, if approved by the appropriate regulatory authorities for marketing and sale, may not gain~~

~~acceptance among physicians, hospitals, dialysis providers, patients and third- party payers. If KORSUVA injection and any product candidates for which we obtain regulatory approval do not gain an adequate level of market acceptance, we may not generate significant product revenues or become profitable. Market acceptance of KORSUVA injection, oral difelikefalin and any future product candidate by physicians, hospitals, dialysis providers, patients and third- party payers will depend on a number of factors, some of which are beyond our control. The degree of market acceptance of KORSUVA injection and any of our product candidates will depend on a number of factors, including: ● the prevalence and severity of adverse events associated with such product or product candidate; ● limitations or warnings contained in the product's FDA- approved labeling, including potential limitations or warnings for such product candidate, that may be more restrictive than other pain management or pruritus products; ● changes in the standard of care for the targeted indications for such product candidate, which could reduce the marketing impact of any claims that we could make following additional FDA approval, if obtained; ● the relative convenience and ease of administration of such product or product candidate; ● cost of treatment versus economic and clinical benefit in relation to alternative treatments or therapies; ● the availability of coverage and adequate reimbursement by third- party payers, such as insurance companies and other healthcare payers, and by government healthcare programs, including Medicare and Medicaid; ● the extent and strength of our marketing and distribution of such product or product candidate; ● the safety, efficacy and other potential advantages over, and availability of, alternative treatments already used to treat acute pain, chronic pain and / or pruritus; ● distribution and use restrictions, if any, imposed by the FDA with respect to such product candidate or to which we agree as part of a mandatory risk evaluation and mitigation strategy or voluntary risk management plan; ● the timing of market introduction of such product or product candidate, as well as competitive products; ● our ability to offer such product or product candidate for sale at competitive prices; 41 ● the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies; and ● the clinical indications for such product or product candidate if approved. Our and our commercial partners' ability to effectively promote and sell KORSUVA injection and our current and future product candidates, if approved, will also depend on pricing and cost effectiveness, including our ability to produce a product at a competitive price and achieve acceptance of the product onto dialysis organization or hospital formularies, and our ability to obtain sufficient third- party coverage or reimbursement. Generally, before we or our commercial partners can attempt to sell a product in a hospital or dialysis provider, it must be approved for addition to that institution's list of drugs approved for use in that institution, or formulary list. In evaluating drugs for inclusion on the formulary list, hospitals and dialysis providers evaluate a variety of factors, including cost. The frequency with which hospitals and dialysis providers add and remove drugs from their formulary lists varies from organization to organization, and institutions often require additional information prior to adding new drugs to their formulary, which may result in substantial delays in our receiving formulary approval for KORSUVA injection. Since most hospitals are members of group purchasing organizations, which leverage the purchasing power of a group of entities to obtain discounts based on the collective buying power of the group, our and our commercial partners' ability to access customers in the hospital marketplace will also depend on our ability to effectively promote KORSUVA injection and our product candidates to group purchasing organizations. We will also need to demonstrate acceptable evidence of safety and efficacy, as well as relative convenience and ease of administration. Market acceptance could be limited depending on the prevalence and severity of any expected or unexpected adverse side effects associated with KORSUVA injection and our product candidates. In addition, the potential market opportunity for KORSUVA injection and for our product candidates is difficult to precisely estimate. Our internal estimates of the potential market opportunity for our products and product candidates include several key assumptions based on our industry knowledge, industry publications, third- party research reports, assessment of competition, and other surveys. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions. If any of these assumptions proves to be inaccurate, then the actual market for our products and product candidates could be smaller than our estimates of our potential market opportunity. If the actual market for our products and product candidates is small, and / or smaller than we expect, our product revenue may be limited and it may be more difficult for us to achieve or maintain profitability. Our and our commercial partners' efforts to educate the medical community and third- party payers on the benefits of KORSUVA injection and our product candidates may require significant resources and may never be successful. Even if the medical community accepts that KORSUVA injection or one of our product candidates is safe and effective for its approved indications, physicians and patients may not immediately be receptive to such product or product candidate and may be slow to adopt it as an accepted treatment of pain or pruritus. It is unlikely that any future labeling approved by the FDA will contain claims that one of our products or product candidates is safer or more effective than competitive products or will permit us to promote such products or product candidate as being superior to competing products. Further, the availability of inexpensive generic forms of products for acute and chronic pain as well as pruritus may also limit acceptance of KORSUVA injection and our product candidates among physicians, patients and third- party payers. If KORSUVA injection and our current and any future product candidate, if approved, does not achieve an adequate level of acceptance among physicians, patients and third- party payers, we may not generate meaningful revenues from KORSUVA injection or our current and future product candidates, and we may not become profitable~~ . We face potential product liability exposure, and if successful claims are brought against us, we may incur substantial liability ~~for KORSUVA injection~~ **and may have to limit commercialization of** ~~or~~ **our** ~~our other current and future~~ product ~~candidates~~ **candidate** ~~that we may develop and may have to limit their commercialization~~ . We face an inherent risk of product liability lawsuits related to the sale of our products to, use of our products by, and testing of our product ~~candidates~~ **candidate** in, seriously ill patients. For example, product liability claims might be brought against us by consumers, healthcare providers or others using, administering or selling our products. We may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, ~~42defects~~ **defects** in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. If we cannot successfully defend ourselves against these claims, we will incur substantial

liabilities. Regardless of merit or eventual outcome, liability claims may result in: ● loss of revenue from decreased demand for our products and / or product ~~candidates~~ **candidate** ; ● impairment of our business reputation or financial stability; ● costs of related litigation; **31** ● substantial monetary awards to patients or other claimants; ● diversion of management attention and scientific resources from our business operations; ● withdrawal of clinical trial participants and potential termination of clinical trial sites or entire clinical programs; ● the inability to successfully commercialize our products and / or product ~~candidates~~ **candidate** ; ● significant negative media attention; ● initiation of investigations by regulators or increased regulatory scrutiny; ● product recalls, withdrawals or labeling, marketing or promotional restrictions; and ● the inability to commercialize our product ~~candidates~~ **candidate** . **For** ~~With respect to KORSUVA injection and~~ any ~~of our other~~ product ~~candidates~~ **candidate** that ~~are~~ **is** approved for commercial sale, we ~~are, and~~ will be ~~,~~ highly dependent upon ~~physician~~ **healthcare provider** and patient perceptions of us and the safety and quality of our products. We could be adversely affected if we are subject to negative publicity. We could also be adversely affected if any of our products or any similar products distributed by other companies prove to be, or are asserted to be, harmful to patients. Because of our dependence upon consumer perceptions, any adverse publicity associated with illness or other adverse effects resulting from patients' use or misuse of our products or any similar products distributed by other companies could have a material adverse impact on our financial condition or results of operations. We have obtained limited product liability insurance coverage for our products and our clinical trials with a $ 15. 0 million annual aggregate coverage limit in the United States and various other coverage limits outside of the United States. However, our insurance coverage may not reimburse us or may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive, and, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. We intend to expand our insurance coverage to include the sale of commercial products for our product ~~candidates~~ **candidate** in development, but we may be unable to obtain commercially reasonable product liability insurance for any products approved for marketing, or at all. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. A successful product liability claim or series of claims brought against us could cause our stock price to fall and, if judgments exceed our insurance coverage, could decrease our cash and adversely affect our business. We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on **our** product ~~candidates~~ **candidate** or indications that may be more profitable or for which there is a greater likelihood of success. Because we have limited financial and managerial resources, we focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of both its regulatory approval and commercialization. As such, we are currently ~~primarily~~ focused on the development of oral difelikefalin for ~~AD- aP, 43NDD- CKD, and~~ NP. As a result, we may have foregone or delayed, or may in the future forgo or delay, pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential. For example, in ~~2022~~ **2023** , we **terminated** ~~de- prioritized~~ the ~~PBC~~ **atopic dermatitis** program as part of our strategy to focus on our ~~nephrology~~ **advanced chronic kidney disease** and ~~dermatology franchises~~ **NP programs. Further, in January 2024, we announced a prioritization of our pipeline to focus our resources on our late- stage clinical program evaluating oral difelikefalin in chronic pruritus associated with NP and terminate our Phase 3 clinical program evaluating oral difelikefalin in pruritus associated with advanced chronic kidney disease** . Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future R & D programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing **,** or other ~~royalty~~ **32royalty** arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. Our future growth may depend on our ability to identify and develop products and if we do not successfully identify and develop product candidates or integrate them into our operations, we may have limited growth opportunities. ~~A~~ **One** component of our business strategy is to continue to develop a ~~pipeline of~~ product ~~candidates by developing products~~ that we believe ~~are~~ **is** a strategic fit with our focus on ~~pain and~~ pruritus therapeutics. However, these business activities may entail numerous operational and financial risks, including: ● difficulty or inability to secure financing to fund development activities for such development; ● disruption of our business and diversion of our management' s time and attention; ● higher than expected development costs; ● exposure to unknown liabilities; ● difficulty in managing multiple **clinical trials** ~~product development programs~~ ; and ● inability to successfully develop new products or clinical failure. We have limited resources to identify and execute the development of products. Moreover, we may devote resources to potential ~~development~~ **developments** that are never completed, or we may fail to realize the anticipated benefits of such efforts. If we do not successfully develop and commercialize product candidates, we may not be able to obtain product revenues in future periods. The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable. If we are not able to obtain, or if there are delays in obtaining, required additional regulatory approvals, we will not be able to commercialize our product candidates as expected, and our ability to generate revenue will be materially impaired. The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate' s clinical development and may vary among jurisdictions. **It** ~~In August 2021, the FDA approved KORSUVA injection for the treatment of moderate- to- severe CKD- aP in adults undergoing hemodialysis in the United States. Our partner, CSL Vifor, submitted an MAA to the EMA in March 2021. On April 27, 2022, the European Commission granted marketing authorization to Kapruvia for the treatment of moderate- to- severe pruritis associated with CKD in adult hemodialysis patients. The marketing authorization approves Kapruvia for use in all member states of the EU, as well as in Iceland, Liechtenstein, and Norway. On April 28, 2022, Kapruvia was also approved in the U. K.~~

~~In August 2022, as part of the Access Consortium, difelikefalin injection was approved in Switzerland under the brand name Kapruvia, as well as in Singapore and Canada under the brand name KORSUVA. In November 2022, difelikefalin injection was approved in the last Access Consortium country, Australia, under the brand name KORSUVA. We have not obtained regulatory approval for our 44other product candidates and it~~ is possible that **neither** ~~none of our existing product candidates, including~~ oral difelikefalin, ~~or~~ **nor** any **potential** product candidates we may seek to develop in the future, will ever obtain regulatory approval. Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA, and similar regulatory authorities ~~outside~~ **in** ~~the~~ **other countries** ~~United States~~. Failure to obtain marketing approval for a product candidate will prevent us from commercializing that product candidate. We expect to continue to rely on third- party CROs **, other vendors,** and consultants to assist us in filing and supporting the applications necessary to gain marketing approvals. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate' s safety and efficacy for that indication. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. Product candidates in later stages of ~~clinical~~ **33clinical** trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. Our future clinical trial results may not be successful. We may also experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including: ● regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site; ● we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites; ● clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs; ● the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate; ● our third- party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all; ● we may have to suspend clinical trials, ~~as in the case of the IND clinical hold placed on our adaptive Phase 3 trial of I. V. difelikefalin for postoperative pain in February 2016, which was subsequently removed in April 2016,~~ or terminate clinical trials of our product ~~candidates~~ **candidate** for various reasons, including a finding that the participants are being exposed to unacceptable health risks; ● regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks; ● changes in marketing approval policies during the development period; ● changes in or the enactment of additional statutes or regulations; ~~45~~ ● changes in regulatory review for each submitted product application; ● the cost of clinical trials of our product ~~candidates~~ **candidate** may be greater than we anticipate; ● the supply or quality of our product ~~candidates~~ **candidate** or other materials necessary to conduct clinical trials of our product ~~candidates~~ **candidate** may be insufficient or inadequate; and ● our product ~~candidates~~ **candidate** may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or institutional review boards to suspend or terminate the trials. In addition, unfavorable changes in our industry or the global economy, including as a result of macroeconomic factors related to inflation, rising interest rates, political turmoil, or ~~pandemics~~ **public health crises** such as ~~COVID- 19~~ **pandemics or other similar outbreaks**, could contribute to some of the events listed above and further impact our ability to progress our clinical trials, submit for marketing approval or commercialize our product candidates, if approved, as planned. Further, if and to the extent, global health concerns prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our additional regulatory submissions, which could affect our ability to obtain marketing approval for ~~any of~~ our product ~~candidates~~ **candidate** ~~, including our MAA to the EMA submitted in March 2021~~. ~~Moreover~~ **34Moreover**, if we are required to conduct additional clinical trials or other testing of our product ~~candidates~~ **candidate** beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product ~~candidates~~ **candidate** or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may: ● be delayed in obtaining marketing approval for our product ~~candidates~~ **candidate**; ● not obtain marketing approval at all; ● obtain approval for indications or patient populations that are not as broad as intended or desired; ● obtain approval with labeling that includes significant use or distribution restrictions or safety warnings; ● be subject to additional post- marketing testing requirements; or ● have the product removed from the market after obtaining marketing approval. Furthermore, regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies, including with respect to third- party technology used in any of our product candidates such as the excipient we intend to use for oral difelikefalin. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post- approval commitments that render the approved product not commercially viable. Finally, even if we were to obtain approval, regulatory authorities may approve ~~any of~~ our product

~~candidates~~ **candidate** for fewer or more limited indications than we request, may grant approval contingent on the performance of costly post- marketing clinical trials, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Any of these scenarios could compromise the commercial prospects for our product ~~candidates~~ **candidate** to assure safe use of the product ~~candidates~~ **candidate**, either as a condition of product candidate approval or on the basis of new safety information. If we experience delays in obtaining approval, if we fail to obtain approval of a product candidate or if the label for a product candidate does not include the labeling claims necessary or desirable for the successful commercialization ~~46of~~ **of** that product candidate, the commercial prospects for such product candidate may be harmed and our ability to generate revenues will be materially impaired. **Our** ~~For our approved products, KORSUVA injection and Kapruvia, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense. Additionally, our~~ product ~~candidates~~ **candidate or any future product candidate**, if approved, could be subject to labeling and other restrictions and market withdrawal and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our ~~products. KORSUVA injection, Kapruvia and any~~ product ~~candidate for which we obtain marketing approval, along with the manufacturing processes, post- approval clinical data (if any), labeling, packaging, distribution, adverse event reporting, storage, recordkeeping, export, import, advertising and promotional activities for such product, will be subject to extensive and ongoing requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post- marketing information and reports, registration and listing requirements, continued compliance with cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping and cGCPs for any clinical trials that we conduct post- approval~~. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including any requirement to implement a Risk Evaluation and Mitigation Strategies, or REMS. If ~~any of~~ our product ~~candidates~~ **candidate** receives marketing approval, the accompanying label may limit the approved use of our drug, which could limit sales of the product. The FDA **or other regulatory authorities** may also impose requirements for costly post- marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. The FDA **and other regulatory authorities** closely ~~regulates~~ **regulate** the post- approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA **and other regulatory authorities** ~~imposes~~ **impose** stringent restrictions on manufacturers' communications regarding off- label use and if we do not market our products for their approved indications, we may be subject to enforcement action for off- label marketing. Violations of the Federal Food, Drug, and Cosmetic Act **or equivalent regulations outside the United States** relating to the promotion ~~of~~ **35of** prescription drugs may lead to investigations alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws. In addition, later discovery of previously unknown **AEs** ~~adverse events~~ or other problems with our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including: ● restrictions on the products, manufacturers, manufacturing facilities or manufacturing process; ● imposition of restrictions on operations, including costly new manufacturing requirements; ● restrictions on the labeling or marketing of a product; ● restrictions on product distribution or use; ● requirements to conduct post- marketing studies or clinical trials; ● warning letters; ● withdrawal of the products from the market; ● refusal to approve pending applications or supplements to approved applications that we submit; ● recall of products and publicity requirements; ~~47~~ ● fines, restitution or disgorgement of profits or revenues; ● suspension or withdrawal of marketing or regulatory approvals; ● refusal to permit the import or export of our products; ● product seizure, detentions or import bans ; or ● injunctions or the imposition of civil or criminal penalties. The FDA' s **or other regulatory authorities'** policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained. Regulatory approval is limited by the FDA **and other regulatory authorities** to those specific indications and conditions for which clinical safety and efficacy have been demonstrated, and we may be subject to fines, penalties or injunctions if we are determined to be promoting the use of our products for unapproved or " off- label " uses, resulting in damage to our reputation and business. When the FDA or comparable foreign regulatory authorities issue regulatory approval for a product candidate, the regulatory approval is limited to those specific indications for which a product is approved. ~~For example, the FDA approved KORSUVA injection for the treatment of moderate- to- severe CKD- AP in adults undergoing hemodialysis indication.~~ If we are not able to obtain FDA approval for any desired future indications for our products and product candidates, our ability to effectively market and sell our products may be reduced and our business may be adversely affected. While physicians may choose to prescribe drugs for uses that are not described in the product' s labeling and for uses that differ from those tested in clinical studies and approved by the regulatory authorities, we are prohibited from marketing and promoting the products for indications that are not specifically approved by the FDA **or other regulatory 36authorities**. These " off- label " uses are common across medical specialties and may constitute an appropriate treatment for some patients in varied circumstances. Regulatory authorities in the United States **and other countries** generally do not restrict or regulate the behavior of physicians in their choice of treatment within the practice of medicine. Regulatory authorities do, however, restrict communications by pharmaceutical companies on off- label use. If the FDA **or other regulatory authorities** ~~determines~~ **determine** that our or our commercial partners' promotional activities constitute promotion of an off- label use, it could request that we modify our promotional materials. Further, off- label promotion could subject us to regulatory or enforcement actions by the FDA and other ~~agencies~~ **authorities**, including issuance of warning letters or untitled letters, suspension or withdraw an approved product from the market, mandatory or voluntary recalls, civil fines, disgorgement of money, operating restrictions, additional reporting requirements and

/ or oversight if we become subject to a corporate integrity agreement or similar agreement, injunctions or criminal prosecution, any of which could significantly harm our business. Failure to obtain marketing approval in international jurisdictions would prevent our product ~~candidates~~ **candidate** from being marketed abroad. In order to market and sell our products in the EU and many other jurisdictions, we or our collaborators or partners must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. ~~For example, our partner, CSL Vifor, submitted an MAA to the EMA in March 2021, which was accepted for review by the EMA. On April 27, 2022, the European Commission granted marketing authorization to Kapruvia for the treatment of moderate- to- severe pruritis associated with CKD in adult hemodialysis patients. The marketing authorization approves Kapruvia for use in all member states of the EU, as well as in Iceland, Liechtenstein, and Norway. On April 28, 2022, Kapruvia was also approved in the U. K. In August 2022, as part of the Access Consortium, difelikefalin injection was approved in Switzerland under the brand name Kapruvia, as well as in Singapore and Canada under the brand name KORSUVA. In 48November 2022, difelikefalin injection was approved in the last Access Consortium country, Australia, under the brand name KORSUVA.~~ Even if we obtain FDA approval of **a** ~~one of our~~ product ~~candidates~~ **candidate**, the regulatory approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or these third parties may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, the failure to obtain approval in one jurisdiction may compromise our or our collaborators' or partners' ability to obtain approval elsewhere. We or our collaborators or partners may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market. Our **agreements with HCR contain various covenants and other provisions, which, if violated, could materially adversely affect our financial condition. During the fourth quarter of 2023, we, through Cara Royalty Sub, entered into the HCR Agreement with HCR, pursuant to which Cara Royalty Sub sold, or agreed to sell, to HCR the Royalties under the Covered License Agreements, in exchange for up to $ 40. 0 million. We have retained all of our right, title and interest in, to and under the Covered License Agreements that relate to any non- intravenous formulation of difelikefalin. Under the terms of the HCR Agreement, Cara received an initial payment of $ 17. 5 million in November 2023. In December 2023, we received an additional $ 20. 0 million less certain advisory fees, upon satisfying the milestone event for pricing for Kapruvia ® (difelikefalin) in Germany being approved above a certain threshold amount per dose. The terms of the HCR Agreement also provide for an additional $ 2. 5 million milestone payment to Cara Royalty Sub upon achievement of a 2024 sales milestone of KORSUVA in Japan. The HCR Agreement will automatically expire, and the payment of Royalties to HCR will cease, when HCR has received payments of Royalties equal to two times the aggregate amount of payments made by HCR under the HCR Agreement if achieved on or prior to December 31, 2029, or 2. 8 times the aggregate amount of payments made by HCR under the HCR Agreement, if the 2029 Threshold is not achieved on or prior to December 31, 2029. In the event of a change of control, Cara Royalty Sub will pay to HCR an amount equal to 2. 8 times the aggregate amount of payments made by HCR less the total net amounts paid by Cara Royalty Sub to HCR as of the effective date of control. In certain situations, Cara Royalty Sub would not be obligated to pay the change of control payment to HCR. After the HCR Agreement expires, all rights to receive the Royalties return to Cara Royalty Sub. In connection with the HCR Agreement, we entered into a Contribution and Servicing Agreement which contains various representations and warranties, covenants, indemnification obligations and other provisions related to the 37contribution of the Covered License Agreement to Cara Royalty Sub and our maintenance and servicing obligations with respect to the Royalties and the Covered License Agreements. In the event we violate these covenants or provisions, we may lose the right to act as the servicer of Cara Royalty Sub and a third- party servicer may be appointed at Cara Royalty Sub' s expense. Our replacement as servicer, if it were to occur, could have a material adverse effect on our financial condition as HCR, by virtue of owning Cara Royalty Sub, would own the Royalties. In connection with the HCR Agreement we also entered into a Pledge and Security Agreement containing various representations, warranties and covenants, and a limited recourse guaranty of Cara Royalty Sub' s obligations under the Purchase and Sale Agreement which is secured by the pledge in favor of HCR all of the capital stock of Cara Royalty Sub. HCR is entitled to foreclose on the capital stock of Cara Royalty Sub following the occurrence of certain remedies events, including, without limitation, a bankruptcy of us or the failure of us to perform our obligations under the Contribution and Servicing Agreement. Such foreclosure, if it were to occur, could have a material adverse effect on our financial condition as HCR, by virtue of owning Cara Royalty Sub, would own the Royalties. Our information systems, or those of others upon whom we rely (such as our CROs, contract manufacturers, contractors, consultants, service providers, collaborators and others) may fail or suffer cybersecurity breaches, loss or leakage of data or other disruptions, which could result in a material disruption of our development programs, compromise sensitive information related to our business, or prevent us from accessing critical information, potentially exposing us to liability that could adversely affect our business. We are increasingly dependent upon information systems, infrastructure and data to operate our business. In the ordinary course of business, we collect, store, transmit and otherwise process confidential information (including but not limited to intellectual property, proprietary business information and personal data). We also have outsourced elements of our operations to third parties, and as a result we manage a number of service providers who have access to our data and information systems and infrastructure. Our reliance on service providers could introduce new cybersecurity risks and vulnerabilities, including supply- chain attacks, and other threats to our business operations. We rely on service providers and**

technologies to operate critical business systems to process sensitive data in a variety of contexts, including, without limitation, cloud- based infrastructure, data center facilities, encryption and authentication technology, personnel email, and other functions. We also rely on third- party service providers to provide other products, **services** ~~including KORSUVA injection and Kapruvia~~ , **parts, or otherwise to operate our business. Our ability to monitor these third parties' information security practices is limited, and these third parties** may **not** have ~~undesirable side effects~~ **adequate information security measures in place. If our third- party service providers experience a security incident or other interruption, we could experience adverse consequences. While we may be entitled to damages if our third- party service providers fail to satisfy their privacy or security- related obligations to us, any award may be insufficient to cover our damages, or we may be unable to recover such award. In addition, supply- chain attacks have increased in frequency and severity, and we cannot guarantee** that ~~may require them to be taken off the market, require them to include safety warnings or otherwise limit their~~ **third** ~~sales. Further,~~ **parties' infrastructure in our supply chain** ~~our~~ **or** ~~product candidates may~~ **our third- party partners' supply chains** have ~~serious adverse events or undesirable side effects~~ **not been compromised. Cybersecurity risks have significantly increased in recent years in part because of the proliferation of new technologies, the use of the internet and telecommunication technologies to conduct financial transactions, especially as personnel are working remotely, and the increased sophistication and activities of organized crime, hackers, terrorists, nation- states and other external parties. To the extent** that ~~may limit dosing~~ **any disruption or cybersecurity breach were to result** in **a loss of, or damage to, our data or information systems, or inappropriate disclosure of confidential or proprietary information, we could incur liability and reputational damage and the further** development **of** ~~, delay or prevent regulatory or marketing approval. Undesirable side effects caused by~~ our product candidates could **be** ~~cause us or regulatory authorities to limit dosage in development or interrupt, delay~~ **delayed . Some actors now engage and are expected to continue to engage in cyberattacks, including without limitation nation- state actors** ~~or~~ **for geopolitical reasons and in conjunction with military conflicts and defense activities. During times of war and other major conflicts, we, and the third parties upon which we rely, may be vulnerable to a heightened risk of these attacks, including retaliatory cyberattacks,** ~~halt~~ **that** ~~clinical trials and~~ could ~~result~~ **materially disrupt our systems and operations, supply chain, and ability to produce, sell and distribute our goods and services. In particular, severe ransomware attacks are becoming increasingly prevalent and can lead to significant interruptions** in **our operations, ability to provide our products or services, loss of sensitive data and income, reputational harm, and diversion of funds. Extortion payments may alleviate the negative impact of** a **ransomware attack, but we may be unwilling or unable to make such payments due to, for example, applicable laws or regulations prohibiting such payments. 38We and the third parties upon which we rely are subject to a variety of evolving threats, including but not limited to social- engineering attacks (including through deep fakes, which may be increasingly** more **difficult to identify** ~~restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. For example, in February 2016, the FDA placed our adaptive trial of I. V. difelikefalin for postoperative pain on IND clinical hold pending a safety review. The clinical hold was~~ **as fake, and phishing attacks), malicious code (such** ~~based on a stopping rule related to elevated serum sodium levels of greater than 150 mmol / L. After the safety review was~~ **as viruses** ~~completed, the FDA removed this clinical hold in April 2016~~ and **worms), malware (including** ~~the clinical trial was resumed in June 2016. If other concerns are raised regarding the safety of a new drug~~ as a result of ~~undesirable side~~ **advanced persistent threat intrusions), denial- of- service attacks, credential stuffing, credential harvesting, personnel misconduct or error, ransomware attacks, supply- chain attacks, software bugs, server malfunctions, software or hardware failures, loss of data or other information technology assets, adware, attacks enhanced or facilitated by AI, telecommunications failures, earthquakes, fires, floods, and other similar threats. Additionally, future or past business transactions (such as acquisitions or integrations) could expose us to additional cybersecurity risks and vulnerabilities, as our systems could be negatively affected by vulnerabilities present in acquired or integrated entities' systems and technologies. Furthermore, we may discover security issues that were not found during due diligence of such acquired or integrated entities, and it may be difficult to integrate companies into our information technology environment and security program. While we have implemented security measures designed to protect against security incidents, there can be no assurance that these measures will be** ~~effects~~ **effective . We take steps designed to detect, mitigate, and remediate vulnerabilities in our information systems (such as our hardware and / or software, including that of third parties upon which we rely). We may not, however, detect and remediate all such vulnerabilities including on a timely basis. Further, we may experience delays in developing and deploying remedial measures and patches designed to address** identified ~~during clinical testing,~~ **vulnerabilities. Vulnerabilities could be exploited and result in a security incident. Any of the previously identified or similar threats could cause a security incident or** ~~the~~ **other** ~~FDA~~ **interruption that could result in unauthorized, unlawful, or accidental acquisition, modification, destruction, loss, alteration, encryption, disclosure of, or access to our sensitive data or our information technology systems, or those of the third parties upon whom we rely. A security incident or other interruption could disrupt our ability (and that of third parties upon whom we rely) to provide our services. We** may ~~order~~ **expend significant resources or modify our business activities to try to protect against security incidents. Additionally, certain data privacy and security obligations may require** us to ~~cease further~~ **implement and maintain specific security measures or industry- standard or reasonable security measures to protect our information technology systems and sensitive data. Applicable data privacy and security obligations may require us to notify relevant stakeholders, including affected individuals, customers, regulators, and investors, of security incidents. Such disclosures are costly, and the disclosure or the failure to comply with such requirements could lead to adverse consequences. If we (or a third party upon whom we rely) experience a security incident or are perceived to have experienced a security incident, we may experience adverse consequences, such as government enforcement actions (for example, investigations, fines, penalties, audits, and**

inspections); additional reporting requirements and / or oversight; restrictions on processing sensitive data (including personal data); litigation (including class claims); indemnification obligations; negative publicity; reputational harm; monetary fund diversions; diversion of management attention; interruptions in our operations (including development **and commercialization of oral difelikefalin** , **if** ~~decline to approve~~ **approved , and availability of** ~~the drug or issue a letter requesting additional~~ data **); financial loss; and other similar harms. Security incidents and attendant consequences may prevent or cause customers to stop using** ~~or~~ **our services, deter new customers from using** ~~information prior to making a final decision regarding whether or~~ **our services, and negatively impact our ability to grow and operate our business. Our contracts may** not ~~to approve~~ **contain limitations of liability, and even where** ~~the~~ **they do,** ~~drug. The number of such requests for additional data or information issued by the FDA in recent years has increased and resulted in substantial delays in the approval of several new drugs. Undesirable side effects caused by I. V. difelikefalin or any of our other~~ - **there** ~~current~~ **can be no assurance that limitations of liability in** ~~or~~ **our contracts are sufficient to protect** ~~future product candidates could also result in denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications or the inclusion of unfavorable information in our product labeling, and in turn prevent~~ us from **liabilities, damages,** ~~commercializing and generating revenues from the sale of I. V. difelikefalin for~~ - **or claims** ~~acute post- operative pain or any other product candidate. Approval of our current or future product candidates may include aspects of product labeling that limit its commercial use, including a Boxed Warning, REMS or other limitations of use. To date, the side effects observed in the completed I. V. difelikefalin clinical trials include dizziness, transient facial tingling, a state of near- sleep, or somnolence, and hypernatremia, an electrolyte disturbance that is defined by an elevated sodium level in the blood, which we believe is secondary, at least in part, to another side effect, aquaresis, that is defined as electrolyte- free urination. As described above, the observation of mild to moderate hypernatremia in our adaptive trial for postoperative pain triggered a stopping rule in the trial protocol and led the FDA to institute an IND clinical hold~~ related to ~~the trial, pending a safety review. Prolonged aquaresis can result in a negative fluid balance if the excreted water is not replaced by oral or~~ **our data privacy** ~~intravenous fluids, and although we recommend steps to control fluid balance, we cannot be certain that such instructions will be followed by healthcare providers and / or patients, and failure to follow such instructions may be accompanied by adverse events associated with negative fluid balance, including disability and death. We believe that one such adverse event, which has been observed, postural tachycardia, an~~ **and security obligations** ~~elevation of heart rate upon standing up, is a physiological reflex that can be triggered as a result of decreased intravascular volume caused by a negative fluid balance. We have observed transient prolactin elevations, which are brief increases in the concentration of the hormone prolactin in the bloodstream, in response to I. V. difelikefalin, which we have measured as a nonselective opioid biomarker since both kappa and mu opioids elicit this effect~~ . We cannot be ~~certain~~ **sure that our insurance coverage will be adequate or sufficient to protect us from or to mitigate liabilities arising out of our privacy and security practices,** that such **coverage** ~~elevations in prolactin~~ will **continue to** be **available on commercially reasonable terms or at** ~~transient, safe, and well tolerated in~~ all ~~patients. In addition~~ , **or** ~~previously developed kappa opioid 49agonists, the pharmacological class of drugs~~ that ~~difelikefalin belongs to, have been associated with poorly tolerated psychiatric side effects,~~ such **coverage** ~~as a feeling of emotional and mental discomfort, or dysphoria, and hallucinations, at high doses, particularly for prior generations of kappa opioid agonists with substantially unrestricted or only partially restricted entry to the CNS. Although we have not observed psychiatric side effects in any difelikefalin clinical trials to date, we cannot be certain that these side effects or others~~ will **pay** ~~not be observed in the~~ future ~~, or that the FDA will not require additional trials or impose more severe labeling restrictions due to these side effects or other concerns. The drug- related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability~~ claims. Any of these occurrences may harm our..... our ability to generate revenues. Risks **39Risks** Related to Our Financial Condition and Capital Requirements We have incurred significant losses from our inception, and ~~although we generated net income in 2020,~~ we anticipate that we may incur losses in the foreseeable future ~~. Our first commercial product was only recently approved, and we may never maintain profitability~~ . We are a ~~commercial~~ **development** - stage biopharmaceutical company. **Until recently** ~~For the last several years~~ , we ~~have~~ **had** focused our efforts primarily on developing KORSUVA injection, Kapruvia and oral difelikefalin **for a number of indications** with the goal of achieving regulatory approval and ~~in August 2021~~ , ~~the FDA approved~~ **more recently, commercializing** KORSUVA injection **and Kapruvia. However, the commercial launches of KORSUVA injection and Kapruvia did not achieve meaningful success and, in January 2024, we made the strategic decision to focus our efforts on developing oral difelikefalin** for the treatment of ~~moderate- to- severe CKD- aP in adults undergoing hemodialysis. In April 2022, the European Commission granted marketing authorization to Kapruvia for the treatment of moderate- to- severe pruritis~~ **pruritus** associated with **NP** ~~CKD in adult hemodialysis patients. The marketing authorization approves Kapruvia for use in all member states of the EU, as well as in Iceland, Liechtenstein, and Norway. In April 2022, Kapruvia was also approved in the U. K. In August 2022, as part of the Access Consortium, difelikefalin injection was approved in Switzerland under the brand name Kapruvia, as well as in Singapore and Canada under the brand name KORSUVA. In November 2022, difelikefalin injection was approved in the last Access Consortium country, Australia, under the brand name KORSUVA~~ . Since inception, we have incurred significant operating and net losses. We incurred net losses of $ **118. 5 million, $** 85. 5 million and $ 88. 4 million for the years ended December 31, **2023,** ~~512022~~ -- **2022** and 2021, respectively. As of December 31, ~~2022~~ **2023** , we had an accumulated deficit of $ ~~566~~ **684** . ~~2~~ **7** million, and we expect to continue to incur significant expenses and operating and net losses in the foreseeable future, as we continue **to** ~~the commercialization of KORSUVA injection and Kapruvia and~~ develop and seek ~~marketing~~ **regulatory** approval for ~~our~~ **oral difelikefalin and any potential future** product candidates. Our financial results may fluctuate significantly from year to year, depending on the timing of our clinical trials ~~, the receipt of additional milestone payments, if any, under our agreements with CSL Vifor, Maruishi and CKDP~~ , the receipt of payments under any future agreements we may enter into, and our expenditures on other R & D activities as well as any payments owed under the License Agreement with Enteris and any future similar

agreements. ~~In addition, we expect to incur significant sales, marketing and manufacturing expenses related to our product candidates, if they are approved by the FDA, and expenses related to the commercialization of KORSUVA injection.~~ As a result, we expect to continue to incur significant losses for the foreseeable future as we: ● continue the development of oral difelikefalin for ~~AD- aP, NDD- CKD, and~~ NP; ● seek regulatory approvals for any other product candidate that successfully completes clinical trials; ● establish a sales, marketing and distribution infrastructure **in the United States** and scale up external manufacturing capabilities to commercialize any ~~other~~ products for which we may obtain regulatory approval; ● maintain, expand and protect our global intellectual property portfolio; ● hire additional clinical, quality control and scientific personnel; and ● add operational, financial and management information systems and personnel, including personnel to support our drug development and potential future commercialization efforts. **Revenues from KORSUVA injection will not be sufficient to enable us to reach profitability.** To become and remain profitable from product sales, we must succeed in developing and eventually commercializing one or more products that generate significant revenue. ~~For example, revenues from KORSUVA injection and Kapruvia royalties may not be sufficient to enable us to reach profitability.~~ In order to commercialize any ~~additional~~ product ~~candidates~~ **candidate**, we will need to be successful in a range of challenging activities, including successful registration of oral difelikefalin, discovering **, developing, licensing or acquiring** additional product candidates and completing preclinical testing and clinical trials for those product candidates, potentially entering into collaboration and license agreements, obtaining regulatory approval for product candidates and manufacturing, marketing and selling approved products and product candidates for which we may obtain regulatory approval. We may never succeed in these activities and, even if we do, may never achieve profitability. Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. If we are required by the FDA or foreign regulatory authorities, to perform studies in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of ~~any of~~ our product ~~candidates~~ **candidate**, our expenses could increase. ~~Even~~ **40Even** if we do achieve profitability from product sales, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our R & D efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment. ~~Our operating history makes it difficult to evaluate our business and prospects. We commenced operations in 2004, and our operations to date have been limited to organizing and staffing our company, business planning, raising capital and advancing our products and product candidates, including KORSUVA injection, Kapruvia and oral difelikefalin, through clinical development. We have not previously demonstrated an ability 52to successfully commercialize a product. With the approval of KORSUVA injection and Kapruvia, we have begun to expand our capabilities to support commercial activities of our commercial partners. We may not be successful in sufficiently adding such capabilities. Consequently, any predictions about our future performance may not be as accurate as they could be if we had a history of successfully developing and commercializing pharmaceutical products.~~ We may need additional funding and may be unable to raise capital when needed, which would force us to delay, reduce or eliminate our product development programs ~~or commercialization efforts~~. Conducting clinical trials, pursuing regulatory approvals, establishing outsourced manufacturing relationships **,** and successfully manufacturing and commercializing our ~~products and~~ product **and product** ~~candidates~~ **candidate** is expensive. We may need to raise additional capital to ~~: ● fund our operations and~~ continue ~~our efforts to hire additional personnel to support~~ the ~~commercialization of KORSUVA injection and Kapruvia; ● qualify and outsource the commercial- scale manufacturing of our products, including KORSUVA injection, under cGMP; ● continue the further~~ development of oral difelikefalin for ~~NDD- CKD, AD, and~~ NP ~~;~~ and ~~●~~ **potentially** in- license **or acquire** other product candidates. ~~We~~ **In January 2024, we announced a prioritization of our pipeline to focus our resources on our late- stage clinical program evaluating oral difelikefalin in chronic pruritus associated with NP and terminate our Phase 3 clinical program evaluating oral difelikefalin in pruritus associated with advanced chronic kidney disease, including our KICK 1 and KICK 2 Phase 3 clinical trials. As part of this strategic update, in the first quarter of 2024, we reduced our global workforce by approximately 50 %. After taking into account our strategic prioritization and reduction in workforce, we** expect that our current unrestricted cash and cash equivalents and available- for- sale marketable securities ~~, including collaborative revenue from our share of the profit from KORSUVA injection,~~ will be sufficient to fund our currently anticipated operating plan into ~~at least the first half of 2024~~ **2026**. Our anticipated operating expenses include contractually committed costs as well as non- contractually committed clinical trial costs for trials that may be delayed or not initiated and other non-committed controllable costs. Because the process of testing product candidates in clinical trials is costly and the timing of progress in these trials is uncertain, it is possible that the assumptions upon which we have based this estimate may prove to be wrong, and we could use our capital resources sooner than we presently expect. Our future funding requirements will depend on many factors, including, but not limited to: ● the ~~success~~ **rate** of ~~the commercialization~~ **progress and costs related to Phase 2 and Phase 3 development** of **oral difelikefalin** ~~KORSUVA injection, Kapruvia~~ and any ~~current and~~ **trials for** future product candidates; ● the ~~cost and timing of manufacturing sufficient supplies of KORSUVA injection for commercialization; ● the~~ rate of progress and costs ~~related to Phase 2 and Phase 3 development of oral difelikefalin and our future product candidates; ● the rate of progress and costs for the submission and review of an NDA~~ for any product candidates that we may in- license or acquire in the future ~~, and the potential that we may need to conduct additional clinical trials to support applications for regulatory approval~~ ; ● the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights associated with our product ~~candidates~~ **candidate**, including any such costs we may be required to expend if our licensors are unwilling or unable to do so; ● the effect of competing technological and market developments; and ● the terms and timing of any collaborative, licensing, co- promotion or other arrangements that we may establish. ~~53Future~~ **Future** capital requirements will also depend on the extent to which we acquire or invest in additional complementary businesses,

products and technologies. Until we can generate a sufficient amount of product revenue, if ever, we expect to finance future cash needs through public or private equity offerings, debt financings, milestone and royalty payments from corporate collaboration and licensing arrangements, as well as through interest income earned on cash and investment balances. We cannot be certain that additional funding will be available on acceptable terms, or at all, and our ability to raise additional capital may be adversely impacted by potential worsening global economic conditions **, including high rates of inflation** and **interest rates,** the continuing disruptions to and volatility in the credit and financial markets in the United States and worldwide **, including** resulting from the ~~COVID- 19 pandemic~~ **ongoing conflicts between Russia and the Ukraine, conflicts in the Middle East, and increasing tensions between China and Taiwan** . If adequate funds are not available, we may be required to delay, reduce the scope of, or eliminate, ~~one or more of~~ our development ~~programs~~ **program** ~~or our commercialization efforts~~ . ~~Risks~~ **41Risks** Related to Our Dependence on Third **PartiesAny** ~~Parties~~We are dependent on third parties to decide to utilize KORSUVA injection and to make it readily available at the point of care throughout their dialysis centers or hospitals. In addition to extensive internal efforts, the successful commercialization of KORSUVA injection will require many third parties, over whom we have no control, to decide to utilize KORSUVA injection and to make it readily available at the point of care throughout their hospitals. These third parties include physicians, dialysis providers, pharmacists and hospital pharmacy and therapeutics committees, which are commonly referred to as P & T committees. Generally, before we can attempt to sell KORSUVA injection in a hospital or dialysis center, it must be approved for addition to that hospital or dialysis center' s list of approved drugs, or formulary list, by the institution' s P & T committee. An institutional P & T committee typically governs all matters pertaining to the use of medications within the institution, including review of medication formulary data and recommendations for the appropriate use of drugs within the institution to the medical staff. The frequency of P & T committee meetings at various institutions varies considerably, and P & T committees often require additional information to aid in their decision- making process, so we may experience substantial delays in obtaining formulary approvals. Additionally, institutions may be concerned that the cost of acquiring KORSUVA injection for use in their institutions will adversely impact their overall pharmacy budgets, which could cause institution staff to resist efforts to add KORSUVA injection to the formulary, or to implement restrictions on the usage of the drug in order to control costs, either initially or later, when the increasing use of KORSUVA injection within their institution begins to significantly impact their budgets. We cannot guarantee that we will be successful in getting the approvals we need from enough P & T committees and overcoming any financial objections raised by institution staff quickly enough to maintain and grow institutional sales of KORSUVA injection. We rely on third parties to perform many essential services for KORSUVA injection and may do so in the future for any products that we commercialize, including services related to warehousing and inventory control, distribution, customer service, accounts receivable management, cash collection and adverse event reporting. If these third parties fail to perform as expected or to comply with legal and regulatory requirements, our ability to commercialize KORSUVA injection or any other product candidate, will be significantly impacted and we may be subject to regulatory sanctions. We retain third- party service providers to perform a variety of functions related to the sale and distribution of KORSUVA injection and may do so in the future for our other current or future product candidates, key aspects of which will be out of our direct control. These service providers provide key services related to warehousing and inventory control, distribution, customer service, accounts receivable management and cash collection, and, as a result, most of our inventory are stored at a single warehouse maintained by one such service provider. Thus, we substantially rely on it as well as other third- party providers that perform services for us, including entrusting our inventories of products to their care and handling. If these third- party service providers fail to comply with applicable laws and regulations, fail to meet expected deadlines, or otherwise do not carry out their contractual duties to us, or encounter physical or natural damage at their facilities, our ability to deliver product to meet commercial demand would be significantly impaired. In addition, we have engaged third parties to perform various other services for us relating to adverse event reporting, safety database management, fulfillment of requests for medical information regarding our product candidates and related services. If the quality or accuracy of the data maintained by these service providers is insufficient, or these third parties otherwise fail to comply with regulatory requirements related to adverse event reporting, we could be subject to regulatory sanctions. 54We are dependent on our collaboration agreements for certain revenues, and if our commercial partners do not perform their obligations under such agreements, we could lose revenues. In October 2020, we entered into a license agreement with Vifor International under which we granted Vifor International an exclusive license solely in the United States to use, distribute, offer for sale, promote, sell and otherwise commercialize our product candidate KORSUVA (difelikefalin) injection for all therapeutic uses relating to the inhibition, prevention or treatment of itch associated with pruritus in hemodialysis and peritoneal dialysis patients in the United States. In May 2018, we entered into an agreement under which we granted Vifor Fresenius Medical Care Renal Pharma Ltd. a license to seek regulatory approval to commercialize, import, export, use, distribute, offer for sale, promote, sell and otherwise commercialize KORSUVA (difelikefalin) injection for all therapeutic uses to prevent, inhibit or treat itch associated with pruritus in hemodialysis and peritoneal- dialysis patients worldwide (excluding the United States, Japan and South Korea). In April 2013, we entered into an agreement with Maruishi under which we granted Maruishi an exclusive license to develop, manufacture and commercialize products containing difelikefalin in Japan. Also, in April 2012, we entered into an agreement with CKDP under which we granted CKDP an exclusive license to develop, manufacture and commercialize products containing difelikefalin in South Korea. Under Vifor Agreement No. 2, we are responsible, at our own cost, to undertake clinical and non- clinical development. We are also responsible to provide all content and subject matter expertise required for registration with the EMA in the EU that will be needed by Vifor Fresenius Medical Care Renal Pharma Ltd. for such registration, including participation in regulatory meetings, as needed. Vifor Fresenius Medical Care Renal Pharma Ltd. will contribute, at its own cost, its clinical development expertise as reasonably useful for such development activities, such as preparing the clinical results that we present to it in a format acceptable to the EMA to obtain marketing approval in the EU. Maruishi and CKDP are required to use commercially reasonable efforts, at their expense, to develop, obtain regulatory

~~approval for and commercialize difelikefalin in Japan and South Korea, respectively. Our receipt of milestone payments and royalties under these agreements is dependent on the continued efforts by CSL Vifor, Maruishi and CKDP, respectively, and their failure to adequately develop or commercialize the licensed products, or any default or inability to meet their payment obligations under their respective agreements, could harm our revenues and business. Any~~ collaboration arrangements that we are a party to ~~, such as our collaboration with CSL Vifor,~~ or may enter into in the future may not be successful, which could adversely affect our ability to develop and **ultimately** commercialize our product ~~candidates~~ **candidate or any potential future product candidate** . Our business model is to **develop and** commercialize our product ~~and product candidates~~ **candidate** in the United States and generally to seek collaboration arrangements with pharmaceutical or biotechnology companies for the development or commercialization of our product ~~candidates~~ **candidate** in the rest of the world. We currently have license agreements with **Maruishi** ~~Vifor Fresenius Medical Care Renal Pharma Ltd.~~ and **CKDP** ~~Vifor International (KORSUVA injection~~ for ~~CKD- aP in dialysis patients)~~ **the intravenous and oral formulations of difelikefalin** , as well as ~~Maruishi~~ **license agreements with respect to our commercially approved products, KORSUVA Injection** and **Kapruvia with CSL Vifor** ~~CKDP (difelikefalin- both I. V. and Oral)~~ . In addition to our existing agreements, we may enter into additional collaboration arrangements in the future on a selective basis. Our existing collaborations and future collaboration arrangements may not be successful. The success of our existing and future collaboration arrangements will depend heavily on the efforts and activities of our collaborators. Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaboration arrangements. Disagreements between parties to a collaboration arrangement regarding clinical development and commercialization matters can lead to delays in the development process or commercializing the applicable product candidate and, in some cases, termination of the collaboration arrangement. These disagreements can be difficult to resolve if neither of the parties has final decision- making authority. Collaborations with pharmaceutical companies and other third parties often are terminated or allowed to expire by the other party. ~~For example, the CSL Vifor, Maruishi and CKDP Agreements may be terminated by our collaborator for our breach or insolvency, CSL Vifor may terminate its respective agreements (in its entirety or with respect to any countries within the Territory upon written notice to us) upon the earlier of (1) acceptance for filing of an NDA covering Licensed Product filed with the FDA (after completion of the Phase 3 program) or (2) the third anniversary of the Effective Date.~~ Maruishi may terminate its agreement with us at will, and CKDP may terminate its agreement with us in certain circumstances relating to patent invalidity or unenforceability or generic entry by a third party, as further described in the section titled " Management' s Discussion and Analysis of Financial Condition and Results of Operations ~~55~~ - Collaboration and License Agreements " ~~above~~ . Any such termination or expiration ~~would~~ **could** adversely affect us financially and could harm our business reputation. Our current collaborations and any future collaborations we might enter into may pose a number of risks, including the following: ● collaborators may not perform their obligations as expected; ● collaborators may not pursue development and commercialization of our ~~products or any~~ product **or product** ~~candidates~~ **candidate** that ~~achieve~~ **achieves** regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding that divert resources or create competing priorities; ● collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing; ● collaborators could fail to make timely regulatory submissions for a product or product candidate; ● collaborators may not comply with all applicable regulatory requirements or may fail to report safety data in accordance with all applicable regulatory requirements; ● collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours; ● product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product ~~candidates~~ **candidate** ; **42** ● a collaborator with marketing and distribution rights to one or more of our products or product ~~candidates~~ **candidate** that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products; ● disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of products and product ~~candidates~~ **candidate** , might lead to additional responsibilities for us with respect to products and product ~~candidates~~ **candidate** , or might result in litigation or arbitration, any of which would be time- consuming and expensive; ● collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation; ● collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and ● collaborations, including our collaboration with Maruishi, may be terminated for the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product ~~candidates~~ **candidate** . ~~Additionally, collaborators may elect not to pursue, or pursue as vigorously, the development or commercialization of our product or product candidates as a result of external factors, such as an acquisition or merger. For example, Vifor Pharma Group recently entered into a merger agreement with CSL Limited, a global specialty 56pharmaceutical company, pursuant to which CSL Limited would acquire all publicly held Vifor Pharma Group shares if such transaction is completed. When biopharma companies are acquired, it is not uncommon for the acquiring company to have a different strategic focus and priorities than those of the acquired company, which could lead to different decisions with respect to product commercialization efforts. Accordingly, if the acquisition is consummated, CSL Limited may choose not to prioritize KORSUVA injection and Kapruvia to the same extent as Vifor Pharma Group would as a standalone company. If this were to occur, it is possible that the commercialization of KORSUVA injection and Kapruvia could suffer, which would have a material~~

~~adverse impact on our business and results of operations~~ . If our current collaborations or any other collaborations we might enter into in the future do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our product ~~candidates~~ **candidate** could be delayed and we may need additional resources to develop our product ~~candidates~~ **candidate** and our product platform. All of the risks relating to our product development, regulatory approval and commercialization described in this Annual Report on Form 10- K also apply to the activities of our collaborators in their respective jurisdictions. Additionally, if any current or future collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate development or commercialization of any product candidate licensed to it by us. If one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our reputation in the business and financial communities could be adversely affected. **If we determine to collaborate in** ~~For KORSUVA injection, Kapruvia and any other~~ **the** ~~current or~~ future ~~product candidates, we may in the future determine to collaborate~~ with additional pharmaceutical ~~and~~ **or** biotechnology companies for ~~their~~ **the** development and potential commercialization ~~. We~~ **of oral difelikefalin or any potential future product candidate, we would** face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for collaboration will depend, among other things, upon our assessment of the collaborator' s resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator' s evaluation of a number of factors. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our product platform or successfully commercialize our products and our business may be materially and adversely affected. ~~Risks~~ **43Risks** Related to Legal and Compliance MattersIf we fail to comply with federal and state healthcare laws, including fraud and abuse, and transparency laws, we could face substantial penalties and our business, results of operations, financial condition and prospects could be adversely affected. As a pharmaceutical company, even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third- party payers, certain federal and state healthcare laws and regulations pertaining to fraud and abuse, transparency and patients' rights may be applicable to our business. The healthcare laws and regulations that may affect our ability, and our partners' and collaborators' ability, to operate include, but are not limited to: ● the federal Anti- Kickback Statute, which regulates, among other things, our marketing practices, educational programs, pricing policies, and relationships with healthcare providers or other entities, by prohibiting, among other things, any person or entity from knowingly and willfully soliciting, receiving, offering or paying any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, the ~~57purchase~~ **purchase** , recommendation, lease, order or furnishing of an item or service reimbursable, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs; ● federal civil and criminal false claims laws, including without limitation the federal civil False Claims Act, and civil monetary penalties law, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false or fraudulent claims for payment or approval from a federal health care program (including Medicare and Medicaid); ● Federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal statutes that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any health care benefit program, regardless of the payer (e. g., public or private) and knowingly and willfully falsifying, concealing, or covering up by any trick, scheme or device a material fact or making any materially false statements in connection with the delivery of, or payment for, health care benefits, items or services relating to healthcare matters; ● federal transparency laws, including the federal Physician Payments Sunshine Act, that requires certain 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 to CMS information related to payments and other transfers of value provided to physicians (defined to include doctors of medicine, dentists, optometrists, podiatrists and chiropractors), other healthcare professionals (such as physician assistants and nurse practitioners), and teaching hospitals, and applicable manufacturers and group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their immediate family members; ● state law equivalents of each of the above federal laws, such as anti- kickback and false claims laws which may apply to items or services reimbursed by any third- party payer, including commercial insurers; and ● state laws that require pharmaceutical companies to comply with the pharmaceutical industry' s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to the pricing of certain drugs, as well as payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state and local laws that require the registration of pharmaceutical sales representatives, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. ~~Because~~ **44Because** of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available under these laws, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Pharmaceutical and other healthcare companies continue to be prosecuted under the federal false claims laws for numerous activities, including those related to

research, sales, marketing and promotional programs. In addition, recent health care reform legislation has strengthened these laws. For example, the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or the Health Care Reform Law, among other things, amends the intent requirement of the federal Anti- Kickback Statute and certain other criminal healthcare fraud statutes. As a result, a person or entity no longer needs to have actual knowledge of these statutes or specific intent to violate them in order to commit a violation. Moreover, the Health Care Reform Law provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti- Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. To the extent that any product we make is sold in a foreign country, we may be subject to similar foreign laws and regulations. If we or our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to significant penalties, including administrative, civil and criminal penalties, damages, fines, disgorgement, exclusion from participation in U. S. federal or state health care programs, contractual damages, reputational harm, imprisonment, diminished profits and future earnings, additional reporting ~~58requirements~~ -- **requirements** and / or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non- compliance with these laws, and the curtailment or restructuring of our operations, any of which could materially adversely affect our ability to operate our business and our financial results. Although an effective compliance program can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management' s attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal and state transparency and fraud and abuse laws may prove costly. If any of the physicians or other healthcare providers or entities with whom we do business, including our partners or collaborators, is found not to be in compliance with applicable laws, it may be subject to significant criminal, civil or administrative sanctions, including but not limited to, exclusions from participation in government healthcare programs, which could also materially affect our business. ~~Changes in and failures to comply with applicable U. S. and foreign privacy and data protection laws, regulations and standards may subject us to liabilities and adversely affect our business, operations and financial performance.~~ We are subject to **stringent and evolving U. S. and foreign laws, regulations and standards, contracts, industry standards, policies and other obligations related to data privacy and security. Our actual or perceived failure to comply with such obligations could lead to regulatory investigations or actions, litigation (including class claims) and mass arbitration demands, fines and penalties, disruptions of our business operations, reputational harm, loss of revenue and profits, and otherwise adversely affect our business, operations and financial performance. We are subject to** or affected by numerous **domestic (both** federal ~~,~~ **and** state **)** and foreign laws and regulations, as well as regulatory guidance, **contracts, industry standards, policies and other obligations** governing the collection, use, disclosure, retention, ~~and~~ security **and other processing** of personal data, such as information that we collect about participants and healthcare providers in connection with clinical trials in the United States and abroad. ~~The~~ **Obligations related to data privacy and security (and consumers' data privacy expectations) are quickly changing, becoming increasingly stringent, and creating uncertainty. Additionally, these obligations may be subject to differing applications and interpretations, which may be inconsistent or conflict among jurisdictions. This evolving** global data protection landscape ~~is rapidly evolving, and implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future. This evolution~~ may create uncertainty in our business, affect our or our service providers' ability to operate in certain jurisdictions or to collect, store, transfer use ~~and~~ **,** share **and otherwise** personal data, result in liability or impose additional costs on us. The cost of compliance with these **obligations** ~~laws, regulations and standards~~ is high and is likely to increase in the future ~~. Any failure~~ **and may necessitate changes to** ~~or~~ **our operations and** ~~perceived failure by us~~ to ~~comply with federal, state,~~ **those of third parties that process personal data on** ~~or~~ **our behalf** ~~foreign laws or self- regulatory standards could result in negative publicity, diversion of management time and effort and proceedings against us by governmental entities or others~~ . In many jurisdictions, enforcement actions and consequences for noncompliance are rising. In the United States, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization by entities subject to the rule, including health plans, healthcare clearinghouses, certain healthcare providers, and their business associates and covered subcontractors that perform services for them that involve the creation, use, maintenance or disclosure of, individually identifiable health information. In the event we are subject to HIPAA and we or our ~~covered~~ **business associates or** subcontractors fail to properly maintain the privacy and security of certain individually identifiable health information, ~~or~~ **45or** we ~~or our~~ - **or** ~~covered~~ **our business associates or** subcontractors are responsible for an inadvertent disclosure or security breach of such individually identifiable health information, we could be subject to enforcement measures, including civil and criminal penalties and fines for violations of state and federal privacy or security standards, such as HIPAA and HITECH, and their respective implementing regulations. Additionally, certain states have adopted ~~comparable~~ **their own** privacy and security laws and regulations **for health information** , some of which may be more stringent than HIPAA. ~~For example~~ **In the past few years** , **numerous U. S. states, following California' s enactment of the CCPA — including Virginia, Colorado, Connecticut, and Utah — have enacted comprehensive privacy laws that impose certain obligations** on ~~June 28~~ **covered businesses** , **including providing specific disclosures in** ~~2018, California enacted the California Consumer Privacy~~ **privacy notices and affording** ~~Act, or CCPA, which takes effect on January 1, 2020. The CCPA gives California~~ residents ~~expanded~~ **with certain** rights **concerning** ~~to access and delete~~ their personal ~~information~~ **data. As applicable** , ~~opt out of~~ **such rights may include the right to access, correct, or delete** certain personal **data** ~~information sharing~~ , and ~~receive detailed information~~ **to opt-** ~~about~~ -- **out** ~~how~~ **of certain data processing activities, such as targeted advertising, profiling, and automated decision- making. To** ~~their~~ -- **the** ~~personal information is used. The CCPA~~ **extent that we are or may become subject to these laws, the exercise of these rights may impact our business and ability**

to ~~provides --~~ **provide** ~~for civil penalties for violations~~ **our products and services. Similar laws are being considered in several other states** , as well as **at the federal and local levels, and we expect more states to pass similar laws in the future. These state laws may allow for statutory fines for noncompliance (for example, under the CCPA, fines can be levied up to $ 7, 500 per intentional violation) and private rights of action. While some of these laws may exempt some data processed in the context of clinical trials, these developments further complicate compliance efforts, and increase legal risk and compliance costs for us, and the third parties upon whom we rely. For example, Washington' s My Health My Data Act (" MHMD ") broadly defines consumer health data, places restrictions on processing consumer health data (including imposing stringent consent requirements), provides consumers certain rights with respect to their health data, and creates** a private right of action **to allow individuals to sue** for **violations** ~~data breaches that is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability. Some observers have noted that the CCPA could mark the beginning~~ of **the law. Outside** ~~a trend toward more stringent privacy legislation in~~ the United States, ~~such as similar~~ **an increasing number of laws, regulations, and industry standards govern data** privacy ~~legislation in Virginia~~ and ~~in Colorado, which could increase our potential liability and adversely affect our business. Our operations abroad may also be subject to increased scrutiny or attention from data protection authorities. Many countries in these regions have established or are in the process of establishing privacy and data~~ security ~~legal frameworks with which we or our partners, collaborators, customers, or service providers must comply~~ . For example, the EU ~~has adopted the General Data Protection Regulation, or~~ GDPR ~~, which went into effect in May 2018~~ and ~~introduced~~ **the UK GDPR impose** strict requirements for processing personal data. ~~The~~ GDPR **may** ~~is likely to~~ increase compliance ~~burden~~ **burdens** on us, including by mandating potentially burdensome documentation requirements and granting certain rights to individuals to control how we collect, use, disclose, retain and **otherwise process personal data** ~~leverage information about them or how we obtain consent from them~~ . The ~~59processing --~~ **processing** of sensitive personal data, such as physical health ~~condition~~ **conditions** , may ~~impose~~ **also be subject to** heightened compliance burdens under the GDPR ~~and is a topic of active interest among foreign regulators and supervisory bodies involved in the review and approval of clinical trials~~ . **Under** ~~In addition,~~ the GDPR ~~provides~~ **, companies may face temporary** ~~for --~~ **or definitive bans on data processing** ~~breach reporting requirements, more robust regulatory enforcement~~ and **other corrective actions;** fines of up to 20 million ~~euros~~ **Euros under the EU GDPR, 17. 5 million pounds sterling under the UK GDPR** or ~~up to~~ **, in each case,** 4 % of ~~the~~ annual global revenue ~~. As we continue~~ **, whichever is greater; or private litigation related** to ~~expand into~~ **processing of personal data brought by classes of data subjects or consumer protection organizations authorized at law to represent their interests. In addition, we may be unable to transfer personal data from Europe and** other ~~foreign~~ **jurisdictions to the United States or other** countries **due to data localization requirements or limitations on cross- border data flows. Europe** and **other** jurisdictions **have enacted laws requiring data to be localized or limiting the transfer of personal data to other countries. In particular** , ~~we~~ **the European Economic Area (EEA) and the United Kingdom (UK) have significantly restricted the transfer of personal data to the United States and other countries whose privacy laws it generally believes are inadequate. Other jurisdictions** may **adopt similarly stringent interpretations of their data localization and cross- border data transfer laws. Although there are currently various mechanisms that may be used to transfer personal data from the EEA and UK to the United States in compliance with law, such as the EEA' s standard contractual clauses, the UK' s International Data Transfer Agreement / Addendum, and the EU- U. S. Data Privacy Framework and the UK extension thereto (which allows for transfers to relevant U. S.- based organizations who self- certify compliance and participate in the Framework), these mechanisms are subject to legal challenges, and there is no assurance that we can satisfy or rely on these measures to lawfully transfer personal data to the United States. If there is no lawful manner for us to transfer personal data from the EEA, the UK, or other jurisdictions to the United States, or if the requirements for a legally- compliant transfer are too onerous, we could face significant adverse consequences, including the interruption or degradation of our operations, the need to relocate part of or all of our business or data processing activities to other jurisdictions (such as Europe) at significant expense, increased exposure to regulatory actions, substantial fines and penalties, the inability to transfer data and work with partners, vendors and other third parties, and injunctions against our processing or transferring of personal data necessary to operate our business. Additionally, companies that transfer personal data out of the EEA and UK to other jurisdictions, particularly to the United States, are subject to increased scrutiny from regulators, individual litigants, 46and activities groups. Some European regulators have ordered certain companies to suspend or permanently cease certain transfers of personal data out of Europe for allegedly violating the GDPR' s cross- border data transfer limitations. In addition to data privacy and security laws, we are or may become contractually subject to industry standards adopted by industry groups. We are also bound by other contractual obligations related to data privacy and security, and our efforts to comply with such obligations may not be successful. We publish privacy policies, marketing materials, and other statements, such as compliance with certain certifications or self- regulatory principles, regarding data privacy and security. If these policies, materials or statements are found to be deficient, lacking in transparency, deceptive, unfair, or misrepresentative of our practices, we [may]** be subject to **investigation** ~~additional laws and regulations that may affect how we conduct business. U. S. and foreign data protection laws~~ , **enforcement actions** ~~regulations and standards are subject to interpretation~~ by ~~various courts and~~ **regulators, or** other ~~governmental authorities, thus creating potentially complex compliance issues~~ **adverse consequences. We may at times fail (** ~~for --~~ **or be perceived to have** ~~us and our future customers and strategic partners. Any liability from failure --~~ **failed) in our efforts** to comply with **our data privacy and security obligations. Moreover, despite our efforts, our personnel or third parties on whom we rely may fail to comply with such obligations, which could negatively impact our business operations. If we or** the **third parties on which we rely fail, or are perceived to have failed, to address or comply with applicable data privacy and security obligations, we could face significant consequences, including but not limited to: government enforcement actions (e. g.,**

investigations, fines, penalties, audits, inspections, and similar); litigation (including class- action claims) and mass arbitration demands; additional reporting requirements **and / or oversight; bans on processing personal data; orders to destroy or not use personal data; and imprisonment of company officials. In particular, plaintiffs have become increasingly more active in bringing privacy- related claims against companies, including class claims and mass arbitration demands. Some** of these ~~laws~~ **claims allow for the recovery of statutory damages on a per violation basis** , ~~to~~ **and, if viable, carry the potential for monumental statutory damages, depending on the volume of data and the number of violations. Any of** ~~the~~ **these events** ~~extent such requirements are deemed to apply to our operations, could adversely affect our financial condition. The costs of complying with privacy and security related legal and regulatory requirements are burdensome and~~ could have a material adverse effect on our ~~results of operations. If the government or other third- party payers fail to provide coverage and adequate reimbursement and payment rates for KORSUVA injection or Kapruvia or any of our other current or future product candidates, if any, or if providers choose to use therapies that are less expensive, our revenue and prospects for profitability will be limited. In both U. S. and international markets, sales of KORSUVA injection, Kapruvia and our future products (if approved) will depend in part upon the availability of coverage and reimbursement from third- party payers. Such third- party payers include government health programs such as Medicare and Medicaid in the United States, managed care providers, private health insurers and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available. Assuming coverage is approved, the resulting reimbursement payment rates might not be adequate. In the United States, KORSUVA injection for the treatment of pruritus in adult hemodialysis patients is expected to be designated as a component of the government' s bundled reimbursement for end stage renal disease treatment after the expiration of the TDAPA period. On October 31, 2019, CMS issued a final rule that revises payment policies and rates under the ESRD PPS for renal dialysis services furnished to beneficiaries on or after January 1, 2020. The final rule also updates the TDAPA. In the final rule, CMS revised ESRD PPS eligibility to focus on innovative drugs and excluded certain drugs from being eligible for the TDAPA. CMS will pay the revised TDAPA adjustment, which is called the Transitional Add- on Payment Adjustment for New and Innovative Equipment and Supplies, or TPNIES, for equipment and supplies that: (1) have been designated by CMS as a renal dialysis service, (2) are new, meaning granted marketing authorization by FDA on or after January 1, 2020, (3) are commercially available by January 1 of the particular calendar year, meaning the year in which the payment adjustment would take effect, (4) have a HCPCS application submitted in accordance with the official Level II HCPCS coding procedures by September 1 of the particular calendar year, (5) are innovative, meaning they meet the substantial clinical improvement criteria specified in the Inpatient Prospective Payment System regulations** - **reputation** ~~and related guidance~~ , ~~and (6) are not capital- related assets. TDAPA went into effect on April 1, 2022, for a minimum of two years, for KORSUVA injection. However, there is no assurance that KORSUVA injection will be able to maintain its price established in the TDAPA period in the post- TDAPA timeframe. On November 2, 2020, CMS issued a final rule outlining its payment policies and rates under the ESRD PPS for the 2021 calendar year. In addition to the annual technical updates to the ESRD PPS, the final rule, among other things, expands eligibility under the TPNIES. In particular, the final rule provided for biannual coding cycles for new HCPCS Level II code applications, revised the definition of " new " to be three (3) years beginning on the date of FDA marketing authorization, and expanded eligibility under the TPNIES to include certain home dialysis capital- related assets. Additionally, in October 2021, CMS issued a final rule that updates the ESRD PPS for calendar year 2022. Further, on June 28, 2022, in its Calendar Year 2023 ESRD PPS proposed rule, CMS issued a request for information, or RFI, to seek input on potential methodologies to add additional money through an add- on adjustment methodology for certain TDAPA drugs that enter the prospective payment system in an existing functional category. The options included in the RFI, if proposed and ultimately approved through Notice and Comment Rulemaking, could result in the provision of additional payments for KORSUVA injection post- TDAPA. Further, on November 7, 2022, CMS published a Calendar Year 2023 ESRD PPS final rule that will, among others, update Medicare payment policies and rates for renal dialysis 60services. This final rule rebases and revises ESRD bundled market basket to a 2020 base year, updates the labor- related share, changes the ESRD PPS methodology for calculating the outlier threshold for adult patients, applies a permanent 5 % cap on decreases in the ESRD PPS wage index, and increases the wage index floor. Also in the final rule, with regard to the RFI in the June 2022 proposed rule, CMS noted that most commenters expressed support for an add- on payment adjustment for new renal dialysis drugs to improve patient access to innovative drugs and that CMS intends to take the received comments into consideration during potential future policy development. As this is an RFI, these provisions have not been proposed or implemented as a rule and there is no guarantee that CMS will formally propose a change in policy in the form presented in the RFI. Additionally, many U. S. hospitals receive a fixed reimbursement amount per procedure for certain surgeries and other treatment therapies they perform, or a pre- determined rate for all hospital inpatient care provided as payment in full. Because, in these instances, the amount of reimbursement that such providers receive may not be based on the actual expenses the provider incurs, providers may choose to use therapies which are less expensive when compared to our product candidates. Accordingly, KORSUVA injection or any of our other current or future product candidates, if approved, will face competition from other therapies and drugs for these limited provider financial resources. We may need to conduct post- marketing studies in order to demonstrate the cost- effectiveness of any future products to the satisfaction of hospitals, other target customers and their third- party payers. Such studies might require us to commit a significant amount of management time and financial and other resources. Our future products might not ultimately be considered cost- effective. Third- party coverage and adequate reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development. Third- party payers, whether U. S. or international, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the United States, no uniform policy of coverage and reimbursement for drug products exists among third- party payers. Therefore, coverage and reimbursement for drug products can differ~~

~~significantly from payer to payer. Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the U. S. and international markets. Third- party coverage and reimbursement for our products or product candidates for which we receive regulatory approval may not be available or adequate in either the U. S. or international markets, which could have a negative effect on our~~ business, **or** ~~results of operations,~~ financial condition, **including but not limited to: loss of customers; interruptions or stoppages in our business operations (including, as relevant, clinical trials); inability to process personal data or to operate in certain jurisdictions; limited ability to develop or commercialize our products; expenditure of time** and ~~prospects~~ **resources to defend any claim or inquiry; adverse publicity; or substantial changes to our business model or operations** . We are subject to recent legislation, regulatory proposals and healthcare payer initiatives that may increase our costs of compliance and adversely affect our ability to market our products, obtain collaborators and raise capital. In March 2010, President Obama signed the Health Care Reform Law, which includes provisions that have changed, and likely will continue to change, health care financing and the delivery of health care in the United States. **The** ~~Among the provisions of the~~ Health Care Reform Law **, among** ~~of importance to the~~ **other** ~~pharmaceutical industry~~ **things, increased the minimum level of Medicaid rebates payable by manufacturers of brand name drugs, required collection of rebates for drugs paid by Medicaid managed** ~~are~~ **care organizations, required manufacturers to participate in a coverage gap discount program, under which** ~~the~~ **they** ~~following: ● an~~ **must agree to offer point- of- sale discounts (increased to 70 percent, effective as of January 1, 2019) off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer' s outpatient drugs to be covered under Medicare Part D; imposed a non- deductible** annual ~~, nondeductible~~ fee on **pharmaceutical** ~~any entity that manufactures~~ **manufacturers** or ~~imports~~ **importers who sell** certain **"** branded prescription drugs **"** ~~and biologic agents, apportioned among these entities according~~ to **specified federal** ~~their market share in certain~~ government ~~healthcare~~ programs ~~; ● an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23. 1 % and 13 % of the average manufacturer price for most branded and generic drugs~~ , **implemented** ~~respectively; ●~~ a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted **,** or injected ~~; ● a new Medicare Part D coverage gap~~ **expanded the types of entities eligible for the 340B drug** discount program ~~, in which manufacturers must now agree to offer 70 % point- of- sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer' s outpatient drugs to be covered under Medicare Part D~~ ; **expanded** ~~61 ● extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations; ● expansion of~~ eligibility criteria for Medicaid programs ~~by, among other things, allowing states to offer Medicaid coverage to additional individuals with income at or below 133 % of the Federal Poverty Level, thereby potentially increasing both the volume of sales and manufacturers' Medicaid rebate liability~~ ; **created** ~~● expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program; ● new transparency requirements under the federal Physician Payments Sunshine Act; ● a new requirement to annually report certain drug samples that manufacturers and distributors provide to licensed practitioners, or to pharmacies of hospitals or other healthcare entities; ● a licensure framework for follow- on biologic products; ●~~ a new Patient- Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; ~~●~~ **and** ~~establishment~~ **established** ~~of~~ a Center for Medicare ~~& Medicaid~~ Innovation at ~~the~~ CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending ~~; and ● expansion of healthcare fraud and abuse laws, including the federal civil False Claims Act and the federal Anti- Kickback Statute, new government investigative powers and enhanced penalties for non- compliance~~ . There have been executive, judicial **,** and Congressional challenges to certain aspects of the Health Care Reform Law. For example, on June 17, 2021 **,** the U. S. Supreme Court dismissed a challenge on procedural grounds that argued the Health Care Reform Law is unconstitutional in its entirety because the " individual mandate " was repealed by Congress. ~~Thus, the Health Care Reform Law will remain in effect in its current form.~~ Further, prior to the Supreme Court ruling, on January 28, 2021, President Biden issued an executive order ~~to~~ **that** ~~initiate~~ **initiated** a special enrollment period for purposes of obtaining health insurance coverage through the Health Care Reform Law marketplace, which began on February 15, 2021 **,** and remained open through August 15, 2021. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver ~~programs~~ **47programs** that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the Health Care Reform Law. In addition, on August 16, 2022, President Biden signed the Inflation Reduction Act of 2022, or IRA, into law, which among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in Health Care Reform Law marketplaces through plan year 2025. The IRA also eliminates the " donut hole " under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out- of- pocket cost and creating a new manufacturer discount program. It is also unclear how any such challenges and the healthcare reform measures of the Biden administration will impact the Health Care Reform Law and our business. In addition, other legislative changes have been proposed and adopted since the Health Care Reform Law was enacted. These changes include, among other things, aggregate reductions to Medicare payments to providers of up to 2 % per fiscal year, which went effective on April 1, 2013 ~~and~~ , ~~following passage of the Bipartisan Budget Act of 2015,~~ and **, due to** subsequent legislative amendments, will remain in effect until ~~2031~~ **2032** , ~~except for a temporary suspension from May 1, 2020 through March 31, 2022 due to the COVID- 19 pandemic~~ , unless additional Congressional action is taken. ~~Under current legislation, the actual reduction in Medicare payments will vary from 1 % in 2022 to up to 4 % in the final fiscal year of this sequester.~~ In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Additionally,

on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory ~~62Medicaid~~ -- **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. Congress is considering additional health reform measures. These new laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on customers for our drugs, if approved, and, accordingly, our financial operations. Further, Congress is considering additional health reform measures. We expect that the Health Care Reform Law, as well as other federal and state healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for KORSUVA injection or any approved product candidate. Any reduction in reimbursement from Medicare or other government healthcare programs may result in a similar reduction in payments from private payers. In addition, there have been several recent U. S. Presidential executive orders, Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform government program reimbursement methodologies for drugs. At the federal level, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates 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. Further, in July 2021, the Biden administration released an executive order that included multiple provisions aimed at prescription drugs. In response to Biden' s executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform. The plan sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. In addition, the IRA, among other things, (1) directs HHS to negotiate the price of certain single- source drugs and biologics covered under Medicare and (2) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions ~~will~~ take effect progressively starting in fiscal year 2023 **. On August 29** , ~~although~~ **2023, HHS announced** ~~they~~ -- **the** ~~may~~ **list of the first ten drugs that will** be subject to **price negotiations, although the Medicare drug price negotiation program is currently subject to** legal challenges. It is ~~currently~~ unclear how the IRA will be implemented but is likely to have a significant impact on the pharmaceutical industry. ~~Further,~~ **In response to** the Biden administration ~~released an additional~~ **' s October 2022** executive order **,** on ~~October~~ **February** 14, ~~2022~~ **2023** , ~~directing~~ HHS **released** ~~to submit~~ a report **outlining** ~~on how the~~ **three** ~~Center for Medicare and Medicaid Innovation can be further leveraged to test~~ new models for **testing by the CMS Innovation Center which will be evaluated on their ability to** ~~lowering~~ --- **lower** ~~drug~~ **the** ~~costs~~ -- **cost of drugs, promote accessibility, and improve quality of care. It is unclear whether the models will be utilized in any health reform measures in the future. Further, on December 7, 2023, the Biden administration announced an initiative to control the price of prescription drugs through the use of march- in rights under the Bayh- Dole Act. On December 8, 2023, the National Institute of Standards and Technology published** for ~~Medicare~~ **comment a Draft Interagency Guidance Framework for Considering the Exercise of March- In Rights which for the first time includes the price of a product as one factor** ~~and~~ -- **an** ~~Medicaid beneficiaries~~ **agency can use when deciding to exercise march- in rights. While march- in rights have not previously been exercised, it is uncertain if that will continue under the new framework** . 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, and, in some cases, to encourage importation from other ~~countries~~ **48countries** and bulk purchasing **. For example, on January 5, 2024, the FDA approved Florida' s Section 804 Importation Program (SIP) proposal to import certain drugs from Canada for specific state healthcare programs. It is unclear how this program will be implemented, including which drugs will be chosen, and whether it will be subject to legal challenges in the United States or Canada. Other states have also submitted SIP proposals that are pending review by the FDA. Any such approved importation plans, when implemented, may result in lower drug prices for products covered by those programs** . The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our drugs. Legislative and regulatory proposals have been made to expand post- approval requirements and restrict sales and promotional activities for drugs. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U. S. Congress of the FDA' s approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post- marketing testing and other requirements. Moreover, the Drug Supply Chain Security Act imposes obligations on manufacturers of pharmaceutical products, among others, related to product tracking and tracing. Legislation and regulations that, among other things, reduce drug prices or require the implementation of costly compliance measures could result in decreased net revenues from our pharmaceutical products and decrease potential returns from our development efforts, and we cannot predict what legislation will be enacted in the future. ~~Further, it is possible that additional governmental action is taken in response to the COVID- 19 pandemic.~~ Governments outside the United States tend to impose strict price controls, which may adversely affect our revenues, if any. In international markets, reimbursement and health care payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. In some countries, particularly the countries of the EU, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a ~~63product~~ -- **product** . To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost- effectiveness of our product candidate to other available therapies. There can be no assurance that our products will be considered cost- effective by third- party payers, that an adequate level of reimbursement will be available or that the third-

party payers' reimbursement policies will not adversely affect our ability to sell our products profitably. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially. Our employees, independent contractors, consultants, and commercial partners may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business. We are exposed to the risk of fraud or other misconduct by our employees, independent contractors, consultants and commercial partners. Misconduct by such individuals could include **inadvertent or** intentional failures to: ● comply with FDA regulations and other similar foreign regulations; ● provide true, complete and accurate information to the FDA; ● comply with manufacturing standards; ● comply with federal and state data privacy, security, fraud and abuse and other healthcare laws and regulations in the United States and similar foreign laws; ● report financial information or data accurately; or ● disclose unauthorized activities to us. ~~In~~ **49In** particular, the promotion, sales and marketing of healthcare items and services, as well as certain business arrangements in the healthcare industry, are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self- dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, including off label uses of our products, structuring and commission (s), certain customer incentive programs, patient assistance programs, and other business arrangements generally. Third party misconduct could also involve the improper use or misrepresentation of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter such misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and financial results, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, individual imprisonment, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and / or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non- compliance with these laws, and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. Our business involves the use of hazardous materials and we **and our third- party manufacturers and suppliers** must comply with environmental laws and regulations, which can be expensive and restrict how we do business. Our **third- party** ~~manufacturing~~ **manufacturers ' and suppliers'** activities involve the controlled storage, use and disposal of hazardous materials **owned by us** , including the components of **oral difelikefalin** ~~our products, product candidates~~ and other hazardous compounds. We **and any third- party manufacturers and suppliers we engage** are subject to **numerous** federal, state and local **environmental, health and safety** laws ~~and~~ **,** regulations **and permitting requirements, including those** governing **laboratory procedures;** the **generation, handling,** use, ~~manufacture,~~ storage, ~~handling~~ **treatment** , ~~release~~ and disposal of ~~,~~ **hazardous** and ~~exposure to~~ **regulated materials and wastes; the emission and discharge of hazardous materials into the ground, air and water; and employee health and safety. Our partners' operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste. In some cases** , these hazardous materials **and various wastes resulting from their use are stored at our contract manufacturers' facilities pending their use and disposal** . ~~Violation~~ **We generally contract with third parties for the disposal** of these **materials and wastes. We cannot eliminate the risk of contamination, which could cause an interruption of our commercialization efforts, research and development efforts and business operations, environmental damage resulting in costly clean- up and liabilities under applicable** laws and regulations ~~could lead to substantial fines~~ **governing the use, storage, handling** and ~~penalties~~ **disposal of these materials and specified waste products. In addition, we cannot entirely eliminate the risk of accidental injury or contamination from these materials or wastes** . Although ~~64we~~ **we** believe that ~~our~~ **the** safety procedures **utilized by our third- party manufacturers** for handling and disposing of these materials **generally** comply with the standards prescribed by these laws and regulations, we cannot **guarantee that this is the case or** eliminate the risk of accidental contamination or injury from these materials. **Under certain environmental laws, we could be held responsible for costs relating to any contamination at our current or past facilities and at third- party facilities.** In ~~the~~ **such an** event ~~of~~ **, we may be held liable for** ~~an~~ **any** ~~accident,~~ **resulting damages and such liability could exceed our resources and** state or federal **or other applicable** authorities may curtail our use of ~~these~~ **certain** materials and **/ or** interrupt our business operations. **Furthermore** ~~In addition~~ ~~, we could~~ **environmental laws and regulations are complex, change frequently and have tended to** become **more stringent. We cannot predict** ~~subject to potentially material liabilities relating to~~ the **impact** ~~investigation and cleanup~~ of ~~any contamination, whether currently unknown~~ **such changes and cannot be certain of** ~~or~~ **our** ~~caused by~~ future ~~releases~~ **compliance** . **Compliance with applicable** ~~Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for~~ environmental **laws and regulations** ~~liability or toxic tort claims that~~ may be **expensive** ~~asserted against us in connection with our storage or disposal of biological~~ , **and** ~~hazardous or radioactive materials. In addition, we may incur substantial costs in order to comply with~~ current or future environmental ~~, health and safety~~ laws and regulations ~~. These current or future laws and regulations~~ may impair our research, **product** development ~~or production~~ **and manufacturing** efforts. ~~Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions. Risks~~ **50Risks** Related to Intellectual PropertyIt is difficult and costly to protect our proprietary rights and as a result we may not be able to ensure their protection and all patents will eventually expire. Our commercial success will depend in part on obtaining and maintaining patent protection and trade secret protection for difelikefalin ~~for our KORSUVA injection or other product candidates~~ and for any other product candidates that

we may develop, license or acquire and the methods we use to manufacture them, as well as successfully defending these patents and trade secrets against third- party challenges. We will only be able to protect our technologies from unauthorized use by third parties to the extent that valid and enforceable patents or trade secrets cover them. The patent prosecution process is expensive and time- consuming, and we may not be able to file and prosecute to issuance all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we may fail to identify patentable aspects of our R & D output before it is too late to obtain patent protection. Moreover, should we enter into additional collaborations we may be required to consult with or cede control to collaborators regarding the prosecution, maintenance and enforcement of our patents. Therefore, these patents and applications may not be successfully prosecuted to issuance and enforced in a manner consistent with the best interests of our business. The patent positions of pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in pharmaceutical or biotechnology patents has emerged to date in the United States. The patent situation outside the United States is also uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third- party patents. The degree of future protection for our proprietary rights is uncertain, because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. Moreover, the patent application process is also subject to numerous risks and uncertainties, and there can be no assurance that we or any of our future development partners will be successful in protecting difelikefalin and any other product candidates that we may develop, license or acquire by obtaining and defending patents. For example: ● we may not have been the first to make the inventions covered by each of our pending patent applications and issued patents; ● we may not have been the first to file patent applications for these inventions; ● others may independently develop similar or alternative technologies or duplicate any of our product candidates or technologies; ~~65~~ ● it is possible that none of the pending patent applications will result in issued patents; ● the issued patents covering our product candidates may not provide a basis for commercially viable active products, may not provide us with any competitive advantages, or may be challenged by third parties; ● we may not develop additional proprietary technologies that are patentable; ● patents of others may have an adverse effect on our business; ● competitors may file trademark infringement claims or challenges to the validity of our trademark (s); ● noncompliance with governmental patent agencies requirements can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction, potentially allowing competitors to enter the market earlier than would otherwise have been the case; **51** ● our competitors, many of whom have substantially greater resources than we do and many of whom have made significant investments in competing technologies, may seek or may have already obtained patents that will limit, interfere with, or eliminate our ability to make, use, and sell our potential product candidates; or ● there may be significant pressure on the U. S. government and international governmental bodies to limit the scope of available patent protection both inside and outside the United States for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns. Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. On September 16, 2011, the Leahy- Smith America Invents Act, or the Leahy- Smith Act, was signed into law. The Leahy- Smith Act includes a number of significant changes to U. S. patent law. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The U. S. Patent Office has developed new regulations and procedures to govern administration of the Leahy- Smith Act, and many of the substantive changes to patent law associated with the Leahy- Smith Act, including and in particular, the first to file provisions, became effective on March 16, 2013. The Leahy- Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our currently pending and future patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition. Patent applications in the United States are generally maintained in confidence for at least 18 months after their earliest effective filing date and in certain circumstances not until granted when no foreign counterpart patent applications are filed. Furthermore, published patent applications may issue at a later date with new and / or amended claims substantially different from those published earlier. Consequently, we cannot be certain we were the first to invent or the first to file patent applications on difelikefalin or any other product candidates that we may develop, license or acquire. Until recent changes to the U. S. Patent Laws, patents and patent applications relating to substantially similar claimed inventions were potentially subject to interference proceedings to determine the first applicant to invent the claimed subject matter. For an interference to be declared against our patents and patent applications, any such interference would be under the 1952 law which was eliminated by the America Invents Act, or AIA, enacted in 2011 and fully effective in 2013. Such an interference would therefore have to relate to a patent or application with an effective filing date before March 16, 2013. No interference with such a patent or application has been declared to date. Therefore, it seems extremely unlikely that we may have to participate in interference proceedings declared by the USPTO to determine priority of invention in the United States against one or more parties claiming the same or similar invention. However, in the unlikely event that such interference was to be declared, the costs of these proceedings could be substantial and it is possible that our efforts would be unsuccessful, resulting in a material adverse effect on our U. S. patent position. The results of these types of proceedings could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result ~~66in~~ **in** our inability to manufacture or commercialize products without infringing third- party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. Such results could have a material adverse effect on our results of operations. In addition, the patentability of claims in pending patent applications covering KORSUVA injection or other difelikefalin- based product can be challenged by third parties during prosecution in the USPTO under the new AIA law of

2013, for example by third party observations and derivation proceedings, and the validity of claims in issued patents can be challenged by third parties in various post- grant proceedings such as Post- Grant Review, Inter- partes Reexamination, and Inter- partes Review proceedings. Furthermore, we may not have identified all U. S. and foreign patents or published applications that affect our business either by blocking our ability to commercialize our drugs or by covering similar technologies that affect our drug market. In addition, some countries, including many in Europe, do not grant patent claims directed to methods of treating humans, and in these countries patent protection may not be available at all to protect our product candidates. ~~Even~~ **52Even** if patents issue, we cannot guarantee that the claims of those patents will be valid and enforceable or provide us with any significant protection against competitive products, or otherwise be commercially valuable to us. We also rely on trade secrets to protect our technology, particularly where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. While we use reasonable efforts to protect our trade secrets, our licensors, employees, consultants, contractors, outside scientific collaborators and other advisors may unintentionally or willfully disclose our information to competitors. Enforcing a claim that a third party illegally obtained and is using our trade secrets is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing to protect trade secrets. Moreover, our competitors may independently develop equivalent knowledge, methods and know- how. If we fail to obtain or maintain patent protection or trade secret protection for difelikefalin or any other product candidate that we may develop, license or acquire, third parties could use our proprietary information, which could impair our ability to compete in the market and adversely affect our ability to generate revenues and achieve profitability. 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. 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 United States 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. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such product candidates might expire before or shortly after such product candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. If we or any current or future collaboration partner are sued for infringing intellectual property rights of third parties, it will be costly and time consuming, and an unfavorable outcome in any litigation would harm our business. Our ability to develop, manufacture, market and sell **difelikefalin** ~~KORSUVA injection~~ or any **potential** ~~of our other current of~~ future product ~~candidates~~ **candidate** **will** ~~depends~~ **depend** upon our ability to avoid infringing the proprietary rights of third parties, and our commercial success **will** ~~depends~~ **depend** upon our ability, and the ability of our collaborators, to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. Numerous U. S. ~~67and~~ **and** foreign issued patents and pending patent applications, which are owned by third parties, exist in the general field of pain management and cover the use of numerous compounds and formulations in our targeted markets. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. Because of the uncertainty inherent in any patent or other litigation involving proprietary rights, we and our licensors may not be successful in defending intellectual property claims by third parties, which could have a material adverse effect on our results of operations. Regardless of the outcome of any litigation, defending the litigation may be expensive, time- consuming and distracting to management. In addition, because patent applications can take many years to issue, there may be currently pending applications, unknown to us, which may later result in issued patents that ~~KORSUVA injection or our other~~ current or **potential** future product candidates may infringe. There could also be existing patents of which we are not aware that ~~KORSUVA injection or~~ **our** ~~our other~~ current or **potential** future product candidates may inadvertently infringe. ~~There~~ **53There** is a substantial amount of litigation involving patent and other intellectual property rights in the biotechnology and biopharmaceutical industries generally. If a third- party claims that we infringe on their products or technology, we could face a number of issues, including: ● infringement and other intellectual property claims which, with or without merit, can be expensive and time consuming to litigate and can divert management' s attention from our core business; ● substantial damages for past infringement which we may have to pay if a court decides that our product infringes on a competitor' s patent; ● a court prohibiting us from selling or licensing our product unless the patent holder licenses the patent to us, which it would not be required to do; ● if a license is available from a patent holder, we may have to pay substantial royalties or grant cross licenses to our patents; and ● redesigning our processes so they do not infringe, which may not be possible or could require substantial funds and time. If we are found to infringe **on** a third party' s intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non- exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product ~~candidates~~ **candidate** or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business. We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and may ultimately be unsuccessful. Competitors may

infringe **on** our issued patents or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent' s claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. ~~68Most~~ -- **Most** of our competitors are larger than we are and have substantially greater resources. They are, therefore, likely to be able to sustain the costs of complex patent litigation longer than we could. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our internal research programs, in- license needed technology, or enter into development partnerships that would help us bring our product ~~candidates~~ -- **candidate** to market. ~~We~~ **54We** may need to license certain intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms. A third party may hold intellectual property, including patent rights that are important or necessary to the development or commercialization of our products. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties. Such a license may not be available on commercially reasonable terms or at all, which could materially harm our business. We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers. As is common in the biotechnology and pharmaceutical industry, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these employees **,** or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management. We may not be able to protect our intellectual property rights throughout the world. Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement rights are not as strong as those in the United States. These products may compete with our product ~~candidates~~ - **candidate** and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries do not favor the enforcement of patents and other intellectual property protection, which could make it difficult for us to stop the infringement of our patents generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license. The validity and enforceability of the patents and applications that cover ~~KORSUVA injection and our~~ difelikefalin ~~product candidates~~ can be challenged by competitors. **In** ~~For KORSUVA injection and in~~ the event that oral difelikefalin or any **potential** future product candidate is approved by the FDA, one or more third parties may challenge the patents covering these products and product candidates, which could result in the invalidation of, or render unenforceable, some or all of the relevant patent claims. For example, if a third ~~69party~~ -- **party** files an Abbreviated New Drug Application, or ANDA, for a generic drug product containing difelikefalin, and relies in whole or in part on studies conducted by or for us, the third party will be required to certify to the FDA that either: (1) the patents listed in the Orange Book have expired; (2) the listed patents have not expired, but will expire on a particular date and approval is sought after patent expiration; or (3) the listed patents are invalid or will not be infringed by the manufacture, use or sale of the third- party' s generic drug product. A certification that the new product will not infringe the Orange Book- listed patents for difelikefalin, or that such patents are invalid, is called a paragraph IV certification. If ~~the~~ **55the** third party submits a paragraph IV certification to the FDA, a notice of the paragraph IV certification must also be sent to us once the third- party' s ANDA is accepted for filing by the FDA. We may then initiate a lawsuit to defend the patents identified in the notice. The filing of a patent infringement lawsuit within 45 days of receipt of the notice automatically prevents the FDA from approving the third- party' s ANDA until the earliest of 30 months or the date on which the patent expires, the lawsuit is settled, or the court reaches a decision in the infringement lawsuit in favor of the third party. If we do not file a patent infringement lawsuit within the required 45- day period, the third- party' s ANDA will not be subject to the 30- month stay. Litigation or other proceedings to enforce or defend intellectual property rights are often very complex in nature, may be very expensive and time- consuming, may divert our management' s attention from our core business, and may result in unfavorable results that could adversely impact our ability to prevent third parties from competing with our products. Risks Related to Employee Matters and Managing **GrowthWe** ~~GrowthOur internal information technology systems, or those of our CROs, contract manufacturers or other contractors or~~

consultants, may fail or suffer cybersecurity breaches, loss or leakage of data and other disruptions, which could result in a material disruption of our development programs, commercialization efforts, compromise sensitive information related to our business or prevent us from accessing critical information, potentially exposing us to liability, which could adversely affect our business. We are increasingly dependent upon information technology systems, infrastructure and data to operate our business. In the ordinary course of business, we collect, store and transmit confidential information (including but not limited to intellectual property, proprietary business information and personal information). It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. We also have outsourced elements of our operations to third parties, and as a result we manage a number of third- party contractors who have access to our confidential information. Despite the implementation of cybersecurity measures, given their size and complexity and the increasing amounts of confidential information that they maintain, our internal information technology systems and those of our third- party CROs, contract manufacturers and other contractors and consultants are potentially vulnerable to breakdown or other damage or interruption from service interruptions, system malfunction, natural disasters, terrorism, war and telecommunication and electrical failures, as well as cybersecurity breaches from inadvertent or intentional actions by our employees, contractors, consultants, business partners and / or other third parties, or from cyber- attacks by malicious third parties (including the deployment of harmful malware, ransomware, denial- of- service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information), which may compromise our system infrastructure or lead to data leakage. Cybersecurity risks have significantly increased in recent years in part because of the proliferation of new technologies, the use of the internet and telecommunication technologies to conduct financial transactions, especially as more employees are working remotely, and the increased sophistication and activities of organized crime, hackers, terrorists, nation- states and other external parties. To the extent that any disruption or cybersecurity breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and reputational damage and the further development and commercialization of our product candidates could be delayed. While we have not experienced any such system failure, accident or cybersecurity breach to date, we cannot assure you that our data protection efforts and our investment in information technology will prevent significant breakdowns, data leakages, breaches in our systems or other cyber incidents that could adversely affect our business. For example, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our programs and the development and commercialization of KORSUVA injection, if approved, could be delayed. In addition, the loss of clinical trial data could result in delays in our marketing approval efforts and significantly increase 70our costs to recover or reproduce the data. Furthermore, significant disruptions of our internal information technology systems or cybersecurity breaches could result in the loss, misappropriation and / or unauthorized access, use, or disclosure of, or the prevention of access to, confidential information (including trade secrets or other intellectual property, proprietary business information and personal information), which could result in financial, legal, business and reputational harm to us. For example, any such event that leads to unauthorized access, use, or disclosure of personal information, including personal information regarding our clinical trial subjects or employees, could harm our reputation directly, compel us to comply with federal and / or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information, which could result in significant legal and financial exposure and reputational damages that could adversely affect our business. We may need to significantly increase the size of our organization, and we may experience difficulties in managing growth. As of March 2, 2023, we had 106 employees. Our management and personnel systems and facilities currently in place may not be adequate to support future growth. In addition, we may not be able to recruit and retain qualified personnel in the future, particularly for sales and marketing positions, due to competition for personnel among pharmaceutical businesses, and the failure to do so could have a significant negative impact on our future product revenues and business results. Our need to effectively manage our operations, growth and various projects requires that we: ● ensure that our consultants and other service providers successfully carry out their contractual obligations, provide high quality results, and meet expected deadlines; ● continue to carry out our own contractual obligations to our licensors and other third parties; and ● continue to improve our operational, financial and management controls, reporting systems and procedures. We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our development and commercialization goals. We depend on skilled personnel to operate our business effectively in a rapidly changing market, and if we are unable to retain existing or hire additional personnel when needed, or manage transitions among members of our leadership team, our ability to develop and sell our products could be harmed. **In January 2024, as part of our pipeline prioritization, we reduced our headcount by approximately 50 %, including the separation of our former Chief Scientific Officer and SVP of Research & Development. Although we believe these employee transitions are in the best interest of our company and our stockholders, these transitions may result in the loss of personnel with deep institutional or technical knowledge. Further, the transition could potentially disrupt our operations and relationships with employees, suppliers, and partners and, as a result, create added costs, operational inefficiencies, decreased employee morale and productivity and increased turnover. In addition, our competitors may seek to use these transitions and the related potential disruptions to gain a competitive advantage over us. Furthermore, these changes increase our dependency on the other members of our leadership team and clinical and preclinical operations teams that remain with us, who are not contractually obligated to remain employed with us and may leave at any time. Any such departure could be particularly disruptive and, to the extent we experience additional turnover, competition for top talent is high such that it may take some time to find a candidate that meets our requirements.** We may not be able to attract or retain qualified management and commercial, scientific , and clinical personnel due to the intense competition for qualified personnel among biotechnology, pharmaceutical and other businesses. If we are not able to attract and retain necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our

development objectives, our ability to raise additional capital and our ability to implement our business strategy. ~~Our industry has experienced a high rate of turnover of management personnel in recent years. We are highly dependent on the skills and leadership of our management team, including our President and CEO. Most recently, we appointed a new President and CEO in November 2021, at which time our former President and CEO, who had served in such position since 2004, transitioned to the role of Senior Advisor to the Company which concluded on June 30, 2022. Further, our senior management may terminate their employment with us at any time.~~ If we ~~are unable to execute an orderly transition and successfully integrate our new CEO into our management team, or if we~~ lose **additional** ~~one or more~~ members of our senior management team, our ability to successfully implement our business strategy could be seriously harmed. Replacing these employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain regulatory approval of and commercialize products successfully. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate additional key personnel. We do not maintain " key person " insurance for any of our executives or other employees. ~~71If~~ **If** we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired. We are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, the Sarbanes- Oxley Act of 2002 and the rules and regulations of The Nasdaq Global Market. Pursuant to Section 404 of the Sarbanes- Oxley Act of 2002, or Section 404, we are required to perform system and process evaluation and testing of our internal control over financial reporting to allow our management to report on the effectiveness of our internal control over financial reporting and, in the past, we have also been required to have our independent registered public accounting firm issue an opinion on the effectiveness of our internal control over financial reporting on an annual basis as a large accelerated filer. However, based on our public float as of June 30, ~~2022~~ **2023**, we qualified as a non- accelerated filer at the end of ~~2022~~ **2023**, which would allow us to forgo the auditor attestation requirement for the fiscal year ended December 31, ~~2022~~ **2023**. However, we have determined to voluntarily comply with the auditor attestation requirement for the fiscal year ended December 31, ~~2022~~ **2023**. ~~During~~ **56During** the evaluation and testing process, if we identify one or more material weaknesses in our internal control over financial reporting, we will be unable to assert that our internal control over financial reporting is effective. Further, we may in the future discover weaknesses in our system of internal financial and accounting controls and procedures that could result in a material misstatement of our financial statements ~~. For example, beginning in April 2022, we began recognizing profit- sharing revenue from the sale of KORSUVA injection in the United States by CSL Vifor. We are dependent on CSL Vifor for timely and accurate information regarding the net revenues from sales of KORSUVA injection in the United States in accordance with applicable accounting standards to accurately report our results of operations. If we do not receive timely and accurate information or incorrectly estimate activity levels associated with the profit share arrangement at a given point in time, we could be required to record adjustments in future periods~~. Moreover, our internal controls over financial reporting will not prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system' s objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected. Moreover, we are aware that the increased prevalence of remote working arrangements ~~implemented in connection with the COVID- 19 pandemic~~ potentially presents additional areas of risk, including cyber and privacy risks, and we are carefully monitoring any impact to our internal controls and procedures. If we are unable to assert that our internal control over financial reporting is effective, or if our independent registered public accounting firm is unable to express an opinion on the effectiveness of our internal control over financial reporting, investors could lose confidence in the reliability of our financial statements, the market price of our stock could decline and we could be subject to sanctions or investigations by The Nasdaq Global Market, the SEC or other regulatory authorities. Risks Related to Ownership of Our Common ~~StockThe~~ **StockIf we fail to meet all applicable requirements of Nasdaq and Nasdaq determines to delist our common stock, the delisting could adversely affect the market liquidity of our common stock and the market price of our common stock could decrease. On February 1, 2024, we received a letter from Nasdaq, notifying us that, for the previous 30 consecutive business day period prior to the date of the letter, the closing bid price for our common stock was below $ 1. 00. In accordance with Nasdaq Listing Rule 5810 (c) (3) (A) we have been provided an initial period of 180 calendar days, or until July 30, 2024, to regain compliance with Nasdaq' s bid price requirement. If, at any time before July 30, 2024, the bid price for our common stock closes at $ 1. 00 or more for a minimum of 10 consecutive business days, we will regain compliance with the bid price requirement, unless Nasdaq staff exercised its discretion to extend this 10- day period pursuant to Nasdaq rules. If we are unable to satisfy the Nasdaq criteria for continued listing, our common stock would be subject to delisting. A delisting of our common stock could negatively impact us by, among other things, reducing the liquidity and market price of our common stock; reducing the number of investors willing to hold or acquire our common stock, which could negatively impact our ability to raise equity financing; decreasing the amount of news and analyst coverage of us; and limiting our ability to issue additional securities or obtain additional financing in the future. In addition, delisting from Nasdaq may negatively impact our reputation and, consequently, our business. The** market price of our common stock has been, and is likely to continue to be, highly volatile, and you may not be able to resell your shares at or above the price you paid for them. Since our initial public offering in January 2014, our stock price has been volatile and it is likely that the trading price of our common stock will continue to be volatile. As a result of this volatility, investors may not be able to sell their common stock at or above the price paid for the shares. The market price for our common stock may be influenced by many factors, including: ● actual or anticipated variations in quarterly or annual operating results ~~; ● the commercial success of KORSUVA injection and Kapruvia and, if approved by the FDA, oral difelikefalin or any future product candidates~~ ; ● delays in the commencement, enrollment and ultimate completion of our clinical trials, including our planned trials for oral difelikefalin; ~~72~~ **● results of clinical trials of oral difelikefalin for the treatment of pruritus in patients with NP, or any**

potential future product candidate or those of our competitors; 57 ● any delay or refusal on the part of the FDA **or other regulatory authorities** in approving ~~an NDA~~ **marketing authorization** for ~~our other current or future product candidates; ● results of clinical trials of~~ oral difelikefalin ~~, such as our announcement of top- line results in June 2022 and data in September 2022 from the proof- of- concept Phase 2 KOMFORT trial of oral difelikefalin for the treatment of pruritus in patients with NP,~~ or any **potential** future product candidate ~~or those of our competitors~~ ; ● failure to meet or exceed financial projections we provide to the public; ● failure to meet or exceed the estimates and projections of the investment community, including securities analysts; ● introduction of competitive products or technologies; ● changes or developments in laws or regulations applicable to ~~our~~ product ~~candidates~~ **candidate** ; ● the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community; ● general trends in our industry or economic and market conditions and overall fluctuations in U. S. equity markets ~~, including as a result of the COVID- 19 pandemic~~ ; ● developments concerning our sources of manufacturing supply, warehousing and inventory control; ● disputes or other developments relating to patents or other proprietary rights; ● additions or departures of key scientific or management personnel; ● announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us; ● capital commitments; ● investors' general perception of our company and our business; ● announcements and expectations of additional financing efforts, including the issuance of debt, equity or convertible securities **or other security instruments** ; ● sales of our common stock, including sales by our directors and officers or significant stockholders; ● changes in the market valuations of companies similar to us; ● announcements by us or our competitors of significant acquisitions, strategic partnerships, or divestitures; ● changes in the structure of healthcare payment systems; and ● the other factors described in this " Risk Factors " section. In addition, the stock market in general, and the market for small pharmaceutical and biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors, such as those related to **high rates of inflation and interest rates and concerns of a recession in the United States or** ~~the~~ **other** ~~COVID- 19 pandemic~~ **major markets, the recent disruptions to and volatility in the credit and financial markets in the United States and worldwide, and geopolitical instability, including resulting from the ongoing conflicts between Russia and the Ukraine, conflicts in the Middle East, and increasing tensions between China and Taiwan** , may negatively affect the market price of our common stock, regardless of our actual operating performance. ~~73Further~~ **58Further** , in the past, stockholders have initiated class action lawsuits against pharmaceutical and biotechnology companies following periods of volatility in the market prices of these companies' stock. Such litigation, if instituted against us, could cause us to incur substantial costs and divert management' s attention and resources from our business. If equity research analysts cease to publish research or reports about us or if they publish unfavorable research or reports about us, our business or our market, our stock price and trading volume could decline. The trading market for our common stock is likely to be influenced by the research and reports that equity research analysts publish about us and our business. We do not have any control over the analysts or the content and opinions included in their reports. The price of our stock could decline if one or more equity research analysts downgrade our stock or issue other unfavorable commentary or research. **Certain** ~~If one or more~~ equity research analysts **who covered us have** ~~ceases~~ **ceased** coverage **, and if further analysts who cover us were to cease coverage** of our company or ~~fails~~ **fail** to publish reports on us regularly, demand for our stock could decrease, which in turn could cause our stock price or trading volume to decline. Our quarterly operating results may fluctuate significantly. We expect our operating results to be subject to quarterly fluctuations. Our operating results will be affected by numerous factors, including: ● ~~our or our partners' or our collaborators' ability to establish the necessary commercial infrastructure to successfully launch KORSUVA injection and Kapruvia without substantial delays, including hiring sales and marketing personnel and contracting with third parties for warehousing, distribution, cash collection and related commercial activities; ●~~ the successful progress of our clinical trials for oral difelikefalin and other potential future product candidates; ● **variations in the level of expenses related to our future development programs; ●** whether the FDA **or other regulatory authorities** ~~requires~~ **require** us to complete additional, unanticipated studies, tests or other activities prior to approving our other current or future product candidates, which would likely further delay any such approval; ● our ability to identify, enter into and maintain third party manufacturing arrangements capable of manufacturing **oral difelikefalin** ~~KORSUVA injection or our~~ **or any potential** ~~other current or~~ future product ~~candidates~~ **candidate** in commercial quantities; ● our execution of other collaborative, licensing or similar arrangements and the timing of payments we may make or receive under these arrangements ~~; ● variations in the level of expenses related to our future development programs~~ ; ● any product liability or intellectual property infringement lawsuit in which we may become involved; ● regulatory developments affecting ~~KORSUVA injection, Kapruvia,~~ oral difelikefalin, any **potential** ~~of our~~ future product candidates, or the product candidates of our competitors; and ● ~~for KORSUVA injection and Kapruvia, and~~ if oral difelikefalin or any **potential** ~~of our~~ future product candidates receives regulatory approval, the level of underlying demand for such product ~~and product candidate~~ and wholesaler buying patterns. If our quarterly or annual operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly or annual fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance. ~~74Raising~~ **Raising** additional funds by issuing securities may cause dilution to existing stockholders and raising funds through lending and licensing arrangements may restrict our operations or require us to relinquish proprietary rights. Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, **royalty arrangements,** grants ~~and~~ **,** license and development agreements in connection with any collaborations **, and other financial instruments** . We do not yet have any committed external source of funds. To the extent that we raise additional capital by issuing equity securities, our existing ~~stockholders~~ **59stockholders** ' ownership will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing and preferred equity financing, if

available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs **,** ~~or KORSUVA injection or~~ product ~~candidates~~ **candidate** or grant licenses on terms that may not be favorable to us. Any debt financing that we enter into may involve covenants that restrict our operations. These restrictive covenants may include limitations on additional borrowing and specific restrictions on the use of our assets as well as prohibitions on our ability to create liens, pay dividends, redeem our stock or make investments. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. The use of our net operating loss carryforwards and research tax credits may be limited. A portion of our net operating loss, or NOL, carryforwards and R & D tax credits may expire and not be used. As of December 31, ~~2022~~ **2023**, we had federal and state NOL carryforwards of approximately $ ~~440~~ **467**. ~~2~~ **0** million and $ ~~348~~ **473**. ~~0~~ **3** million, respectively, and we also had federal and state R & D tax credit carryforwards of approximately $ ~~23~~ **27**. ~~9~~ **5** million and $ ~~2~~ **4**. ~~9~~ **5** million, respectively. Our NOL carryforwards will begin expiring in 2026 for federal purposes (to the extent such federal NOLs are generated in taxable years beginning on or before December 31, 2017) and 2027 for state purposes if we have not used them prior to that time, and our federal R & D tax credits will begin expiring in 2025 unless previously used. The federal NOLs arising in 2018 and forward have an unlimited carryforward period and losses from 2018- 2020 may be carried back five years due to the Coronavirus Aid, Relief, and Economic Security Act of 2020, or the CARES Act. It is uncertain if and to what extent various states will conform to the TCJA, as modified by the CARES Act. To the extent that we have not exchanged our Connecticut R & D tax credits for a tax refund, those tax credits carry forward indefinitely. Additionally, our ability to use any NOL and R & D tax credit carryforwards to offset taxable income or tax, respectively, in the future will be limited under Internal Revenue Code Sections 382 and 383, respectively, if we have a cumulative change in ownership of our stock of more than 50 % within a three- year period. The completion of our initial public offering in 2014 and our follow- on public offerings in 2015, 2017, 2018 and 2019, together with private placements and other transactions that have occurred, may have triggered such ownership changes. We conducted a 382 analysis in the first quarter of 2021. This analysis showed a limited change of ownership had occurred, and the amount of NOL carryforwards and R & D tax credits that could be utilized annually in the future to offset taxable income or tax, respectively. In addition, since we will need to raise substantial additional funding to finance our operations, we may undergo ownership changes in the future. Any such annual limitation may significantly reduce the utilization of the NOL carryforwards and R & D tax credits before they expire. In addition, certain states have in the past suspended use of NOL carryforwards for certain taxable years (including Connecticut which currently limits the use of NOL carryforwards by 50 % and without limitation legislation enacted by California in June 2020 that suspends the use of California NOLs and limits the use of California R & D tax credits for certain years), and other states are considering similar measures. As a result, we may incur higher state income tax expense in the future. Depending on our future tax position, limitations on our ability to use NOL carryforwards in states in which we are subject to income tax could have an adverse impact on our results of operations and financial condition. ~~75New --~~ **New** or future changes to tax laws could materially adversely affect our company. On December 22, 2017, President Trump signed into law the TCJA, which significantly amends the Internal Revenue Code of 1986, which was modified by the CARES Act. We continue to examine the impact these changes may have on our business. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the TCJA and CARES Act, or any other future changes in tax laws, is uncertain and our business and financial condition could be adversely affected. For example, proposals have recently been made in Congress (which have not yet been enacted) that include tax law changes that could have a material adverse impact on us. The impact of the TCJA and CARES Act and any future changes in tax laws on holders of our common stock is also uncertain and could be adverse. **60** ~~Further, beginning in our tax year ending December 31, 2022, as a result of the TCJA, current R & D expenditures incurred in the United States must be capitalized for tax purposes, and amortized over a period of five years (fifteen years in the case of R & D performed outside the United States). As such, the deferred tax asset for intangible assets will materially increase in lieu of NOL carryforwards, offset by a change in valuation allowance. Because we do not intend to pay dividends on our common stock, your returns will be limited to any increase in the value of our stock. We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business and do not anticipate declaring or paying any cash dividends on our common stock for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock, if any. Investors seeking cash dividends should not purchase our common stock. Provisions in our corporate charter documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management and hinder efforts to acquire a controlling interest in us, and the market price of our common stock may be lower as a result. There are provisions in our certificate of incorporation and bylaws, as amended, that may make it difficult for a third party to acquire, or attempt to acquire, control of our company, even if a change in control was considered favorable by you and other stockholders. For example, our Board of Directors has the authority to issue up to 5, 000, 000 shares of preferred stock and to fix the price, rights, preferences, privileges, and restrictions of the preferred stock without any further vote or action by our stockholders. The issuance of shares of preferred stock may delay or prevent a change in control transaction. As a result, the market price of our common stock and the voting and other rights of our stockholders may be adversely affected. An issuance of shares of preferred stock may result in the loss of voting control to other stockholders. Our charter documents also contain other provisions that could have an anti- takeover effect, including: ● our Board of Directors are divided into three classes, with only one class of directors elected each year; ● our stockholders are entitled to remove directors only for cause upon a 66 2 / 3 % vote; ● our stockholders are not permitted to take actions by~~

written consent; ● our stockholders are not permitted to call a special meeting of stockholders; and ● our stockholders must give us advance notice of their intent to nominate directors or submit proposals for consideration at stockholder meetings. In addition, we are subject to the anti- takeover provisions of Section 203 of the Delaware General Corporation Law, which regulates corporate acquisitions by prohibiting Delaware corporations from engaging in specified business combinations with particular stockholders of those companies. These provisions could discourage potential acquisition 76