Risk Factors Comparison 2024-02-22 to 2023-03-02 Form: 10-K

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Our business involves significant risks, some of which are described below. You should carefully consider these risks, as well as other information in this Annual Report on Form 10- K, including our financial statements and the notes thereto and " Management' s Discussion and Analysis of Financial Condition and Results of Operations. " The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations, cash flows, the trading price of our common stock and our growth prospects. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business operations. Risks Related to our Financial Condition and Capital Requirements We **are not profitable and** have incurred significant losses since our inception **,** and ~~will~~ **we expect to** incur **operating** losses in the future **as we commercialize IBSRELA ® and XPHOZAH ®** , ~~which makes it difficult~~ **incur manufacturing and development costs** for **tenapanor** ~~us to assess our future viability; although our financial statements have been prepared on a going concern basis~~ , ~~our current level of cash~~ and **incur research and development costs related** ~~short-term investments alone is not sufficient~~ to **potential new product candidates** ~~meet our operating plans for the next twelve months, raising substantial doubt regarding our ability to continue as a going concern~~ . In March 2022, we commenced the commercialization of our first product, IBSRELA ® (tenapanor) for the treatment of irritable bowel syndrome with constipation (~~"~~IBS- C ~~"~~) in adult patients and have generated ~~limited~~ **approximately $ 95. 6 million in net** revenue from product sales **through** ~~to date. We are not profitable and have incurred losses in each year since our inception in October 2007, and we do not know whether or when we will become profitable. We continue to incur significant commercialization, development and other expenses related to our ongoing operations. As of~~ December 31, ~~2022~~ **2023 . In October 2023** , we ~~had~~ **received U. S. Food** ~~an~~ **and Drug Administration (FDA)** ~~accumulated deficit of $ 780. 1 million. We expect to continue to incur substantial operating losses for the foreseeable future as we commercialize IBSRELA, seek to gain~~ approval for XPHOZAH ® (tenapanor) for the ~~control~~ **reduction** of serum phosphorus in ~~adult~~ **adults** ~~patients~~ with chronic kidney disease (~~"~~CKD ~~"~~) on dialysis ~~; prepare~~ **as add- on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy. In November 2023, we commenced the commercialization of XPHOZAH and generated approximately $ 2. 5 million in net revenue from product sales through December 31, 2023. We are not profitable and have incurred losses in each year since our inception in October 2007, and we do not know whether or when we will become profitable. We continue to incur significant commercialization, development and other expenses related to our ongoing operations. As of December 31, 2023, we had an accumulated deficit of $ 846. 2 million. We expect to continue to incur operating losses** for ~~, and~~ **the foreseeable future as we** commercialize **IBSRELA and** XPHOZAH, ~~if approved; incur manufacturing and development cost for tenapanor; and~~ incur manufacturing and development costs for tenapanor ~~.. Ernst & Young LLP~~ , ~~our independent registered public accounting firm for the fiscal year ended December 31, 2022, has included an~~ **and incur research** ~~explanatory paragraph in their opinion that accompanies our audited financial statements as of the year ended December 31, 2022, indicating our current liquidity position raises substantial doubt about our ability to continue as a going concern. We plan to address our operating cash flow requirements with our current cash~~ and **development costs related to** ~~short- term investments, cash generated from the sales of IBSRELA, and if approved, cash generated from the sales of XPHOZAH, our~~ potential **new product candidates** ~~receipt of anticipated milestone payments from our collaboration partners, our potential receipt of anticipated payments from our collaboration partner, Kyowa Kirin, Co., Ltd. (" KKC ") in connection with the transaction entered into with KKC in April 2022 (" 2022 KKC Amendment ") which amended our License Agreement entered into with KKC in 2017; with additional financing sources and through the implementation of cash preservation activities to reduce or defer discretionary spending~~ . There are no assurances that our efforts to meet our operating cash flow requirements will be successful. If our current cash **, cash equivalents** and short- term investments as well as our plans to meet our operating cash flow requirements are not sufficient to fund necessary expenditures and meet our obligations ~~for at least the next twelve months~~ , our liquidity, financial condition **,** and business prospects will be materially affected. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. Further, the net losses we incur may fluctuate significantly from quarter- to- quarter and year- to- year, such that a period- to- period comparison of our results of operations may not be a good indication of our future performance. Our ability to utilize our net operating loss carryforwards and certain other tax attributes may be limited. We have substantial net operating loss and tax credit carryforwards for Federal and California income tax purposes. Such net operating losses and tax credits carryforwards may be reduced as a result of certain intercompany restructuring transactions. In addition, the future utilization of such net operating loss and tax credit carryforwards and credits ~~will~~ **may** be subject to limitations, pursuant to Sections 382 and 383 of the Internal Revenue Code of 1986, as amended (the ~~"~~Code ~~"~~). In general, if a corporation undergoes an " ownership change, " generally defined as a cumulative change of more than 50 percentage points (by value) in its equity ownership by certain stockholders over a three- year period, the corporation' s ability to use its pre- change net operating loss (~~"~~NOL ~~"~~) carryforwards and other pre- change tax attributes (such as research and development tax credits) to offset its post- change income or taxes may be limited. We have experienced ownership changes in the past and may experience additional ownership changes in the future, as a result of subsequent changes in our stock ownership, some of which are outside our control. Accordingly, we may not be able to utilize a material portion of our NOL carryforwards, even if we achieve profitability **.** We will require additional financing for the foreseeable future as we invest in the commercialization of IBSRELA ~~,~~ and ~~prepare for and commercialize~~ XPHOZAH in the U. S. ~~, if approved~~ **and incur research and development costs related to potential new**

product candidates . The inability to access necessary capital when needed on acceptable terms, or at all, could force us to reduce our efforts to commercialize IBSRELA or **XPHOZAH, or to** delay or limit ~~the commercialization of XPHOZAH, if approved. Since~~ our **pursuit** ~~inception, most~~ of **potential new product candidates** ~~our resources have been dedicated to our research and development activities, including developing tenapanor.~~ We believe that we will continue to expend substantial resources for the foreseeable future, including ~~,~~ costs associated with our efforts to commercialize IBSRELA **and** ~~, which we began selling in the U. S. in March 2022; costs associated with our efforts to pursue approval for our NDA for~~ XPHOZAH; conducting pediatric clinical trials for IBSRELA ~~and XPHOZAH, if approved~~ ; ~~and~~ manufacturing for IBSRELA and ~~, if approved~~ XPHOZAH **and research and development related to potential new product candidates** . Our future funding requirements will depend on many factors, including, but not limited to: • the extent to which we are able to generate product revenue from sales of IBSRELA **and** ~~; • whether we are successful in securing approval for our NDA for~~ XPHOZAH ~~, and the time and cost associated with securing such approval~~ ; • the availability of adequate third- party reimbursement for IBSRELA and ~~, if approved, the sales price and the availability of adequate third- party reimbursement for~~ XPHOZAH; • the manufacturing, selling and marketing costs associated with IBSRELA and ~~, if approved,~~ XPHOZAH **; • whether or when XPHOZAH, along with other oral ESRD- related drugs without an injectable or intravenous equivalent, are bundled into the ESRD prospective payment system (ESRD PPS), the manner in which such introduction into the ESRD PPS may occur, including the length of any applicable TDAPA period and the amount of the add- on payment available during the TDAPA period and whether, and the extent to which, the ESRD PPS base rate is adjusted following any applicable TDAPA period** ; • our ability to maintain our existing collaboration partnerships and to establish additional collaboration partnerships, in- license / out- license, joint ventures or other similar arrangements and the financial terms of such agreements; • the timing, receipt and amount of any milestones that may be received from our collaboration partners in connection with tenapanor, if any ~~• the timing, receipt, and amount of revenue, if any, that may be received from KKC in connection with the 2022 KKC Amendment~~ ; • the timing, receipt, and amount of royalties we may receive as a result of sales of tenapanor by our collaboration partners in China **,** and Canada, if any; • the cash requirements for the discovery and / or development of other potential product candidates, including RDX013 and RDX020; • the time and cost necessary to respond to technological and market developments; • the costs of filing, prosecuting, maintaining, defending and enforcing any patent claims and other intellectual property rights, including litigation costs and the outcome of such litigation, ~~including~~ **and** costs of defending any claims of infringement brought by others in connection with the development, manufacture or commercialization of tenapanor or any of our product candidates; and • the payment of interest and principal related to our loan and security agreement entered into with SLR Investment Corp. ~~in February 2022~~ **, as amended to date** . Additional funds may not be available when we need them on terms that are acceptable to us, or at all. If adequate funds are not available to us on a timely basis, we may be required to limit or reduce our commercialization of IBSRELA ~~,~~ or ~~delay or limit the commercialization of XPHOZAH~~ **XPOHZAH** , ~~if approved, or~~ delay or limit additional clinical trials for tenapanor **, or delay or limit our pursuit of potential new product candidates** . Additionally, our inability to access capital on a timely basis and on terms that are acceptable to us may force us to restructure certain aspects of our business or identify and complete one or more strategic collaborations or other transactions in order to fund the commercialization of IBSRELA or XPHOZAH ~~, if approved,~~ through the use of alternative structures. We have generated limited revenue from product sales and may never be profitable. We began selling IBSRELA in the U. S. in March 2022 ~~,~~ and have generated ~~limited~~ **approximately $ 95. 6 million in net** revenue from product sales ~~to date~~ **through December 31, 2023. On October 17, 2023, our NDA for XPHOZAH was approved by the U. S. Food and Drug Administration' s (U. S. FDA). In November, we commenced the commercialization of XPHOZAH and generated approximately $ 2. 5 million in net revenue from product sales through December 31, 2023** . We have no other products approved for sale. ~~We are preparing to resubmit our NDA for XPHOZAH following the U. S. Food and Drug Administration' s (" FDA ") Center for Drug Evaluation and Research, Office of New Drugs (" OND ") decision to grant our appeal of the Complete Response Letter (" CRL ") for the NDA for XPHOZAH. There can be no assurances that our NDA for XPHOZAH will be approved by the FDA. There can be no assurances that we will be successful in increasing the amount of product revenue from sales of IBSRELA.~~ There can be no assurances that we will generate sufficient product revenue from sales of IBSRELA and ~~, if approved,~~ XPHOZAH ~~,~~ to cover our expenses. Our ability to generate product revenue from sales or pursuant to milestone or royalty payments depends heavily on many factors, including but not limited to: • our ability to successfully commercialize ~~IBSRELA~~ **ISBRELA and XPHOZAH and to increase market share for both products** ; • ~~obtaining~~ **maintaining sufficient** market acceptance of IBSRELA as a viable treatment option for IBS- C; • **obtaining market acceptance of XPHOZAH; •** our ability to obtain and sustain an adequate level of coverage and reimbursement for IBSRELA **and XPHOZAH** by third- party payors; • whether ~~we~~ **or when XPHOZAH, along with other oral ESRD- related drugs without an injectable or intravenous equivalent,** are ~~successful~~ **bundled into the ESRD PPS, the manner** in **which such introduction into the ESRD PPS may** ~~our~~ **occur** ~~efforts~~ **, including the length of any applicable TDAPA period and the amount of the add- on payment available during the TDAPA period and whether, and the extent** to ~~secure approval for our NDA for XPHOZAH~~ **which, the ESRD PPS base rate is adjusted following any applicable TDAPA period** ; • establishing and maintaining supply and manufacturing relationships with third parties that can provide an adequate (in amount and quality) supply of product to support the market demand for IBSRELA and ~~, if approved,~~ XPHOZAH; • addressing any competing technological and market developments; • maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets, and know- how, and our ability to develop, manufacture and commercialize our product candidates and products without infringing intellectual property rights of others; and • attracting, hiring, and retaining qualified personnel. With respect to our commercialization of IBSRELA ~~,~~ and ~~if we are successful in obtaining regulatory approval to market~~ XPHOZAH, our revenue will be dependent, in part, upon the size of the markets in the U. S. ~~and~~ **,** the label for which approval ~~is~~ **was** granted, accepted price for the product, and the ability to get reimbursement at any price. While there is significant uncertainty related to the insurance coverage and reimbursement of newly approved products in general in the U. S., there is additional uncertainty related to insurance coverage and reimbursement for drugs, like XPHOZAH, which **is being** ~~, if approved, will be~~ marketed for the ~~control~~ **reduction** of serum phosphorus in ~~adult~~ **adults** ~~patients~~ with **chronic kidney disease (** CKD **)** on dialysis ~~or~~ **as add- on therapy in patients who have an inadequate response to phosphate binders** ~~for~~ **or who** ~~another other related indication. If we~~ are **intolerant of any dose of phosphate binder therapy. Our** ~~successful in obtaining regulatory approval to market XPHOZAH for such indication, our~~ ability to generate and sustain future revenues from sales of XPHOZAH, ~~may~~ **will** be **significantly** dependent upon whether and when XPHOZAH, along with other oral end stage renal disease (~~"~~ESRD ~~"~~)- related drugs without an injectable or intravenous equivalent, are bundled into the ESRD **PPS** ~~prospective payment system~~, and the manner in which such introduction into the ESRD **PPS** ~~prospective payment system~~ may occur. See " **—** Third- party payor coverage and reimbursement status of newly ~~approved~~ **commercialized** products are uncertain. Failure to obtain or maintain adequate coverage and reimbursement for IBSRELA and ~~, if approved,~~ XPHOZAH could limit our ability to market those products and decrease our ability to generate revenue **" and " — In the event no legislative or regulatory action is taken to further delay the inclusion of oral only ESRD related drugs in the ESRD PPS, XPHOZAH will become part of the ESRD PPS on January 1, 2025, and will no longer be separately paid for under Part D, and as a result the revenue that we may generate on sales of XPHOZAH will be negatively and materially impacted** " below. Additionally, if the number of adult patients for IBSRELA **and /** or ~~, if approved~~ XPHOZAH ~~,~~ is not as significant as we estimate, ~~the indication approved by regulatory authorities for XPHOZAH is narrower than we expect,~~ coverage and reimbursement for either IBSRELA or XPHOZAH ~~, if approved,~~ are not available in the manner and to the extent we expect, or the reasonably accepted population for treatment is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from the sale of IBSRELA or XPHOZAH ~~, if approved~~. Even if we achieve profitability in the future, we may not be able to sustain profitability in subsequent periods. Our failure to generate adequate revenue from product sales would likely depress our market value and could impair our ability to raise capital, expand our business, discover or develop other product candidates or continue our operations. A decline in the value of our common stock could cause our stockholders to lose all or part of their investment. Principal Risks Related to Our Business We are substantially dependent on the successful commercialization of IBSRELA, and there is no guarantee that we will ~~achieve~~ **maintain** sufficient market acceptance for IBSRELA, **grow market share for IBSRELA,** secure **and maintain** adequate coverage and reimbursement for IBSRELA, or generate sufficient revenue from product sales of IBSRELA. We began selling IBSRELA in the U. S. in March 2022. The overall commercial success of IBSRELA will depend on a number of factors, including the following: • the ability of the third- party manufacturers we contract with to provide an adequate (in amount and quality) supply of product to support the market demand for IBSRELA **; • our ability to obtain and sustain an adequate level of coverage and reimbursement for IBSRELA by third- party payors** ; • the effectiveness of IBSRELA as a treatment for adult patients with IBS- C; • the size of the treatable patient population; • **our ability to continue to increase the market share of IBSRELA; •** the effectiveness of our sales, market access and marketing efforts; • whether physicians view IBSRELA as a safe and effective treatment for adult patients with IBS- C, which will impact the adoption of IBSRELA by physicians for the treatment of IBS- C; • the availability, perceived advantages, relative cost, relative safety and relative efficacy of IBSRELA compared to alternative and competing treatments; • the prevalence and severity of adverse side effects of IBSRELA; • our potential involvement in lawsuits in connection with enforcing intellectual property rights in and to IBSRELA; • our potential involvement in third- party interference, opposition, derivation or similar proceedings with respect to our patent rights directed to IBSRELA, and avoiding other challenges to our patent rights and patent infringement claims; and • a continued acceptable safety and tolerability profile of IBSRELA following approval. The amount of potential revenue we may achieve from the commercialization of IBSRELA is subject to these and other factors, and may be unpredictable from quarter- to- quarter. If the number of patients in the market for IBSRELA or the price that the market can bear is not as significant as we estimate, or if we are not able to **continue to** secure ~~adequate~~ **and maintain** physician and patient acceptance of IBSRELA or adequate coverage and reimbursement for IBSRELA, we may not generate sufficient revenue from sales of IBSRELA. Any failure of IBSRELA to ~~achieve~~ **maintain** market acceptance, **continue to increase market share, obtain and maintain** sufficient third- party coverage or reimbursement, or **achieve** commercial success would adversely affect our results of operations. ~~We are pursuing regulatory approval for XPHOZAH.~~ There ~~can be no assurances that we will be successful in obtaining such regulatory approval. We are pursuing regulatory approval for XPHOZAH. To date, we have invested a significant amount of our efforts and financial resources in the research and development of XPHOZAH. On July 28, 2021, we received a CRL from the FDA' s Division of Cardiology and Nephrology (" Division ") regarding our NDA for XPHOZAH. According to the CRL, the Division determined that the magnitude of the treatment effect observed in our Phase 3 clinical trials was small and of unclear clinical significance. Following an End- of- Review Type A meeting (" End of Review Meeting ") in October 2021, with the Division, we submitted a Formal Dispute Resolution Request (" FDRR ") in December 2021. The FDRR was focused on demonstrating that the data submitted in the NDA supported the clinical significance of the treatment effect of tenapanor in the control of serum phosphorus in adult patients with CKD on dialysis. On February 4, 2022, we received an Appeal Denied Letter (" ADL") from the Office of Cardiology, Hematology, Endocrinology and Nephrology (" OCHEN "). On February 18, 2022, we submitted an appeal of the ADL to the OND. In April 2022, we received an interim response from the OND requesting additional input from the Cardiovascular and Renal Drug Advisory Committee (" CRDAC "). A CRDAC meeting was held in November 2022 with the Committee voting that the benefits of XPHOZAH outweigh its risks nine to four as a monotherapy and ten to two, with one abstention, in combination with phosphate binder therapy. In December 2022, the OND granted our appeal of the CRL for the NDA for XPHOZAH and directed the Division to work with us to develop an appropriate label for the commercialization of XPHOZAH. We believe that a label could reflect an indication for patients whose hyperphosphatemia is insufficiently managed on binder therapy. On February 13, 2023, we participated in a Type A meeting with the Division where we discussed the~~

~~resubmission of the NDA, and the information to be contained in the resubmitted NDA. We currently expect to resubmit the NDA for XPHOZAH early in the second quarter of 2023. Within 30 days of resubmitting the NDA, we expect to receive notification from the Division as to the classification of the resubmission (Class 1 or Class 2) at which point the expected timing for review will also be known (2- months for a Class 1 and 6- months for a Class 2) as well as a goal review date. We currently that the FDA will act upon the XPHOZAH NDA in the second half of 2023, and that, if approved, we will launch XPHOZAH in the second half of 2023. There can be no assurances that the granting of our appeal to the CRL and resubmission of our NDA will result in approval of our NDA for XPHOZAH. Even if we are successful in obtaining approval for the NDA, the delay in obtaining such approval may result in delay in the regulatory process for our partners, which could have a material adverse effect on our business and results of operations. Even if we are successful in obtaining regulatory approval for XPHOZAH, there~~ is no guarantee that we will achieve sufficient market acceptance for XPHOZAH, secure **and maintain** adequate coverage and reimbursement for XPHOZAH or generate sufficient revenue from product sales of XPHOZAH. ~~We may not be successful in obtaining FDA approval for XPHOZAH, and if we are able to obtain approval, there~~ **There** is no guarantee that we will achieve sufficient market acceptance for XPHOZAH, secure **and maintain** adequate coverage and reimbursement for XPHOZAH or generate sufficient revenue from product sales of XPHOZAH. **The** ~~If we are successful in obtaining approval for XPHOZAH, the~~ commercial success of XPHOZAH will depend on a number of factors, including the following: • the ability of the third- party manufacturers we contract with to provide an adequate (in amount and quality) supply of product to support the market demand for both IBSRELA and XPHOZAH; • whether or not the content and breadth of the label **that has been** approved by the **U. S.** FDA for XPHOZAH ~~may~~ **will** materially and adversely impact our ability to commercialize the product for the approved indication ~~; • whether or when XPHOZAH, along with other oral ESRD- related drugs without an injectable or intravenous equivalent, are bundled into the ESRD prospective payment system, and the manner in which such introduction into the ESRD prospective payment system may occur~~ ; • the prevalence and severity of adverse side effects of XPHOZAH; • acceptance of XPHOZAH as safe, effective and well- tolerated by patients and the medical community ~~, and, the extent to which the issuance of a CRL by the FDA has impacted the potential acceptance of XPHOZAH as safe, effective and well- tolerated~~ ; • our ability to manage the commercialization of IBSRELA and XPHOZAH and the complex pricing and reimbursement negotiations that may arise with marketing products containing the same active ingredient at different doses for separate indications; • the availability, perceived advantages, relative cost, relative safety and relative efficacy of XPHOZAH compared to alternative and competing treatments; • obtaining and sustaining an adequate level of coverage and reimbursement for XPHOZAH by third- party payors; • our potential involvement in lawsuits in connection with enforcing intellectual property rights in and to XPHOZAH; • our potential involvement in third- party interference, opposition, derivation or similar proceedings with respect to our patent rights, and avoiding other challenges to our patent rights and patent infringement claims; and • a continued acceptable safety and tolerability profile of XPHOZAH following approval. ~~IBSRELA and /~~ **In the event no legislative** or ~~, if approved and commercialized~~ **regulatory action is taken to further delay the inclusion of oral only ESRD related drugs in the ESRD PPS** , XPHOZAH **will become part of** ~~, may cause undesirable side effects or have other~~ -- **the ESRD PPS** properties that could limit the commercial success......; • additional restrictions may be imposed on **January 1** ~~the marketing of the particular product or the manufacturing processes for the product or any component thereof~~ , **2025** ~~including the imposition of a Risk Evaluation and Mitigation Strategy (" REMS ") which could require creation of a Medication Guide or patient package insert outlining the risks of such side effects for distribution to patients~~ , **and** ~~a communication plan to educate healthcare providers of the drugs' risks, as well~~ **will** as other elements to assure safe use...... of pharmaceutical products. There can be no **longer** ~~assurances that we will~~ be **separately** successful in our efforts to hire,...... the costs of the product will be paid for ~~by health maintenance~~ **under Part D** , ~~managed care, pharmacy benefit,~~ and **as a result** ~~similar healthcare management organizations, or reimbursed by government authorities, private health insurers, and other~~ -- **the revenue that** ~~third- party payors. If coverage and reimbursement are not available, or are available only to limited levels,~~ we ~~, or our collaboration partners,~~ may **generate on sales of** ~~not be able to successfully commercialize IBSRELA, or~~ XPHOZAH **will** ~~, if approved. Even if coverage is provided, the approved reimbursement amount may not~~ be **negatively** ~~high enough to allow us to establish or maintain pricing sufficient to realize a return on our investment. There is significant uncertainty related to the insurance coverage~~ and **materially impacted** ~~reimbursement of newly approved products~~ . In **January 2011** ~~the U. S.~~ , ~~the principal decisions about coverage and reimbursement for new drugs are typically made by~~ the Centers for Medicare & Medicaid Services (~~"~~CMS ~~"~~), an agency within the United States Department of Health and Human Services responsible for administering the Medicare program, ~~as CMS decides whether and to what extent a new drug will be covered and reimbursed under Medicare. Private payors tend to follow the coverage reimbursement policies established by CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for products such as ours. There is increased uncertainty related to insurance coverage and reimbursement for drugs, like XPHOZAH, which, if approved, may be marketed for the control of serum phosphorus in adult patients with CKD on dialysis or for another other related indication. In January 2011, CMS~~ implemented **the ESRD PPS,** a new prospective payment system for dialysis treatment. Under the ESRD **PPS** ~~prospective payment system~~ , CMS generally makes a single bundled payment to the dialysis facility for each dialysis treatment that covers all items and services routinely required for dialysis treatments furnished to Medicare beneficiaries in Medicare-certified ESRD facilities or at their home, including the cost of certain ~~routine~~ drugs **defined by CMS to be part of the renal dialysis service** . The inclusion of oral medications without injectable or intravenous equivalents in the bundled payment was initially delayed **by CMS** until January 1, 2014, and through several subsequent legislative actions ~~was~~ **has been** delayed until January 1, 2025. ~~As a result, absent~~ **Absent** further legislation or regulation on this matter, beginning in **January** 2025, oral ESRD- related drugs without injectable or intravenous equivalents ~~may~~ **, including XPHOZAH and all other phosphate lowering medications, will** be included in the ESRD bundle and separate Medicare payment for these drugs will no longer be available, as is the case today under Medicare Part D. **successful in our efforts to hire,retain,and incentivize qualified**

individuals,generate sufficient sales leads,comply with regulatory requirements applicable to the marketing and sale of drug products and effectively manage a ~~contraindication;• ~~**geographically dispersed sales and marketing team.If** we **fail or are delayed in the development of our internal sales,marketing and distribution capabilities,the commercialization of IBSRELA,and if approved,XPHOZAH** could be ~~sued and held liable for harm caused to patients;• the product may become less competitive;and • our reputation may suffer.Any of the foregoing events could prevent us,or a collaboration partner,from achieving or maintaining market acceptance of IBSRELA and / or XPHOZAH,and could result in the loss of significant revenue to us,which would materially and~~ adversely **impacted** ~~affect our results of operations and business~~ .Third- party payor coverage and reimbursement status of newly commercialized products are uncertain.Failure to obtain or maintain adequate coverage and reimbursement for IBSRELA and **,if approved,** XPHOZAH could limit our ability to market those products and decrease our ability to generate revenue.The pricing,coverage and reimbursement of IBSRELA and XPHOZAH **,if approved,** must be adequate to support a commercial infrastructure.The availability and adequacy of coverage and reimbursement by governmental and private payors are essential for most patients to be able to afford treatments.Sales of IBSRELA and **,if approved and commercialized,** XPHOZAH,will depend substantially,both domestically and abroad,on the extent to which the costs of the product will be ~~paid for by health maintenance,managed~~ While it is too early to project the full impact that bundling may have on sales of XPHOZAH ~~, if approved and commercialized,~~ and on our business **,** should XPHOZAH be brought into the bundle in 2025, or at any time, we may be unable to sell XPHOZAH ~~, if approved,~~ to dialysis providers on a profitable basis **. See " — In the event no legislative or regulatory action is taken to further delay the inclusion of oral only ESRD related drugs in the ESRD PPS, XPHOZAH will become part of the ESRD PPS on January 1, 2025, and will no longer be separately paid for under Part D, and as a result the revenue that we may generate on sales of XPHOZAH will be negatively and materially impacted " above for a more detailed discussion related to the risks that may occur if XPHOZAH is brought into the bundle** . Outside the U. S., international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost- containment initiatives in Europe, Canada, Japan, China and other countries has and will continue to put pressure on the pricing and usage of IBSRELA and XPHOZAH, even if regulatory approval is received in such countries. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. Other countries allow companies to fix their own prices for medicinal products, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the U. S., the reimbursement for our products may be reduced compared with the U. S. and may be insufficient to generate commercially reasonable revenue and profits. Moreover, increasing efforts by governmental and third- party payors in the U. S. and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, these caps may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of IBSRELA ~~,~~ and ~~if approved and commercialized,~~ XPHOZAH, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations, and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. We rely completely on third parties **, including certain single- source suppliers,** to manufacture IBSRELA and XPHOZAH. If they are unable to comply with applicable regulatory requirements, unable to source sufficient raw materials, experience manufacturing or distribution difficulties or are otherwise unable to manufacture sufficient quantities to meet demand, our commercialization of IBSRELA and ~~, if approved and commercialized,~~ XPHOZAH ~~and our development efforts for tenapanor~~ may be materially harmed. We do not currently have, nor do we plan to acquire, the infrastructure or capability internally to manufacture IBSRELA or XPHOZAH on a commercial scale, or to manufacture our drug supplies for use in the conduct of our nonclinical and clinical studies. **Our success depends upon our ability to enter into new supplier agreements and maintain our relationships with suppliers who are critical and necessary to the production of our drug supply.** The facilities used by our contract ~~manufacturers~~ **manufacturing organizations (CMOs)** to manufacture our drug supply are subject to inspection by the **U. S.** FDA. Our ability to control the manufacturing process of our product candidates is limited to the contractual requirements and obligations we impose on our **CMOs** ~~contract manufacturer~~ . Although they are contractually required to do so, we are completely dependent on our **CMOs** ~~contract manufacturing partners~~ for compliance with the regulatory requirements, known as current Good Manufacturing Practice requirements (~~"~~cGMPs ~~"~~), for manufacture of both active drug substances and finished drug products. The manufacture of pharmaceutical products requires significant expertise and capital investment. Manufacturers of pharmaceutical products often encounter difficulties in commercial production. These problems may include difficulties with production costs and yields, quality control, including stability of the product and quality assurance testing, and shortages of qualified personnel, as well as compliance with federal, state and foreign regulations and the challenges associated with complex supply chain management. Even if our **CMOs** ~~contract manufacturers~~ do not experience problems and commercial manufacturing is achieved, their maximum or available manufacturing capacities may be insufficient to meet commercial demand. Finding alternative manufacturers or adding additional manufacturers requires a significant amount of time and involves significant expense. New manufacturers would need to develop and implement the necessary production techniques and processes, which along with their facilities, would need to be inspected and approved by the regulatory authorities in each applicable territory. In addition, the raw materials necessary to make API for our products are acquired from a limited number of sources. Any delay or disruption in the availability of these raw materials could result in production disruptions, delays or higher costs with consequent adverse effects on us. If our **CMOs** ~~contract manufacturers~~ fail to adhere to applicable GMP or other regulatory requirements, experience delays or disruptions in the availability of raw materials or experience manufacturing or distribution problems, we may suffer significant consequences, including the inability to meet our product requirements for our clinical development programs, and ~~if tenapanor is commercialized for any indication,~~ such events could result in product seizures or recalls, loss of product approval, fines and sanctions, reputational damage, shipment delays, inventory shortages, inventory write- offs and other product- related charges and increased manufacturing costs. As a result, or if maximum or available manufacturing capacities are insufficient to meet demand, our development or our commercialization efforts for IBSRELA and / or ~~, if approved,~~ XPHOZAH may be materially harmed **. Our future results depend on CMOs, many of whom are our single source manufacturers. Many of our CMOs are currently single source manufacturers. While we try to obtain multiple sources whenever possible, similar to other commercial pharmaceutical companies, three stages of our manufacturing process are currently completed by a single source, which exposes us to a number of risks related to our supply chain, including delivery failure and drug shortages. To date, we have no qualified alternative sources for these single source CMOs. Our manufacturing and commercial supply agreements with our CMOs, including our single source CMOs, contain or are likely to contain pricing provisions that are subject to adjustment based on factors outside of our control, including changes in market prices. Substantial increases in the prices for necessary materials and equipment, whether due to supply chain or logistics issues or due to inflation, would increase our operating costs and could reduce our margins. Any attempts to increase the announced or expected prices of IBSRELA and / or XPHOZAH in response to increased costs could be viewed negatively by the public and could adversely affect our business, prospects, financial condition, and results of operations. An inability to continue to source product from any of these CMOs, which could be due to regulatory actions or requirements affecting the supplier, adverse financial or other strategic developments experienced by a CMO, labor disputes or shortages, unexpected demands, or quality issues, could adversely affect our ability to satisfy demand for our products, which could adversely and materially affect our product sales and operating results, which could significantly harm our business. Furthermore, qualifying alternate suppliers or developing our own manufacturing capability for certain highly customized stages of our manufacturing process may be time consuming and costly. There can be no assurance that our business, financial condition, and results of operations will not be materially and adversely affected by supply chain disruptions. Any disruption in the supply chain, whether or not from a single source CMO, could temporarily disrupt production of our drug supply until an alternative supplier is fully qualified by us or until such CMO is able to perform. There can be no assurance that we would be able to successfully retain an alternative CMO on a timely basis, on acceptable terms, or at all. Changes in business conditions, force majeure, governmental changes, and other factors beyond our control or which we do not presently anticipate, could also affect our CMOs' ability to deliver components to us on a timely basis. Any of the foregoing could materially and adversely affect our results of operations, financial condition, and prospects** . Our operating activities may be restricted as a result of covenants related to the indebtedness under our loan and security agreement **with SLR, as amended,** and we may be required to repay the outstanding indebtedness in an event of default, which could have a materially adverse effect on our business. On February 23, 2022, we entered into a loan and security agreement with SLR ~~Investment Corp.~~ (~~“~~Lender ~~”~~) pursuant to which the Lender agreed to provide us with a loan facility for up to $ 50. 0 million with a maturity date of March 1, 2027, and on August 1, 2022 ~~and~~ **,** February 9 **, 2023 and October 17** , 2023, we entered into amendments to the loan and security agreement (collectively, the ~~“~~2022 Loan Agreement ~~.”~~). The loan was funded in the amount of $ 27. 5 million on February 23, 2022 and ~~the remaining~~ **an additional amount of** $ 22. 5 million **was drawn on October 19, 2023. We** may **draw an additional $ 50. 0 million on or before March 15, 2024, and we expect to draw this additional $ 50. 0 million prior to expiry of the option on March 15, 2024. In addition, subject to the Lender approval of its investment committee, we may** be ~~funded~~ **able to draw up to an additional $ 50 million** by December ~~20~~ **31** , ~~2023~~ **2026** ~~upon the satisfaction of both (i) receipt from the FDA of approval of the NDA for XPHOZAH on or prior to November 30, 2023 and (ii) our achievement of certain product revenue milestone targets described in the 2022 Loan Agreement~~ . Until we have repaid all funded indebtedness, the **2022** ~~loan~~ **Loan** ~~and security agreement~~ **Agreement** subjects us to various customary covenants, including requirements as to financial reporting and insurance and restrictions on our ability to dispose of our business or property, to change our line of business, to liquidate or dissolve, to enter into any change in control transaction, to merge or consolidate with any other entity or to acquire all or substantially all the capital stock or property of another entity, to incur additional indebtedness, to incur liens on our property, to pay any dividends or other distributions on capital stock other than dividends payable solely in capital stock, to redeem capital stock, to enter into licensing agreements, to engage in transactions with affiliates, and to encumber our intellectual property. Our business may be adversely affected by these restrictions on our ability to operate our business. We are permitted to make interest only payments on the loan facility through ~~March~~ **December 31,** ~~2024~~ **2026** , with principal repayments commencing on ~~April~~ **January** 1, ~~2024~~ **2027** ~~, however, this interest only period will be extended to March 2025 with principal repayments delayed to April 1, 2025 if (i) we secure approval from the FDA for our NDA for XPHOZAH by November 30, 2023 or (ii) we achieve certain product revenue targets described in the 2022 Loan Agreement for the year ended December 31, 2023~~ . In addition, we may be required to repay the outstanding indebtedness under the loan facility if an event of default occurs under the **2022** ~~loan~~ **Loan** ~~and security agreement~~ **Agreement** . An event of default will occur if, among other things, we fail to make payments under the **2022** ~~loan~~ **Loan** ~~and security agreement~~ **Agreement** ; we breach any of our covenants under the **2022** ~~loan~~ **Loan** ~~and security agreement~~ **Agreement** , subject to specified cure periods with respect to certain breaches; the Lender determines that a material adverse change has occurred; we or our assets become subject to certain legal proceedings, such as bankruptcy proceedings; we are unable to pay our debts as they become due; or we default on contracts with third parties which would permit the Lender to accelerate the maturity of such indebtedness or that could have a material adverse change on us. We may not have enough available cash or be able to raise additional funds through equity or debt financings to repay such indebtedness at the time any such event of default occurs. In this case, we may be required to limit or reduce our activities necessary to commercialize IBSRELA and / or ~~, if approved,~~ XPHOZAH, or delay or limit clinical trials for tenapanor or other product candidates. The Lender could also exercise its rights as collateral agent to take possession of and to dispose of the collateral securing the term loans, which collateral includes substantially all of our property (excluding intellectual property, which is subject to a negative pledge). Our business, financial condition and results of operations could be materially adversely affected as a result of any of these events. Additional Risks Related to Our Business and Industry Clinical drug development involves a lengthy and expensive process with an uncertain outcome. Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. For example, while the results of our Phase 2 clinical trial evaluating RDX013 for the treatment of hyperkalemia demonstrated an acceptable safety and tolerability profile for RDX013 and supported proof of concept in its ability to lower serum potassium levels, with statistically significant reductions compared to placebo after eight days of treatment, the study did not meet its primary endpoint of significantly reducing serum potassium levels compared to placebo after four weeks of treatment. We currently expect that the next step for the program will be to evaluate a new formulation that potentially enhances subject compliance and the efficacy of RDX013 in an additional Phase 2 clinical study at such time as we have determined that our available resources support conducting such an additional clinical study. There can be no assurances that any additional clinical study that we determine to conduct with RDX013 will be successful. Additionally, if we conduct additional clinical trials with RDX013 or any other product candidates, we could encounter delays in our future development if any clinical trials are suspended or terminated by us, by the ~~IRBs~~ **institutional review boards** of the institutions in which the trial is being conducted, or by the **U. S.** FDA or other regulatory authorities. Such authorities may suspend or terminate a clinical trial due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the **U. S.** FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. In addition, identifying and qualifying patients to participate in any clinical trials is critical to the success of the clinical trials. The timing of any future clinical trials, including any additional RDX013 clinical trial that we may determine to conduct, will depend, in part, on the speed at which we can recruit patients to participate in testing our product candidates. Patients may be unwilling to participate in our clinical studies because of concerns about adverse events observed with the current standard of care, competitor products and / or other investigational agents, in each case for the same indications and / or similar patient populations. In addition, patients currently receiving treatment with the current standard of care or a competitor product may be reluctant to participate in a clinical trial with an investigational drug, or our inclusion and exclusion criteria for our clinical trials may present challenges in identifying acceptable patients. As a result, the timeline for recruiting patients and conducting clinical trials may be delayed. These delays could result in increased costs, delays in advancing our development of the program, or termination of the clinical studies altogether. Any of these occurrences may significantly harm our business, financial condition and prospects. We will rely on third parties to conduct all of our nonclinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may be unable to obtain regulatory approval for additional products or commercialize our product candidates. We do not have the ability to independently conduct nonclinical studies or clinical trials. We rely on medical institutions, clinical investigators, contract laboratories, and other third parties, such as Contract Research Organizations (“ CROs ”), to conduct clinical trials on our product candidates. The third parties with whom we contract for execution of the clinical trials play a significant role in the conduct of these trials and the subsequent collection and analysis of data. However, these third parties are not our employees, and except for contractual duties and obligations, we control only certain aspects of their activities and have limited ability to control the amount or timing of resources that they devote to our programs. Although we rely, and will continue to rely, on these third parties to conduct our nonclinical studies and our clinical trials, we remain responsible for ensuring that each of our studies and clinical trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards and our reliance on third parties does not relieve us of our regulatory responsibilities. We, and these third parties are required to comply with current GLPs for nonclinical studies, and good clinical practices (“ GCPs ”) for clinical studies. GLPs and GCPs are regulations and guidelines enforced by the **U. S.** FDA, the Competent Authorities of the Member States of the European Economic Area (“ EEA ”) and comparable foreign regulatory authorities for all of our products in nonclinical and clinical development, respectively. Regulatory authorities enforce GCPs through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our third- party contractors fail to comply with applicable regulatory requirements, including GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the **U. S.** FDA, the European Medicines Agency (“ EMA ”), or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. There can be no assurance that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations. In addition, our clinical trials must be conducted with product produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which could add additional costs and could delay the regulatory approval process. We face substantial competition, and our competitors may discover, develop or commercialize products faster or more successfully than us. The biotechnology and pharmaceutical industries are highly competitive, and we face significant competition from companies in the biotechnology, pharmaceutical and other related markets that are researching and marketing products designed to address diseases that we are currently developing products to treat. ~~We are aware of~~ **Competition for IBSRELA largely comes from** three prescription products marketed for certain patients with IBS- C **that we are aware of** , including Linzess (linaclotide), Amitiza (lubiprostone) and Trulance (plecanatide). Generic lubiprostone is also available in the U. S. **Additionally, over- the- counter products not indicated for IBS- C are commonly used to treat the constipation component of IBS- C, alone and in combination with the IBS- C- indicated prescription therapies.** XPHOZAH ~~, if approved will compete~~ **is indicated to reduce serum phosphorus in adults** with **chronic kidney disease (CKD) on dialysis as add- on therapy in patients who have an inadequate response to** phosphate binders **or who are intolerant of any dose of**

phosphate binder therapy . The various types of phosphate binders commercialized in the U. S. include the following: Calcium acetate (several prescription brands including PhosLo and Phoslyra); Lanthanum carbonate (Fosrenol); Sevelamer hydrochloride (Renagel); Sevelamer carbonate (Renvela); Sucroferric oxyhydroxide (Velphoro); and Ferric citrate (Auryxia). All of the listed phosphate binders are available as generics in the U. S., with the exception of Velphoro and Auryxia. Additionally, over- the- counter calcium carbonate, such as Tums and Caltrate, is also used to bind phosphorus. In addition to the currently available phosphate binders, we are aware of at least four ~~other~~ **phosphate** binders in development, including fermagate (Alpharen), an iron- based binder in Phase 3 being developed by Opko Health, Inc., PT20, an iron- based binder in Phase 3 being developed by Shield Therapeutics, AP- 301 **, a binder** in Phase ~~2~~ **3** being developed by Alebund Pharmaceutical (Hong Kong) Limited, and ~~lanthanum~~ **Oxylanthanum** ~~dioxycarbonate~~ **Carbonate** (~~Renazorb~~ **OLC**), which has demonstrated pharmacodynamic bioequivalence to Fosrenol. ~~Renazorb~~ **OLC** is being developed by Unicycive Therapeutics, which has announced its plans to ~~file an NDA~~ **seek U. S. FDA approval** via the 505 (b) (2) pathway ~~in mid- 2023~~ . Additionally, Chugai and Alebund are developing EOS789 **/ AP- 306** , an inhibitor of phosphate transporters NaPi- 2b, PiT- 1, and PiT- 2, thus far studied in a ~~phase~~ **Phase** ~~1~~ **2** clinical trial. It is possible that our competitors' drugs may be less expensive and more effective than our product candidates, or may render our product candidates obsolete. It is also possible that our competitors will commercialize competing drugs or treatments before we or our collaboration partners can launch any products developed from our product candidates. We also may face increased competition in the future as new companies enter into our target markets. Many of our competitors have materially greater name recognition and financial, manufacturing, marketing, research and drug development resources than we do. Additional mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Large pharmaceutical companies in particular have extensive expertise in preclinical and clinical testing and in obtaining regulatory approvals for drugs. In addition, academic institutions, government agencies, and other public and private organizations conducting research may seek patent protection with respect to potentially competitive products or technologies. These organizations may also establish exclusive collaboration partnerships or licensing relationships with our competitors. We may experience difficulties in managing our current activities and growth given our level of managerial, operational, financial and other resources. While we have continued to work to optimize our management composition, personnel and systems to support our current activities for future growth, these resources may not be adequate for this purpose. Our need to effectively execute our business strategy requires that we: • manage any commercialization activities in which we may engage effectively; • manage our clinical trials effectively; • manage our internal development efforts effectively while carrying out our contractual obligations to licensors, contractors, collaborators, government agencies and other third parties; • continue to improve our operational, financial and management controls, reporting systems and procedures; and • retain and motivate our remaining employees and potentially identify, recruit, and integrate additional employees. If we are unable to maintain or expand our managerial, operational, financial and other resources to the extent required to manage our development and commercialization activities, our business will be materially adversely affected. If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of IBSRELA and / or ~~, if approved,~~ XPHOZAH. We face an inherent risk of product liability as a result of the clinical testing of our product candidates and our **commercialization** ~~commercial launch~~ of IBSRELA and ~~will face further risk following the commercial launch of XPHOZAH~~ - **XPOHZAH** ~~in the second half of 2023, if approved~~ . For example, we may be sued if any product we develop **and / or commercialize** allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability, and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in: • decreased demand for the product; • injury to our reputation; • withdrawal of clinical trial participants; • costs to defend the related litigation; • a diversion of management' s time and our resources; • substantial monetary awards to trial participants or patients; • regulatory investigations, product recalls or withdrawals, or labeling, marketing or promotional restrictions; • loss of revenue; and • the inability to commercialize or co- promote IBSRELA and / or ~~, if approved,~~ XPHOZAH. Our inability to obtain and maintain sufficient product liability insurance at an acceptable cost and scope of coverage to protect against potential product liability claims could prevent or inhibit the commercialization of any products we develop. Although we maintain product liability insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies also have various exclusions and deductibles, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. Moreover, 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. If we fail to attract, retain and motivate our executives, senior management and key personnel, our business will suffer. Recruiting and retaining qualified scientific, clinical, medical, manufacturing, and sales and marketing personnel is critical to our success. We are highly dependent on our executives, senior management and certain other key employees. The loss of the services of our executives, senior management or other key employees could impede the achievement of our development and commercial objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executives, senior management and other key 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 successfully develop, gain marketing approval of and commercialize products. We may be unable to hire, train or motivate these key personnel on acceptable terms given the intense competition among numerous biopharmaceutical companies for similar personnel, particularly in our geographic regions. If we are unable to continue to attract and retain high quality personnel, our ability to grow and pursue our business strategy will be limited. Actual or perceived failures to comply with applicable data protection, privacy and security laws, regulations, standards and other requirements could adversely affect our business, results of operations, and financial condition. The global data protection landscape is rapidly evolving, and we are or may become subject to numerous state, federal and foreign laws, requirements and regulations governing the collection, use, disclosure, retention, and security of personal data, such as information that we may collect in connection with clinical trials in the U. S. and abroad. Implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future, and we cannot yet determine the impact future laws, regulations, standards, or perception of their requirements may have on our business. This evolution may create uncertainty in our business; affect our ability to operate in certain jurisdictions, or to collect, store, transfer use and share personal information; necessitate the acceptance of more onerous obligations in our contracts; result in liability; or impose additional costs on us. The cost of compliance with these laws, regulations and standards is high and is likely to increase in the future. Any failure or perceived failure by us to comply with federal, state or foreign laws or regulation, our internal policies and procedures or our contracts governing our processing of personal information could result in negative publicity, government investigations and enforcement actions, claims by third parties and damage to our reputation, any of which could have a material adverse effect on our operations, financial performance and business. As our operations and business grow, we may become subject to or affected by new or additional data protection laws and regulations and face increased scrutiny or attention from regulatory authorities. In the U. S., the Health Insurance Portability and Accountability Act of 1996, as amended, and regulations promulgated thereunder (collectively ~~“~~HIPAA ~~”~~) imposes, among other things, certain standards relating to the privacy, security, transmission, and breach reporting of individually identifiable health information. We may obtain health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy and security requirements under HIPAA. Depending on the facts and circumstances, we could be subject to significant penalties if we violate HIPAA. Certain states have also adopted comparable privacy and security laws and regulations, some of which may be more stringent than HIPAA. Such laws and regulations will be subject to interpretation by various courts and other governmental authorities, thus creating potentially complex compliance issues for us and our future customers and strategic partners. For example, the California Consumer Privacy Act (~~"~~CCPA ~~"~~) went into effect on January 1, 2020. The CCPA creates individual privacy rights for California consumers and increases the privacy and security obligations of entities handling certain personal information. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that has increased the likelihood of, and risk associated with data breach litigation. Further, the California Privacy Rights Act (~~"~~CPRA ~~"~~) generally went into effect on January 1, 2023 and significantly amends the CCPA. It imposes additional data protection obligations on covered businesses, including additional consumer rights processes, limitations on data uses, new audit requirements for higher risk data, and opt outs for certain uses of sensitive data. It also creates a new California data protection agency authorized to issue substantive regulations and could result in increased privacy and information security enforcement. Additional compliance investment and potential business process changes may also be required. Similar laws have passed in ~~Virginia, Connecticut, Utah and Colorado, and have been proposed in~~ other states and **are continuing to be** at the **state and** federal level, reflecting a trend toward more stringent privacy legislation in the U. S. The enactment of such laws could have potentially conflicting requirements that would make compliance challenging. In the event that we are subject to or affected by HIPAA, the CCPA, the CPRA or other domestic privacy and data protection laws, any liability from failure to comply with the requirements of these laws could adversely affect our financial condition. Furthermore, the Federal Trade Commission (~~“~~FTC ~~”~~) **also has authority** ~~and many state Attorneys General continue~~ to **initiate** ~~enforce~~ **enforcement actions** ~~federal and state consumer protection laws~~ against ~~companies for online collection~~ **entities that mislead customers about HIPAA compliance** , **make deceptive statements about privacy and data sharing in privacy policies, fail to limit third-party** use **of personal health information** , ~~dissemination and security~~ **fail to implement policies to protect personal health information or engage in other unfair** practices that **harm customers** ~~appear to be unfair or deceptive. For~~ - **or** ~~example,~~ **that may violate Section 5 (a) of the FTC Act.** ~~according~~ **According** to the FTC, failing to take appropriate steps to keep consumers’ personal information secure can constitute unfair acts or practices in or affecting commerce in violation of Section 5 (a) of the Federal Trade Commission Act. The FTC **and many state Attorneys General continue to enforce federal and state consumer protection laws against companies for online collection, use, dissemination and security practices that appear to be unfair or deceptive, including on websites, to regulate the presentation of website content. The FTC** expects a company’ s data security measures to be reasonable and appropriate in light of the sensitivity and volume of consumer information it holds, the size and complexity of its business, and the cost of available tools to improve security and reduce vulnerabilities. We are also or may become subject to rapidly evolving data protection laws, rules and regulations in foreign jurisdictions. For example, in Europe, the European Union General Data Protection Regulation (~~“~~GDPR ~~”~~) went into effect in May 2018 and imposes strict requirements for processing the personal data of individuals within the European Economic Area (~~“~~EEA ~~”~~). Companies that must comply with the GDPR face increased compliance obligations and risk, including more robust regulatory enforcement of data protection requirements and potential fines for noncompliance of up to € 20 million or 4 % of the annual global revenues of the noncompliant company, whichever is greater. Among other requirements, the GDPR regulates transfers of personal data subject to the GDPR to third countries that have not been found to provide adequate protection to such personal data, including the U. S. ~~; in July 2020~~ **and the efficacy and longevity of current transfer mechanisms between the EEA** , **and the United States remains uncertain. Case law from** the Court of Justice of the ~~EU~~ **European Union** (~~“~~CJEU ~~”~~) **states that reliance** ~~limited how organizations could lawfully transfer personal data from the EU / EEA to the U. S. by invalidating the Privacy Shield for purposes of international transfers and imposing further restrictions~~ on the ~~use of~~ standard contractual clauses ~~. In March 2022,~~ **- a standard form of contract approved by** the **European Commission as** ~~U. S. and~~ - **an**

~~EU announced~~ **adequate personal data transfer mechanism- alone may not necessarily be sufficient in all circumstances and that transfers must be assessed on** a ~~new regulatory regime intended to replace~~ **case- by- case basis. On July 10, 2023,** the ~~invalidated~~ **European Commission adopted its Adequacy Decision in** ~~regulations~~ --- **relation to the** ~~; however, this~~ new EU- **US** ~~U. S.~~ Data Privacy Framework **(DPF), rendering the DPF effective** ~~has~~ - **as** ~~not been implemented beyond~~ **a GDPR transfer mechanism to U. S. entities self- certified under the DPF. We expect the existing legal complexity** ~~an~~ **and** ~~executive order signed by President Biden on October 7~~ **uncertainty regarding international personal data transfers to continue. In particular** , ~~2022 on Enhancing Safeguards for~~ **we expect the DPF Adequacy Decision to be challenged and international transfers to the** United States ~~Signals Intelligence Activities. European court~~ and **to other jurisdictions more generally to continue to be subject to enhanced scrutiny by** ~~regulatory~~ **regulators . As a result, we may** ~~decisions subsequent to the CJEU decision of July 2020~~ have ~~taken a restrictive approach~~ to **make certain** ~~international~~ - **operational changes and we will have to implement revised standard contractual clauses and other relevant documentation for existing** data transfers **within required time frames** . Relatedly, following the United Kingdom' s withdrawal from the EEA and the European Union, and the expiry of the transition period, companies have had to comply with both the GDPR and the GDPR as incorporated into United Kingdom national law, the latter regime having the ability to separately fine up to the greater of £ 17. 5 million or 4 % of global turnover. **On October 12, 2023, the UK Extension to the DPF came into effect (as approved by the UK Government), as a data transfer mechanism from the United Kingdom to U. S. entities self- certified under the DPF.** As we continue to expand into other foreign countries and jurisdictions, we may be subject to additional laws and regulations that may affect how we conduct business. Although we work to comply with applicable laws, regulations and standards, our contractual obligations and other legal obligations, these requirements are evolving and may be modified, interpreted and applied in an inconsistent manner from one jurisdiction to another, and may conflict with one another or other legal obligations with which we must comply. Any failure or perceived failure by us or our employees, representatives, contractors, consultants, CROs, collaborators, or other third parties to comply with such requirements or adequately address privacy and security concerns, even if unfounded, could result in additional cost and liability to us, damage our reputation, and adversely affect our business and results of operations. We and our collaborators, CROs and other contractors and consultants depend on information technology systems, and any failure of these systems could harm our business. Security breaches, loss of data, and other disruptions could compromise sensitive information related to our business or prevent us from accessing critical information and expose us to liability, which could adversely affect our business, results of operations and financial condition. We and our collaborators, CROs, and other contractors and consultants collect and maintain information in digital form that is necessary to conduct our business, and we are increasingly dependent on information technology systems and infrastructure to operate our business. In the ordinary course of our business, we and our collaborators, CROs and other contractors and consultants collect, store and transmit large amounts of confidential information, including intellectual property, proprietary business information **, clinical trial data** and personal information **(collectively, Confidential Information)** . It is critical that we and our collaborators, CROs and other contractors and consultants do so in a secure manner to maintain the confidentiality and integrity of such ~~confidential~~ **Confidential** ~~information~~ **Information** . We have established physical, electronic and organizational measures designed to safeguard and secure our systems to prevent a data compromise, and rely on commercially available systems, software, tools, and monitoring to provide security for our information technology systems and the processing, transmission and storage of ~~digital~~ **Confidential** ~~information~~ **Information** . We have also outsourced elements of our information technology infrastructure, and as a result a number of third- party vendors may or could have access to our ~~confidential~~ **Confidential** ~~information~~ **Information** . Our information technology systems and infrastructure, and those of our current and any future collaborators, CROs, contractors and consultants and other third parties on which we rely, are vulnerable to attack, damage and interruption from computer viruses, malware (e. g., ransomware), natural disasters, terrorism, war, telecommunication and electrical failures, cyber- attacks or cyber- intrusions over the Internet, phishing attacks and other social engineering schemes, attachments to emails, human error, fraud, denial or degradation of service attacks, sophisticated nation- state and nation- state- supported actors or unauthorized access or use by persons inside our organization, or persons with access to systems inside our organization. The risk of a security breach or disruption or data loss, particularly through cyberattacks or cyber intrusion, including by computer hackers, foreign governments and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. In addition, the prevalent use of mobile devices that access ~~confidential~~ **Confidential** ~~information~~ **Information** increases the risk of data security breaches, which could lead to the loss of ~~confidential~~ **Confidential** ~~information~~ **Information** or other intellectual property. We may also face increased cybersecurity risks due to our reliance on internet technology and the number of our employees who are working remotely, which may create additional opportunities for cybercriminals to exploit vulnerabilities. Furthermore, because the techniques used to obtain unauthorized access to, or to sabotage, systems change frequently and often are not recognized until launched against a target, we may be unable to anticipate these techniques or implement adequate preventative measures. We may also experience security breaches that may remain undetected for an extended period. Even if identified, we may be unable to adequately investigate or remediate incidents or breaches due to attackers increasingly using tools and techniques that are designed to circumvent controls, to avoid detection, and to remove or obfuscate forensic evidence. The costs to us to mitigate network security problems, bugs, viruses, worms, malicious software programs and security vulnerabilities could be significant, and while we have implemented security measures to protect our data security and information technology systems, our efforts to address these problems may not be successful, and these problems could result in unexpected interruptions, delays, cessation of service and other harm to our business and our competitive position. **There can also be no assurance that our and our collaborators', CROs', CMOs, contractors', consultants' and other service providers' cybersecurity risk management program and processes, including policies, controls or procedures, will be fully implemented, complied with or effective in protecting our systems, networks and Confidential Information.** We and certain of our service providers are from time to time subject to cyberattacks and security incidents. We do not believe that we have experienced any significant system failure, accident or security breach to date, but if such an event were to occur and cause interruptions in our operations, it could result in a material disruption to our business. In addition, such a breach may require notification to governmental agencies, the media or individuals pursuant to various federal and state privacy and security laws, if applicable. Moreover, if a computer security breach affects our systems or those of our collaborators, CROs or other contractors, or results in the unauthorized release of personally identifiable information, our reputation could be materially damaged. **Any adverse impact** ~~We would also be exposed~~ to ~~a risk~~ **the availability, integrity or confidentiality** of ~~loss or~~ **our or third- party systems or Confidential Information can result in legal claims or proceedings (such as class actions), regulatory** ~~litigation~~ - **investigations** and ~~potential liability~~ **enforcement actions, fines and penalties, negative reputational impacts that cause us to lose existing or future customers, and / or significant incident response, system restoration or remediation and future compliance costs** , which could materially adversely affect our business, results of operations and financial condition. If we fail to maintain proper and effective internal controls, our ability to produce accurate and timely financial statements could be impaired, which could harm our operating results, our ability to operate our business and investors' views of us and could have a material adverse effect on the price of our common stock. Our failure to implement and maintain effective internal controls over financial reporting could result in errors in our financial statements that could result in a restatement of our financial statements and cause us to fail to meet our reporting obligations. If we cannot in the future favorably assess the effectiveness of our internal controls over financial reporting, investor confidence in the reliability of our financial reports may be adversely affected, which could have a material adverse effect on the trading price of our common stock. We have formed in the past, and may form in the future, collaboration partnerships, joint ventures and / or licensing arrangements, and we may not realize the benefits of such collaborations. We have current collaboration partnerships for the commercialization of tenapanor in certain foreign countries, and we may form additional collaboration partnerships, create joint ventures or enter into additional licensing arrangements with third parties in the U. S. and abroad that we believe will complement or augment our existing business. In particular, we have formed collaboration partnerships with ~~KKC~~ **Kyowa Kirin** for commercialization of tenapanor for hyperphosphatemia in Japan; with **Shanghai Fosun Pharmaceutical Industrial Development Co. Ltd. (** Fosun Pharma **)** for commercialization of tenapanor for hyperphosphatemia and IBS- C in China and related territories; ~~and~~ in Canada with Knight **Therapeutics, Inc. (Knight)** for commercialization of tenapanor for IBS- C and hyperphosphatemia **; and with METiS Therapeutics, Inc. (METiS) for the development and commercialization of a portfolio of TGR5 agonist compounds for all therapeutic areas** . We face significant competition in seeking appropriate collaboration partners, and the process to identify an appropriate partner and negotiate appropriate terms is time- consuming and complex. Any delays in identifying suitable additional collaboration partners and entering into agreements to develop our product candidates could also delay the commercialization of our product candidates, which may reduce their competitiveness even if they reach the market. There is no guarantee that our current collaboration partnerships or any such arrangements we enter into in the future will be successful, or that any collaboration partner will commit sufficient resources to the development, regulatory approval, and commercialization effort for such products, or that such alliances will result in us achieving revenues that justify such transactions. We ~~received a CRL from the FDA regarding our NDA for XPHOZAH. Following the OND' s decision to grant our appeal of the CRL, we are preparing to resubmit our NDA for XPHOZAH. There can be no assurances that the granting of our appeal of the CRL and resubmission of our NDA will result in approval of our NDA for XPHOZAH. Even if we are successful in obtaining approval for the NDA, the delay in obtaining such approval may result in delay in the regulatory process for our partners, which could have a material adverse effect on our business and results of operations. The ongoing effects of the COVID- 19 pandemic, or any other outbreak of epidemic diseases, or the perception of their effects, could have a material adverse effect on our business, financial condition, results of operations or cash flows. Outbreaks of epidemic, pandemic, or contagious diseases, such as the current novel coronavirus (" COVID- 19 ") pandemic or, historically, the Ebola virus, Middle East Respiratory Syndrome, Severe Acute Respiratory Syndrome or the H1N1 virus, could disrupt our business. Economic and health conditions related to the COVID- 19 pandemic in the U. S. and across most of the globe remain uncertain and continue to evolve. The continuing effects of the coronavirus pandemic may result in delays in the manufacture of tenapanor, or in the delivery of key intermediates or raw materials required to manufacture tenapanor or delays in clinical development activities by us, or our collaboration partners. Such effects could also materially and negatively impact our ability to successfully commercialize IBSRELA and / or, if approved, XPHOZAH, or the ability of our collaboration partners to successfully commercialize such products, if approved for marketing and sale by the foreign regulatory authorities, including our ability, and that of our collaboration partners to educate physicians and patients about the benefits, administration and use of the product. • Although we have reopened our offices and invited our personnel to return to the office, we continue to permit our personnel to work remotely, which could negatively impact productivity, or disrupt, delay, or otherwise adversely impact our business. In addition, this could increase our cyber-security risk, create data accessibility concerns, and make us more susceptible to communication disruptions, any of which could adversely impact our business operations or delay necessary interactions with local and federal regulators, ethics committees, manufacturing sites, research or clinical trial sites and important agencies and contractors. • The FDA and comparable foreign regulatory agencies may continue to experience operational interruptions or delays, which may impact timelines for regulatory submission, trial initiation and regulatory approval. The full effects of the COVID- 19 remain unknown. The extent to which the outbreak may continue to impact our business, including, our commercialization and manufacturing will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as access to physician offices for our commercial and medical teams, business closures or supply chain or business disruptions. We~~ may engage in strategic transactions that could impact our liquidity, increase our expenses and present significant distractions to our management. We may consider strategic transactions, such as acquisitions of companies, asset purchases, and / or in- licensing of products, product candidates or technologies. In addition, if we are unable to access capital on a timely basis and on terms that are acceptable to us, we may be forced to further restructure certain aspects of our business or identify and complete one or more strategic collaborations or other transactions in order to fund the commercialization of IBSRELA **and** ~~, our continued efforts to seek approval for our NDA for~~ XPHOZAH **,** and / or the development of discovery and developmental assets through the use of alternative structures. Additional potential transactions that we may consider include a variety of different business arrangements, including spin- offs, spin outs, collaboration partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any such transaction may require us to incur non- recurring or other charges, may increase our near- and long- term expenditures and may pose significant integration challenges or disrupt our management or business, which could adversely affect our operations and financial results. For example, these transactions may entail numerous operational and financial risks, including: • up- front, milestone and royalty payments, equity investments and financial support of new research and development candidates including increase of personnel, all of which may be substantial; • exposure to unknown liabilities; • disruption of our business and diversion of our management' s time and attention in order to develop acquired products, product candidates or technologies; • incurrence of substantial debt or dilutive issuances of equity securities; • higher- than- expected acquisition and integration costs; • write- downs of assets or goodwill or impairment charges; • increased amortization expenses; • difficulty and cost in combining the operations and personnel of any acquired businesses with our operations and personnel; • impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership; and • inability to retain key employees of any acquired businesses. Accordingly, although there can be no assurance that we will undertake or successfully complete any transactions of the nature described above, any transactions that we do complete may be subject to the foregoing or other risks and could have a material adverse effect on our business, results of operations, financial condition and prospects. Our CMOs manufacture tenapanor API outside of the U. S., **our collaboration partners outside of the U. S. have sought** and ~~we~~ **obtained and** may **continue to** seek and obtain approval to commercialize **tenapanor** ~~IBSRELA and XPHOZAH~~ outside of the U. S., and as a result a variety of risks associated with international operations could materially adversely affect our business. **Our** ~~We or our~~ collaboration partners **have sought and obtained and** may ~~decide~~ **continue** to seek **and obtain marketing approval for tenapanor outside the U. S. Furthermore, we may seek and obtain** marketing approval for IBSRELA or XPHOZAH **in other territories** outside **of** the U. S. Additionally, we have contractual agreements with CMOs involving the manufacture of tenapanor API outside of the U. S., and may otherwise engage in business outside of the U. S., including entering into additional contractual agreements with third parties. We are subject to additional risks related to entering these international business markets and relationships, including: • different regulatory requirements for drug approvals in foreign countries; • differing U. S. and foreign drug import and export rules; • reduced protection for intellectual property rights in foreign countries; • unexpected changes in tariffs, trade barriers and regulatory requirements; • different reimbursement systems, and different competitive drugs; • economic weakness, including inflation, or political instability in particular foreign economies and markets; • compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; • foreign taxes, including withholding of payroll taxes; • foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country; • workforce uncertainty in countries where labor unrest is more common than in the U. S.; • production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; • potential liability resulting from development work conducted by these distributors; and • business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters. Our business involves the use of hazardous materials and we and third- parties with whom we contract must comply with environmental laws and regulations, which can be expensive and restrict how we do business. We and manufacturers and suppliers with whom we may contract are subject to laws and regulations governing the use, manufacture, storage, handling, and disposal of hazardous materials, including the components of our tenapanor and our product candidates. In some cases, these hazardous materials and various wastes resulting from their use are stored at our and our manufacturers' facilities pending their use and disposal. We cannot eliminate the risk of contamination, which could cause an interruption of our commercialization efforts, and business operations, and could result in environmental damage requiring costly clean- up and resulting in liabilities under applicable laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products. We cannot guarantee that the safety procedures utilized by third- party manufacturers and suppliers with whom we may contract will comply with the standards prescribed by laws and regulations or will eliminate the risk of accidental contamination or injury from these materials. In such an event, we may be held liable for any resulting damages and such liability could exceed our resources and state or federal or other applicable authorities may curtail our use of certain materials and / or interrupt our business operations. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. We do not currently carry biological or hazardous waste insurance coverage. We may be adversely affected by earthquakes or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster. We currently occupy a leased facility located in the San Francisco Bay Area, which in the past has experienced severe earthquakes. We do not carry earthquake insurance. Earthquakes or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our leased facilities, including our California facility, that damaged critical infrastructure ~~,~~ **supporting access to systems** such as our enterprise financial systems or manufacturing resource planning and enterprise quality systems, or that otherwise disrupted operations, it may be difficult or **time consuming** ~~, in certain cases, impossible for us~~ to ~~continue our~~ **restore some** business ~~for a substantial period~~ of ~~time~~ **our business functions** . The disaster recovery and business continuity plans we have in place currently are ~~limited~~ **not holistic in coverage** and **may** ~~are unlikely to~~ prove ~~adequate~~ **inadequate** in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business. Risks Related to Government Regulation Despite having received regulatory approval for IBSRELA ~~,~~ and ~~even if we receive regulatory approval for~~ XPHOZAH, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense. Additionally, IBSRELA and ~~, if approved,~~ XPHOZAH could be subject to 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. Even ~~if~~ **after** a drug is approved by the **U. S.** FDA or foreign regulatory authorities, the manufacturing processes, labeling, packaging, distribution, pharmacovigilance, storage, advertising, promotion and recordkeeping for the product will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs and GCP regulations for any clinical trials that we conduct post- approval. As such, we and our third- party CMOs will be subject to continual review and periodic inspections to assess compliance with regulatory requirements. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, and quality control. Regulatory authorities may also impose significant restrictions on a product' s indicated uses or marketing or impose ongoing requirements for potentially costly post- marketing studies. Furthermore, any new legislation addressing drug safety issues could result in delays or increased costs to assure compliance. We will also be required to report certain adverse reactions and production problems, if any, to the **U. S.** FDA, and to comply with requirements concerning advertising and promotion for our products. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product' s approved label. As such, we may not promote our products for indications or uses for which they do not have **U. S.** FDA approval. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with our third- party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things: • warning or untitled letters or fines; • restrictions on the marketing or manufacturing of the product, withdrawal of the product from the market or voluntary or mandatory product recalls; • injunctions or the imposition of civil or criminal penalties; • suspension or revocation of existing regulatory approvals; • suspension of any of our ongoing clinical trials; • refusal to approve pending applications or supplements to approved applications submitted by us; • restrictions on our or our CMOs' operations; or • product seizure or detention, or refusal to permit the import or export of products. Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to commercialize IBSRELA and ~~, if approved,~~ XPHOZAH. If regulatory sanctions are applied or if regulatory approval is withdrawn, the value of our company and our operating results will be adversely affected. In addition, the **U. S.** FDA' s policies may change, and additional government regulations may be enacted. 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, which would adversely affect our business, prospects and ability to achieve or sustain profitability. We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the U. S. or abroad. Disruptions at the **U. S.** FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire and retain key leadership and other personnel, or otherwise review and process regulatory submissions in a timely manner, which could negatively impact our business. The ability of the FDA to review and process regulatory submissions can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, ~~and~~ policy changes **, and other events that may otherwise affect the FDA' s ability to perform routine functions** . ~~Average review~~ **For example, over the last several years, the U. S. government has shut down several** times ~~at~~ **and certain regulatory agencies, such as** the ~~agency~~ **FDA,** have ~~fluctuated in recent years as a result~~ **had to furlough critical FDA employees and stop critical activities** . Disruptions at the **U. S.** FDA and other agencies may also slow the time necessary for new drugs to be reviewed and / or approved by necessary government agencies, which would adversely affect our business. If a prolonged government shutdown occurs, or if global health concerns prevent the **U. S.** FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the **U. S.** FDA or other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business. We and our CMOs are subject to significant regulation with respect to manufacturing IBSRELA and XPHOZAH. The manufacturing facilities on which we rely may not continue to meet regulatory requirements or may not be able to meet supply demands. All entities involved in the preparation of product for commercial sale, or product candidates for clinical trials, including our existing **CMOs** ~~contract manufacturers~~ are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in late- stage clinical studies must be manufactured in accordance with cGMP regulations. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of contaminants or to inadvertent changes in the properties or stability of our products or product candidates that may not be detectable in final product testing. We or our CMOs must supply all necessary documentation in support of an NDA or comparable regulatory filing on a timely basis and must adhere to cGMP regulations enforced by the **U. S.** FDA and other regulatory agencies through their facilities inspection programs. The facilities and quality systems of some **,** or all **,** of our **CMOs** ~~third- party contractors~~ must pass a pre- approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the manufacture of our product or the associated quality systems for compliance with the regulations applicable to the activities being conducted. Although we oversee the CMOs, we cannot control the manufacturing process of, and are completely dependent on, our **CMOs** ~~contract manufacturing partners~~ for compliance with the regulatory requirements. If these facilities do not pass a pre- approval plant inspection, regulatory approval of the products may not be granted or may be substantially delayed until any violations are corrected to the satisfaction of the regulatory authority, if ever. In addition, we have no control over the ability of our **CMOs** ~~contract manufacturers~~ to maintain adequate quality control, quality assurance and qualified personnel. The regulatory authorities also may, at any time following approval of a product for sale, audit the manufacturing facilities of our **CMOs** ~~third- party contractors~~ . If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and / or time consuming for us or a third party to implement, and that may include the temporary or permanent suspension of a clinical study or commercial sales or the temporary or permanent suspension of production or closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business. If we or any of our third- party manufacturers fail to maintain regulatory compliance, the **U. S.** FDA or other applicable regulatory authority can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new drug product, withdrawal of an approval, or suspension of production. As a result, our business, financial condition, and results of operations may be materially harmed. Additionally, if supply from one approved manufacturer is interrupted, an alternative manufacturer would need to be qualified through an NDA, a supplemental NDA or equivalent foreign regulatory filing, which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines. These factors could cause us to incur higher costs and could cause the delay or termination of clinical studies, regulatory submissions, required approvals, or commercialization of our product candidates. Furthermore, if our suppliers fail to meet contractual requirements and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical studies may be delayed, or we could lose potential revenue. If we fail to comply or are found to have failed to comply with **U. S.** FDA and other regulations related to the promotion of our products for unapproved uses, we could be subject to criminal penalties, substantial fines or other sanctions and damage awards. The regulations relating to the promotion of products for unapproved uses are complex and subject to substantial interpretation by the **U. S.** FDA and other government agencies. With respect to the commercialization of IBSRELA and / or ~~, if approved,~~ XPHOZAH **,** we will be restricted from marketing the product outside of its approved labeling, also referred to as off- label promotion. However, physicians may nevertheless prescribe an approved product to their patients in a manner that is inconsistent with the approved label, which is an off- label use. We have implemented compliance and training programs designed to ensure that our sales and marketing practices comply with applicable regulations regarding off- label promotion. Notwithstanding these programs, the **U. S.** FDA or other government agencies may allege or find that our practices constitute prohibited promotion of our product candidates for unapproved uses. We also cannot be sure that our employees will comply with company policies and applicable regulations regarding the promotion of products for unapproved uses. Over the past several years, a significant number of pharmaceutical and biotechnology companies have been the target of inquiries and investigations by various federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of products for unapproved uses and other sales practices, including the Department of Justice and various U. S. Attorneys' Offices, the Office of Inspector General of the Department of Health and Human Services, the **U. S.** FDA, the FTC and various state Attorneys General offices. These investigations have alleged violations of various federal and state laws and regulations, including claims asserting antitrust violations, violations of the ~~FFDCA~~ **Federal Food, Drug, and Cosmetic Act** , the False Claims Act, the Prescription Drug Marketing Act, anti- kickback laws, and other alleged violations in connection with the promotion of products for unapproved uses, pricing and Medicare and / or Medicaid reimbursement. Many of these investigations originate as " qui tam " actions under the False Claims Act. Under the False Claims Act, any individual can bring a claim on behalf of the government alleging that a person or entity has presented a false claim, or caused a false claim to be submitted, to the government for payment. The person bringing a qui tam suit is entitled to a share of any recovery or settlement. Qui tam suits, also commonly referred to as " whistleblower suits, " are often brought by current or former employees. In a qui tam suit, the government must decide whether to intervene and prosecute the case. If it declines, the individual may pursue the case alone. If the **U. S.** FDA or any other governmental agency initiates an enforcement action against us or if we are the subject of a qui tam suit and it is determined that we violated prohibitions relating to the promotion of products for unapproved uses, we could be subject to substantial civil or criminal fines or damage awards and other sanctions such as consent decrees and corporate integrity agreements pursuant to which our activities would be subject to ongoing scrutiny and monitoring to ensure compliance with applicable laws and regulations. Any such fines, awards or other sanctions would have an adverse effect on our revenue, business, financial prospects and reputation. IBSRELA and / or ~~, if approved,~~ XPHOZAH may cause or contribute to adverse medical events that we are required to report to regulatory agencies and if we fail to do so we could be subject to sanctions that would materially harm our business. We are required to report certain information about adverse medical events if our products may have caused or contributed to those adverse events. The timing of our obligation to report is triggered by the date we become aware of the adverse event as well as the nature of the event. We may fail to report adverse events we become aware of within the prescribed timeframe. We may also fail to appreciate that we have become aware of a reportable adverse event, especially if it is not reported to us as an adverse event or if it is an adverse event that is unexpected or removed in time from the use of our products. If we fail to comply with our reporting obligations, the **U. S.** FDA or a foreign regulatory agency could take action, including criminal prosecution, the imposition of civil monetary penalties, seizure of our products or delay in approval or clearance of future products. Our employees, independent contractors, principal investigators, CROs, collaboration partners, consultants **, CMOs** and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements. We are exposed to the risk that our employees, independent contractors, principal investigators, CROs, collaboration partners, consultants **, CMOs** and vendors may engage in fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless and / or negligent conduct or unauthorized activities that violate any of the following: **U. S.** FDA regulations, including those laws that require the reporting of true, complete and accurate financial and other information to the **U. S.** FDA; manufacturing standards; or federal and state healthcare fraud and abuse laws and regulations. Specifically, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self- dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. These activities also include the improper use 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 misconduct by employees and other third parties, 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 comply with such laws or regulations. Additionally, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. 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, including the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgements, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, individual imprisonment, other sanctions, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations. Failure to obtain regulatory approvals in foreign jurisdictions would prevent us from marketing our products internationally. In order to market any product in the EEA (which is composed of the 27 Member States of the European Union plus Norway, Iceland and Liechtenstein), and many other foreign jurisdictions, separate regulatory approvals are required. In the EEA, medicinal products can only be commercialized after obtaining a Marketing Authorization (~~"~~ MA ~~"~~). Before the MA is granted, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk- benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy. The approval procedures vary among countries and can involve additional clinical testing, and the time required to obtain approval may differ from that required to obtain **U. S.** FDA approval. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Approval by the **U. S.** FDA does not ensure approval by regulatory authorities in other countries, and approval by one or more foreign regulatory authorities does not ensure approval by regulatory authorities in other foreign countries or by the **U. S.** FDA. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. The foreign regulatory approval process may include all of the risks associated with obtaining **U. S.** FDA approval. We may not be able to file for regulatory approvals or to do so on a timely basis, and even if we do file, we may not receive necessary approvals to commercialize our products in any market. We and our collaboration partners are subject to healthcare laws, regulation and enforcement; our failure or the failure of any such collaboration partners to comply with these laws could have a material adverse effect on our results of operations and financial conditions. We and our collaboration partners are subject to additional healthcare statutory and regulatory requirements and enforcement by the federal government and the states and foreign governments in which we conduct our business. The laws that may affect our ability to operate as a commercial organization include: • the federal Anti- Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation; • federal false claims laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third- party payors that are false or fraudulent. In addition, 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 false claims statutes; • the federal Civil Monetary Penalties law, which prohibits, among other things, offering or transferring remuneration to a federal healthcare beneficiary that a person knows or should know is likely to influence the beneficiary' s decision to order or receive items or services reimbursable by the government from a particular provider or supplier; • federal criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters. Similar to the federal Anti- Kickback Statute, a person or entity does not need to have actual knowledge of these statutes or specific intent to violate them in order to have committed a violation; • the federal ~~physician~~ **Physician Payments** ~~sunshine~~ **Sunshine Act** requirements under the **Affordable Care Act (** ACA **)**, which requires manufacturers of drugs, devices, biologics, and medical supplies to report annually to CMS information related to payments and other transfers of value to physicians, (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain non- physician practitioners (physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, anesthesiologist assistants and certified nurse midwives), and teaching hospitals, and ownership and investment interests held by physicians (as defined by the statute) 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 payor, including commercial insurers; • state laws that require pharmaceutical companies to comply with the pharmaceutical industry' s voluntary compliance guidelines and the applicable 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 payments and other transfers of value to physicians and other healthcare providers or pricing information and marketing expenditures; and • European and other foreign law equivalents of each of the laws, including reporting requirements detailing interactions with and payments to healthcare providers. Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. The risk of our being found in violation of these laws is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. 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. If our operations are found to be in violation of any of the laws described above or any other governmental laws and regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment, any of which could adversely affect our ability to market our products and adversely impact our financial results. Legislative or regulatory healthcare reforms in the U. S. may make it more difficult and costly for us to obtain regulatory clearance or approval of our product candidates and to produce, market and distribute our products after clearance or approval is obtained. From time to time, legislation is drafted and introduced in Congress that could significantly change the statutory provisions governing the regulatory clearance or approval, manufacture, and marketing of regulated products or the reimbursement thereof. In addition, **U. S.** FDA regulations and guidance are often revised or reinterpreted by the FDA in ways that may significantly affect our business and our products. Any new regulations or revisions or reinterpretations of existing regulations may impose additional costs or lengthen review times of our product candidates. We cannot determine what effect changes in regulations, statutes, legal interpretation or policies, when and if promulgated, enacted or adopted may have on our business in the future. Such changes could, among other things, require: • additional clinical trials to be conducted prior to obtaining approval; • changes to manufacturing methods; • recall, replacement, or discontinuance of one or more of our products; and • additional record keeping. Each of these would likely entail substantial time and cost and could materially harm our business and our financial results. In addition, delays in receipt of or failure to receive regulatory clearances or approvals for any future products would harm our business, financial condition and results of operations. In addition, the full impact of recent healthcare reform and other changes in the healthcare industry and in healthcare spending is currently unknown, and may adversely affect our business model. In the U. S., the ACA was enacted in 2010 with a goal of reducing the cost of healthcare and substantially changing the way healthcare is financed by both government and private insurers. Since its enactment, there have been judicial, executive and Congressional challenges to certain aspects of the ACA. The ACA, among other things, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, and created 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 manufacturer' s outpatient drugs to be covered under Medicare Part D. Other legislative changes have been proposed and adopted in the U. S. since the ACA was enacted. These new laws, among other things, included aggregate reductions of Medicare payments to providers that will remain in effect through 2032, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022, unless additional action is taken by Congress, additional specific reductions in Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and an increase in the statute of limitations period for the government to recover overpayments to providers from three to five years. More recently, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which ~~eliminates~~ **eliminated** the statutory Medicaid drug rebate cap **beginning January 1** , ~~currently set~~ **2024. The rebate was previously capped** at 100 % of a drug ~~'~~ **'** s average ~~manufacturer~~ - **manuacturer** price ~~, beginning January 1, 2024~~ . Recently, there has also been heightened governmental scrutiny over the manner in which drug manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. On August 16, 2022, the Inflation Reduction Act of 2022 (the ~~"~~ IRA ~~"~~) was signed into law. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023), and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). **Under the IRA, small molecule drugs and biologics first become eligible for price negotiation seven and eleven years, respectively, after FDA approval.** The IRA permits the Secretary of the Department of Health and Human Services to implement many of these provisions through guidance, as opposed to regulation, for the initial years. ~~For~~ **On August 29, 2023, HHS announced the list of the first ten drugs** that **will be subject to price negotiations. HHS has issued** and **will continue to issue guidance implementing** ~~other~~ -- **the** ~~reasons~~ **IRA, although the Medicare drug price negotiation program is currently subject to legal challenges. While the impact of the IRA on the pharmaceutical industry cannot yet be fully determined** , it is **likely to** ~~currently unclear how the IRA will~~ be ~~effectuated~~ **significant** . Additionally, individual states have become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access, and to encourage importation from other countries and bulk purchasing. We cannot predict the reform initiatives that may be adopted in the future or whether initiatives that have been adopted will be repealed or modified. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare may adversely affect the demand for any drug products for which we may obtain regulatory approval, our ability to set a price that we believe is fair for our products, our ability to obtain coverage and reimbursement approval for a product, our ability to generate revenues and achieve or maintain profitability, and the level of taxes that we are required to pay. If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the U. S., we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, results of operations and financial condition. With the commercial launch of IBSRELA, we participate in the Medicaid Drug Rebate Program (“MDRP ”) and other federal and state government pricing programs in the U. S., and we may participate in additional government pricing programs in the future. These programs generally require manufacturers to pay rebates or otherwise provide discounts to government payors in connection with drugs that are dispensed to beneficiaries of these programs. Medicaid drug rebates are based on pricing data that we will be obligated to report on a monthly and quarterly basis to ~~the U. S. Centers for Medicare & Medicaid Services (“~~CMS ~~”)~~, the federal agency that administers the MDRP and Medicare programs. For the MDRP, these data include the average manufacturer price (“AMP ”) and the best price (“BP ”) for each drug. If we become aware that our MDRP price reporting submission for a prior period was incorrect or has changed as a result of recalculation of the pricing data, we must resubmit the corrected data for up to three years after those data originally were due. In addition, there is increased focus by the Office of Inspector General within the U. S. Department of Health and Human Services on the methodologies used by manufacturers to calculate AMP, and BP, to assess manufacturer compliance with MDRP reporting requirements. If we fail to provide information timely or are found to have knowingly submitted false information to the government, we may be subject to civil monetary penalties and other sanctions, including termination from the MDRP, which would result in payment not being available for our covered drugs under Medicaid. Failure to make necessary disclosures and / or to identify overpayments could result in allegations against us under the Federal False Claims Act and other laws and regulations. Federal law requires that a manufacturer that participates in the MDRP also participate in the Public Health Service' s 340B drug pricing program (“340B program ”) in order for federal funds to be available for the manufacturer' s drugs under Medicaid. We participate in the 340B program, which is administered by the Health Resources and Services Administration (“HRSA ”), and requires us to charge statutorily defined covered entities no more than the 340B " ceiling price " for our covered drugs. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low- income patients. The 340B ceiling price is calculated using a statutory formula, which is based on the AMP and rebate amount for the covered drug as calculated under the MDRP. In general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. We are obligated to report 340B ceiling prices to HRSA on a quarterly basis, and HRSA publishes them to 340B covered entities. HRSA has finalized regulations regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities for 340B- eligible drugs. HRSA has also finalized an administrative dispute resolution process through which 340B covered entities may pursue claims against participating manufacturers for overcharges, and through which manufacturers may pursue claims against 340B covered entities for engaging in unlawful diversion or duplicate discounting of 340B drugs. In order to be eligible to have drug products paid for with federal funds under Medicaid and purchased by certain federal agencies and grantees, we also participate in the U. S. Department of Veterans Affairs (“VA ”) Federal Supply Schedule (“FSS ”) pricing program. Under the VA / FSS program, we are obligated to report the Non- Federal Average Manufacturer Price (“Non- ~~FAMP~~ - **FAM** ") for our covered drugs to the VA and charge certain federal agencies no more than the Federal Ceiling Price, which is calculated based on Non- FAMP using a statutory formula. These four agencies are the VA, the U. S. Department of Defense, the U. S. Coast Guard, and the U. S. Public Health Service (including the Indian Health Service). We are also required to pay rebates on products purchased by military personnel and dependents through the TRICARE retail pharmacy program. If we fail to provide timely information or are found to have knowingly submitted false information, we may be subject to civil monetary penalties. Individual states continue to consider and have enacted legislation to limit the growth of healthcare costs, including the cost of prescription drugs and combination products. A number of states have either implemented or are considering implementation of drug price transparency legislation that may prevent or limit our ability to take price increases at certain rates or frequencies. Requirements under such laws include advance notice of planned price increases, reporting price increase amounts and factors considered in taking such increases, wholesale acquisition cost information disclosure to prescribers, purchasers, and state agencies, and new product notice and reporting. Such legislation could limit the price or payment for IBSRELA and, if ~~approved and~~ launched, XPHOZAH, and a number of states are authorized to impose civil monetary penalties or pursue other enforcement mechanisms against manufacturers who fail to comply with drug price transparency requirements, including the untimely, inaccurate, or incomplete reporting of drug pricing information. If we are found to have violated state law requirements, we may become subject to penalties or other enforcement mechanisms, which could have a material adverse effect on our business. Pricing and rebate calculations are complex, vary among products and programs, and are often subject to interpretation by us, governmental or regulatory agencies, and the courts. The terms, scope and complexity of these government pricing programs change frequently, as do interpretations of applicable requirements for pricing and rebate calculations. Responding to current and future changes may increase our costs and the complexity of compliance will be time consuming. Any required refunds to the U. S. government or responding to a government investigation or enforcement action would be expensive and time consuming and could have a material adverse effect on our business, results of operations and financial condition. Price recalculations under the MDRP also may affect the ceiling price at which we are required to offer products under the 340B program. Civil monetary penalties can be applied if we are found to have knowingly submitted any false price or product information to the government, if we fail to submit the required price data on a timely basis, or if we are found to have charged 340B covered entities more than the statutorily mandated ceiling price. In the event that CMS were to terminate our Medicaid rebate agreement, no federal payments would be available under Medicaid or Medicare for IBSRELA or, if ~~approved and~~ launched, XPHOZAH. We cannot offer any assurances that our submissions will not be found to be incomplete or incorrect. Risks Related to Intellectual Property Our success will depend on our ability to obtain, maintain and protect our intellectual property rights **.** Our success and ability to compete depend in part on our ability to obtain, maintain and enforce issued patents, trademarks and other intellectual property rights and proprietary technology in the U. S. and elsewhere. If we cannot adequately obtain, maintain and enforce our intellectual property rights and proprietary technology, competitors may be able to use our technologies or the goodwill we have acquired in the marketplace and erode or negate any competitive advantage we may have and our ability to compete, which could harm our business and ability to achieve profitability and / or cause us to incur significant expenses. We rely on a combination of contractual provisions, confidentiality procedures and patent, trademark, copyright, trade secret and other intellectual property laws to protect the proprietary aspects of our products, product candidates, brands, technologies, trade secrets, know- how and data. These legal measures afford only limited protection, and competitors or others may gain access to or use our intellectual property rights and proprietary information. Our success will depend, in part, on preserving our trade secrets, maintaining the security of our data and know- how and obtaining, maintaining and enforcing other intellectual property rights. We may not be able to obtain, maintain and / or enforce our intellectual property or other proprietary rights necessary to our business or in a form that provides us with a competitive advantage. Failure to obtain, maintain and / or enforce intellectual property rights necessary to our business and failure to protect, monitor and control the use of our intellectual property rights could negatively impact our ability to compete and cause us to incur significant expenses. The intellectual property laws and other statutory and contractual arrangements in the U. S. and other jurisdictions we depend upon may not provide sufficient protection in the future to prevent the infringement, use, violation, or misappropriation of our patents, trademarks, data, technology, and other intellectual property rights and products by others; and may not provide an adequate remedy if our intellectual property rights are infringed, misappropriated, or otherwise violated by others. We rely in part on our portfolio of issued and pending patent applications in the U. S. and other countries to protect our intellectual property and competitive position. However, it is also possible that we may fail to identify patentable aspects of inventions made in the course of our development, manufacture and commercialization activities before it is too late to obtain patent protection on them. If we fail to timely file for patent protection in any jurisdiction, we may be precluded from doing so at a later date. Although we enter into non- disclosure and confidentiality agreements with parties who have access to patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, suppliers, consultants, advisors, and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. Furthermore, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the U. S. and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in any of our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. Moreover, should we become a licensee of a third party’ s patents or patent applications, depending on the terms of any future in- licenses to which we may become a party, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain or enforce the patents, covering technology in- licensed from third parties. Therefore, these patents and patent applications may not be prosecuted, maintained and / or enforced in a manner consistent with the best interests of our business. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business. The patent positions of companies, including our patent position, may involve complex legal and factual questions that have been the subject of much litigation in recent years, and, therefore, the scope of any patent claims that we have or may obtain cannot be predicted with certainty. Accordingly, we cannot provide any assurances about which of our patent applications will issue, the breadth of any resulting patent, whether any of the issued patents will be found to be infringed, invalid or unenforceable or will be threatened or challenged by third parties, that any of our issued patents have, or that any of our currently pending or future patent applications that mature into issued patents will include, claims with a scope sufficient to protect our products and services. Our pending and future patent applications may not result in the issuance of patents or, if issued, may not issue in a form that will be advantageous to us. The coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. We cannot offer any assurances that the breadth of our granted patents will be sufficient to stop a competitor from developing, manufacturing and commercializing a product or technologies in a non- infringing manner that would be competitive with one or more of our products or technologies, or otherwise provide us with any competitive advantage. Furthermore, any successful challenge to these patents or any other patents owned by or licensed to us after patent issuance could deprive us of rights necessary for our commercial success. Further, there can be no assurance that we will have adequate resources to enforce our patents. Patents have a limited lifespan. In the U. S., the natural expiration of a utility patent is generally 20 years from the earliest effective non- provisional filing date. Though an issued patent is presumed valid and enforceable, its issuance is not conclusive as to its validity or its enforceability and it may not provide us with adequate proprietary protection or competitive advantages against competitors with similar products or services. Patents, if issued, may be challenged, deemed unenforceable, invalidated, narrowed or circumvented. Proceedings challenging our patents or patent applications could result in either loss of the patent, or denial of the patent application or loss or reduction in the scope of one or more of the claims of the patent or patent application. Any successful challenge to our patents and patent applications could deprive us of exclusive rights necessary for our commercial success. In addition, defending such challenges in such proceedings may be costly. Thus, any patents that we may own may not provide the anticipated level of, or any, protection against competitors. Furthermore, an adverse decision may result in a third party receiving a patent right sought by us, which in turn could affect our ability to develop, manufacture or commercialize our products or technologies. Some of our patents and patent applications may in the future be co- owned with third parties. If we are unable to obtain an exclusive license to any such third- party co- owners’ interest in such patents or patent applications, such co- owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products, services and technology. In addition, we may need the cooperation of any such co- owners of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us. The degree of future protection for our proprietary rights is uncertain, and we cannot ensure that: • Any of our patents, or any of our pending patent applications, if issued, will include claims having a scope sufficient to protect our products or product candidates; • Any of our pending patent applications will issue as patents; • We were the first to make the inventions covered by each of our patents and pending patent applications; • We were the first to file patent applications for these inventions; • Others will not develop, manufacture and / or commercialize similar or alternative products or technologies that do not infringe our patents; • Any of our challenged patents will **ultimately** be found to ~~ultimately~~ be valid and enforceable; • Any patents issued to us will provide a basis for an exclusive market for our commercially viable products or technologies will provide us with any competitive advantages or will not be challenged by third parties; • We will develop additional proprietary technologies or products that are separately patentable; or • Our commercial activities or products will not infringe upon the patents of others. We may become subject to third- party claims alleging infringement, misappropriation or violation of such third parties' patents or other intellectual property rights and / or third- party claims seeking to invalidate our patents, which would be costly, time consuming and, if successfully asserted against us, delay or prevent the development, manufacture or commercialization of our products or product candidates. Our commercial success depends, in part, on our ability to develop, manufacture or commercialize our products and product candidates without infringing, misappropriating or otherwise violating the intellectual property rights of third parties. There have been many lawsuits and other proceedings asserting infringement or misappropriation of patents and other intellectual property rights in the pharmaceutical and biotechnology industries, and companies in the industry have used intellectual property litigation to gain a competitive advantage. While we take steps to ensure that we do not infringe upon, misappropriate or otherwise violate the intellectual property rights of others, there can be no assurances that we will not be subject to claims alleging that the manufacture, use or sale of IBSRELA or XPHOZAH or of any other product candidates infringes existing or future third- party patents, or that such claims, if any, will not be successful. Because patent applications can take many years to issue and may be confidential for 18 months or more after filing, and because pending patent claims can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use or sale of IBSRELA or XPHOZAH or other product candidates. Moreover, we may face patent infringement claims from non- practicing entities that have no relevant product revenue and against whom our own patent portfolio may thus have no deterrent effect. We may be unaware of one or more issued patents that would be infringed by the manufacture, sale or use of IBSRELA or XPHOZAH or our other product candidates. Third parties may initiate legal proceedings alleging that we are infringing, misappropriating or otherwise violating their intellectual property rights. These proceedings could cause us to pay substantial damages, including treble damages and attorney' s fees if we are found to be willfully infringing a third party' s patents. We may be required to indemnify future collaboration partners against such claims. We are not aware of any threatened or pending claims related to these matters, but in the future **,** litigation may be necessary to defend against such claims. If a patent infringement suit were brought against us, we could be forced to stop or delay development, manufacturing or sales of the product or product candidate that is the subject of the suit. As a result of patent infringement claims, or in order to avoid potential claims, we may choose to seek, or be required to seek, a license from the third party and would most likely be required to pay license fees or royalties or both. These licenses may not be available on acceptable terms, or at all. Even if we were able to obtain a license, we may be unable to maintain such licenses and the rights may be nonexclusive, which would give our competitors access to the same intellectual property. Ultimately, we could be prevented from commercializing a product, or forced to redesign it if, as a result of actual or threatened patent infringement claims, we are unable to enter into licenses on acceptable terms, or unable to maintain such licenses when granted. Even if we are successful in defending against such claims, such litigation can be expensive and time consuming to litigate and would divert management' s attention from our core business. Any of these events could harm our business significantly. We also could be ordered to pay substantial damages, including treble damages and attorney' s fees if we are found to be willfully infringing a third party' s patents or other intellectual property right. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third party patents are valid and enforceable, and infringed by the use of our products and / or technologies, which could have a negative impact on the commercial success of our current and any future products or technologies. If we were to challenge the validity of any such third party U. S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U. S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U. S. patent. We will have similar burdens to overcome in foreign courts in order to successfully challenge a third party claim of patent infringement. Even if we are successful in defending against such claims, such litigation can be expensive and time consuming to litigate and would divert management' s attention from our core business. Any of these events could harm our business significantly. In addition to infringement claims against us, third parties may also raise similar claims before administrative bodies in the U. S. or abroad. Such mechanisms include reexamination, post grant review, inter parties review, derivation or opposition proceedings before the United States Patent and Trademark Office ("USPTO ") or other jurisdictional body relating to our intellectual property rights or the intellectual property rights of others. If third parties prepare and file patent applications in the U. S. that also claim technology similar or identical to ours, we may have to participate in interference or derivation proceedings in the USPTO to determine which party is entitled to a patent on the disputed invention. We may also become involved in similar opposition proceedings in the European Patent Office or similar offices in other jurisdictions regarding our intellectual property rights with respect to our products and technology. Since patent applications are confidential for a period of time after filing, we cannot be certain that we were the first to file any patent application related to our product candidates. Such administrative proceedings could result in revocation of or amendment to our patents in such a way that they no longer cover our products or product candidates. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we, our patent counsel, and the patent examiner were unaware during prosecution. If a third party were to prevail on a legal assertion of invalidity and / or unenforceability, we may lose at least part, and perhaps all, of the patent protection on our products or technologies. Such a loss of patent protection would have a material adverse impact on our business, financial condition, results of operations, and prospects. If ~~our intellectual property related to IBSRELA, XPHOZAH, RDX013 or any future product candidates is not adequate or if~~ we are not able to successfully enforce our intellectual property rights, the commercial value of IBSRELA, ~~if approved,~~ XPHOZAH, **RDX013** or other product candidates may be adversely affected and we may not be able to compete effectively in our market. The ~~strength~~ **enforceability** of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions ~~and~~ **, the answers to which** can be uncertain. The patent applications that we own or license may fail to result in issued patents in the U. S. or in foreign countries. Additionally, our research and development efforts may result in product candidates for which patent protection is limited or not available. Even if patents do ~~successfully~~ issue, third parties may challenge the validity, enforceability ~~or~~ **,** scope **or infringement** thereof, which may result in such patents being narrowed, invalidated ~~or~~ **,** held unenforceable **or not infringed** . For example, U. S. patents can be challenged by any person before the new USPTO Patent Trial and Appeals Board at any time before one year after that person is served an infringement complaint based on the patents. Patents granted by the European Patent Office may be similarly opposed by any person within nine months from the publication of the grant. Similar proceedings are available in other jurisdictions, and in the U. S., Europe and other jurisdictions third parties can raise questions of validity with a patent office even before a patent has granted. Furthermore, even if ~~they are~~ unchallenged, our patents and patent applications may not ~~adequately protect our intellectual property or~~ prevent others from designing around our **patent** claims. For example, a third party may develop a competitive product that provides therapeutic benefits similar to one or more of our product candidates but has a sufficiently different composition to fall outside the scope of our patent protection. If the breadth or strength of protection provided by the patents and patent applications we hold or pursue with respect to IBSRELA, XPHOZAH, RDX013 or any future product candidates is successfully challenged, then our ability to commercialize such product could be negatively affected, and we may face unexpected competition that could have a material adverse impact on our business. Further, we have reported that we have completed the data analysis from our Phase 2 clinical trial evaluating the safety and efficacy of RDX013 for the treatment of hyperkalemia, and that we currently expect that the next steps for the RDX013 program will be to evaluate a new formulation that potentially enhances subject compliance and the efficacy of RDX013 in an additional Phase 2 clinical study. We currently expect to delay further development of RDX013 until such time as we have determined that our available resources support conducting such additional formulation work and an additional clinical study. As a result of this delay in our development program for RDX013, the period of time during which we or our collaboration partners could market RDX013 under patent protection ~~would~~ **could** be reduced. Even where laws provide **intellectual property and / or regulatory** protection, costly and time- consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and the outcome of such litigation would be uncertain. If we or one of our collaboration partners were to initiate legal proceedings against a third party to enforce a patent covering a product or product candidate, the defendant could counterclaim that our patent is invalid **, unenforceable** and / or ~~unenforceable~~ **not infringed** . In patent litigation in the U. S. **and other jurisdictions** , defendant counterclaims alleging invalidity **, unenforceability** and / or ~~unenforceability~~ **noninfringement** are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including ~~lack of~~ novelty, ~~obviousness~~ **nonobviousness and** ~~or non-~~ enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. The outcome following legal assertions of invalidity ~~and~~ **,** unenforceability **and noninfringment** is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity **,** ~~and / or~~ unenforceability ~~against~~ **or non- infringement of** our intellectual property related to a product or a product candidate, we ~~would~~ **could** lose ~~at least~~ part, and ~~perhaps~~ **possibly** all, of the patent protection on such product or product candidate. Such a loss of patent protection ~~would~~ **could** have a material adverse impact on our business. Moreover, our competitors could counterclaim that we infringe their intellectual property ~~,~~ and ~~some~~ **may attempt to prevent us from commercializing a product. Although the composition and use** of **IBSRELA are currently claimed by** ~~our~~ **four (4) issued patents** ~~competitors have substantially greater intellectual property portfolios than~~ **that are listed in the U. S. FDA' s Orange Book,** we ~~do~~ **cannot assure that we will be successful in defending against third parties asserting that any of our patents are invalid, unenforceable or not infringed by the third parties' products, or in competing against third parties seeking to introduce generic versions of IBSRELA or any of our future products. In the U. S., the Hatch- Waxman Act provides non- patent regulatory exclusivity for five years from the date of the first U. S. FDA approval of a drug containing a new chemical entity (NCE). The U. S. FDA is prohibited during those five years from approving an Abbreviated New Drug Application (ANDA) that references the NDA that has been granted NCE exclusivity. However, if any patents are listed in the U. S. FDA Orange Book for such NCE- containing drug, a generic manufacturer may file an ANDA that references a NDA product with granted NCE exclusivity after four years from the first NDA approval date provided it is accompanied by a Paragraph IV certification asserting that each Orange Book listed patent is invalid, unenforceable, or that the generic product does not infringe the Orange Book listed patents. The Hatch- Waxman Act does not prevent a third party from filing, or the U. S. FDA from approving, another full NDA (i. e. not an ANDA) for an already- approved drug where the third party has conducted its own pre- clinical and clinical trials to independently demonstrate safety and effectiveness without reliance on the original NDA data. In cases where NCE exclusivity has been granted for an NDA, as in the case of IBSRELA, if an ANDA sponsor has provided a Paragraph IV certification to the U. S. FDA when filing an ANDA, the ANDA sponsor must also send a notice thereof to the NCE NDA owner. The NCE NDA owner may then initiate a patent infringement lawsuit in response to the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the NCE NDA owner' s receipt of a notice of the Paragraph IV certification automatically prevents the U. S. FDA from approving the ANDA until the earlier of 30 months after the NCE NDA owner' s receipt of the Paragraph IV certification notice or a final decision in the**

infringement case in favor of the ANDA sponsor. There can be no assurances that an ANDA that references our IBSRELA NDA and includes a Paragraph IV certification will not be filed, or that we will be successful in enforcing our Orange Book listed patents against such ANDA sponsor . We also rely on trade secret protection and confidentiality agreements to protect proprietary know- how that may not be patentable, processes for which patents may be difficult to obtain and / or enforce and any other elements of our drug discovery and development processes that involve proprietary know- how, information or technology that is not covered by patents. Although we require all of our employees, consultants, advisors and any third parties who have access to our proprietary know- how, information or technology, to assign their inventions to us, and endeavor to execute confidentiality agreements with all such parties, we cannot be certain that we have executed such agreements with all parties who may have helped to develop our intellectual property or who had access to our proprietary information, nor can we be certain that our agreements will not be breached by such consultants, advisors or third parties, or by our former employees. The breach of such agreements by individuals or entities who were actively involved in the discovery and design of our products or potential drug candidates, or in the development of our discovery and design platform could require us to pursue legal action to protect our trade secrets and confidential information, which ~~would~~ **could** be expensive, and the outcome of which would be unpredictable. If we are not successful in prohibiting the continued breach of such agreements, our business could be negatively impacted. We cannot guarantee that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the U. S. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the U. S. and abroad. If we are unable to prevent material disclosure of the intellectual property related to our technologies to third parties, we will not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition. Although we have obtained patent term extension in the U. S. under the Hatch- Waxman Act, extending the term of ~~marketing~~ exclusivity for tenapanor, if we do not obtain patent term extension in foreign countries under similar legislation, our business may be materially harmed. **Furthermore, we have obtained patent term adjustment in the U. S. under the American Inventors Protection Act extending the patent term for certain patents covering tenapanor. U. S. Patent No. 8, 541, 448 covering tenapanor was subject to patent term adjustment (PTA) under the American Inventors Protection Act for delays by the United States Patent and Trademark Office in granting the patent. Additionally,** ~~Following~~ **following** the approval by the **U. S.** FDA for our NDA to market tenapanor for IBS- C, ~~we obtained~~ **this patent was granted** patent term ~~restoration~~ **extension (PTE)** under the Hatch- Waxman Act **and together with PTA provides us with exclusivity for tenapanor and uses thereof** until August 1, 2033 ~~for U. S. patent no. 8, 541, 448 covering our approved product or the use thereof~~ . The Hatch- Waxman Act allows a maximum of one patent to be extended per **U. S.** FDA approved product. **Extension and / or adjustment of patent term (collectively "** Patent ~~term extension~~ **Restoration ")** also may be available in certain foreign countries upon regulatory approval of our product candidates. Despite seeking ~~patent~~ **Patent Restoration** ~~term extension~~ for tenapanor **in all countries where it is available** , ~~we~~ **it** may not be granted ~~patent term extension~~ in any foreign country because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the term of ~~extension~~ **patent protection subject to Patent Restoration** , as well as the scope of patent protection during any such ~~extension~~ **Patent Restoration** , afforded by the governmental authority could be less than we request **or could change due to changes to applicable Patent Restoration laws or regulations or interpretations thereof** . If we are unable to obtain ~~patent~~ **Patent** ~~term~~ **Term** ~~extension or restoration~~ **Restoration** in any particular ~~foreign~~ country, or the term of any such extension is less than we request, **or is changed due to changes in applicable laws or regulations or interpretations thereof,** the period during which we will have ~~the~~ **exclusive** ~~right~~ **rights** to ~~exclusively market~~ our product in such ~~foreign~~ country ~~will~~ **could** be shortened and our competitors may obtain approval of competing products following our **non- extended / adjusted** patent expiration, and our revenue could be reduced, possibly materially ~~. Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non- compliance with these requirements~~ . The USPTO and various foreign patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions to maintain patent applications and issued patents. Noncompliance with these 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. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case. We may not be able to enforce our intellectual property rights throughout the world. The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the U. S. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to life sciences. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Europe' s ~~planned~~ **new** Unified Patent Court may, in particular, present uncertainties for our ability to protect and enforce our patent rights against competitors in Europe. In 2012, the European Patent Package (~~"~~EU Patent Package ~~"~~) regulations were passed with the goal of providing a single pan- European Unitary Patent and a new European Unified Patent Court (~~"~~UPC ~~"~~), for litigation involving European patents. Implementation of the EU Patent Package **entered into force on June 1,** ~~will likely occur in the first half of~~ 2023. Under the UPC, all European patents, including those issued prior to ratification of the European Patent Package, will by default automatically fall under the jurisdiction of the UPC. The UPC will provide our competitors with a new forum to centrally revoke our European patents ~~,~~ and allow for the possibility of a competitor to obtain pan- European injunctions. It will be several years before we will understand the scope of patent rights that will be recognized and the strength of patent remedies that will be provided by the UPC. Under the EU Patent Package as currently proposed, we will have the right to opt our patents out of the UPC over the first seven years of the court' s existence, but doing so may preclude us from realizing the benefits of the new unified court **. In addition, geo- political actions in the United States and in foreign countries could increase the uncertainties and costs surrounding the prosecution or maintenance of our patent applications or those of any current or future licensors and the maintenance, enforcement or defense of our issued patents or those of any current or future licensors. For example, the United States and foreign government actions related to Russia' s conflict in Ukraine may limit or prevent filing, prosecution, and maintenance of patent applications in Russia. Government actions may also prevent maintenance of issued patents in Russia. These actions could result in abandonment or lapse of our patents or patent applications, resulting in partial or complete loss of patent rights in Russia. In addition, a decree was adopted by the Russian government in March 2022, allowing Russian companies and individuals to exploit inventions owned by patentees from the United States without consent or compensation. Consequently, we would not be able to prevent third parties from practicing our inventions in Russia or from selling or importing products made using our inventions in and into Russia. Accordingly, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected** . Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and attention from other aspects of our business. Furthermore, while we intend to protect our intellectual property rights in our expected significant markets, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our products. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate. In addition, changes in the law and legal decisions by courts in the U. S. and foreign countries may affect our ability to obtain and enforce adequate intellectual property protection for our technology. We may be subject to claims that we or our employees have misappropriated the intellectual property, including know- how or trade secrets, of a third party, or claiming ownership of what we regard as our own intellectual property. Many of our employees, consultants and contractors were previously employed at or engaged by other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Some of these employees, consultants and contractors, executed proprietary rights, non-disclosure and non- competition agreements in connection with such previous employment. Although we try to ensure that our employees, consultants and contractors do not use the intellectual property and other proprietary information or know- how or trade secrets of others in their work for us, and do not perform work for us that is in conflict with their obligations to another employer or any other entity, we may be subject to claims that we or these employees, consultants and contractors have used or disclosed such intellectual property, including know- how, trade secrets or other proprietary information. In addition, an employee, advisor or consultant who performs work for us may have obligations to a third party that are in conflict with their obligations to us, and as a result such third party may claim an ownership interest in the intellectual property arising out of work performed for us. We are not aware of any threatened or pending claims related to these matters, but in the future litigation may be necessary to defend against such claims. If we fail ~~in~~ **to** ~~defending~~ --- **defend** any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, or access to consultants and contractors. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management. In addition, while we typically require our employees, consultants and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own, which may result in claims by or against us related to the ownership of such intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our management and scientific personnel. Risks Related to Our Common Stock Our stock price may **continue to** be volatile and our stockholders may not be able to resell shares of our common stock at or above the price they paid. The trading price of our common stock is highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. These factors include those discussed in this " Risk Factors " section and others such as: • the success or lack of success with regards to our commercialization of IBSRELA **and** ~~; • announcements of regulatory decisions regarding our NDA seeking marketing approval for~~ XPHOZAH ~~; • the success or lack of success with regards to our commercial launch of XPHOZAH, if approved~~ ; • results of regulatory inspections of our facilities or those of our CMOs, or specific label restrictions or patient populations for XPHOZAH' s use ~~, if approved~~ , or changes or delays in the regulatory review process; • announcements regarding whether XPHOZAH ~~, if approved,~~ alone or with other oral only medications, will be included in the ESRD **PPS** ~~prospective payment system~~ , and the time and manner in which such transition is achieved; • announcements relating to our current or future collaboration partnerships; • announcements of therapeutic innovations or new products by us or our competitors; • adverse actions taken by regulatory agencies with respect to our product label, our clinical trials, manufacturing supply chain or sales and marketing activities; • changes or developments in laws or regulations applicable to our approved products or our product candidates; • the success of our testing and clinical trials; • failure to meet any of our projected timelines or goals with regard to the commercialization of IBSRELA **and** ~~, the commercial launch of XPHOZAH~~ - **XPOHZAH** ~~, if approved~~ , or the clinical development and commercialization of any of our product candidates; • the success of our efforts to acquire or license or discover additional product candidates; • any intellectual property infringement actions in which we may become involved; • the success of our efforts to obtain adequate intellectual property protection for our product candidates; • announcements concerning our competitors or the pharmaceutical industry in general; • achievement of expected product sales and profitability; • manufacture, supply or distribution shortages; • actual or anticipated fluctuations in our operating results; • **U. S.** FDA or other U. S. or foreign regulatory actions affecting us or our industry or other healthcare reform measures in the U. S.;

• changes in financial estimates or recommendations by securities analysts; • trading volume of our common stock; • sales of our common stock by us, our executive officers and directors or our stockholders in the future; • sales of debt securities and sales or licensing of assets; • general economic and market conditions and overall fluctuations in the U. S. equity markets; and • the loss of any of our key scientific or management personnel. In addition, the stock markets in general, and the markets for pharmaceutical, biopharmaceutical and biotechnology stocks in particular, have experienced extreme volatility that may have been unrelated to the operating performance of the issuer. These broad market fluctuations may adversely affect the trading price or liquidity of our common stock. In the past, when the market price of a stock has been volatile, holders of that stock have sometimes instituted securities class action litigation against the issuer. If any of our stockholders were to bring such a lawsuit against us, we could incur substantial costs defending the lawsuit and the attention of our management would be diverted from the operation of our business, which could seriously harm our financial position. Any adverse determination in litigation could also subject us to significant liabilities. If we sell shares of our common stock in future financings, stockholders may experience immediate dilution and, as a result, our stock price may decline. We may from time to time issue additional shares of common stock at a discount from the current trading price of our common stock. As a result, our stockholders would experience immediate dilution upon the purchase of any shares of our common stock sold at such discount. In addition, as opportunities present themselves, we may enter into financing or similar arrangements in the future, including the issuance of debt securities, preferred stock or common stock. If we issue common stock or securities convertible into common stock, our common stockholders ~~would~~ **will** experience additional dilution and, as a result, our stock price may decline **. We will no longer be a " smaller reporting company " in 2024 and as a result we are or will be subject to certain enhanced disclosure requirements which will require us to incur significant expenses and expend time and resources. We will no longer be a " smaller reporting company, " in 2024 and, as a result, we are or will be required to comply with various disclosure and compliance requirements that did not previously apply to us. Compliance with these additional requirements increases our legal and financial compliance costs and causes management and other personnel to divert attention from operational and other business matters to these additional public company reporting requirements. In addition, if we are not able to comply with changing requirements in a timely manner, the market price of our stock could decline and we could be subject to delisting proceedings by the Nasdaq Global Market, or sanctions or investigations by the Securities and Exchange Commission (SEC) or other regulatory authorities, which would require additional financial and management resources. We are not required to reflect the change in our smaller reporting company status and comply with the increased disclosure obligations until our quarterly report for the quarter ending March 31, 2024, the first quarter in our fiscal year ending December 31, 2024. We will need to reassess, as of June 30, 2024, whether we will continue to qualify as a large accelerated filer for filings beyond the fiscal year ending December 31, 2024** . General Risk Factors We incur significant costs as a result of operating as a public company, and our management will devote substantial time to new compliance initiatives. We may fail to comply with the rules that apply to public companies, including Section 404 of the Sarbanes- Oxley Act of 2002, which could result in sanctions or other penalties that would harm our business. We incur significant legal, accounting and other expenses as a public company, including costs resulting from public company reporting obligations under the Securities Exchange Act of 1934, as amended (~~"~~Exchange Act ~~"~~) and regulations regarding corporate governance practices. The listing requirements of The Nasdaq Global Market require that we satisfy certain corporate governance requirements relating to director independence, distributing annual and interim reports, stockholder meetings, approvals and voting, soliciting proxies, conflicts of interest and a code of conduct. Our management and other personnel will need to devote a substantial amount of time to ensure that we comply with all of these requirements. Moreover, the reporting requirements, rules and regulations will increase our legal and financial compliance costs and will make some activities more time consuming and costly. Any changes we make to comply with these obligations may not be sufficient to allow us to satisfy our obligations as a public company on a timely basis, or at all. These reporting requirements, rules and regulations, coupled with the increase in potential litigation exposure associated with being a public company, could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors or board committees or to serve as executive officers, or to obtain certain types of insurance, including directors' and officers' insurance, on acceptable terms. We are subject to Section 404 of The Sarbanes- Oxley Act of 2002 (~~"~~Section 404 ~~"~~) and the related rules of the ~~Securities and Exchange Commission ("~~SEC ~~")~~ which generally require, among other things, our management **and independent registered public accounting firm** to report on the effectiveness of our internal control over financial reporting ~~, subject to certain exceptions applicable to non- accelerated filers~~ . Our compliance with Section 404 requires that we incur substantial expense and expend significant management efforts. During the course of our review and testing of our internal controls, we may identify deficiencies and be unable to remediate them before we must provide the required reports. Furthermore, if we have a material weakness in our internal controls over financial reporting, we may not detect errors on a timely basis and our financial statements may be materially misstated. We or our independent registered public accounting firm may not be able to conclude on an ongoing basis that we have effective internal control over financial reporting, which could harm our operating results, cause investors to lose confidence in our reported financial information and cause the trading price of our stock to fall. In addition, as a public company we are required to file accurate and timely quarterly and annual reports with the SEC under the Exchange Act. Any failure to report our financial results on an accurate and timely basis could result in sanctions, lawsuits, delisting of our shares from The Nasdaq Global Market or other adverse consequences that would materially harm our business. We may be adversely affected by the global economic environment. Our ability to attract and retain collaboration partners or customers, invest in and grow our business and meet our financial obligations depends on our operating and financial performance, which, in turn, is subject to numerous factors, including the prevailing economic conditions and financial, business and other factors beyond our control, such as the rate of unemployment, the number of uninsured persons in the U. S., presidential elections, other political influences and inflationary pressures. Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets, including the current inflationary environment and rising interest rates. **Adverse developments that affect financial institutions, transactional counterparties, or other third parties, or concerns or rumors about these events, have in the past and may in the future lead to market- wide liquidity problems.** For example, **on March 10, 2023, Silicon Valley Bank (SVB) was closed by the California Department of Financial Protection and Innovation, which appointed the U. S. Federal Deposit Insurance Corporation (FDIC) as receiver. Similarly,** ~~the~~ **other** ~~2008 global~~ **institutions have been and may continue to be swept into receivership. We currently have no borrowing or deposit exposure to directly impacted institutions and have not experienced an adverse impact to our liquidity or to our business operations,** financial ~~crisis caused extreme volatility and disruptions in~~ **condition, or results of operations as a result of** ~~the~~ **these** ~~capital~~ **recent events. However, uncertainty may remain over liquidity concerns in the broader financial services industry,** and ~~credit markets~~ **there may be unpredictable impacts to our business and our industry** . We cannot anticipate all the ways in which the global economic climate and global financial market conditions could adversely impact our business in the future. We are exposed to risks associated with reduced profitability and the potential financial instability of our collaboration partners or customers, many of which may be adversely affected by volatile conditions in the financial markets. For example, unemployment and underemployment, and the resultant loss of insurance, may decrease the demand for healthcare services and pharmaceuticals. If fewer patients are seeking medical care because they do not have insurance coverage, our collaboration partners or customers may experience reductions in revenues, profitability and / or cash flow that could lead them to reduce their support of our programs or financing activities. If collaboration partners or customers are not successful in generating sufficient revenue or are precluded from securing financing, they may not be able to pay, or may delay payment of, accounts receivable that are owed to us. In addition, volatility in the financial markets could cause significant fluctuations in the interest rate and currency markets. We currently do not hedge for these risks. The foregoing events, in turn, could adversely affect our financial condition and liquidity. In addition, if economic challenges in the U. S. result in widespread and prolonged unemployment, either regionally or on a national basis, or if certain provisions of the Patient Protection and ACA, as amended by the Health Care and Education Reconciliation Act, collectively known as the ACA, are repealed, a substantial number of people may become uninsured or underinsured. To the extent economic challenges result in fewer individuals pursuing or being able to afford our product candidates once commercialized, our business, results of operations, financial condition and cash flows could be adversely affected. Provisions in our charter documents and under Delaware law could discourage a takeover that stockholders may consider favorable and may lead to entrenchment of management. Our amended and restated certificate of incorporation and amended and restated bylaws contain provisions that could significantly reduce the value of our shares to a potential acquirer or delay or prevent changes in control or changes in our management without the consent of our board of directors. The provisions in our charter documents include the following: • a classified board of directors with three- year staggered terms, which may delay the ability of stockholders to change the membership of a majority of our board of directors; • no cumulative voting in the election of directors, which limits the ability of minority stockholders to elect director candidates; • the exclusive right of our board of directors to elect a director to fill a vacancy created by the expansion of the board of directors or the resignation, death or removal of a director, which prevents stockholders from being able to fill vacancies on our board of directors; • the required approval of at least two- thirds of the shares entitled to vote to remove a director for cause, and the prohibition on removal of directors without cause; • the ability of our board of directors to authorize the issuance of shares of preferred stock and to determine the price and other terms of those shares, including preferences and voting rights, without stockholder approval, which could be used to significantly dilute the ownership of a hostile acquirer; • the ability of our board of directors to alter our bylaws without obtaining stockholder approval; • the required approval of at least two- thirds of the shares entitled to vote at an election of directors to adopt, amend or repeal our bylaws or repeal the provisions of our amended and restated certificate of incorporation regarding the election and removal of directors; • a prohibition on stockholder action by written consent, which forces stockholder action to be taken at an annual or special meeting of our stockholders; • the requirement that a special meeting of stockholders may be called only by the chairman of the board of directors, the chief executive officer, the president or the board of directors, which may delay the ability of our stockholders to force consideration of a proposal or to take action, including the removal of directors; and • advance notice procedures that stockholders must comply with in order to nominate candidates to our board of directors or to propose matters to be acted upon at a stockholders' meeting, which may discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer' s own slate of directors or otherwise attempting to obtain control of us. In addition, these provisions would apply even if we were to receive an offer that some stockholders may consider beneficial. We are also subject to the anti- takeover provisions contained in Section 203 of the Delaware General Corporation Law. Under Section 203, a corporation may not, in general, engage in a business combination with any holder of 15 % or more of its capital stock unless the holder has held the stock for three years or, among other exceptions, the board of directors has approved the transaction. Claims for indemnification by our directors and officers may reduce our available funds to satisfy successful third- party claims against us and may reduce the amount of money available to us. Our amended and restated certificate of incorporation and amended and restated bylaws provide that we will indemnify our directors and officers, in each case to the fullest extent permitted by Delaware law. In addition, as permitted by Section 145 of the Delaware General Corporation Law, our amended and restated bylaws and our indemnification agreements that we have entered into with our directors and officers provide that: • We will indemnify our directors and officers for serving us in those capacities or for serving other business enterprises at our request, to the fullest extent permitted by Delaware law. Delaware law provides that a corporation may indemnify such a person if such person acted in good faith and in a manner such person reasonably believed to be in or not opposed to the best interests of the registrant and, with respect to any criminal proceeding, had no reasonable cause to believe such person' s conduct was unlawful. • We may, in our discretion, indemnify employees and agents in those circumstances where indemnification is permitted by applicable law. • We are required to advance expenses, as incurred, to our directors and officers in connection with defending a proceeding, except that such directors or officers shall undertake to repay such advances if it is ultimately determined that such person is not entitled to indemnification. • We will not be obligated pursuant to our amended and restated bylaws to indemnify a person with respect to proceedings initiated by that person against us or our other indemnities, except with respect to proceedings authorized by our board of directors or brought to enforce a right to indemnification. • The rights conferred in our amended and restated bylaws are not exclusive, and we are authorized to enter into indemnification agreements with our directors, officers, employees and agents and to obtain insurance to indemnify such persons. • We may not retroactively amend our amended and restated bylaw provisions to reduce our indemnification obligations to directors, officers, employees and agents. We do not currently intend to pay dividends on our common stock, and, consequently, our stockholders' ability to achieve a return on their investment will depend on appreciation in the price of our common stock. We do not currently intend to pay any cash dividends on our common stock for the foreseeable future. We currently intend to invest our future earnings, if any, to fund our growth. Additionally, the terms of our **2022** ~~loan~~ **Loan** ~~and security agreements~~ **Agreement** could restrict our ability to pay dividends. Therefore, our stockholders are not likely to receive any dividends on our common stock for the foreseeable future. Since we do not intend to pay dividends, our stockholders' ability to receive a return on their investment will depend on any future appreciation in the market value of our common stock. There is no guarantee that our common stock will appreciate or even maintain the price at which our holders have purchased it. ~~The continuing impact of " Brexit " may have a negative effect on our business. Following a national referendum and subsequent legislation the United Kingdom formally withdrew from the European Union, commonly referred to as " Brexit " and ratified a trade and cooperation agreement governing its future relationship with the European Union. Among other things, the agreement became effective in 2021, addresses trade, economic arrangements, law enforcement, judicial cooperation and governance. Because the agreement merely sets forth a framework that in many respects requires complex additional bilateral negotiations between the United Kingdom and the European Union significant uncertainty remains about how the precise terms of the relationship between the parties will differ from the terms before withdrawal. We cannot yet predict the full implications of Brexit, including whether it will increase our operational costs or otherwise have a negative effect on our business, financial condition or results of operations, which could reduce the price of our common stock.~~