Risk Factors Comparison 2024-03-05 to 2023-03-07 Form: 10-K

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Investing in our securities involves a high degree of risk. Below is a summary of the material factors that make an investment in our common stock speculative or risky. This summary does not address all of the risks that we face. Additional discussion of the risks summarized in this risk factor summary, as well as other risks that we face, can be found below under the heading " Part 1, Item 1A, Risk Factors " and should be carefully considered, together with other information in this Form 10- K and our other filings with the SEC, before making an investment decision regarding our common stock. ● Our prospects are highly dependent on our ~~first~~ **existing** commercial ~~product~~ **products** , TAVALISSE ® (fostamatinib disodium hexahydrate) and ~~our recently launched second commercial product~~ REZLIDHIA ~~™~~ **®** (olutasidenib) **, and our upcoming commercialization later this year of GAVRETO (pralsetinib) which we recently acquired from Blueprint Medicines Corporation (Blueprint)** . To the extent that the commercial success of our products in the US and respective territories outside of the US is diminished or **halted** ~~is not commercially successful~~ , our business, financial condition and results of operations may be adversely affected, and the price of our common stock may decline. ● We may not be able to successfully develop or commercialize our product candidates if problems arise in the clinical testing and **/ or** approval process. There is a high risk that drug discovery and development efforts might not generate successful product candidates. If the results of our clinical trials do not meet the primary efficacy endpoints, or if the top- line data from the results of our clinical trials may not ultimately meet the requirements for an NDA approval by the FDA and other ~~national~~ regulatory authorities, the commercial prospects of our business may be harmed, and our ability to generate product revenues may be delayed or eliminated **. ● Our strategy to expand our hematology and oncology pipeline on our own, or through acquisitions or in- licensing of early or late- stage products or companies, or through partnerships with pharmaceutical and biotechnology companies, as well as academic institutions and government organizations, may not be successful** . ● Even if we, or any of our collaborative partners, are able to continue to commercialize our products or any product candidate that we, or they, develop, the product may become subject to unfavorable pricing regulations, unfavorable health technology assessments (HTA) ~~assessment~~ , third- party payor reimbursement practices or labeling restrictions, all of which may vary from country to country and any of which could harm our business. ● If we are unable to successfully market and distribute our products and retain experienced commercial personnel, our business will be substantially harmed. ● ~~Our business was adversely affected and could be materially and adversely affected in the future by the evolving effects of the COVID- 19 pandemic as a result of the potential future impacts on our commercialization efforts, supply chain, regulatory, clinical development and corporate development activities and other business operations, in addition to the impact of a global economic slowdown. ●~~ We are subject to stringent and evolving **healthcare regulatory,** privacy and information security laws, regulations, rules, policies and contractual obligations, and changes in such laws, regulations, rules, policies, contractual obligations and our actual or perceived failure to comply with such requirements could subject us to significant investigations, **audits,** fines, penalties, and claims, any of which may have a material adverse effect on our business, financial condition, results of operations or prospects. ● If manufacturers obtain approval for generic versions of our products, or of products with which we compete, our business may be harmed. ● Unforeseen safety issues could emerge with our products that could require us to change the prescribing information to add warnings, limit use of the product, and / or result in litigation. Any of these events could have a negative impact on our business. ● We rely and may continue to rely on third **-** party distribution facilities for the sale of our products and potential sale of any of our product candidates. If any or all of them become subject to adverse findings from inspections or face other difficulties to operate, then the distribution of our products may be interrupted or otherwise adversely affected. ● We lack the capability to manufacture compounds for clinical development and we intend to rely on third parties for commercial supply, manufacturing and distribution, if any, of our product candidates which receive regulatory approval and we may be unable to obtain required material or product in a timely manner, at an acceptable cost or at a quality level required to receive regulatory approval. ● Any product for which we have obtained regulatory approval, or for which we obtain approval in the future, is subject to, or will be subject to, extensive ongoing regulatory requirements by the FDA, EMA **, MHRA** and other comparable regulatory authorities, and if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, we may be subject to penalties, we ~~will~~ **may** be unable to generate revenue from the sale of such products, our potential for generating positive cash flow ~~will~~ **may** be diminished, and the capital necessary to fund our operations will be increased **. Additionally, approval of a drug under the accelerated drug approval program may be withdrawn or the labeled indication of the drug changed if trials fail to verify clinical benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug** . ● If our corporate collaborations or license agreements are unsuccessful, or if we fail to form new corporate collaborations or license agreements, our research and development efforts could be delayed. ● Our success is dependent on **securing** intellectual property rights **and data exclusivity and other regulatory rights (such as orphan exclusivity, pediatric extensions and supplementary protection certificate)** held by us and third parties, and our interest in such rights is complex and uncertain. ● If a dispute arises regarding the infringement or misappropriation of the proprietary rights of others, such dispute could be costly and result in delays in our research and development activities, partnering and commercialization activities. **3** ● If our competitors develop technologies that are more effective than ours, our commercial opportunity will be reduced or eliminated. ● If product liability lawsuits are successfully brought against us, we may incur substantial liabilities and may be required to limit commercialization of our products. ~~3PART~~ **PART** IItem 1. BusinessOverviewWe are a biotechnology company dedicated to ~~discovering,~~ developing and providing novel therapies that significantly improve the lives of patients with hematologic

disorders and cancer. **We** ~~Our pioneering research focuses~~ -- **focus** on **products that address** signaling pathways that are critical to disease mechanisms. Our first product approved by the FDA is TAVALISSE (fostamatinib disodium hexahydrate) tablets, the only approved oral spleen tyrosine kinase (SYK) inhibitor ~~,~~ for the treatment of adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. The product is also commercially available in Europe and the United Kingdom (UK) (as TAVLESSE), and in Canada ~~and~~ **,** Israel **and Japan** (as TAVALISSE) for the treatment of chronic ITP in adult patients. Our second FDA **-** approved product is REZLIDHIA (olutasidenib) capsules for the treatment of adult patients with relapsed or refractory (R / R) acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase- 1 (IDH1) mutation as detected by an FDA- approved test. We began our commercialization of REZLIDHIA ~~(olutasidenib)~~ in December 2022. We in- licensed olutasidenib from Forma Therapeutics, Inc. **, now Novo Nordisk** (Forma), with exclusive, worldwide rights for its development, manufacturing and commercialization **.** We **continue** ~~conducted a Phase 3 clinical trial evaluating fostamatinib for the treatment of warm autoimmune hemolytic anemia (wAIHA) and announced that we did not file a supplemental New Drug Application (sNDA) for this indication considering the top-~~ **to advance** ~~- line data results and guidance received from the FDA. We announced the completion of the FOCUS Phase 3 clinical trial of fostamatinib for the treatment of hospitalized high- risk patients with COVID- 19. Fostamatinib is currently being studied in a National Institute of Health (NIH) / National Heart, Lung, and Blood Institute (NHLBI) sponsored Accelerating COVID- 19 Therapeutic Inventions and Vaccines Phase 2 / 3 trial (ACTIV- 4 Host Tissue Trial) for the treatment of COVID- 19 in hospitalized patients. Our other --~~ **the development of** ~~clinical programs include~~ our interleukin receptor- associated ~~kinase~~ **kinases 1 and 4** (~~IRAK~~ **IRAK1 / 4**) inhibitor program, **in** ~~and~~ - **an open- label, Phase 1b trial to determine the tolerability and preliminary efficacy of the drug in patients with lower- risk myelodysplastic syndrome (MDS) who are refractory or resistant to prior therapies. In February 2024, we entered into an Asset Purchase Agreement with Blueprint to purchase certain assets comprising the right to research, develop, manufacture and commercialize GAVRETO (pralsetinib) in the US. GAVRETO (pralsetinib) is a once daily, small molecule, oral, kinase inhibitor of wild- type rearranged during transfection (RET) and oncogenic RET fusions. GAVRETO is approved by the FDA for the treatment of adult patients with metastatic RET fusion- positive non- small cell lung cancer (NSCLC) as detected by an FDA- approved test. GAVRETO is also approved under accelerated approval based on overall response rate and duration response rate, for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion- positive thyroid cancer who require systemic therapy and who are radioactive iodine- refractory (if radioactive iodine is appropriate). We have strategic development collaborations with the University of Texas MD Anderson Cancer Center (MD Anderson) to expand our evaluation of REZLIDHIA (olutasidenib) in AML and other hematologic cancers, and with Collaborative Network for Neuro-Oncology Clinical Trials (CONNECT) to conduct a Phase 2 clinical trial to evaluate REZLIDHIA (olutasidenib) in combination with temozolomide as maintenance therapy in newly diagnosed pediatric and young adult patients with high- grade glioma (HGG) harboring an IDH1 mutation. We have** a receptor- interacting serine / threonine- protein kinase **1** (RIPK1) inhibitor program in clinical development with **our** partner Eli Lilly and Company (Lilly). **We also** ~~In addition, we~~ have product candidates in clinical development with partners BerGenBio ASA (BerGenBio) and Daiichi Sankyo (Daiichi). ~~Business~~ **4Business** UpdatesTAVALISSE in ITPIn ~~2022~~ **2023** , ~~our~~ **we recognized $ 93. 7 million of TAVALISSE** net product sales ~~of TAVALISSE were $ 75. 8 million~~ , a ~~20~~ **24** % increase compared to **$ 75. 8 million in** ~~2021~~ **2022** . The increase in our net product sales was primarily driven by the increase in quantities sold as **a result of increased number of patients under therapy, as** well as the increase in price per bottle of TAVALISSE **,** ~~. These increases were~~ partially offset by the increase in revenue reserves ~~mainly~~ **primarily** due to ~~higher rebates on recent contracts entered with certain Pharmacy Benefits Managers (PBMs), and~~ higher government ~~program~~ rebates. ~~Our~~ **Typically, our** first quarter net sales are ~~typically~~ impacted by the first quarter reimbursement issues such as the resetting of co- pays and the Medicare donut hole. ~~We continue to deploy resources to enable our field- based employees to engage with health care providers, either in- person or virtually. These engagements have enabled our field team to cover existing prescribers, as well as develop relationships with new prescribers to appropriately market TAVALISSE. In the third quarter of 2021, we expanded our sales force by increasing our number of territories.~~ REZLIDHIA in R / R AML with ~~mIDHIOn~~ - **mIDH1In** ~~December 1, 2022~~ **2023** , ~~the FDA approved~~ **we recognized $ 10. 6 million of** REZLIDHIA ~~(olutasidenib) capsules for the treatment of adult patients with R / R AML with a susceptible IDH1 mutation as detected by an FDA- approved test. The recommended dosage of REZLIDHIA is 150 mg taken orally twice daily until disease progression or unacceptable toxicity. We in- licensed olutasidenib from Forma with exclusive, worldwide rights for its development, manufacturing and 4commercialization. On December 22, 2022, we began the commercialization of REZLIDHIA in the US and made it available to patients. In 2022, we recorded~~ net product sales ~~of~~ **, compared to** $ 0. 9 million ~~from sale~~ **in 2022. The increase was primarily due to increased quantities sold as we began our commercialization** of REZLIDHIA **in December 2022 following the FDA approval** . **Our commercial effort focuses on growing awareness of** REZLIDHIA ~~is highly synergistic with~~ **within key institutions** ~~our existing hematology- oncology focused commercial and medical affairs infrastructure. We incurred operating expenses in 2022 and will continue to incur such expenses in the future associated with our commercial launch activities for REZLIDHIA in the US. Specifically~~ , ~~our commercial efforts focus on targeting hematologists~~ and ~~hematologist- oncologists~~ **among targeted healthcare professionals (HCPs)** who manage patients with R / R AML ~~. We also plan to enter partnerships with third parties to commercialize REZLIDHIA outside the US. For further discussions and other updates on REZLIDHIA (olutasidenib), refer to " Commercial Products -- REZLIDHIA in R / R AML~~ with mIDH1 ~~" section below~~ . ~~Pursuant to~~ **We in- licensed olutasidenib from Forma, with exclusive, worldwide rights for development, manufacturing and commercialization of olutasidenib for any uses, including for the treatment of AML and other malignancies. In accordance with the terms of** the license and transition services agreement ~~with Forma entered on July 27, 2022, Forma provided us an exclusive license to develop, manufacture and commercialize olutasidenib, Forma's proprietary inhibitor of mutated IDH1 (mIDH1), for any uses worldwide, including for the treatment of AML and other~~

~~malignancies. On October 14, 2022, Novo Nordisk A / S (Novo Nordisk) announced the completion of the acquisition of Forma. Following this acquisition, Forma became a wholly owned subsidiary of Novo Nordisk. In accordance with the terms of the license and transition services agreement~~ , we paid ~~Forma~~ an upfront fee of $ 2. 0 million, with the potential to pay up to $ 67. 5 million additional payments upon achievement of specified development and regulatory milestones and up to $ 165. 5 million additional payments upon achievement of certain commercial milestones. In addition, subject to the terms and conditions of the license and transition services agreement, Forma would be entitled to tiered royalty payments on net sales of licensed products at percentages ranging from low- teens to mid- thirties, as well as certain portions of our sublicensing revenue, subject to certain standard reductions and offsets. **In** ~~As of December 31,~~ 2022, certain milestones were met which entitled Forma to receive a $ 17. 5 million milestone ~~payment~~ **payments** ~~, of which, $ 15~~ . ~~0 million~~ **No new milestone** was **met in 2023** ~~outstanding and included within accounts payable on our balance sheet~~ . For further discussions ~~of~~ **including** ~~the~~ **other** ~~license~~ **recent developments on REZLIDIA (olutasidenib), please refer to the " REZLIDHIA (olutasidenib) in AML, Other Hematologic Cancers** and ~~transition services agreement~~ **Glioma " and " Commercial Products – REZLIDHIA in R / R AML** with **mIDH1** ~~Forma, see " Note 4- Sponsored Research and License Agreements and Government Contract~~ " **section s** ~~to our " Notes to Financial Statements " contained~~ in ~~" Part II,~~ Item **1** ~~8, Financial Statements and Supplementary Data "~~ of this Annual Report on Form 10- K **, below. GAVRETO (pralsetinib) in metastatic RET fusion- positive NSCLC and advanced thyroid cancersOn February 22, 2024, we entered into an Asset Purchase Agreement with Blueprint to purchase certain assets comprising the right to research, develop, manufacture and commercialize GAVRETO (pralsetinib) in the US. Under the terms of the agreement, we agreed to pay Blueprint a purchase price of $ 15. 0 million, $ 10. 0 million of which is payable upon our first commercial sale of GAVRETO (pralsetinib) and an additional $ 5. 0 million of which is payable on the first anniversary of the closing date of the agreement, subject to certain conditions. Blueprint is also eligible to receive up to $ 97. 5 million in future commercial milestone payments and up to $ 5. 0 million in future regulatory milestone payments, in addition to tiered royalties ranging from 10 % to 30 %. Simultaneously and in conjunction with entering into the Asset Purchase Agreement, we also entered into certain supporting agreements, including a customary transition agreement, pursuant to which, during the transition period, Blueprint will transition regulatory and distribution responsibility for GAVRETO (pralsetinib) to us. We also agreed to purchase certain drug product inventories from Blueprint. We believe GAVRETO will be highly synergistic with our current product portfolio, and we expect to leverage our existing commercial infrastructure to ensure current and newly prescribed GAVRETO patients have continued access to this important treatment option. We intend to distribute and market GAVRETO for approved indications in RET fusion- positive NSCLC and advanced thyroid cancers, and we expect to complete the transition of the asset and to start recognizing product sales in the third quarter of 2024. 5GAVRETO (pralsetinib) is a once daily, small molecule, oral, kinase inhibitor of wild- type RET and oncogenic RET fusions. Currently, GAVRETO (pralsetinib) is one of only two approved RET inhibitors on the market for patients. GAVRETO is approved by the FDA for the treatment of adult patients with metastatic RET fusion- positive NSCLC as detected by an FDA- approved test. GAVRETO is also approved for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion- positive thyroid cancer who require systemic therapy and who are radioactive iodine- refractory (if radioactive iodine is appropriate). This indication was approved by the FDA under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial. Discussions with the FDA regarding confirmatory requirements are ongoing. GAVRETO has been co- marketed by Blueprint and Genentech, a member of Roche Group (Roche), to patients in the US since September 2020 pursuant to a collaboration agreement between Blueprint and Roche, which was terminated effective in February 2024. The patent portfolio covering pralsetinib contains patents and patent applications directed to compositions of matter for pralsetinib, including solid forms, formulations, and methods of use and manufacture. Pralsitenib is covered as a composition of matter in a US issued patent that has an expiration date in November 2036 and subject to extensions. Patents that have been issued or are expected to be issued covering pralsetinib will have statutory expiration dates between 2036 and 2041. Patent term adjustments, patent term extensions, and supplementary protection certificates could result in later expiration dates. The FDA granted GAVRETO (pralsetinib) new chemical entity exclusivity until September 2025 and orphan drug exclusivity until September 2027 with respect to the approval for treatment of adult patients with metastatic RET fusion- positive NSCLC as detected by an FDA- approved test. The FDA also granted GAVRETO (pralsetinib) two orphan drug exclusivities until December 2027 with respect to FDA approval for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion- positive thyroid cancer who require systemic therapy and who are radioactive iodine- refractory (if radioactive iodine is appropriate), and for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET- mutant medullary thyroid carcinoma who require systemic therapy. RET is involved in the physiological development of some organ systems. RET is a receptor tyrosine kinase that activates multiple downstream pathways involved in cell proliferation and survival. RET can be activated by mutation or when a portion of the RET gene that encodes the kinase domain is joined to part of another gene creating a fusion gene that encodes an aberrantly activated RET fusion protein. RET alterations, such as fusions or mutations, drive the growth of multiple tumor types. It is estimated that over 230, 000 adult patients in the US will be diagnosed with lung cancer in 2024. NSCLC is the most common type of lung cancer in the US accounting for 80- 85 % of all lung cancer diagnoses. RET activating fusions are key disease drivers in NSCLC. RET fusions are implicated in approximately 1- 2 % of patents with NSCLC. GAVRETO (pralsetinib) faces competition for RET fusion- positive NSCLC and advanced thyroid cancers from Lilly' s selpercatinib. In addition, other commercially available therapies used to treat RET fusion- positive NSCLC include cabozantanib and platinum- based chemotherapy regimens with or without pembrolizumab,**

atezolizumab, nivolumab / ipilumumab, cemiplimab or tremelimumab- durvalumab. Pralsetinib may also face competition from other drug candidates in development for RET- altered cancers, as well as multi- kinase inhibitors with RET activity being evaluated in clinical trials . R289, an Oral IRAK1 / 4 Inhibitor for ~~Autoimmune, Inflammatory and~~ Hematology- Oncology **, Autoimmune, and Inflammatory** DiseasesWe continue to advance the development of our IRAK1 / 4 **inhibitor** program, ~~completing~~ **following** the evaluation of a new pro- drug formulation of R835, R289, in single- ascending and multiple ascending dose studies with positive safety results in 2021. In January 2022, we received clearance from the FDA on our clinical trial design to explore R289 in ~~low~~ **lower** - risk MDS. The open- label, Phase 1b trial will determine the tolerability and preliminary efficacy of R289 in patients with ~~low~~ **lower** - risk MDS who are refractory or resistant to prior therapies. In December 2022, we announced that we dosed the first patient in our Phase 1b trial of R289. The Phase 1b trial of R289 is expected to enroll approximately ~~22~~ **34** patients **(up to 24 participants with lower risk MDS who receive study treatment in dose escalation phase, and up to 10 participants with lower- risk MDS who receive study treatment in the dose expansion phase)** . The primary objective of the trial is ~~safety~~ **6safety** , with secondary and exploratory objectives to assess preliminary efficacy and characterize the pharmacokinetic and pharmacodynamic profile of R289. The safety and efficacy data from this Phase 1b trial, along with the safety and pharmacokinetic / pharmacodynamic data from the completed first- in- human study in heathy volunteers, are intended to be used to determine the recommended Phase 2 dose for future clinical development of R289 targeting lower- risk MDS. **To date, target enrollment in the second cohort of the trial has been completed and we are currently enrolling patients in the third cohort. Preliminary results are expected by the end of 2024. REZLIDHIA (olutasidenib) in AML, Other Hematologic Cancers and GliomaIn December 2023, we entered into a Strategic Collaboration Agreement with the University of Texas MD Anderson Cancer Center (MD Anderson), a comprehensive cancer research, treatment, and prevention center. The collaboration will expand our evaluation of REZLIDHIA (olutasidenib) in AML and other hematologic cancers. Under the Strategic Collaboration Agreement, we will jointly lead the clinical development efforts with MD Anderson to evaluate the potential of olutasidenib to treat newly diagnosed and R / R patients with AML, higher- risk MDS, and advanced myeloproliferative neoplasms, in combination with other agents. The collaboration will also support the evaluation of olutasidenib as monotherapy in patients with IDH1 mutated clonal cytopenia of undermined significance and lower- risk MDS, as well as maintenance therapy in post- hematopoietic stem cell transplant patients. Under the Strategic Collaboration Agreement, we will provide MD Anderson the study materials and $ 15. 0 million in time- based milestone payments as compensation for services to be provided for the studies, over the five- year collaboration term, unless terminated earlier as provided for in the agreement. In December 2023, we provided $ 2. 0 million funding to MD Anderson. In January 2024, we announced our collaboration with Collaborative Network for Neuro- Oncology Clinical Trials (CONNECT), an international collaborative network of pediatric cancer centers, to conduct a Phase 2 clinical trial to evaluate REZLIDHIA (olutasidenib) in combination with temozolomide as maintenance therapy in newly diagnosed pediatric and young adult patients with high- grade glioma (HGG) harboring an IDH1 mutation. Under the collaboration, CONNECT will include olutasidenib in CONNECT' s TarGet- D, a molecularly guided Phase 2 umbrella clinical trial for HGG. Our sponsored arm will study post- radiotheraphy administration of olutasidenib in combination with temozolomide followed by olutasidenib monotheraphy as maintenance treatment in newly diagnosed pediatric and young adult patients (less than 39 years old) with IDH1 mutation positive HGG, including diffuse intrinsic pontine glioma, an aggressive brain tumor with limited treatment options. Under the collaboration, we will provide funding up to $ 3. 0 million and study material over the four- year collaboration. Global Strategic Partnership with LillyLilly is continuing to advance R552, an investigational, potent and selective RIPK1 inhibitor. Lilly has initiated the Phase 2a trial studying R552 in adult patients with moderately to severely active rheumatoid arthritis. The trial plans to enroll 100 patients globally. RIPK1 is implicated in a broad range of key inflammatory cellular processes and plays a key role in tumor necrosis factor signaling, especially in the induction of pro- inflammatory necroptosis. The program also includes RIPK1 compounds that cross the blood- brain barrier (central nervous system (CNS)- penetrants) to address neurodegenerative diseases such as Alzheimer' s disease and amyotrophic lateral sclerosis. Under the Lilly Agreement, we are responsible for 20 % of the development costs for R552 in the US, Europe, and Japan, up to a specified cap. Lilly is responsible for funding the remainder of all development activities for R552 and other non- CNS disease development candidates. Under the Lilly Agreement, we have the right to opt- out of co- funding the R552 development activities in the US, Europe and Japan at two different specified times and as a result receive lesser royalties from sales. Prior to us providing our first opt- out notice as discussed below, we were required to fund our share of the R552 development activities in the US, Europe, and Japan up to a maximum funding commitment of $ 65. 0 million through April 1, 2024. On September 28, 2023, we entered into an amendment to the Lilly Agreement which provides, among other things, that if we exercise our first opt- out right, we have the right to opt- in to co- funding of R552 development, upon us providing notice to Lilly within 30 days of certain events, as specified in the Lilly Agreement. If we decide to exercise our opt- in right, we will be required to continue to share in global development costs, and if we later exercise our second opt- out right (no later than April 1, 2025), our share in global development costs will be up to a specified cap through December 31, 2025, as provided for in the Lilly Agreement. On September 29, 2023, we provided 7the first opt- out notice to Lilly. We will continue to fund our share of the R552 development activities up to $ 22. 6 million through April 1, 2024 as provided for in the amended Lilly Agreement. Through December 31, 2023, Lilly billed us $ 18. 6 million of the funding development costs.** Fostamatinib in Hospitalized COVID- 19 ~~patientsIn~~ **patientsWe** ~~April~~ **previously announced in November** ~~2021~~ **2022 the** ~~, we reported positive~~ top- line results from ~~a multi- center, Phase 2 clinical trial sponsored by~~ the ~~NIH / NHLBI, evaluating the safety of fostamatinib, our oral SYK inhibitor, for the treatment of hospitalized patients with COVID- 19. The trial met its primary endpoint of safety comparable to standard of care (SoC) and showed broad and consistent improvement in numerous efficacy~~

endpoints, including mortality, ordinal scale assessment, and number of days in the intensive care unit (ICU). In May 2021, the trial data were submitted as part of a request for an Emergency Use Authorization (EUA) from the FDA for fostamatinib as a treatment for hospitalized patients with COVID- 19. In August 2021, the FDA informed us that the clinical data submitted from the NIH / NHLBI- sponsored Phase 2 trial were insufficient to support an EUA. In September 2021, the data from the NIH / NHLBI- sponsored Phase 2 trial was published in Clinical Infectious Diseases, an official publication of the Infectious Disease Society of America. 5In July 2022, we completed the enrollment of our FOCUS Phase 3 clinical trial to evaluate the safety and efficacy of fostamatinib in hospitalized COVID- 19 patients without respiratory failure that have certain high- risk prognostic factors with 280 patients. The trial had originally targeted a total of 308 patients; however , we determined the trial would be sufficiently powered with 280 patients to potentially provide a clinically meaningful result and determine the efficacy and safety of fostamatinib in hospitalized COVID- 19 patients. On November 1, 2022, we announced the top- line results from the FOCUS trial. The trial approached but did not meet statistical significance (p = 0. 0603) in the primary efficacy endpoint of the number of days on oxygen through Day 29. All prespecified **Upon further analysis, we discovered an error by the biostatistical contract research organization (CRO) in the application of a statistical stratification factor. The biostatistical CRO misinterpreted receipt of prior COVID- 19 treatment of interest 14 days before randomization (regardless of continuation post randomization), as those medications taken 14 days before the date of randomization and ended prior to the day of randomization. After correcting for this statistical error, the primary endpoint of the study was met; those who received fostamatinib had lower mean days on oxygen than those who received placebo (4. 8 vs. 7. 6 days, p = 0. 0136). Further, fostamatinib showed significance or trend towards significance in all** secondary endpoints **in of reducing mortality and morbidity compared to placebo after correcting for** the study numerically favored **error. The results were presented at the IDWeek 2023 held on October 11- 15, 2023 in Boston, Massachusetts. During our continued analysis regarding** fostamatinib over placebo, including mortality, time to sustained recovery, change in ordinal scale assessment **hospitalized COVID- 19 patients** , **we provided** and number of days in the **updated analysis to** ICU. We are evaluating the opportunity and discussing next steps with the FDA and in collaboration with our partner, the US Department of Defense **(DOD)** . In June **Given the end of the federal COVID- 19 Public Health Emergency (PHE) in May** 2021 **2023 , and based on feedback from the FDA, DOD and other advisors regarding the program' s regulatory requirements, costs, timeline and potential for success** , we announced that fostamatinib has been selected **decided not to submit an Emergency Use Authorization (EUA)** for - **or** the NIH **sNDA. The Accelerating COVID- 19 Therapeutic Inventions and Vaccines Phase 2 / 3 trial (** ACTIV- 4 Host Tissue Trial in hospitalized patients with **), conducted and sponsored by the National Institute of Health (NIH) / National Heart, Lung, and Blood Institute (NHLBI), is a randomized, placebo- controlled trial of therapies, including fostamatinib, targeting the host response to** COVID- 19 **in hospitalized patients** . The ACTIV- 4 Host Tissue Trial **evaluated** , initiated and funded by NHLBI, is a randomized, placebo- controlled trial of therapies, including fostamatinib, targeting the host response to COVID- 19 in hospitalized patients. The ACTIV- 4 Host Tissue Trial is evaluating fostamatinib in a targeted population of approximately 600 hospitalized patients with COVID- 19, 300 fostamatinib versus 300 placebo. An **During the first quarter of 2023, an** interim analysis of the trial was completed by the Data and Safety Monitoring Board **(DSMB)** with a recommendation for the trial to continue. Fostamatinib in wAIHA In June **September** 2022 **2023** , we announced top **the DSMB recommended that the fostamatinib study arm of the ACTIV - 4 Host Tissue** line efficacy and safety data results from our FORWARD study, a Phase 3 pivotal trial **Trial platform cease** of fostamatinib, an oral SYK inhibitor, in patients with wAIHA, which we initiated in March 2019. We completed the enrollment of our FORWARD study in November 2021 with 90 patients enrolled and completed the treatment period for the last patient under the study in April 2022 . **Based on** The results of the trial did not demonstrate statistical significance in the primary efficacy endpoint of durable hemoglobin response in the overall study population. For more detailed discussions of the results of the trial, refer to " Clinical Stage Programs " section below. We conducted an in- depth analysis of these -- **the DSMB** data to better understand differences in patient characteristics and outcomes and submitted these findings to the FDA. In October 2022, we announced that we received guidance from the FDA ' s review of **a conditional power analysis, the DSMB determined that** these **there** findings. Based **was an extremely low likelihood of fostamatinib providing benefits related to the primary outcome (oxygen free days) or other secondary outcomes in patients hospitalized and** on **oxygen therapy for COVID- 19. No safety concerns were identified. The NIH / NHLBI concurs with** the result of **DSMBs recommendation and has asked** the trial **investigators** and the guidance from the FDA, we did not file a supplemental New Drug Application (sNDA) for this indication. Global Strategic Partnership with LillyWe have a global exclusive license and collaboration agreement with Lilly (the Lilly Agreement) entered in February 2021, to **cease enrollment** develop and commercialize R552 , **complete follow** a RIPK1 inhibitor, for the treatment of non - central nervous system (non- CNS) diseases. In addition, the collaboration is aimed at developing additional RIPK1 inhibitors for the treatment of central nervous system (CNS) diseases. Pursuant to the terms of the license agreement, we granted to Lilly the exclusive rights to develop and commercialize R552 and related RIPK1 inhibitors in all indications worldwide. We are responsible for 20 % of the development costs for R552 in the US, Europe, and Japan, up to a specified cap. Lilly is responsible for **participants already enrolled** funding the remainder of all development activities for R552 and other non- CNS disease development candidates. We have the right to opt- out of co- funding the R552 development activities in the US , Europe and **complete study closeout** Japan at two different specified times . **The** If we exercise our first opt- out right (no later than September 30, 2023), we are required to fund our share of the R552 development activities in the US, Europe, and Japan up to a maximum funding commitment of $ 65. 0 million through April 1, 2024. Through December 31, 2022, Lilly billed us $ 15. 1 million of the funding development costs and the amounts were fully - **full study data** paid as of December 31, 2022. Under the Lilly Agreement, we were responsible for performing and funding initial discovery and identification of CNS disease development candidates, and following candidate selection, Lilly will be **analyzed** responsible for performing and funding all future development and commercialization of the CNS disease development candidates. In June

2022, Lilly provided notice of continuance pursuant to the terms of the Lilly Agreement, whereby Lilly elected its option to lead the identification and selection of CNS penetrant lead candidate. Lilly is continuing to advance R552, with an **and disseminated** initial Phase 2a trial in active rheumatoid arthritis. This initial Phase 2a trial in approximately 100 patients with moderately to severely active rheumatoid arthritis is anticipated to 6begin in the first half of 2023 and will involve global recruitment. RIPK1 is implicated in a broad range of key inflammatory cellular processes and plays a key role in Tumor Necrosis Factor signaling, especially in the induction of pro- inflammatory necroptosis. The program also includes RIPK1 compounds that cross the blood-brain barrier (CNS- penetrants) to address neurodegenerative diseases such as **previously planned** Alzheimer' s disease and Amyotrophic Lateral Sclerosis. The Phase 2a trial analysis is expected by the end of 2024 . Patent Infringement LawsuitIn June 2022, we received a notice letter regarding an Abbreviated New Drug Application (ANDA) submitted to the FDA by Annora Pharma Private Limited (Annora), requesting approval to market a generic version of TAVALISSE. On **In** July 25, 2022, we filed a lawsuit in the **US** United States District Court for the District of New Jersey against Annora and its subsidiaries for infringement of certain of our US patents **. Litigation continues, and no trial date is currently set** . For a more detailed discussion of this litigation matter, see " Part I, Item 3, Legal Proceedings " of this Annual Report on Form 10- K. Update on Current and Potential Future Impact of COVID- 19 on our BusinessThe COVID- 19 pandemic has adversely impacted , and may continue to adversely impact, our business and operations. **Although** The degree to which the **World Health Organization declared the end of** COVID- 19 **PHE in May 2023, the degree to which another global** pandemic may affect our **future** business and operations in the future **and financial condition** will depend on developments that are highly uncertain and beyond our knowledge or control. **As** The ultimate potential future impact of the COVID- 19 pandemic on our business and financial condition is highly uncertain and subject to change, and as such, we cannot ascertain the full extent of the **future** impacts **it may have** on our sales of our products, our ability to continue to secure new collaborations and support existing collaboration efforts with our partners and our clinical and regulatory activities. Periodic resurgence of COVID- 19 cases negatively impacted and may continue to impact our ability to grow our product sales. When COVID- 19 cases surged, we have observed reduced patient- doctor interactions and our representatives had fewer visits with health care providers. We continue to monitor the effects of the COVID- 19 pandemic and continues to undertake safety measures to keep our staff, patients, investigators and stockholders safe. We have a Crisis Management Team (CMT) that implements and monitors our business continuity plans to prevent or minimize business disruption and ensure the safety and well- being of our personnel. We also have a COVID- 19 Headquarters Policy (Plan) in place to provide guidelines when working onsite. We continue to evaluate the workplace for compliance with the local, state and federal guidance and may modify or update at any time to ensure the safety of our employees, contractors and visitors. During the first quarter of 2022, we updated our Plan as we move towards a hybrid schedule, reinstituting more in- person interactions beginning April 2022. We endeavor to provide the safest and most effective work environment under the circumstances, but we cannot guarantee that employees who come to the office will not be exposed to COVID- 19 while at the office. It will be the responsibility of all employees to participate and cooperate in safety and cleaning protocols. We expect all employees, contractors, and visitors to our facility to comply with the Plan. With respect to our supply chain, we did not experience significant disruptions in the supply chain for our commercial product . See also " Part I, Item 1A, Risk Factors " of this Annual Report on Form 10- K for additional information on risks and uncertainties related to the ongoing COVID- 19 pandemic. 7StrategyOur **8StrategyOur** goal is to establish ourselves as a successful commercial stage biopharmaceutical company with significant development capabilities. We aim to expand our commercial business in the US on our own and globally through partnerships. We **recently** expanded our hematology - **and** oncology portfolio with our recently launched commercial **commercialized** product REZLIDHIA **and our upcoming commercialization of GAVRETO later this year** , which is **we believe are** highly synergistic with **and complementary to** our existing hematology - **and** oncology focused commercial infrastructure. We continue our research **to maintain a strong commercial** and **medical affairs team in the US to enable us to execute successfully on our commercialization strategy to grow TAVALISSE in chronic ITP, REZLIDHIA in mIDH1 R / R AML, and GAVRETO in NSCLC and advanced thyroid cancers. For the expansion of fostamatinib outside of the US, we entered into partnerships. We continue our** development of novel therapies designed to significantly improve the lives of patients with hematological disorders and cancer. We continue to maintain a strong commercial team in the US to enable us to execute successfully on our commercialization strategy for TAVALISSE in chronic ITP and REZLIDHIA for treatment of R / R AML patients with a susceptible IDH1 mutation as detected by an FDA- approved test. We entered into partnerships for the expansion of fostamatinib outside of US, and will be focusing on the further development of **our products** the utility of fostamatinib and olutasidenib in other indications on our own or through our partners. We also aim to expand **our portfolio with additional commercial products and / or additional candidates for** our development pipeline **,** on our own and / or **in partnership** with partnerships with pharmaceuticals - **pharmaceutical** and biotechnology companies to further develop **as well as academic institutions** and **government organizations** market additional product candidates . In particular, the key elements that we believe are value drivers, which we plan to continue to execute include: ● growing sales of TAVALISSE in **chronic** the estimated over $ 2. 0 billion global ITP **and** market; ● expanding our hematology- oncology portfolio with REZLIDHIA **in mIDH1** for treatment of R / R AML **; ● successfully commercializing** patients with a susceptible IDH1 mutation, a well- identified patient population of approximately 1, 000 patients, part of an **and growing sales** AML market estimated to have an incidence of **GAVRETO** 20, 000 cases in the US **in NSCLC** and **advanced thyroid cancers** estimated 120, 000 cases globally ; and ● expanding our development pipeline on our own and / or with collaboration partner (s). Our Product PortfolioThe following table summarizes our portfolio: 8Commercial **9Commercial** ProductsTAVALISSE / Fostamatinib in ITPDisease background. Chronic **ITPChronic** ITP affects an estimated 81, 300 adult patients in the US. In patients with ITP, the immune system attacks and destroys the body' s own blood platelets, which play an active role in blood clotting and healing. ITP patients can suffer extraordinary bruising, bleeding and fatigue as a result of low platelet counts. Current therapies for ITP include steroids, blood platelet production boosters that imitate thrombopoietin (TPO) and

splenectomy ~~. Orally- available fostamatinib program~~ . Taken in tablet form, fostamatinib blocks the activation of SYK inside immune cells. ITP is typically characterized by the body producing antibodies that attach to healthy platelets in the blood stream. Immune cells recognize these antibodies and affix to them, which activates the SYK enzyme inside the immune cell, and triggers the destruction of the antibody and the attached platelet. When SYK is inhibited by fostamatinib, it interrupts this immune cell function and allows the platelets to escape destruction. The results of our Phase 2 clinical trial, in which fostamatinib was orally administered to 16 adults with chronic ITP, published in Blood, showed that fostamatinib significantly increased the platelet counts of certain ITP patients, including those who had failed other currently available agents. Our Fostamatinib for Immune Thrombocytopenia (FIT) Phase 3 clinical program had a total of 150 ITP patients which were randomized into two identical multi- center, double- blind, placebo- controlled clinical trials. The patients were diagnosed with persistent or chronic ITP, and had blood platelet counts consistently below 30, 000 per microliter of blood. Two- thirds of the subjects received fostamatinib orally at 100 mg twice daily (bid) and the other third received placebo on the same schedule. Subjects were expected to remain on treatment for up to 24 weeks. At week four of treatment, subjects who failed to meet certain platelet counts and met certain tolerability thresholds could have their dosage of fostamatinib (or corresponding placebo) increased to 150 mg bid. The primary efficacy endpoint of this program was a stable platelet response by week 24 with platelet counts at or above 50, 000 per microliter of blood for at least four of the final six qualifying blood draws. In August ~~2015, the FDA granted our request for Orphan Drug designation for fostamatinib for the treatment of ITP. In August~~ 2016, we announced the results of the first FIT study, reporting that fostamatinib met the study' s primary efficacy endpoint. The study showed that 18 % of patients receiving fostamatinib achieved a stable platelet response compared to none receiving a placebo control ~~(p = 0. 0261)~~ . In October 2016, we announced the results of the second FIT study, reporting that the response rate (16 % in the treatment group, versus 4 % in the placebo group) was consistent with the first study, although the difference was not statistically significant. In the ITP double- blind studies, the most commonly ~~–~~reported adverse reactions occurring in at least 5 % of patients treated with TAVALISSE were diarrhea, hypertension, nausea, dizziness, increased alanine aminotransferase, increased aspartate aminotransferase, respiratory infection, rash, abdominal pain, fatigue, chest pain, and neutropenia. Serious adverse drug reactions occurring in at least 1 % of patients treated with TAVALISSE in the ITP double- blind studies were febrile neutropenia, diarrhea, pneumonia, and hypertensive crisis. **A post- hoc analysis from our Phase 3 clinical program in adult patients with chronic ITP, highlighting the potential benefit of using TAVALISSE in earlier lines of therapy, was published in the British Journal of Haematology in July 2020. In addition, a report describing the long- term safety and durable efficacy of TAVALISSE with up to five years of treatment was published in Therapeutic Advances in Hematology in 2021. The FDA granted our request for orphan drug designation for fostamatinib for the treatment of ITP in August 2015.** TAVALISSE was approved by the FDA in April 2018 for the treatment of ITP in adult patients who have had an insufficient response to a previous treatment, and successfully launched in the US in May 2018. In January 2020, the European Commission (EC) granted **a centralized** ~~our Marketing Authorization Application (MAA~~ **MA** ~~) in Europe~~ for fostamatinib (TAVLESSE) **valid throughout the European Union (EU) and in the UK, after the departure of the UK from the EU,** for the treatment of chronic ITP in adult patients who are refractory to other treatments ~~. In February 2020, Kissei Pharmaceutical Co., Ltd. (Kissei) was granted orphan drug designation from the Japanese Ministry of Health, Labor and Welfare for R788 (fostamatinib) in chronic idiopathic thrombocytopenic purpura for fostamatinib in chronic ITP~~ . In December 2022, Japan' s Pharmaceuticals and Medical Devices Agency (PMDA) approved the NDA for fostamatinib in chronic ITP. A post- hoc analysis from our..... TAVALISSE in Canada and Israel. Competitive **10Competitive** landscape for TAVALISSEOur industry is intensely competitive and subject to rapid and significant technological change. TAVALISSE is competing with other existing therapies. In addition, a number of companies are pursuing the development of pharmaceuticals that target the same diseases and conditions that we are targeting. For example, there are existing therapies and drug candidates in development for the treatment of ITP that may be alternative therapies to TAVALISSE. Currently, corticosteroids remain the most common first line therapy for ITP, occasionally in conjunction with intravenous immunoglobulin (IVIg) or anti- Rh (D) to help further augment platelet count recovery, particularly in emergency situations. However, it has been estimated that frontline agents lead to durable remissions in only a small percentage of newly ~~–~~diagnosed adults with ITP. Moreover, concerns with steroid- related side effects often restrict therapy to approximately four weeks. As such, many patients progress to persistent or chronic ITP, requiring other forms of therapeutic intervention. In long- term treatment of chronic ITP, patients are often cycled through several therapies over time in order to maintain a sufficient response to the disease. Other approaches to treat ITP are varied in their mechanism of action, and there is no consensus about the sequence of their use. Options include splenectomy, thrombopoietin receptor agonists (TPO- ~~RAs~~ **Ras**) and various immunosuppressants (such as rituximab). The response rate criteria of the above- mentioned options vary, precluding a comparison of response rates for individual therapies. Even with the above treatment options, a significant number of patients remain severely thrombocytopenic for long durations and are subject to risk of spontaneous or trauma- induced hemorrhage. The addition of fostamatinib to the currently available treatment options could be beneficial because it has a different mechanism of action than any of the therapies that are currently available. Fostamatinib is a potent and relatively selective SYK inhibitor, and its inhibition of Fc receptors and B- cell receptors of signaling pathways make it a potentially broad immunomodulatory agent. Other products in the US that are approved by the FDA to increase platelet production through binding to TPO receptors on megakaryocyte precursors include PROMACTA ® (Novartis International AG (Novartis)), Nplate ® (Amgen, Inc.) and DOPTELET ® (Swedish Orphan Biovitrum AB). In the longer term, we may eventually face competition from potential manufacturers of generic versions of our marketed products, including the proposed generic version of TAVALISSE that is the subject of an ANDA submitted to the FDA by Annora, which, if approved and allowed to enter ~~10the~~ -- **the** market, it could result in significant decreases in the revenue derived from sale of TAVALISSE and thereby materially harm our business and financial condition. ~~Fostamatinib~~ **Commercial activities, including sales and marketingOur marketing and sales efforts are focused on hematologists and hematologist-**

oncologists in ~~Global MarketsWe~~ the US who manage chronic adult ITP patients.We have a fully integrated commercial team consisting of sales,marketing,market access,and commercial operations functions.Our sales team promotes our products in the US using customary pharmaceutical company practices,and we concentrate our efforts on hematologists and ~~hematologists~~ **hematologist** - oncologists.Our products are sold initially through third- party wholesale distribution and specialty pharmacy channels and group purchasing organizations before being ultimately prescribed to patients.To facilitate our commercial activities in the US,we also enter into arrangements with various third parties,including advertising agencies,market research firms and other sales- support- related services as needed.We believe that our commercial team and distribution practices are adequate to ensure that our marketing efforts reach relevant customers and deliver our products to patients in a timely and compliant fashion.Also,to help ensure that all eligible patients in the US have appropriate access to our products,we have established a reimbursement and patient support program called Rigel OneCare (ROC).Through ROC,we provide co- pay assistance to qualified,commercially insured patients to help minimize out- of- pocket costs and ~~also~~ provide free product to uninsured or under- insured patients who meet certain established clinical and financial eligibility criteria.In addition,ROC is designed to provide reimbursement support,such as information related to prior authorizations,benefits investigations and appeals. **We** have entered into various license **and commercial** agreements to commercialize fostamatinib globally **, but** ~~. The following describes the arrangements~~ we ~~have in place with~~ **retain the global rights to fostamatinib outside of the respective territories under such license and commercial agreements. Our collaborative partner** Grifols **S. A. (Grifols) launched TAVLESSE in the UK and certain countries in 11Europe including Germany** , ~~Kissei~~ **France** , **Italy and Spain, and continues a phased rollout across the rest of Europe. Our collaborative partner** Medison Pharma Trading AG (Medison Canada) and Medison Pharma Ltd. (Medison Israel, and together with Medison Canada, Medison) ~~,~~ **launched TAVALISSE in Canada** and ~~Knight Therapeutics International SA~~ **Israel. Further, our collaborative partner Kissei Pharmaceutical Co., Ltd.** (~~Knight~~ **Kissei**) **launched TAVALISSE in Japan** ~~. We retain the global rights to fostamatinib outside of the Grifols, Kissei, Medison and Knight territories~~ . Fostamatinib in Europe / ~~TurkeyIn~~ **TurkeyWe have** ~~January 2019, we entered into~~ a commercialization license agreement with Grifols ~~with~~ **entered in January 2019, for** exclusive rights to commercialize fostamatinib for human diseases, including chronic ITP and **autoimmune hemolytic anemia (** AIHA **)** , and non- exclusive rights to develop, fostamatinib in their territory. Grifols territory includes Europe, the UK, Turkey, the Middle East, North Africa and Russia (including Commonwealth of Independent States). We are responsible for performing and funding certain development activities for fostamatinib for ITP and AIHA and Grifols is responsible for all other development activities for fostamatinib in such territories. We remain responsible for the manufacturing and supply of fostamatinib for all development and commercialization activities under the agreement. Under the terms of the agreement, we received an upfront cash payment of $ 30. 0 million and will be eligible to receive regulatory and commercial milestones of up to $ 297. 5 million. In January 2020, the EC granted a MA for fostamatinib for the treatment of chronic ITP in adult patients who are refractory to other treatments. With this approval, we received a $ 20. 0 million non- refundable milestone payment, consisted of a $ 17. 5 million payment due upon **Market Authorization Application (** MAA **)** approval by the EMA of fostamatinib for the first indication and a $ 2. 5 million creditable advance royalty payment due upon EMA approval of fostamatinib in the first indication. We ~~will~~ **are** also **entitled to** receive ~~tiered~~ **stepped double- digit** royalty payments ~~ranging from the mid- teens to~~ **based on tiered net sales which may reach** 30 % of net sales of fostamatinib in the Grifols ~~Territory~~ **territory** . Fostamatinib in Japan / Asia **We have** ~~In October 2018, we entered into~~ an exclusive license and supply agreement with Kissei **entered in October 2018,** to develop and commercialize fostamatinib in all current and potential indications in **Kissei' s territory, which includes** Japan, China, Taiwan and the Republic of Korea. Kissei is a Japan- based pharmaceutical company addressing patients' unmet medical needs through its research, development and commercialization efforts, as well as through collaborations with partners. Under the terms of the agreement, we received an upfront cash payment of $ 33. 0 million, with the potential for an additional $ 147. 0 million in development and commercial milestone payments, and will receive product transfer price payments in the mid to upper twenty percent range based on tiered net sales for the exclusive supply of fostamatinib. Kissei receives exclusive rights to fostamatinib in ITP and all future indications in **Kissei' s territory** ~~Japan, China, Taiwan, and the Republic of Korea~~ . In September 2019, Kissei initiated a Phase 3 trial in Japan of fostamatinib in adult **Japanese** patients with chronic ITP. The efficacy and safety of orally administered fostamatinib was assessed by comparing it with placebo in a randomized, double- blind study. Japan has the third highest prevalence of chronic ITP in the world behind the US and Europe. In February 2020, Kissei was granted orphan drug designation from the Japanese Ministry of Health, Labor and Welfare for R788 (fostamatinib) in chronic ITP. In December 2021, Kissei reported positive top- line results for a Phase 3 clinical trial ~~of fostamatinib in adult Japanese patients with chronic ITP~~ , meeting its primary endpoint. The Phase 3 clinical trial showed that patients receiving fostamatinib achieved a stable platelet response significantly higher than patients receiving a placebo control. ~~A stable platelet response was defined as achieving greater than or equal to 50, 000 platelets per microliter of blood on at least four of the last six scheduled visits between weeks 14 and 24 of treatment.~~ Based on the positive Phase 3 results, in April 2022, Kissei submitted an NDA to Japan' s PMDA for fostamatinib in chronic ITP. With this milestone event, ~~during the second quarter of 2022,~~ we received $ 5 **. 0 million non- refundable and non- creditable payment from Kissei. In December 2022, Japan' s PMDA approved TAVALISSE for the treatment of chronic ITP. With this milestone event, we received $ 20** . 0 million non- refundable and non- creditable payment from Kissei based on the terms of our collaboration agreement ~~, and such amount was recognized as revenue in the second quarter of 2022~~ . In ~~December~~ **April** ~~2022~~ **2023** , **Kissei launched** ~~Japan' s PMDA approved~~ TAVALISSE for ~~the treatment of~~ chronic ITP ~~. With this milestone event, we are entitled to receive $ 20. 0 million non- refundable and non- creditable 11payment from Kissei based on the terms of our collaboration agreement, and such amount was recognized as revenue~~ in **Japan** ~~the fourth quarter of 2022. The amount was subsequently collected in January 2023~~ . Fostamatinib in Canada / Israel **We have two** ~~In October 2019, we entered into~~ exclusive commercial and license agreements with Medison **entered in October 2019,** to commercialize fostamatinib in all potential indications in Canada and Israel. Under

the terms of the agreements, we received an upfront payment of $ 5. 0 million with the potential for approximately $ 35. 0 million in regulatory and commercial milestones. In addition, we will receive royalty payments beginning at 30 % of net sales. Under our agreement with Medison for the Canada territory, we have the option to buy back all rights to the product upon ~~regulatory~~ **12regulatory** approval in Canada for the indication of AIHA. The buyback provision, if exercised, would require both parties to mutually agree on commercially reasonable terms for us to purchase back the rights, taking into account Medison' s investment and the value of the rights, among others. Pursuant to this exclusive commercialization license agreement, in August 2020, we entered into a commercial supply agreement with Medison. In November 2020, Health Canada approved the New Drug Submission for TAVALISSE for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to other treatments. In August 2021, Medison Israel received the licenses for registrational approval from the Ministry of Health, which ~~triggered the first milestone that is the regulatory approval~~ **event entitled us to receive $ 0. 1 million** of ~~the product in Israel for the first indication, for a~~ non- refundable **milestone** payment ~~of $ 0. 1 million~~. In November 2022, Medison Israel made its first commercial sale of TAVALISSE **and obtained its national reimbursement in February 2023**. Fostamatinib in Latin AmericaIn May 2022, we entered into commercial license agreement with Knight **Therapeutics International SA (Knight)** for the commercialization of fostamatinib for approved indications in Latin America, consisting of Mexico, Central and South America, and the Caribbean (Knight territory). Pursuant to such commercial license agreement, we received a $ 2. 0 million one- time, non- refundable, and non- creditable upfront payment, with potential for up to an additional $ 20. 0 million in regulatory and sales- based commercial milestone payments, and will receive twenty- to mid- thirty percent, tiered, escalated net- sales based royalty payments for products sold in the Knight territory. We are also responsible for the exclusive manufacture and supply of fostamatinib for all future development and commercialization activities under a Commercial and Supply Agreement. **In August 2023, Knight submitted the MAA for regulatory approval in Mexico, Colombia and Brazil for fostamatinib for the treatment of adult patients with ITP who had insufficient response to a previous treatment.** REZLIDHIA in R / R AML with **mIDH1mIDH1** ~~mIDH1Disease background. mIDH1~~ alterations are seen in AML **, MDS** , glioma, chondrosarcoma, and intrahepatic cholangiocarcinoma. It is estimated that there are approximately 1, 000 adult patients, a well- identified patient population, with mIDH1 R / R AML, part of an AML market estimated to have an incidence of **approximately** 20, 000 cases in the US and estimated 120, 000 cases globally. Despite having approved treatment options for R / R AML patients who are mIDH1 positive, an unmet need remains. Olutasidenib ~~may represent~~ **, an oral, small molecule drug designed to selectively bind to and inhibit mIDH1, is** a treatment option with durable remissions, reduced QTc potential, and a stable pharmacokinetics profile that enables a consistent drug exposure over time ~~. In July 2022, we entered into a license and transition agreement with Forma for an exclusive license to develop, manufacture and commercialize olutasidenib, Forma' s proprietary inhibitor of mIDH1, for any uses worldwide, including for the treatment of R / R AML and other malignancies. Olutasidenib is an oral, small molecule drug designed to selectively bind to and inhibit mIDH1~~. This targeted agent has the potential to provide therapeutic benefit by reducing 2- hydroxyglutarate levels and restoring normal cellular differentiation. IDH1 is a natural enzyme that is part of the normal metabolism of all cells. When mutated, IDH1 activity can promote blood malignancies and solid tumors. ~~Orally- available olutasidenib~~ **Olutasidenib** ~~program~~ **was designated by the FDA as an orphan drug for the treatment of AML, which provides orphan drug market exclusivity from the time of marketing approval on December 1, 2022**. REZLIDHIA (olutasidenib) is ~~an oral, small molecule, inhibitor of mIDH1~~ designed to bind to and inhibit mIDH1 to reduce 2- hydroxyglutarate levels and restore normal cellular differentiation of myeloid cells. REZLIDHIA is a novel, non- intensive monotherapy treatment in the R / R AML setting demonstrating a CR CRh rate of 35 % in patients with over 90 % of those responders in complete remission. **On** ~~The safety of REZLIDHIA 150 mg administered twice daily was evaluated in 153 adults with relapsed or refractory AML with an IDH1 mutation. 12On~~ December 1, 2022, the FDA has approved REZLIDHIA ~~(olutasidenib)~~ capsules for the treatment of adult patients with R / R AML with IDH1 mutation as detected by an FDA ~~-~~ approved test. On December 22, 2022, we began the commercialization of REZLIDHIA and made it available to patients. The recommended dosage of REZLIDHIA is 150 mg taken orally twice daily until disease progression or unacceptable toxicity. The FDA approval was based on the NDA for olutasidenib for the treatment of m1DH1 R / R AML submitted by Forma, that had a PDUFA action date for the application of February 15, 2023. The NDA application was supported with **a** ~~Forma' s~~ Phase 2 registrational trial for olutasidenib in mIDH1 R / R AML. Interim results from **the** ~~Forma' s~~ Phase 2 registrational trial were reported at the American Society of Clinical Oncology (ASCO) annual meeting in June 2021. The interim results of this trial of 153 patients showed that olutasidenib demonstrated a favorable tolerability profile as a monotherapy in patients with R / R AML who have a ~~susceptible~~ **13susceptible** mIDH1, and achieved a ~~composite~~ complete remission (CR) ~~, or CR~~ plus CR with partial hematologic recovery (CRh) rate of 33. 3 % (30 % CR and 3 % CRh), the primary efficacy endpoint. While a median duration of CR / CRh was not yet reached, a sensitivity analysis (with a hematopoietic stem cell transplant, ~~or HCST,~~ as the end of a response) indicated the median duration of CR / CRh was 13. 8 months. The overall response rate, comprised CR, CRh, ~~CRi~~ **Cri** , partial response, and morphologic leukemia- free state (MLFS), was 46 % and the median duration of **overall response rate (** ORR **)** was 11. 7 months. The median overall survival ~~(OS)~~ was 10. 5 months. For patients with CR / CRh, the median ~~OS~~ **overall survival** was not reached, but the estimated 18- month survival was 87 %. The most frequently reported treatment emergent adverse events were nausea, constipation, increased white blood cell count, decreased ~~RBC~~ **red blood cell** count, pyrexia, febrile neutropenia, and fatigue. **In** ~~Subsequently, Forma presented the first Phase 2 results of olutasidenib used in combination with azacitidine, including safety / tolerability data, at the American Society of Hematology (ASH) Annual Meeting in December 2021. Olutasidenib was designated by the FDA as an orphan drug for the treatment of acute myeloid leukemia in April 2017. On~~ November ~~3,~~ 2022, we announced the presentation of five posters highlighting data from our commercial and clinical hematology- oncology portfolio at the 64th **American Society of Hematology (** ASH **)** Annual Meeting and Exposition which was held in December 2022. An updated interim analysis from the Phase 2 registrational trial of

olutasidenib in patients with R / R AML demonstrated robust efficacy and safety results. The registrational cohort of the Phase 2 trial enrolled 153 patients with mIDH1 R / R AML who received olutasidenib monotherapy 150 mg twice daily. The efficacy evaluable population was 147 patients who received their first dose at least six months prior to the interim analysis cutoff date of June 18, 2021. The primary endpoint was a CR / CRh defined as less than 5 % blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50, 000 / microliter and absolute neutrophil count > 500 / microliter). ~~Overall response rate comprises CR, CRh, CR with incomplete blood count recovery, partial response and MLFS.~~ The results from the updated interim analysis of patients with mIDH1 R / R AML demonstrated a 35 % CR CRh rate with a median duration of 25. 9 months **. The ORR a secondary end point, was 48 %, and was defined as the rate of CR, CRh, CR with incomplete blood count recovery (Cri), partial remission (which required recovery of neutrophil and platelet counts consistent with a CR), or MLFS** . Olutasidenib was effective in a broad range of patients including those with prior high- intensity chemotherapy and / or post- venetoclax. The abstract concluded that the observed activity is clinically meaningful and represents a therapeutic advance in the treatment of this patient population. In this pivotal cohort, olutasidenib was well tolerated with an adverse event profile largely characteristic of symptoms or conditions experienced by patients undergoing treatment for AML or of the underlying disease itself. ~~On~~ **In** November ~~10,~~ 2022, we **also** announced the publication of data in The Lancet Haematology, which summarizes the Phase 1 results of the Phase 1 / 2 trial of olutasidenib. The objectives of the first phase of the multi- center, open- label Phase 1 / 2 trial were to assess the safety, pharmacokinetic and pharmacodynamic profile, and clinical activity of olutasidenib, both as monotherapy and in combination with azacitidine, in patients with treatment- naïve or R / R AML or ~~myelodysplastic syndrome (~~ MDS ~~)~~ harboring IDH1 mutations. The published data suggest that olutasidenib, with or without azacitidine, was well- tolerated and was associated with improvements in clinical efficacy endpoints in patients with mIDH1 AML. This trial showed that olutasidenib has the potential to provide an additional treatment option for mIDH1 AML. In January 2023, we announced that REZLIDHIA ~~(olutasidenib)~~ has been added by the National Comprehensive Cancer Network (NCCN) to the latest NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for AML. REZLIDHIA is now included as a recommended targeted therapy for adult patients with R / R AML with IDH1 mutation. ~~13In~~ **In** February 2023, we announced peer- reviewed publication data in Blood Advances, which summarize clinical results from the Phase 2 registrational trial of REZLIDHIA ~~(olutasidenib)~~ in patients with mIDH1 R / R AML. The published data demonstrate that REZLIDHIA induced durable remissions and transfusion independence with a well- characterized safety profile. The observed efficacy is clinically meaningful and represents a therapeutic advance in this poor prognosis patient population with limited treatment options. REZLIDHIA demonstrated both a high rate of response and an extended median duration of complete response of 28. 1 months, which is more than a year longer than what is reported with the **Standard of Care (** SoC **)** . ~~We plan to pursue strategic actions to further~~ **In June 2023, we announced the second REZLIDHIA publication in Blood Advances, a review article examining the preclinical and clinical** ~~develop~~ **development , and the positioning of** olutasidenib ~~for~~ **in** the **mIDH1 AML** treatment ~~of~~ **landscape. The review concluded that** ~~other~~ -- **the approval** ~~malignancies and expansion~~ of **REZLIDHIA** ~~commercialization. Commercial activities, including sales and marketing~~REZLIDHIA ~~is~~ **a critical addition to the mIDH1 AML treatment landscape** ~~highly synergistic with our existing hematology- oncology focused commercial and medical affairs infrastructure~~ . **Further, the available data support the use of REZLIDHIA as monotherapy in** ~~Our commercial efforts will focus on targeting hematologists and hematologist- oncologists who manage patients with~~ R / R AML **patients who have failed intensive chemotheraphy or venetoclax plus hypomethylating agents (HMA) combination therapy. 14In June 2023, we announced presentation of data from an analysis from the Phase 2 study of REZLIDHIA in 17 patients** with mIDH1 **AML who were previously treated** ~~. We plan to enter collaborations~~ with ~~third~~ **venetoclax. Data was featured in a poster presentation at the European Hematology Association 2023 Hybrid Congress. The data support olutasidenib induced durable remissions in** ~~parties~~ **patients with mIDH1 AML in this poor- prognosis patient population who were R / R** to **venetoclax- based treatment** ~~commercialize REZLIDHIA outside of US~~ . Competitive landscape for REZLIDHIAThere is currently one other product approved in the US for patients with IDH1 mutation. The FDA granted approval to TIBSOVO ® (ivosidenib), an oral targeted IDH1 mutation inhibitor, (i) in July 2018, for adult patients with R / R AML with a susceptible IDH1 mutation, (ii) in May 2019, for newly diagnosed AML with a susceptible IDH1 mutation who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy, (iii) in August 2021, for adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation as detected by an FDA- approved test, ~~and~~ (iv) in May 2022, in combination with azacitidine (azacitidine for injection) for newly diagnosed AML with a susceptible IDH1 mutation, as detected by an FDA- approved test in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy **, and (v) in October 2023, for adult patients with R / R MDS with a susceptible IDH1 mutation, as detected by an FDA- approved test** . In addition, some clinicians may utilize non- targeted treatments for patients with mIDH1 R / R AML, including use of venetoclax combinations, hypomethylating agents, other chemotherapy regimens, or investigational agents that may be available to them. **Commercial activities, including sales and marketingWe believe REZLIDHIA is highly synergistic with our existing hematology- oncology focused commercial and medical affairs infrastructure. Our commercial effort focuses on growing awareness of REZLIDHIA within key institutions, and among targeted HCPs who manage patients with R / R AML with mIDH1. We plan to enter collaborations with third parties to commercialize REZLIDHIA outside of US. GAVRETO (pralsetinib) in metastatic RET fusion- positive NSCLC and advanced thyroid cancersPlease refer to related discussions above under " Business Updates ", titled " GAVRETO (pralsetinib) in metastatic RET fusion- positive NSCLC and advanced thyroid cancers " in Item 1 of this Annual Report on Form 10- K.** Clinical Stage ProgramsR289, an Oral IRAK1 / 4 Inhibitor for ~~Autoimmune, Inflammatory and~~ Hematology- Oncology **, Autoimmune, and Inflammatory DiseasesDuring** ~~DiseasesOrally Available IRAK- 1 / 4 Inhibitor Program. During~~ the second quarter of 2018, we selected R835, the active metabolite of R289, a proprietary molecule from our ~~IRAK~~ **IRAK1** ~~1~~ / 4 **inhibitor** ~~preclinical development~~ program, for human clinical trials. This

investigational candidate is an orally administered, potent and selective inhibitor of IRAK1 and IRAK4 that blocks inflammatory cytokine production in response to toll- like receptor (TLR) and the interleukin- 1 receptor (IL- 1R) family signaling. TLRs and IL- 1Rs play a critical role in the innate immune response and dysregulation of these pathways can lead to a variety of inflammatory conditions ~~including psoriasis, rheumatoid arthritis, inflammatory bowel disease and gout (among others)~~ . R835 prevents cytokine release in response to TLR and IL- 1R activation in vitro. R835 is active in multiple rodent models of inflammatory disease including psoriasis, arthritis, lupus, multiple sclerosis and gout. Preclinical studies show that R835 inhibits both the IRAK1 and IRAK4 signaling pathways, which play a key role in inflammation and immune responses to tissue damage. Dual inhibition of IRAK1 and IRAK4 allows for more complete suppression of pro- inflammatory cytokine release than inhibition of either one individually. In October 2019, we announced results from a Phase 1 clinical trial of R835 in healthy subjects to assess safety, tolerability, pharmacokinetics (PK) and pharmacodynamics. The Phase 1 trial was a randomized, placebo- controlled, double- blind trial in 91 healthy subjects, ages 18 to 55. The Phase 1 trial showed positive tolerability and PK data as well as established proof- of- mechanism by demonstrating the inhibition of inflammatory cytokine production in response to a lipopolysaccharide (LPS) challenge. ~~14We~~ **15We** continue to advance the development of our IRAK1 / 4 **inhibitor** program, ~~completing~~ **following** the evaluation of a new pro- drug formulation of R835, R289, in single- ascending and multiple ascending dose studies with positive safety results in 2021. In January 2022, we received clearance from the FDA on our clinical trial design to explore R289 in ~~low~~ **lower** - risk MDS. The open- label, Phase 1b trial will determine the tolerability and preliminary efficacy of R289 in patients with ~~low~~ **lower** - risk MDS who are refractory or resistant to prior therapies. In December 2022, we announced that we dosed the first patient in our Phase 1b trial of R289. The Phase 1b trial of R289 is expected to enroll approximately ~~22~~ **34** patients **(up to 24 participants with lower risk MDS who receive study treatment in dose escalation phase, and up to 10 participants with lower- risk MDS who receive study treatment in the dose expansion phase)** . The primary objective of the trial is safety, with secondary and exploratory objectives to assess preliminary efficacy and characterize the pharmacokinetic and pharmacodynamic profile of R289. The safety and efficacy data from this Phase 1b trial, along with the safety and pharmacokinetic / pharmacodynamic data from the completed first- in- human study in heathy volunteers, are intended to be used to determine the recommended Phase 2 dose for future clinical development of R289 targeting lower- risk MDS. **To date, target enrollment in the second cohort of the trial has been completed and we are currently enrolling patients in the third cohort. Preliminary results are expected by the end of 2024.** Fostamatinib in Hospitalized COVID- 19 **PatientsCOVID** ~~PatientsDisease background. COVID~~ - 19 is the infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus- 2 (SARS- CoV- 2). SARS- CoV- 2 primarily infects the upper and lower respiratory tract and can lead to acute respiratory distress syndrome ~~(ARDS)~~ . Additionally, some patients develop other organ dysfunction including myocardial injury, acute kidney injury, shock resulting in endothelial dysfunction and subsequently micro and macrovascular thrombosis. Much of the underlying pathology of SARS- CoV- 2 is thought to be secondary to a hyperinflammatory immune response associated with increased risk of thrombosis. SYK is involved in the intracellular signaling pathways of many different immune cells. **The** ~~Therefore,~~ SYK inhibition may improve outcomes in patients with COVID- 19 via inhibition of key Fc gamma receptor and c- type lectin receptor mediated drivers of pathology, such as inflammatory cytokine release by monocytes and macrophages, production of NETs by neutrophils, and platelet aggregation. Furthermore, SYK inhibition in neutrophils and platelets may lead to decreased thromboinflammation, alleviating organ dysfunction in critically ill patients with COVID- 19. Rigel- led Phase 3 Trial. In November 2020, we launched our FOCUS Phase 3 clinical trial to evaluate the safety and efficacy of fostamatinib in hospitalized COVID- 19 patients without respiratory failure that have certain high- risk prognostic factors. In January 2021, we were awarded $ 16. 5 million from the **DOD** ~~US Department of Defense~~ ' s Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense ~~(JPEO- CBRND)~~ to support this Phase 3 clinical trial. This multi- center, double- blind, placebo- controlled, adaptive design study randomly assigns either fostamatinib plus SoC or matched placebo plus SoC (1: 1) to targeted evaluable patients. Treatment is administered orally twice daily for 14 days with follow up to day 60. In December 2021, we expanded the inclusion criteria to include patients with more severe disease (NIAID Ordinal Scale 6) to more accurately reflect the clinically predominant patient population hospitalized with COVID- 19 and help speed enrollment. In collaboration with the FDA and **DOD** ~~Department of Defense~~ , we also updated the primary endpoint for the trial from progression to severe disease within 29 days, to the number of days on oxygen through day 29. This endpoint allows for closer comparison of the results with earlier results from the NIH / NHLBI Phase 2 clinical trial with fostamatinib and various other NIH- sponsored trials, such as the ACTIV- 4 Host Tissue Trial, which uses a similar outcome measure as a primary endpoint. In July 2022, we completed enrollment with 280 patients. The trial had originally targeted a total of 308 patients; however, we determined the trial would be sufficiently powered with 280 patients to potentially provide a clinically meaningful result and determine the efficacy and safety of fostamatinib in hospitalized COVID- 19 patients. ~~On~~ **We previously announced in** November ~~1,~~ 2022 ~~, we announced~~ the top- line results ~~of~~ **from** the FOCUS **Phase 3 clinical** trial ~~. The trial approached but~~ **to evaluate the safety and efficacy of fostamatinib in hospitalized COVID- 19 patients without respiratory failure that have certain high- risk prognostic factors** did not meet statistical significance ~~(p = 0. 0603)~~ in the primary efficacy endpoint of the number of days on oxygen through Day 29. ~~All prespecified~~ **Upon further analysis, we discovered an error by the biostatistical CRO in the application of a statistical stratification factor. The biostatistical CRO misinterpreted receipt of prior COVID- 19 treatment of interest 14 days before randomization (regardless of continuation post randomization), as those medications taken 14 days before the date of randomization and ended prior to the day of randomization. After correcting for this statistical error, the primary endpoint of the study was met; those who received fostamatinib had lower mean days on oxygen than those who received placebo (4. 8 vs. 7. 6 days, p = 0. 0136). Further, fostamatinib showed significance or trend towards significance in all** secondary endpoints ~~in~~ **of reducing mortality and morbidity compared to 16placebo after correcting for** the ~~trial numerically favored~~ **error. The results were recently presented at the IDWeek 2023 held on**

October 11- 15, 2023 in Boston, Massachusetts. During our continued analysis regarding fostamatinib ~~over placebo, including mortality, time to sustained recovery, change~~ in ~~ordinal scale assessment~~ **hospitalized COVID- 19 patients** , **we provided** ~~and number of days in~~ the **updated analysis to** ~~ICU. We are evaluating the opportunity and discussing next steps with~~ the FDA and ~~in collaboration with~~ our partner, the ~~US Department~~ **DOD. Given the end** of ~~Defense~~ **the federal COVID- 19 PHE in May 2023, and based on feedback from the FDA, DOD and other advisors regarding the program' s regulatory requirements, costs, timeline and potential for success, we decided not to submit an EUA or sNDA** . NIH / NHLBI- sponsored Phase 2 Trial. In September 2020, we announced a Phase 2 clinical trial sponsored by the NIH / NHLBI to evaluate the safety of fostamatinib for the treatment of hospitalized COVID- 19 patients. This multi- center, double- blind, placebo- controlled trial randomly assigned fostamatinib or matched placebo (1: 1) to 59 evaluable patients. Treatment was administered orally twice daily for 14 days, and a follow- up period to day 60. The primary endpoint of this trial was cumulative incidence of Serious Adverse Events (SAEs) through day 29. The trial also included multiple secondary endpoints designed to assess the early efficacy and clinically relevant endpoints of disease course. ~~15The~~ -- **The** trial completed the enrollment in March 2021. In April 2021, we announced that the Phase 2 clinical trial met its primary endpoint of safety. Fostamatinib reduced the incidence of SAEs by half. By day 29, there were three SAEs in the fostamatinib plus SoC group of thirty patients compared to six SAEs in the placebo plus SoC group of twenty- nine patients (p = 0. 23). Of these, there was a reduction for the disease related SAE of hypoxia in the fostamatinib group compared to placebo (1 vs 3, respectively; p = 0. 29). The data from the NIH / NHLBI- Sponsored Phase 2 trial was published in Clinical Infectious Diseases, an official publication of the Infectious Disease Society of America in September 2021. In May 2021, the NIH / NHLBI Phase 2 clinical data were submitted as part of a request for an EUA from the FDA for fostamatinib as a treatment for hospitalized patients with COVID- 19. In August 2021, the FDA informed us that the clinical data submitted from the NIH / NHLBI- sponsored Phase 2 trial of fostamatinib to treat hospitalized patients suffering from COVID- 19 was insufficient for an EUA. ACTIV- 4 Host Tissue Phase 2 / 3 Trial. In June 2021, we announced that fostamatinib had been selected for the NIH ACTIV- 4 Host Tissue Trial in hospitalized patients with COVID- 19. The ACTIV- 4 Host Tissue Trial, initiated and funded by NHLBI, is a randomized, placebo- controlled trial of therapies, including fostamatinib, targeting the host response to COVID- 19 in hospitalized patients. The master protocol for this trial was designed to be flexible in the number of study arms, the use of a single placebo group, and the stopping and adding of new therapies. Eligible participants include patients hospitalized for COVID- 19 with laboratory- confirmed SARS- CoV- 2 infection and a new need for oxygen therapy. The primary outcome is oxygen- free days through day 28. Secondary outcomes include 28- day hospital mortality, use of mechanical ventilation, and severity of disease as measured by World Health Organization (WHO) scale scores. The ACTIV- 4 Host Tissue Trial is evaluating fostamatinib in a targeted population of approximately 600 hospitalized patients with COVID- 19, 300 fostamatinib versus 300 placebo. ~~An~~ **During the first quarter of 2023, an** interim analysis of the trial was completed by the **DSMB** ~~Data and Safety Monitoring Board~~ with a recommendation for the trial to continue **. In September 2023, the DSMB recommended that the fostamatinib study arm of the ACTIV- 4 Host Tissue Trial platform cease enrollment. Based on the DSMB' s review of a conditional power analysis, the DSMB determined that there was an extremely low likelihood of fostamatinib providing benefits related to the primary outcome (oxygen free days) or other secondary outcomes in patients hospitalized and on oxygen therapy for COVID- 19. No safety concerns were identified. The NIH / NHLBI concurs with the DSMBs recommendation and has asked the trial investigators to cease enrollment, complete follow- up for participants already enrolled, and complete study closeout. The full study data will be analyzed and disseminated as previously planned** . Imperial College of London Phase 2 Trial. In July 2020, we announced a Phase 2 clinical trial sponsored by Imperial College of London to evaluate the efficacy of fostamatinib for the treatment of COVID- 19 pneumonia. This is a two- stage, open label, controlled clinical trial with patients randomized (1: 1: 1) to fostamatinib plus SoC, ruxolitinib plus SoC, or SoC alone. Treatment was administered twice daily for 14 days and patients receive a follow- up assessment at day 14 and day 28 after the first dose. The primary endpoint of this trial is progression from mild to severe COVID- 19 pneumonia within 14 days in hospitalized patients (WHO COVID- 19 Severity Scale 3- 4). In April 2022, Imperial College of London completed a pre- planned interim analysis of the primary endpoint, patients progressing from mild or moderate (modified WHO COVID- 19 scale 3- 4) to severe disease (modified WHO COVID- 19 scale ≥ 5) within 14 days, in the Phase 2 MATIS trial. The independent data monitoring committee determined that the fostamatinib plus SoC arm did not meet the prespecified criteria for continuation to the next stage of the trial. No safety concerns were identified. The trial remains blinded and Imperial College of London plans to share results with us and scientific community once the trial is complete. ~~Other Publications. Researchers at MIT and Harvard led a screen to identify FDA- approved compounds that reduce MUC1 protein abundance. MUC1 is a biomarker used to predict the development of ALI and ARDS and correlates with poor clinical outcomes. In June 2020, the results were presented, and of the 3, 713 compounds that were screened, fostamatinib was the only compound identified which both decreased expression of MUC1 and is FDA approved. Fostamatinib~~ **17Fostamatinib** ~~demonstrated preferential depletion of MUC1 from epithelial cells without affecting cell viability. The research was focused on drug repurposing for the much lower risk of toxicity and the ability of FDA- approved treatments to be delivered on a shortened timescale, which is critical for patients afflicted with lung disease resulting from COVID- 19. In addition, the~~ in **warm AIHA (wAIHA) AIHA** ~~vitro studies led by the Amsterdam University Medical Center at the University of Amsterdam, showed that R406, the active metabolite of fostamatinib, blocked macrophage hyperinflammatory responses to a combination of immune complexes formed by anti- Spike IgG in serum from severe COVID- 19 patients. Anti- Spike IgG levels are known to correlate with the severity of COVID- 19. These results, presented in July 2020, suggest that by inhibiting anti- Spike IgG- mediated hyperinflammation, R406 could potentially play a role in the prevention of cytokine storms as well as pulmonary edema and thrombosis associated with severe COVID- 19. 16In December 2020, the Journal of Infectious Diseases published research from NIH which demonstrated that R406, the active metabolite of fostamatinib, was able to inhibit NETosis ex vivo in donor plasma from patients with COVID- 19. NETosis is a unique type of~~

~~cell death resulting in the release of NETs. NETs contribute to thromboinflammation and have been associated with mortality in COVID- 19. These data provide insights for how fostamatinib may mitigate neutrophil- associated mechanisms contributing to COVID- 19 immunopathogenesis. Fostamatinib in wAIHADisease background. Autoimmune hemolytic anemia~~ is a rare, serious blood disorder where the immune system produces antibodies that result in the destruction of the body' s own red blood cells. Symptoms can include fatigue, shortness of breath, rapid heartbeat, jaundice or enlarged spleen ~~. While no medical treatments are currently approved for AIHA, physicians generally treat acute and chronic cases of the disorder with corticosteroids, other immuno- suppressants, or splenectomy~~. Research has shown that inhibiting SYK with fostamatinib may reduce the destruction of red blood cells. **We conducted a** ~~AIHA affects an estimated 45, 000 Americans, and approximately 36, 000 of those patients have~~ wAIHA ~~, where no approved treatment options currently exist. Orally- available fostamatinib program. We completed our Phase 2 clinical trial, also known as the SOAR study, in patients with wAIHA. This trial was an open- label, multi- center, two- stage study that evaluated the efficacy and safety of fostamatinib in patients with wAIHA who had previously received treatment for the disorder but have relapsed. The primary efficacy endpoint of this study was to achieve increased hemoglobin levels by week 12 of greater than 10 g / dL, and greater than or equal to 2 g / dL higher than baseline. In November 2019, we announced updated data that in a Phase 2 open- label study of fostamatinib in patients with wAIHA, data showed that 44 % (11 / 25) of evaluable patients met the primary efficacy endpoint of a Hgb level > 10 g / dL with an increase of ≥ 2 g / dL from baseline by week 24. Including one late responder at week 30, the overall response rate was 48 % (12 / 25). Adverse events were manageable and consistent with those previously reported with fostamatinib. In February 2022, the American Journal of Hematology published the data from our Phase 2 clinical trial of fostamatinib in adults with wAIHA who have failed at least one prior treatment. The published data demonstrate that fostamatinib rapidly and durably increased hemoglobin (Hgb) levels, with clinically meaningful Hgb responses observed in nearly half of the patients, and a safety and tolerability profile consistent with the existing fostamatinib safety database of patients across multiple disease programs studied. In January 2021, we announced that the FDA had granted Fast Track designation to fostamatinib for the treatment of wAIHA. The FDA previously granted fostamatinib Orphan Drug designation for the treatment of wAIHA in January 2018. In March 2019, we initiated our wAIHA pivotal~~ Phase 3 clinical trial of fostamatinib, known as the FORWARD study **that was initiated in March 2019**. The clinical trial protocol calls for a placebo- controlled study of 90 patients with primary or secondary wAIHA who have failed at least one prior treatment. The primary endpoint ~~is~~ **was** a durable ~~Hgb~~ **hemoglobin** response, defined as ~~Hgb~~ **hemoglobin** > 10 g / dL and > 2 g / dL increase from baseline and durability measure, with the response not being attributed to rescue therapy. In ~~November 2020, we reached an agreement with the FDA on the durable response measure for the primary efficacy endpoint of the trial as well as the inclusion of additional secondary endpoints. In November 2021, we completed the enrollment of this study. In April 2022, we completed the treatment period for the last patient under the trial. In~~ June 2022, we announced **the** top- line efficacy and safety data from the ~~FORWARD~~ study ~~with 90 patients. Patients were randomized 1: 1 to receive fostamatinib or matching placebo twice daily for 24 weeks. The primary efficacy endpoint of Hgb response was defined as achieving a Hgb ≥ 10 g / dL with an increase from baseline ≥ 2 g / dL on three consecutive available visits during the 24- week treatment period~~. The trial did not demonstrate statistical significance in the primary efficacy endpoint of durable hemoglobin response in the overall study population ~~. The trial also included key secondary endpoints, including hemoglobin response on at least one visit, change in Hgb from baseline of ≥ 2 g / dL, use of permitted rescue therapy after week 4, change in Hgb from baseline to end of treatment and change from baseline to week 24 in FACIT- F scale~~. Across the trial' s overall patient population, fostamatinib was generally well- tolerated. The safety profile of the product was consistent with prior clinical experience and no new safety issues were discovered. The most common adverse events (≥ 10 %) with fostamatinib and placebo were diarrhea, hypertension, fatigue, pyrexia, nausea, and dyspnea. Treatment- related SAEs were 6. 7 % (3 / 45) for fostamatinib and 4. 4 % (2 / 45) for placebo. There were five deaths on the trial (2 with fostamatinib and 3 with placebo), all of which were determined to be unrelated to study drug. The safety results were consistent with the overall safety profile data collected to date, which includes more than 5, 000 patients ~~17across~~ -- **across** multiple diseases. We conducted an in- depth analysis of these data to better understand differences in patient characteristics and outcomes and submitted these findings to the FDA. In October 2022, we announced that we received guidance from the FDA' s review of these findings. Based on the result of the trial and the guidance from the FDA, we did not file an sNDA for this indication. Of the 90 patients that completed the FORWARD study, 71 (79 %) enrolled in the open- label extension study **, with the last patient visit** ~~. We plan on closing this study~~ in **December** 2023. Partnered Clinical Programs **R552 – Lilly Lilly is continuing to advance R552 and has initiated the Phase 2a trial studying R552 in adult patients with moderately to severely active rheumatoid arthritis. The trial plans to enroll 100 patients globally. RIPK1 is implicated in a broad range of key inflammatory cellular processes and plays a key role in tumor necrosis factor signaling, especially in the induction of pro- inflammatory necroptosis. The program also includes RIPK1 compounds that cross the blood- brain barrier (CNS- penetrants) to address neurodegenerative diseases such as Alzheimer' s disease and amyotrophic lateral sclerosis.** BGB324 – BerGenBio We have an exclusive, worldwide research, development and commercialization agreement with BerGenBio for our investigational AXL receptor tyrosine kinase inhibitor, ~~BGB324 /~~ R428 (now referred to as bemcentinib **(BGB324**) ~~. In October 2022, BerGenBio announced the initiation of a Phase 1b / 2a trial evaluating bemcentinib in combination with the current SoC, checkpoint inhibitor pembrolizumab and doublet chemotheraphy, for the treatment of first line non- small cell lung cancer patients harboring serine / threonine kinase 11 mutations~~. In February 2023, BerGenBio ~~also~~ announced positive data from **the** Phase 2 trial of bemcentinib in combination with pembrolizumab in patients with **second** ~~2L non-~~ **line** ~~small cell lung cancer (~~NSCLC ~~)~~. The treatment with bemcentinib in combination with pembrolizumab demonstrated long survival benefit and sustained disease control, particularly in patients with AXL TPS > 5, substantiating the relevance of AXL as a target and bemcentinib' s selective inhibition capabilities in NSCLC. ~~The product~~ **Also in March 2023, BerGenBio announced** ~~is~~ **its** ~~also being investigated~~ **first patient dosed** in **a** Phase ~~2 clinical~~ **1B / 2A** ~~trials~~ **trial evaluating bemcentinib**

in **first- line NSCLC** patients **harboring STK11 mutations** ~~with AML and COVID- 19. Bemcentinib is being studied in over 600 patients, demonstrating its safety as a monotherapy and in combination with chemotheraphy and immune checkpoint inhibition~~ . DS- 3032 ~~- -~~ DaiichiDS- 3032 is an investigational oral selective inhibitor of the murine double minute 2 (MDM2) protein investigated by Daiichi in three Phase 1 clinical trials for solid and hematological malignancies including AML, acute lymphocytic leukemia, chronic myeloid leukemia in blast phase, lymphoma and MDS. Preliminary safety and efficacy data from a Phase 1 trial of DS- 3032 suggests that DS- 3032 may be a promising treatment for hematological malignancies including R / R AML and high- risk MDS. In September 2020, worldwide rights to DS- 3032 (milademetan) ~~were~~ **18were** out- licensed from Daiichi to Rain Oncology Inc., formerly Rain Therapeutics Inc. (Rain). ~~In July 2021,~~ Rain **had** ~~announced that it~~ initiated a Phase 3 trial to evaluate the efficacy and safety of milademetan ~~(RAIN- 32)~~ for the treatment of ~~well- differentiated /~~ **patients with unresectable or metastatic** dedifferentiated liposarcoma, a rare cancer originating from fat cells located in the soft tissues of the body ~~and~~ **,** in ~~August 2022~~ **2021 . In May 2023** , Rain announced **that** the ~~completion of enrollment of~~ **trial did not meet** its ~~Phase 3 trial for~~ **primary endpoint of progression free survival by blinded independent central review compared to the standard of care. Based on the topline results, Rain does not expect to pursue further development of** milademetan in **dedifferentiated** liposarcoma. In ~~late~~ **December** ~~2021~~ **2023** , Rain ~~commenced~~ **announced that it has entered into a definitive merger agreement with Pathos Al, Inc. (Pathos), and the transaction was completed in January 2024. Pathos has continued interest in further developing miladematan for cancer patients using** its **propriety PathOS Platform** ~~second clinical trial for RAIN- 32 in patients with MDM2- amplified advance solid tumors, and in November 2022, Rain provided an interim analysis of the trial which showed that the drug safety profile of milademetan is preliminary consistent with its prior Phase 1 trial~~ . Research, Preclinical and Clinical Development ProgramsWe have retained a selected team of experts in drug discovery and preclinical development to leverage our existing proprietary collection of inhibitors, small- molecule compound libraries and large database of associated phenotypic and biochemical assay results of therapeutic interest. We maintain leading expertise on specific areas of operation such as inhibition of SYK, IRAK1 / 4, RIPK1 and mIDH1 kinases to assist clinical development and commercial affairs, as well as to expand and explore additional opportunities for such inhibitors in the clinical space. Our preclinical operations involve collaborations with clinical research organizations, leading investigators from universities and research organizations around the world, and strategic collaborations with other pharmaceutical companies. We have assembled a team of experts in drug development to design and implement clinical trials and to analyze the data derived from these trials. The clinical development group possesses expertise in project management ~~18and~~ -- **and** regulatory affairs. We work with external clinical research organizations with expertise in managing clinical trials, drug formulation, and the manufacture of clinical trial supplies to support our drug development efforts. **We also have strategic development collaborations with MD Anderson and CONNECT to conduct evaluation of REZLIDHIA (oluatasidenib) in AML, other hematologic cancers and glioma.** Commercialization and Sponsored Research and License Agreements For a discussion of our Commercialization and Sponsored Research and License, see " Note 4 ~~- -~~ Sponsored Research and License Agreements and Government ~~Contract~~ **Contracts** " to our " Notes to Financial Statements " contained in " Part II, Item 8, Financial Statements and Supplementary Data " of this Annual Report on Form 10- K. Intellectual PropertyWe are able to protect our technology from unauthorized use by third parties only to the extent that it is covered by valid and enforceable patents or is effectively maintained as a trade secret. Accordingly, patents and other proprietary rights are an essential element of our business. **We** ~~As of December 31, 2022, we owned~~ -- **own** or ~~had~~ **have** exclusive license to ~~48~~ **an extensive portfolio of** pending patent applications and ~~376~~ issued and active patents in the US, as well as corresponding pending foreign patent applications and issued foreign patents. Our policy is to file patent applications to protect technology, inventions and improvements to inventions that are commercially important to the development of our business. We seek US and international patent protection for a variety of technologies, including ~~new screening methodologies and other research tools,~~ target molecules that are associated with disease states identified in our screens ~~,~~ and lead compounds that can affect disease pathways. We also ~~intend to seek patent protection or~~ rely upon trade secret rights to protect other technologies that may be used to discover and validate targets and that may be used to identify and develop novel drugs. We seek protection, in part, through confidentiality and proprietary information agreements. We are a party to various license agreements that give us rights to use technologies in our research and development. ~~We~~ **19We** currently hold a number of issued patents in the US, as well as corresponding applications that allow us to pursue patents in other countries, some of which have been allowed and / or granted and others ~~of which~~ **currently being prosecuted that** we expect to be granted. Specifically, in most cases where we hold a US issued patent, the subject matter is covered at least by an application filed under the Patent Cooperation Treaty (PCT), which is then used or has been used to pursue protection in certain countries that are members of the treaty. Our patents extend for varying periods according to the date of patent filing or grant and the legal term of patents in the various countries where patent protection is obtained. Some of these patents may be eligible for patent term extensions, depending on their subject matter and length of time required to conduct clinical trials. Our material patents relate to fostamatinib, an oral SYK inhibitor, that is the active pharmaceutical ingredient in TAVALISSE, and olutasidenib, an oral mIDH1 inhibitor that is the active pharmaceutical ingredient in REZLIDHIA. These patents will expire at various dates from 2026 to 2032 for fostamatinib ~~and~~ **,** from 2035 to 2039 for olutasidenib **and from 2036 to 2041 for pralsetinib** . Fostamatinib. Fostamatinib ~~2023.Accordingly,the term of the' 458 patent has been extended to~~ September 2031 **,after taking into account a patent term adjustment and extension rules** .Additional patents covering fostamatinib composition of matter,methods for use,formulations,methods for making and intermediates expire at various dates from 2023 to 2041. ~~As of December 31,2023,we owned 7 pending patent applications and 43 issued and active patents in the US for fostamatinib.~~ Corresponding applications have been filed in foreign jurisdictions under the PCT,and are at various stages of prosecution.Of note, **a** ~~patents~~ **patent** covering fostamatinib as a composition of matter and in compositions for use treating various diseases ~~are~~ **has been granted by the European Patent Office.Olutasidenib.Olutasidenib is covered as a composition of matter in a US** issued ~~in Europe~~ **patent that has an expected expiration date of** is covered as a

composition of matter in a US issued patent that has an expected expiration date of September 2031, after taking into account..... that has an expected expiration date of December 2036, after taking into account patent term extension rules. Additional patents covering olutasidenib compositions of matter, methods for use, solid forms, methods for making and intermediates expire at various dates from 2035 to 2042. Several corresponding applications have been filed in foreign jurisdictions under the PCT and are at various stages of prosecution. **In all, we have exclusive license to 9 pending patent applications and 17 issued and active patents in the US for olutasidenib, as well as corresponding pending foreign patent applications and issued foreign patents. Pralsetinib. Please refer to related discussions above under " Business Updates ", titled " GAVRETO (pralsetinib) in metastatic RET fusion- positive NSCLC and advanced thyroid cancers " in Item 1 of this Annual Report on Form 10- K.** ~~19Competition --~~ **Competition** The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. Many of the drugs that we are attempting to discover will be competing with existing therapies. In addition, a number of companies are pursuing the development of pharmaceuticals that target the same diseases and conditions that we are targeting. We face, and will continue to face, intense competition from pharmaceutical and biotechnology companies, as well as from academic and research institutions and government agencies, both in the US and abroad. Some of these competitors are pursuing the development of pharmaceuticals that target the same diseases and conditions as our research programs. Our major competitors include fully integrated pharmaceutical companies that have extensive drug discovery efforts and are developing novel small molecule and biologics pharmaceuticals. We also face significant competition from organizations that are pursuing the same or similar technologies, including the discovery of targets that are useful in compound screening, as the technologies used by us in our drug discovery efforts. Competition may also arise from: ● new or better methods of target identification or validation; ● generic version of our products or of products with which we compete; **20** ● other drug development technologies and methods of preventing or reducing the incidence of disease; ● new small molecules; or ● other classes of therapeutic agents. Our competitors or their collaborative partners may utilize discovery technologies and techniques or partner with collaborators in order to develop products more rapidly or successfully than we or our collaborators are able to do. Many of our competitors, particularly large pharmaceutical companies, have substantially greater financial, technical and human resources and larger research and development staffs than we do. 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 and may establish exclusive collaborative or licensing relationships with our competitors. We believe that our ability to compete is dependent, in part, upon our ability to create, maintain and license scientifically advanced technology and upon our and our collaborators' ability to develop and commercialize pharmaceutical products based on this technology, as well as our ability to attract and retain qualified personnel, obtain patent protection or otherwise develop proprietary technology or processes and secure sufficient capital resources for the expected substantial time period between technological conception and commercial sales of products based upon our technology. The failure by any of our collaborators or us, including our commercial team, in any of those areas may prevent the successful commercialization of our potential drug targets. Many of our competitors, either alone or together with their collaborative partners, have significantly greater experience than we do in: ● identifying and validating targets; ● screening compounds against targets; and ● undertaking preclinical testing and clinical trials. Accordingly, our competitors may succeed in obtaining patent protection, identifying or validating new targets or discovering new drug compounds before we do. ~~20Our --~~ **Our** competitors might develop technologies and drugs that are more effective or less costly than any that are being developed by us or that would render our technology and product candidates obsolete and noncompetitive. In addition, our competitors may succeed in obtaining the approval of the FDA or other regulatory agencies for product candidates more rapidly. Companies that complete clinical trials, obtain required regulatory agency approvals and commence commercial sale of their drugs before us may achieve a significant competitive advantage, including certain patent and FDA marketing exclusivity rights that would delay or prevent our ability to market certain products. Any drugs resulting from our research and development efforts, or from our joint efforts with our existing or future collaborative partners, might not be able to compete successfully with competitors' existing or future products or obtain regulatory approval in the US or elsewhere. We face and will continue to face intense competition from other companies for commercial and collaborative arrangements with pharmaceutical and biotechnology companies, for establishing relationships with academic and research institutions and for licenses to additional technologies. These competitors, either alone or with their collaborative partners, may succeed in developing technologies or products that are more effective than ours. Our ability to compete successfully will depend, in part, on our ability to: ● identify and validate targets; ● discover candidate drug compounds that interact with the targets we identify; ● attract and retain scientific and product development personnel; **21** ● obtain patent or other proprietary protection for our new drug compounds and technologies; ● enter commercialization agreements for our new drug compounds; and ● ~~to~~ obtain and maintain an appropriate reimbursement price and positive recommendations by HTA bodies. ITPThere are existing therapies and drug candidates in development for the treatment of ITP that may be alternative therapies to TAVALISSE. Currently, corticosteroids remain the most common first line therapy for ITP, occasionally in conjunction with intravenous immuglobulin (IVIg) or anti- Rh (D) as added agents to help further augment platelet count recovery, particularly in emergency situations. However, it has been estimated that frontline agents lead to durable remissions in only a small percentage of newly- diagnosed adults with ITP. Moreover, concerns with steroid- related side effects often restrict therapy to approximately four weeks. As such, many patients progress to persistent or chronic ITP, requiring other forms of therapeutic intervention. The FDA can approve an ANDA for a generic version of a branded drug without the ANDA applicant undertaking the clinical testing necessary to obtain approval to market a new drug. In September 2019, the FDA published product- specific bioequivalence guidance on fostamatinib disodium to let potential ANDA applicants understand the data the FDA would expect to see for approval of a generic version of TAVALISSE. The earliest an ANDA may be filed by a generic company was April 17, 2022. The ANDA process can result in generic competition if the patents at issue are not upheld or if the generic competitor

is found not to infringe our patents. Other approaches to treat ITP are varied in their mechanism of action, and there is no consensus about the sequence of their use. Options include splenectomy, TPO- Ras, and various immunosuppressants (such as rituximab). The response rate criteria of the above- mentioned options vary, precluding a comparison of response rates for individual therapies. According to the most recent ITP guideline from the ASH, there was a lack of evidence to support strong recommendations for various management approaches. In general, strategies that avoided medication side effects were favored. A large focus was placed on shared decision- making especially with regard to second- line therapy. Even with the above treatment options, a significant number of patients remain severely thrombocytopenic for long durations and are subject to risk of spontaneous or trauma- induced hemorrhage. The addition of fostamatinib to the treatment options could be beneficial since it has a different mechanism of action than the TPO agonists. Fostamatinib is ~~21a~~ **a** potent and relatively selective SYK inhibitor, and its inhibition of Fc receptors and B- cell receptors signaling pathways make it a potentially broad immunomodulatory agent. Other products in the US that are approved by the FDA to increase platelet production through binding and TPO receptors on megakaryocyte precursors include PROMACTA (Novartis), Nplate (Amgen, Inc.) and DOPTELET (Dova Pharmaceuticals). AML with IDH1 MutationThere is currently one other product approved in the US for patients with IDH1 mutation. TIBSOVO (ivosidenib), an oral targeted IDH1 mutation inhibitor, is an FDA **-** approved drug for (i) adult patients with R / R AML with a susceptible IDH1 mutation, (ii) newly diagnosed AML with a susceptible IDH1 mutation who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy, (iii) for adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation as detected by an FDA- approved test, and (iv) in combination with azacitidine (azacitidine for injection), for newly diagnosed AML with a susceptible IDH1 mutation, as detected by an FDA- approved test in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. TIBSOVO is a registered trademark of Servier Pharmaceuticals LLC, a wholly owned, indirect subsidiary of Les Laboratoires Servier. In addition, some clinicians may utilize non- targeted treatments for patients with mIDH1 R / R AML, including use of venetoclax combinations, hypomethylating agents, other chemotherapy regimens, or investigational agents that may be available to them **. 22Metastatic RET fusion- positive NSCLC and advanced thyroid cancersPlease refer to related discussions above under " Business Updates ", titled " GAVRETO (pralsetinib) in metastatic RET fusion- positive NSCLC and advanced thyroid cancers "** . Government RegulationGovernment authorities in the US, at the federal, state and local level, and in other countries and jurisdictions, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, sampling, tracking and tracing, sales, post- approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the US and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations, such as those governing personal information and information security, require the expenditure of substantial time and financial resources. Review and Approval of Drugs in the US In the US, the FDA approves and regulates drugs under the Federal Food, Drug, and Cosmetic Act (FDCA) and implementing regulations. The failure to comply with requirements under the FDCA and other applicable laws at any time during the product development process, approval process or after approval may subject an applicant and / or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties. A drug product candidate must be approved by the FDA through the new drug application (NDA). An applicant seeking approval to market and distribute a new drug product in the US must typically undertake the following: ● completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA' s good laboratory practice regulations; ● submission to the FDA of an IND, which must take effect before human clinical trials may begin; ● approval by an independent institutional review board (IRB) for each clinical site before each clinical trial may be initiated; ● performance of adequate and well- controlled human clinical trials in accordance with good clinical practices (GCP) to establish the safety and efficacy of the proposed drug product for each indication; ~~22~~ ● preparation and submission to the FDA of an NDA requesting marketing for one or more proposed indications; ● review by an FDA advisory committee, if requested by the FDA; ● satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practices (cGMP), requirements and to assure that the facilities, methods and controls are adequate to preserve the product' s identity, strength, quality and purity; ● satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data; ● payment of user fees and securing FDA approval of the NDA; and ● compliance with any post- approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and potentially post- market requirement, or PMR, and commitment, or PMC, studies. ~~Before~~ **23Before** an applicant begins testing a compound with potential therapeutic value in humans, the drug candidate enters the preclinical testing stage. Preclinical studies include laboratory evaluation as well as in vitro and animal studies to assess product chemistry, formulation, and toxicity, as well as the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, are submitted to the FDA as part of an IND. Some long- term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and long- term toxicity studies, may continue after the IND is submitted. An IND is an exemption from the FDCA that allows an unapproved new drug to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer an investigational drug to humans. In support of the IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments. In addition, the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature, among other things, are submitted to

the FDA as part of an IND. The FDA requires a 30- day waiting period after the submission of each IND before clinical trials may begin. At any time during this 30- day period, or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin or resume. An IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. An IRB can suspend or terminate approval of a clinical trial. Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Human clinical trials are typically conducted in sequential phases, which may overlap or be combined: ● Phase 1. The drug is initially introduced into a small number of healthy human subjects or, in certain indications such as cancer, patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage. ● Phase 2. The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage. ● Phase 3. These clinical trials are commonly referred to as " pivotal " studies, which denote a study that presents the data that the FDA or other relevant regulatory agency will use to determine whether or not to ~~23approve~~ **approve** a drug. The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well- controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, identify adverse effects, establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product. ● Phase 4. Post- approval studies may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In most cases the FDA requires at least two adequate and well-controlled Phase 3 clinical trials to demonstrate the efficacy of the drug. A single Phase 3 trial with other confirmatory evidence may be sufficient in rare instances, such as where the study is a large multicenter trial demonstrating internal consistency and a statistically very persuasive finding of a clinically meaningful effect on mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. Concurrent with clinical trials, companies often complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with current good manufacturing practices (cGMP) ~~requirements~~ **24requirements**. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final drug. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life. The FDA or the sponsor or the data monitoring committee may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Review and Approval of Drugs in the EU and the UKSimilar rules governing clinical trials to those in place in the US apply in the ~~European Union (~~EU ~~)~~ and the UK, with a clinical trial application ~~(CTA)~~ required to be submitted for each clinical trial to each EU Member State' s national competent authority ~~(NCA)~~ and an independent Ethics Committee. Following the UK' s exit from the EU, commonly referred to as Brexit, and the end of the transition period that was in place until the end of 2020, clinical trials that take place in the UK will be seen by the EMA as trials that have taken place in a " third country " and will only be considered during the course of a marketing authorization application if they are carried out on a basis that is in line with the regulations governing clinical trials in the EU. As of January 31, 2022, clinical trials in the EU must be conducted in accordance with the requirements of the EU Clinical Trials Regulation (EU) No 536 / 2014 (CTR) that has amended the system of approval for clinical trials in the EU. Under the CTR as of January 31, 2023, sponsors must apply for authorizations through the Clinical Trials Information System (CTIS), the new clinical trials portal and database that allows a coordinated and streamlined application and authorization process for clinical trials and ethical approvals throughout the EU. The UK has not applied the CTR, and is currently revising its own clinical trials framework, and therefore its regulatory framework on clinical trials is not aligned with the EU CTR. This may result in trials that take place in the UK potentially carrying less weight when applying for a marketing authorization in the EU. Review of an NDA by the FDA If clinical trials are successful, the next step in the drug development process is the preparation and submission to the FDA of an NDA. The NDA is the vehicle through which drug applicants formally propose that the FDA approve a new drug for marketing and sale in the US for one or more indications. The NDA must contain a description of the manufacturing process and quality control methods, as well as results of preclinical tests, toxicology studies, clinical trials and proposed labeling, among other things. The submission of most NDAs is subject to an application user fee and the sponsor of an approved NDA is also subject to annual program user fees. These fees are typically increased annually. Following submission of an NDA, the FDA conducts a preliminary review of an NDA to determine whether the application is sufficiently complete to permit substantive review. The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency' s threshold determination that it is ~~24sufficiently~~ **sufficiently** complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in- depth substantive review. The FDA has agreed to goals to review and act within ten months from filing for standard review NDAs and within six months for NDAs that have been designated for " priority review **.** " ~~.~~ Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and

facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease or condition to be treated by the drug, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. ~~The~~ **25The** FDA is required to refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. On the basis of the FDA' s evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA' s satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA intends to review such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post- approval studies, including Phase 4 clinical trials, be conducted to further assess the drug' s safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post- market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and submission to FDA of an sNDA, which may require FDA review and approval prior to implementation. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs. Expedited approval pathwaysThe FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life- threatening disease or condition. These programs are referred to as Fast Track designation, Breakthrough Therapy designation and Priority Review designation. In addition, accelerated approval offers the potential for approval based on a surrogate or intermediate clinical endpoint. In May 2014, the FDA published a final Guidance for Industry titled " Expedited Programs for Serious Conditions Drugs and Biologics, " which provides guidance on the FDA programs that are intended to facilitate and expedite development and review of new drug candidates as well as threshold criteria generally applicable to concluding that a drug candidate is a candidate for these ~~25expedited~~ -- **expedited** development and review programs. The FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life- threatening disease or condition, and nonclinical or clinical data demonstrate the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product' s application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA' s review clock for a Fast Track application does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process. A product may be designated as a Breakthrough Therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life- threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing available therapies on one or more ~~clinically~~ **26clinically** significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to Breakthrough Therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross disciplinary project lead for the review team; rolling review; and, taking other steps to design the clinical trials in an efficient manner. FDA intends to review applications for standard review drug products within ten months of the 60- day filing date; and, applications for priority review drugs within six months. Priority review can be applied to drugs that the FDA determines treat a serious condition, and if approved, would offer a significant improvement in safety or effectiveness. The FDA determines, on a case- by- case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. Accelerated approval pathwayThe FDA may grant accelerated approval to a drug for a serious or life- threatening condition that provides a meaningful therapeutic advantage to patients over available treatments based upon a determination that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated

approval for such drug for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality (IMM) and that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval. For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a drug. The accelerated approval pathway is most often used in settings in which the course of a disease is long, and an extended period of time is required to measure the intended clinical benefit of a drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the ~~26development~~ -- **development** and approval of drugs for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit. The accelerated approval pathway is contingent on a sponsor' s agreement to conduct, in a diligent manner, additional post- approval confirmatory studies to verify and describe the drug' s clinical benefit. As a result, a drug candidate approved on this basis is subject to rigorous post- marketing compliance requirements, including the completion of Phase 4 or post- approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post- approval studies, or confirm a clinical benefit during post- marketing studies, would allow the FDA to withdraw the drug from the market on an expedited basis. In addition, all promotional materials for drugs approved under accelerated regulations are subject to prior review by the FDA. ~~Post~~ **27Post** - Approval Requirements Drugs manufactured or distributed pursuant to FDA, EMA and MHRA approvals are subject to pervasive and continuing regulation by the FDA, EMA and MHRA and other national competent authorities in the EU including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, tracking and tracing, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third- party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post- market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and consistent with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off- label uses, and a company that is found to have improperly promoted off- label uses may be subject to significant liability. However, physicians may, in their independent medical judgment, prescribe legally available products for off- label uses. The FDA does not regulate the behavior of physicians in their choice of treatments but the FDA does restrict manufacturer' s communications on the subject of off- label use of their products. In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, and its implementing regulations, as well as the Drug Supply Chain Security Act, or DSCSA, which regulate the distribution and tracing of prescription drugs and prescription drug samples at the federal level, and set minimum standards for the regulation of drug distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCA imposes requirements to track and trace drug products, ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market. Many jurisdictions, including the EU and the UK, require each marketing authorization holder, national competent authority and the EMA to operate a pharmacovigilance system to ensure that the safety of all medicines is monitored throughout their use. The overall EU pharmacovigilance system operates through cooperation between the EU Member States, EMA and the EC. ~~27Orphan~~ -- **Orphan** Drug Designation and Exclusivity Under the Orphan Drug Act, the FDA may designate a drug product as an " orphan drug " if it is intended to treat a rare disease or condition, generally meaning that it affects fewer than 200, 000 individuals in the US, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the US for treatment of the disease or condition will be recovered from sales of the product. A company must request orphan drug designation before submitting an NDA for the drug and rare disease or condition. Orphan drug designation does not shorten the goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the application fee. After the FDA grants Orphan ~~Drug~~ **drug** ~~Designation~~ **designation** , the name of the drug and its potential orphan- designated use are disclosed publicly by the FDA. ~~If~~ **28If** a product with orphan designation

receives the first FDA approval for the disease or condition for which it has such designation, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor' s marketing application for the same drug for the same indication for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different drug for the same rare disease or condition, nor does it block the approval of the same drug for different indications. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity. Orphan exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same drug for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand. In the EU and UK, under Regulation (EC) 141 / 2000 and the UK Human Medicines Regulation 2012 (as amended), respectively, medicinal products may be granted an orphan drug designation if they are used to treat or prevent life- threatening or chronically debilitating conditions that affect no more than five in 10, 000 people in the EU / UK and for which there is no satisfactory method of diagnosis, prevention or treatment when the application is made, or when the medicinal product is of significant benefit to those affected by the condition. In addition, orphan drug designation can be granted to drugs used to treat or prevent life- threatening or chronically debilitating conditions which, for economic reasons, would be unlikely to be developed without incentives. The application for orphan designation must be submitted to and approved by the EMA in respect of the EU or to the MHRA for Great Britain before an application is made for marketing authorization for the product. Medicinal products which benefit from orphan status, which they successfully maintain post- grant of the marketing authorization, can benefit from up to ten years of market exclusivity in respect of the approved indication. This prevents regulatory authorities in the EU or Great Britain, as the case may be, from granting marketing authorizations for similar medicinal products for the same therapeutic indication, unless another applicant can show that the similar medicinal product in question is safer, more effective or clinically superior to the orphan- designated product or if the marketing authorization holder consents to the second orphan medicinal product application, or where the marketing authorization holder cannot supply the needs of the market. The ten- year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify the maintenance of market exclusivity. Conversely, the 10- year exclusivity period can be further extended by 2 years, when pediatric studies are conducted in accordance with an agreed pediatric investigation plan (PIP) and in completion of all the legal requirements. However, the general pharmaceutical legislative framework, as well as the framework applicable to orphan and pediatric medicinal products in the EU, is under review. The EC expects to publish its position on this in March 2023. Although the final proposals are not yet formally known, it is expected that there will be a reduction in applicable regulatory exclusivities which will significantly affect all medicinal products that will be authorized after the legislative changes have taken effect, including a reduction in the 10- year orphan market exclusivity, which will be modulated according to certain parameters. ~~28Pediatric --~~ **Pediatric** studies and exclusivityUnder the Pediatric Research Equity Act of 2003, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With enactment of the Food and Drug Administration Safety and Innovation Act of 2012 (the FDASIA), sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The applicant, the FDA and the FDA' s internal review committee must then review the information submitted, consult with each other and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time. ~~The~~ **29The** FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in FDASIA. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation. Pediatric exclusivity is another type of non- patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non- patent and orphan exclusivity. This six- month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA' s request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application. In the EU and the UK, a six- month extension to a supplementary protection certificate may be granted, subject to certain circumstances, upon the completion of an agreed pediatric investigation plan (PIP). However, within the EU, regulatory protections afforded to medicinal products such as data exclusivity, marketing protection, market exclusivity for orphan indications and pediatric extensions are currently under review and could be curtailed in future years. **ANDA** ~~Abbreviated New Drug Applications~~ for generic drugsIn 1984, with passage of the Hatch- Waxman Amendments to the FDCA, Congress established an abbreviated regulatory scheme allowing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs. To obtain approval of a generic drug, an applicant must submit an ANDA to the agency. An ANDA is a comprehensive submission that contains, among other things, data and information pertaining to the active pharmaceutical ingredient, bioequivalence, drug product formulation, specifications and stability of the generic drug, as well as analytical methods, manufacturing process validation data and quality control procedures. ANDAs are " abbreviated "

because they generally do not include preclinical and clinical data to demonstrate safety and effectiveness. Instead, in support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference listed drug (RLD). Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form and the strength of the drug. An applicant may submit an ANDA suitability petition to request the FDA' s prior permission to submit an abbreviated application for a drug that differs from the RLD in route of administration, dosage form, or strength, or for a drug that has one different active ingredient in a fixed combination drug product (i. e., a drug product with multiple active ingredients). At the same time, the FDA must also determine that the generic drug is " bioequivalent " to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if " the rate and extent of absorption of the drug do not ~~29show~~ -- **show** a significant difference from the rate and extent of absorption of the listed drug. " Upon approval of an ANDA, the FDA indicates whether the generic product is " therapeutically equivalent " to the RLD in its publication " Approved Drug Products with Therapeutic Equivalence Evaluations, " also referred to as the " Orange Book. " Physicians and pharmacists may consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA' s designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient. 505 (b) (2) **NDAAs** ~~New Drug ApplicationsAs~~ an alternative path to FDA approval for modifications to formulations or uses of products previously approved by the FDA pursuant to an NDA, an applicant may submit an NDA under Section 505 (b) (2) of the FDCA. Section 505 (b) (2) was enacted as part of the Hatch- Waxman Amendments and permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by, or for, the applicant, and for ~~which~~ **30which** the applicant has not obtained a right of reference. If the 505 (b) (2) applicant can establish that reliance on the FDA' s previous findings of safety and effectiveness is scientifically and legally appropriate, it may eliminate the need to conduct certain preclinical studies or clinical trials of the new product. The FDA may also require companies to perform additional bridging studies or measurements, including clinical trials, to support the change from the previously approved reference drug. The FDA may then approve the new drug candidate for all, or some, of the label indications for which the reference drug has been approved, as well as for any new indication sought by the 505 (b) (2) applicant. Hatch- Waxman patent certification and the 30- month stayIn seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent whose claims cover the applicant' s product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA' s Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. To the extent that the Section 505 (b) (2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would. Specifically, the applicant must certify that (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product. The ANDA applicant may also elect to submit a statement certifying that its proposed ANDA label does not contain (or carve out) any language regarding the patented method- of- use rather than certify to a listed method- of- use patent, known as a Section VIII statement. If the applicant does not challenge the listed patents, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired. A certification that the new product will not infringe the already approved product' s listed patents, or that such patents are invalid, is called a Paragraph IV certification. If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit, or a decision in the infringement case that is favorable to the ANDA applicant. Patent term extensionAfter NDA approval, owners of relevant drug patents may apply for up to a five- year patent extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory process. The allowable patent term extension is typically calculated as one- half the time between the effective date of an IND application and the submission date of a NDA, plus the time between NDA submission date and the NDA approval date up to a maximum of five years. The time can be shortened if the FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years from the date of product ~~30approval~~ -- **approval** . Only one patent applicable to an approved drug is eligible for extension and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended and the application for the extension must be submitted prior to the expiration of the patent in question. However, we may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Exclusivity under the Hatch- Waxman AmendmentsIn addition, under the Hatch- Waxman Amendments, the FDA may not approve an ANDA or 505 (b) (2) NDA referencing a particular drug until any applicable period of non- patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non- patent data exclusivity for a new drug containing a new chemical entity (NCE). For the purposes of this provision, an NCE is a drug that contains no active moiety that has previously been approved by ~~the~~ **31the** FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA or 505 (b) (2) NDA may not be submitted to the FDA until the expiration of five years from the date

the NDA is approved, unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval. The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three- year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three- year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five- year NCE exclusivity, an award of three- year exclusivity does not block the FDA from accepting ANDAs or 505 (b) (2) NDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product; it does, however, block the FDA from approving ANDAs or 505 (b) (2) NDAs during the period of exclusivity. The FDA typically makes decisions about awards of data exclusivity shortly before a product is approved. FDA **EUASection** ~~Emergency Use AuthorizationSection~~ 564 of the FDCA (21 U. S. C. § 360bbb- 3) allows the FDA to authorize the shipment of drugs, biological products (including vaccines), or medical devices that either lack required approval, licensure, or clearance (unapproved products), or are approved but are to be used for unapproved ways to diagnose, treat, or prevent serious diseases or conditions in the event of an emergency declaration by the **US Department of Health and Human Services (** ~~HHS~~ **DHHS)** Secretary. On February 4, 2020, then- HHS Secretary Alex M. Azar II determined that a public health emergency exists for COVID- 19 and declared that it justifies the authorization of emergency use of in vitro diagnostics for COVID- 19, pursuant to Section 564 of the FDCA. On March 2, 2020, March 24, 2020, and March 27, 2020, Secretary Azar issued corresponding declarations for personal respiratory protective devices; for medical devices, including alternative products used as medical devices; and, for drugs and biological products. The determination and these declarations were published in the Federal Register on February 7, 2020, March 10, 2020, March 27, 2020, and April 1, 2020, respectively. While the emergency determination and declaration are effective, the FDA may authorize the use of an unapproved product or an unapproved use of an approved product if it concludes that: • an agent referred to in the emergency declaration could cause a serious or life- threatening disease or condition; • it is reasonable to believe that the authorized product may be effective in diagnosing, treating, or preventing that disease or condition or a serious or life- threatening disease or condition caused by an approved product or a product marketed under an EUA; ~~31~~ • the known and potential benefits of the authorized product, when used for that disease or condition, outweigh known and potential risks, taking into consideration the material threat of agents identified in the emergency declaration; • there is no adequate, approved, and available alternative to the authorized product for diagnosing, preventing, or treating the relevant disease or condition; • any other criteria prescribed by the FDA is satisfied. Medical products that are granted an EUA are only permitted to commercialize their products under the terms and conditions provided in the authorization. The FDCA authorizes FDA to impose such conditions on an EUA as may be necessary to protect the public health. Consequently, postmarketing requirements will vary across EUAs. In addition, FDA has, on occasion, waived requirements for drugs marketed under an EUA. ~~Generally~~ **32Generally** , EUAs for unapproved products or unapproved uses of approved products require that manufacturers distribute factsheets for healthcare providers, addressing significant known and potential benefits and risk, and the extent to which benefits and risks are unknown, and the fact that FDA has authorized emergency use; and, distribution of factsheets for recipients of the product, addressing significant known and potential benefits and risk, and the extent to which benefits and risks are unknown, the option to accept or refuse the product, the consequences of refusing, available alternatives, and the fact that FDA has authorized emergency use. Generally, EUAs for unapproved products and, per FDA' s discretion, EUAs for unapproved uses of approved products, include requirements for adverse event monitoring and reporting, and other recordkeeping and reporting requirements. Note, however, that approved products are already subject to equivalent requirements. In addition, FDA may include various requirements in an EUA as a matter of discretion as deemed necessary to protect the public health, including restrictions on which entities may distribute the product, and how to perform distribution (including requiring that distribution be limited to government entities), restrictions on who may administer the product, requirements for collection and analysis of safety and effectiveness data, waivers of cGMP, and restrictions applicable to prescription drugs or restricted devices (including advertising and promotion restrictions). The FDA may revoke an EUA where it is determined that the underlying health emergency no longer exists or warrants such authorization, if the conditions for the issuance of the EUA are no longer met, or if other circumstances make revocation appropriate to protect the public health or safety. **On May 11** ~~It is difficult to predict when the determination and declaration will be revoked or ended , which will impact the marketing of products under existing EUAs and the availability of new EUAs based on the determination and declaration. For example, in January~~ 2023, ~~Congress proposed legislation that would end other --~~ **the** COVID- 19 **PHE declared under** ~~- related emergency declarations, if passed, and the White House has issued a statement that those --~~ **the Public Health Services Act expired** ~~declarations will end on May 11, 2023~~ . FDA officials have stated that this will not impact FDA' s ability to authorize ~~treatments~~ **medical countermeasures** for emergency use, such that existing EUAs will remain in effect and the agency may continue to issue new EUAs going forward when criteria for issuance are met. This is nonetheless subject to change. Pharmaceutical Coverage, Pricing and Reimbursement In the US and ~~markets in~~ other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third- party payors to reimburse all or part of the associated healthcare costs. Third- party payors include federal and state government health programs such as Medicare and Medicaid, commercial health insurers, managed care organizations, and other organizations. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. For example, in the US, there have been several recent US Congressional inquiries and proposed federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform government program reimbursement methodologies for drugs. This includes the Consolidated Appropriations Act of 2021, which addressed ~~32several --~~ **several** drug price reporting and transparency measures, such as a new requirement for

prescription drug plan sponsors and Medicare Advantage organizations to develop tools to display Medicare Part D prescription drug benefit information in real time and for insurance companies and employer- based health plans to report information on pharmacy benefit and drug costs to the Secretaries of the Departments of Health and Human Services, Labor and the Treasury. Additionally, on March 11, 2021, Congress enacted the American Rescue Plan Act of 2021, which included among its provisions a sunset of the provision in the Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act (**collectively,** the Affordable Care Act) that capped pharmaceutical manufacturers' rebate liability under the Medicaid Drug Rebate Program (MDRP). Under the Affordable Care Act, manufacturers' rebate liability was capped at 100 % of the average manufacturer price for a covered outpatient drug. ~~Effective~~ **As of** January 1, 2024, manufacturers' MDRP rebate liability ~~will~~ **is** no longer ~~be~~ capped, potentially resulting in a manufacturer paying more in MDRP rebates than it receives on the sale of certain covered outpatient drugs. In August 2022, President Biden signed into law the Inflation Reduction Act of 2022 (IRA), which implements substantial changes to the Medicare program, including drug pricing reforms and changes to the Medicare Part D benefit design. Among other reforms, the IRA imposes inflation rebates on drug manufacturers for products reimbursed under Medicare Parts B and D if the prices of those products increase faster than inflation; implements changes to the Medicare Part D benefit that, beginning in 2025, will cap beneficiary annual out- of- pocket spending at $ 2, 000, while imposing new discount obligations for pharmaceutical manufacturers; and, beginning in 2026, establishes a " maximum fair price " for a fixed number of pharmaceutical and biological products covered under ~~Medicare~~ **33Medicare** Parts B and D following a price negotiation process with the Centers for Medicare and Medicaid Services (CMS). ~~On~~ **CMS has also taken steps to implement the IRA, including: on** February 9, 2023, **issuing** ~~CMS issued~~ guidance that further clarified the scope of the Medicare Part B and Part D inflationary rebates, including a detailed discussion of which Part B and Part D products are eligible for such rebates and how the rebates are calculated **; on June 30, 2023, issuing guidance detailing the requirements and parameters of the first round of price negotiations, to take place during 2023 and 2024, for products subject to the " maximum fair price " provision that would become effective in 2026; on August 29, 2023, releasing the initial list of ten drugs subject to price negotiations; on November 17, 2023, releasing guidance outlining the methodology for identifying certain manufacturers eligible to participate in a phase- in period where discounts on applicable products will be lower than those required by the Medicare Part D Manufacturer Discount Program; and on December 14, 2023, releasing a list of 48 Medicare Part B products that had an adjusted coinsurance rate based on the inflationary rebate provisions of the IRA for the time period of January 1, 2024 to March 31, 2024** . At the state level, legislatures ~~have~~ **are** increasingly ~~passed~~ **passing** legislation and ~~implemented~~ **implementing** regulations designed to control pharmaceutical and biological product pricing, including limitations on reimbursement, discounts, restrictions on certain product access and marketing, cost disclosure ~~;~~ **(** including disclosures for certain price increases or launches of costly drugs **)** , and transparency measures, and, in some cases, to encourage importation from other countries and bulk purchasing. Thus, even if a product candidate is approved, sales of the product will depend, in part, on the extent to which third- party payors provide coverage and establish adequate reimbursement levels for the product. It is likely that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for a pharmaceutical manufacturer' s products or additional pricing pressure. In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost- effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third- party payor not to cover a product candidate could reduce physician utilization once the product is approved and have an adverse effect on sales, results of operations and financial condition. Additionally, a payor' s decision to provide coverage for a product does not imply that adequate reimbursement will be approved at a rate that covers our costs, including research, development, manufacture, sale and distribution. Further, one payor' s determination to provide coverage for a drug product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor. The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of drugs have been a focus in this effort. Governments and third- party payors have shown significant interest in implementing cost- containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Increasingly, the third- party payors who reimburse patients or healthcare providers, such as government and private insurance plans, are requiring that drug companies provide them with predetermined discounts from list prices, and are seeking to reduce the prices charged or the amounts reimbursed for medical products. Adoption of price controls and cost- containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company' s revenue generated from the sale of any approved products. Coverage policies and third- party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future. ~~33In~~ **In** the EU, pricing and reimbursement methods can differ in each Member State. Some Member States and the UK may require that health technology assessments (HTA) be completed to obtain reimbursement or pricing approval. The outcome of HTA assessments is decided on a national basis and some Member States may decide not to reimburse the use of medicines or may reduce the rate of reimbursement. In December 2021, the EU adopted a new Regulation on Health Technology Assessment which allows Member States to carry out joint clinical assessments and operate joint clinical consultations. It is expected that the new Regulation will come into effect in 2025. ~~Healthcare~~ **34Healthcare** and Privacy Law and Regulation Healthcare providers and third- party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third- party payors and customers are subject to broadly applicable federal and state fraud and abuse laws, anti- kickback laws, false claims laws, laws requiring

reporting of payments to physicians and teaching physicians and other healthcare providers, patient privacy laws and regulations and other healthcare laws and regulations that may constrain business and / or financial arrangements. Restrictions under applicable healthcare laws and regulations, include the following: ● the federal Anti- Kickback Statute, which is a criminal law that prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid. The term " remuneration " has been broadly interpreted to include anything of value. The intent standard under the federal Anti- Kickback Statute was amended by the Affordable Care Act to a stricter standard such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. The federal Anti- Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers **, pharmacies** , purchasers, and formulary managers on the other, including, for example, consulting / speaking arrangements, discount and rebate offers, grants, charitable contributions, and patient support offerings, among others. A conviction for violation of the federal Anti- Kickback Statute can result in criminal fines and / or imprisonment and requires mandatory exclusion from participation in federal health care programs. Exclusion may also be imposed if the government determines that an entity has committed acts that are prohibited by the federal Anti- Kickback Statute. Although there are a number of statutory exceptions and regulatory safe harbors to the federal Anti- Kickback Statute protecting certain common business arrangements and activities from prosecution or regulatory sanctions, the exceptions and safe harbors are drawn narrowly, and practices that involve remuneration to those who prescribe, purchase, or recommend pharmaceutical and biological products, including certain discounts, or engaging such individuals as speakers or consultants, may be subject to scrutiny if they do not fit squarely within an exception or safe harbor. Moreover, a claim including items or services resulting from a violation of the federal Anti- Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act; ● the federal civil and criminal false claims laws and civil monetary penalty laws, including the civil False Claims Act, which prohibits, among other things, (i) knowingly presenting, or causing to be presented, claims for payment of government funds that are false or fraudulent; (ii) knowingly making, or using or causing to be made or used, a false record or statement material to a false or fraudulent claim; (iii) knowingly making, using or causing to made or used a false record or statement material to an obligation to pay money to the government; or (iv) knowingly concealing or knowingly and improperly avoiding, decreasing, or concealing an obligation to pay money to the federal government. Private individuals, commonly known as " whistleblowers, " can bring FCA qui tam actions, on behalf of the government and may share in amounts paid by the entity to the government in recovery or settlement. Pharmaceutical companies have been investigated and / or subject to government enforcement actions asserting liability under the FCA in connection with their alleged off- label promotion of drugs, purportedly concealing price concessions in the pricing information submitted to the government for government price reporting purposes, and allegedly providing free product to customers with the expectation that the customers would bill federal healthcare programs for the product. In addition, a claim including items or services resulting ~~34from --~~ **from** a violation of the federal Anti- Kickback Statute constitutes a false or fraudulent claim for purposes of the FCA. Moreover, manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to " cause " the submission of false or fraudulent claims. FCA liability is potentially significant in the healthcare industry because the statute provides for treble damages and significant mandatory penalties per false or fraudulent claim or statement for violations. Such per- claim penalties are currently set at $ 13, ~~508~~ **946** to $ 27, ~~018~~ **894** per false claim or statement for penalties assessed after January ~~30~~ **15** , ~~2023~~ **2024** , with respect to violations occurring after November 2, 2015. Criminal ~~penalties~~ **35penalties** , including imprisonment and criminal fines, are also possible for making or presenting a false, fictitious or fraudulent claim to the federal government; ● the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for, among other things, executing or attempting to execute a scheme to defraud any healthcare benefit program, including any third- party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statements or representations, or making false statements relating to healthcare benefits, items or services. Similar to the federal Anti- Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation; ● HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, which impose HIPAA- covered entities and their business associates obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security, ~~accesibility~~ **accessibility** and transmission of individually identifiable health information, including protected health information (PHI). While the vast majority of HIPAA obligations do not apply to pharmaceutical companies, the requirements inform privacy and security practices across the industry and may impact interactions with health care providers. ~~Moerver~~ **Moreover** , HITECH created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions; ● the federal payment transparency tracking and reporting requirements known as the federal Physician Payments Sunshine Act, implemented as the Open Payments Program, which requires certain manufacturers of drugs, devices, biologics and medical supplies, among others, to report annually to CMS, within the ~~US Department of Health and Human Services (HHS~~ **DHHS** ~~)~~ , information related to payments and other transfers of value made by that entity to US- licensed physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified registered nurse anesthetists, certified nurse midwives, and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members **. Failure to timely, accurately, and completely**

submit the required information for all payments, transfers of value and ownership or investment interests may result in civil monetary penalties; ● state laws that require the reporting of certain pricing information, including information pertaining to and justifying price increases, prohibit prescription drug price gouging; or impose payment caps on certain pharmaceutical products deemed by the state to be " high cost " ; and ● analogous state and foreign laws and regulations, such as state anti- kickback and false claims laws, which may be broader in scope than analogous federal laws and may apply to sales or marketing arrangements and claims involving healthcare items or services regardless of payor. Some state, local and foreign laws require pharmaceutical companies to comply with the pharmaceutical industry' s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, restrict payments that may be made to healthcare providers and other potential referral sources, and / or require drug manufacturers to report information related to payments and transfers of value made to physicians and other health care providers or entities or marketing expenditures. In addition, there are state and local laws that require registration of sales representatives; state laws that require drug manufacturers to report information related to drug pricing; data privacy and security laws and regulations in foreign jurisdictions that may be more stringent than those in the US (such as the EU' s General Data Protection Regulation (EU GDPR), which became effective in May 2018); federal and state laws governing the privacy and security of personal information (including health information) many of ~~35which~~ -- **which** differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts; and state laws related to insurance fraud in the case of claims involving private insurers. ~~Efforts~~ **36Efforts** to ensure that our business arrangements will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, individual imprisonment, additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non- compliance with these laws, possible exclusion from participation in federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. Healthcare Reform The US **federal** and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the US Congress enacted the Affordable Care Act, which included changes to the coverage and payment for drug products under government health care programs. This law was designed to expand access to health insurance coverage for uninsured and underinsured individuals while containing overall healthcare costs. There have been numerous judicial and Congressional challenges to certain aspects of the Affordable Care Act, as well as efforts to repeal or replace certain aspects of the Affordable Care Act. For example, ~~Congress has considered legislation that would repeal, or repeal and replace, all or part of~~ the ~~Affordable Care Act. While Congress has not passed comprehensive repeal legislation, several bills affecting the implementation of certain taxes under the Affordable Care Act have been enacted. The~~ Tax Cuts and Jobs Act of 2017 ~~includes~~ **included** a provision that repealed the tax- based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the " individual mandate **.** " ~~.~~ Further, the Consolidated Appropriations Act of 2020 fully repealed the Affordable Care Act' s mandated " Cadillac " tax on **certain** high- cost employer- sponsored health coverage and **the** medical device **excise** tax **on non- exempt medical devices,** and also eliminated the health insurer tax. The Bipartisan Budget Act of 2018 (BBA) amended the Affordable Care Act to increase from 50 % to 70 % the point- of- sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the " donut hole. " Under the IRA, this coverage gap will be eliminated beginning January 1, 2025. The IRA also requires pharmaceutical manufacturers to pay 10 % of the negotiated price of brands, biologics, and biosimilar products, when Medicare Part D beneficiaries are in the initial coverage phase, and 20 % of the negotiated price during the catastrophic phase of Medicare Part D coverage. In December 2018, CMS published a new final rule permitting further collections and payments to and from certain Affordable Care Act qualified health plans and health insurance issuers under the Affordable Care Act risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. On June 17, 2021, the US Supreme Court dismissed the most recent judicial challenge to the Affordable Care Act brought by several states without specifically ruling on the constitutionality of the law. It is unclear how future actions before the Supreme Court, other such litigation, and the healthcare reform measures of the Biden administration will impact the Affordable Care Act. Other legislative changes have been proposed and adopted in the US since the Affordable Care Act was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $ 1. 2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation' s automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2 % per fiscal year, which went into effect in April 2013, and, due to subsequent legislative amendments, will remain in effect ~~into~~ **through the first six months of the fiscal year** ~~2031~~ **2032 sequestration order** , unless additional Congressional action is taken (with the exception of a temporary suspension **, and later a temporary reduction,** instituted during the COVID- 19 pandemic that expired on July 1, 2022). ~~To offset the temporary suspension during the COVID- 19 pandemic, in 2030, reductions in Medicare payments will be 2. 25 % for the first half of the year, and 3 % in the second half of the year. The sequestration was temporarily halted from May 1, 2020 to March 31, 2022 as a result of various legislation, and later reduced to 1 % from April 2022 to until July 1, 2022.~~ In January ~~362013~~ -- **2013** , former President Obama signed into law the American Taxpayer Relief Act of 2012 (ATRA), which, among other things, further reduced Medicare payments to several providers,

including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. In addition, there has been heightened governmental scrutiny in the US of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to ~~product~~ **37product** pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. For example, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which among other changes, eliminates the statutory Medicaid drug rebate cap, currently set at 100 % of a drug' s average manufacture price, for single source and innovator multiple source drugs, beginning January 1, 2024. The American Rescue Plan Act also temporarily increased premium tax credit assistance for individuals eligible for subsidies under the ~~ACA~~ **Affordable Care Act** for 2021 and 2022 and removed the 400 % federal poverty level limit that otherwise applies for purposes of eligibility to receive premium tax credits. The IRA extended this increased tax credit assistance and removal of the 400 % federal poverty limit through 2025. The Biden administration has also taken executive actions to address drug pricing and other healthcare policy changes. For example, in response to a July 9, 2021 Executive Order from President Biden that included several prescription drug initiatives, on September 9, 2021, the **DHHS** ~~Department of Health and Human Services~~ issued a Comprehensive Plan for Addressing High Drug Prices that identified potential legislative policies and administrative tools that Congress and the agency can pursue in order to make drug prices more affordable and equitable, improve and promote competition throughout the prescription drug industry, and foster scientific innovation. Additionally, on September 12, 2022, President Biden issued an Executive Order to promote biotechnology and biomanufacturing innovation. The Order noted several methods through which the Biden Administration would support the advancement of biotechnology and biomanufacturing in healthcare, and instructed the **DHHS** ~~Department of Health and Human Service~~ to submit, within 180 days of the Order, a report assessing how to use biotechnology and biomanufacturing to achieve medical breakthroughs, reduce the overall burden of disease, and improve health outcomes. In August 2022, President Biden signed into law the IRA, which implements substantial changes to the Medicare program, including drug pricing reforms and changes to the Medicare Part D benefit design. Among other reforms, the IRA imposes inflation rebates on drug manufacturers for products reimbursed under Medicare Parts B and D if the prices of those products increase faster than inflation; implements changes to the Medicare Part D benefit that, beginning in 2025, will cap benefit annual out- of- pocket spending at $ 2, 000, while imposing new discount obligations for pharmaceutical manufacturers; and, beginning in 2026, establishes a " maximum fair price " for a fixed number of pharmaceutical and biological products covered under Medicare Parts B and D following a price negotiation process with CMS. On October 14, 2022 President Biden issued an Executive Order on Lowering Prescription Drug Costs for Americans, which instructed the Secretary of the **DHHS** ~~Department of Health and Human Services~~ to consider whether to select for testing by the CMS Innovation Center new health care payment and delivery models that would lower drug costs and promote access to innovative drug therapies for beneficiaries enrolled in the Medicare and Medicaid programs. ~~The Executive Order further directed the Secretary of the Department of Health and Human Services to submit, within 90 days after the date of the Executive Order, a report regarding any models that may lead to lower cost- sharing for commonly used drugs and support value- based payment that promotes high- quality care.~~ On February 14, 2023, the **DHHS** ~~Department of Health and Human Services~~ issued a report in response to the October 14, 2022, Executive Order, which, among other things, selects three potential drug affordability and accessibility models to be tested by the CMS Innovation Center. Specifically, the report addresses: (1) a model that would allow Part D Sponsors to establish a " high- value drug list " setting the maximum co- payment amount for certain common generic drugs at $ 2; (2) a Medicaid- focused model that would establish a partnership between CMS, manufacturers, and state Medicaid agencies that would result in multi- state outcomes- based agreements for certain cell and gene therapy drugs; and (3) a model that would adjust Medicare Part B payment amounts for Accelerated Approval Program drugs to advance the developments of novel treatments. It remains to be seen how these drug pricing initiatives will affect the broader pharmaceutical industry. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. **For example, several recently passed state laws require disclosures to state agencies and / or commercial purchasers with respect to price increases and new product launches that exceed certain pricing thresholds as identified in the relevant statutes. Some of these laws and regulations contain ambiguous requirements that government officials have not yet clarified. Given the lack of clarity in the laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent federal and state laws and regulations. Some states have also established prescription drug affordability boards that are tasked with identifying certain high- cost prescription products that may pose affordability challenges for consumers and payors, conducting cost reviews on such products, and, in some circumstances, imposing upper payment limits on such products.** Policy changes, including potential modification or repeal of all or parts of the ~~ACA~~ **Affordable Care Act** or the implementation of new health care legislation, could result in significant changes to the health care system, which may prevent us from being able to generate revenue, attain profitability or commercialize our drugs. We expect that additional state and federal healthcare reform measures will be ~~37adopted~~ -- **adopted** in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand or lower pricing for our product candidates, or additional pricing pressures. ~~Outside~~ **38Outside** the US, ensuring adequate coverage and payment for our products will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of our product candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in

delays in our commercialization efforts. Third- party payors are challenging the prices charged for medical products and services, and many third- party payors limit reimbursement for newly approved health care products. Recent budgetary pressures in many EU countries are also causing governments to consider or implement various cost- containment measures, such as price freezes, increased price cuts and rebates. If budget pressures continue, governments may implement additional cost- containment measures. Cost- control initiatives could decrease the price we might establish for products that we may develop or sell, which would result in lower product revenues or royalties payable to us. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. ~~Further~~ **Scientific and Medical AdvisorsWe utilize scientists** , **key opinion leaders and physicians** ~~it is possible that additional governmental action is taken in response~~ to ~~the COVID~~ **advise us on scientific and medical matters as part of our ongoing commercialization activities and research and product development efforts, including experts in clinical trial design, preclinical development work, chemistry, biology, immunology, oncology and immuno** - ~~19 pandemic~~ **oncology. Certain of our consultants receive non- employee options to purchase our common stock and certain of our scientific and medical advisors receive honorarium for time spent assisting us** . Manufacturing and Raw MaterialsWe currently do not have the manufacturing capabilities or experience necessary to produce our products or any product candidates for clinical trials. We currently use one active pharmaceutical ingredient manufacturer and one finished goods manufacturer for each of our products. We do not own or operate manufacturing or distribution facilities or resources for clinical or commercial production and distribution of our product for commercial use or for preclinical and clinical trials. We assign internal personnel to manage and oversee third parties working on our behalf under contract. These third parties manufacture raw materials, the active pharmaceutical ingredients and finished drug product for commercial distribution and for use in clinical studies. We currently rely on and will continue to rely on these third- party contract manufacturers to produce sufficient quantities of our products. Human Capital ResourcesAs of December 31, ~~2022~~ **2023** , we have ~~155~~ **147** full- time employees. Of these employees, ~~84~~ **83** were engaged in commercial activities, ~~40~~ **37** were engaged in research and development activities, and ~~31~~ **27** were engaged in general and administrative activities. We also engage temporary employees and consultants. In November 2021, we ~~announced our plan to exit~~ **exited our** early- stage research ~~and~~ **to** focus **our** resources on our mid to late- stage development programs and commercial efforts **,** which resulted in elimination of positions primarily in **our** research organization. In October 2022, we ~~announced a~~ **made an additional** reduction in our workforce primarily in our development and administration groups. None of our employees are represented by a collective bargaining arrangement, and we believe our relationship with our employees is good. We aim to provide a stimulating and rewarding work environment, with recognition for accomplishments and the opportunity to advance our employees' careers while sharing in the excitement of our growth and success. We know that our success depends on the experience, intellect, and talent of our highly motivated team, and we truly value the people who make our organization great. We provide a collaborative work environment that is both personally fulfilling and enables our employees to work together to achieve the purpose and goals of the organization. Our human capital efforts focus on maintaining a sufficient number of skilled employees in each respective department. Recruiting and retaining experienced and qualified sales and marketing personnel to successfully commercialize our product and scientific personnel to continue to perform research and development work in the future will be critical to our business success. Our ability to recruit, develop and retain highly skilled talent is a significant determinant of our success. To facilitate talent attraction, retention, and development, we strive to be an inclusive, diverse, and safe workplace with opportunities for our employees to grow and develop in their careers, ~~supported~~ **39supported** by competitive compensation, opportunities for equity ownership, development opportunities that enable continued learning and growth and employment packages that promote well- being across all aspects of our employees' lives, including health care, retirement planning and paid time off. ~~38The~~ -- **The** health, safety, and wellness of our employees is a priority in which we have always invested and intend to continue to do. We provide our employees with access to a variety of innovative, flexible, and convenient health and wellness programs. Additionally, we offer programs to help support employees physical and mental health by providing tools and resources to help them improve or maintain their health status, encourage engagement in healthy behaviors, and offer choices where possible so they are customized to meet their needs. ~~In light of the COVID- 19 pandemic, we have undertaken and plan to continue to undertake, safety measures to keep our employees' health, safety, and wellness a priority. We implemented significant changes that we determined were in the best interest of our employees, as well as the communities in which we operate, in compliance with government regulations. We endeavor to provide the safest and most effective work environment under the circumstances, but we cannot guarantee that employees who come to the office will not be exposed to COVID- 19 while at the office. It will be the responsibility of all employees to participate and cooperate in safety and cleaning protocols. We expect all employees, contractors, and visitors to our facility to comply with our COVID- 19 guidelines plan.~~ We provide compensation and benefits programs to help meet the needs of our employees. In addition to base compensation, these programs include annual bonuses, Stock Award Plans, Employee Stock Purchase Plans, 401 (k), healthcare and insurance benefits, paid time off, health and fitness benefits and various additional employee programs. We have robust annual performance review processes for reviewing employees' performance and pay. **Environmental** ~~Scientific and Medical AdvisorsWe utilize scientists~~ , ~~key opinion~~ **Social and Governance (ESG) Our approach to ESG factors is consistent with our mission and our corporate values. We are committed to conducting our business in a safe and environmentally sustainable manner that promotes the health of patients, our employees, our community and the environment. ESG oversight is exercised both at the Board level and through our executive** ~~leaders~~ **leadership . The Corporate Governance, Health Care Compliance Oversight** and ~~physicians to advise us~~ **Nominating Committee has oversight responsibility over our ESG strategy and policies and is briefed by management** on ~~scientific and medical~~ matters **related to ESG** as **appropriate. For more information** ~~part of our ongoing commercialization activities~~ and ~~research and product development~~ **the latest on our ESG** efforts, ~~including experts in clinical trial design~~ **please refer to our Proxy Statement for the 2024 Annual Meeting of**

Stockholders to be filed with the SEC. Additionally , ~~preclinical development work, chemistry, biology, immunology, oncology and immuno~~ **our full ESG report is available on our website at www. rigel. com / investors / esg. Information in our ESG Report is not incorporated by reference into this Form 10** - **K** ~~oncology. Certain of our consultants receive non- employee options to purchase our common stock and certain of our scientific and medical advisors receive honorarium for time spent assisting us~~ . Corporate InformationOur principal executive office is currently located at 611 Gateway Boulevard, Suite 900, South San Francisco, CA 94080. Prior to expiration of our previous lease agreement in January 2023, our principal executive office was in 1180 Veterans Boulevard, South San Francisco, California 94080. Our telephone number is (650) 624- 1100. Available InformationWe electronically file with the ~~Securities and Exchange Commission (~~ SEC ~~)~~ our Annual Report on Form 10- K, Quarterly Reports on Form 10- Q, Current Reports on Form 8- K, proxy and information statements **,** and amendments to such reports and statements filed or furnished pursuant to Section 13 (a) or 15 (d) of the Exchange Act. We make copies of these reports available free of charge on or through our website at www. rigel. com, as soon as reasonably practicable after we electronically file these reports with, or furnish them to, the SEC. The information found on our website is not part of or incorporated by reference into this Annual Report on Form 10- K. The SEC also maintains an internet site that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC at www. sec. gov. ~~39Item~~ **40Item** 1A. Risk ~~FactorsIn~~ -- **Factors In** evaluating our business, you should carefully consider the following risks, as well as the other information contained in this Annual Report on Form 10- K. These risk factors could cause our actual results to differ materially from those contained in forward- looking statements we have made in this Annual Report on Form 10- K and those we may make from time to time. If any of the following risks actually occurs, our business, financial condition and operating results could be harmed. The risks and uncertainties described below are not the only ones facing us. Additional risks and uncertainties not presently known to us, or that we currently see as immaterial, may also harm our business. Risks Related to Our Business and Our IndustryIf the market opportunities for our products and product candidates are smaller than we believe they are, our revenues may be adversely affected, and our business may suffer. Certain of the diseases that our products and our other product candidates being developed to address are in underserved and underdiagnosed populations. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who will seek treatment utilizing our products or product candidates, may not be accurate. If our estimates of the prevalence or number of patients potentially on therapy prove to be inaccurate, the market opportunities for ~~fostamatinib~~ **our products** and our other product candidates may be smaller than what we believe they are, our prospects for generating expected revenue may be adversely affected and our business may suffer. We may need to continue to increase the size of our organization and we may encounter difficulties with managing our growth, which could adversely affect our business and results of operations. While we have substantially increased the size of our organization particularly in our sales force in the third quarter of 2021, we also implemented two separate reductions in workforce in November 2021 and October 2022, and may need to add additional qualified personnel and resources to support our commercial activities and expected growth. Our current infrastructure may be inadequate to support our development and commercialization efforts and expected growth. Future growth will impose significant added responsibilities on members of management, including the need to identify, recruit, maintain and integrate additional employees, and may take time away from running other aspects of our business, including commercialization of our products and development of our other product candidates. Our future financial performance and our ability to sustain successful commercialization of our products and our ability to commercialize other product candidates that may receive regulatory approval will depend, in part, on our ability to manage any future growth effectively. In particular, as we continue to commercialize our products, we will need to support the training and ongoing activities of our sales force and will likely need to continue to expand the size of our employee base for managerial, operational, financial and other resources. To that end, we must be able to successfully: ● manage our development efforts effectively; ● integrate additional management, administrative and manufacturing personnel; ● further develop our marketing and sales organization; and ● maintain sufficient administrative, accounting and management information systems and controls. We may not be able to accomplish these tasks or successfully manage our operations and, accordingly, may not achieve our research, development, and commercialization goals. Our failure to accomplish any of these goals, including as a result of business or other interruptions resulting from ~~the~~ **a** potential ~~future impacts of the COVID- 19~~ pandemic ~~, if any~~ **or global economic slowdown** , could adversely affect our business and operations. **may** be ~~successful~~ **unable to expand our product pipeline,which could limit our growth and revenue potential** .Our business is focused on the development and commercialization of novel therapies that significantly improve the lives of patients with hematologic disorders and cancer.In this regard,we **are pursuing** ~~continue to pursue~~ internal drug discovery efforts ~~or partnerships with pharmaceutical and biotech companies,as well as academic institutions and government organizations,~~ with the goal of identifying new product candidates to advance into clinical trials. ~~Our~~ **Internal** discovery efforts to identify new product candidates require substantial technical,financial and human resources.These **internal** discovery efforts may initially show promise in identifying potential product candidates,yet ultimately fail to yield product candidates for clinical development for a number of reasons.For example,potential product candidates may,on later stage clinical trial,be **shown to** There is a high risk that drug discovery and development efforts might not generate successful product candidates. ~~At the present time, a significant portion of our operations are focused on various stages of drug identification and development.~~ We currently have ~~various~~ product candidates in the clinical testing stage **and may further pursue to expand our clinical testing efforts** . In our industry, it is statistically unlikely that the limited number of compounds that we have identified as potential product candidates will actually lead to successful product development efforts. We have invested a significant portion of our efforts and ~~40financial~~ -- **financial** resources into ~~the~~ **clinical** development ~~of fostamatinib~~ . Our ability to generate product revenue, which will not occur until after regulatory approval, if ever, will depend on the successful development, regulatory approval and eventual commercialization ~~of one~~ of our product candidates. Our compounds in clinical trials and our future leads for potential drug compounds are subject to the risks and failures inherent in the development of pharmaceutical products. These risks

include, but are not limited to, the inherent difficulty in selecting the right drug and drug target and avoiding unwanted side effects, as well as unanticipated problems relating to product development, testing, enrollment, obtaining regulatory approvals, obtaining and maintaining reimbursement in national markets and positive recommendation from HTA bodies, maintaining regulatory compliance, manufacturing, competition and costs and expenses that may exceed current estimates. In future clinical trials, we or our partners may discover additional side effects and / or a higher frequency of side effects than those observed in previously completed clinical trials. The results of preliminary and mid- stage clinical trials do not necessarily predict clinical or commercial success, and larger later- stage clinical trials may fail to confirm the results observed in the previous clinical trials. Similarly, a clinical trial may show that a product candidate is safe and effective for certain patient populations in a particular indication, but other clinical trials may fail to confirm those results in a subset of that population or in a different patient population, which may limit the potential market for that product candidate. With respect to our own compounds in development, we have established anticipated timelines with respect to the initiation of clinical trials based on existing knowledge of the compounds. However, we cannot provide assurance that we will meet any of these timelines for clinical development. Additionally, the initial results of a completed earlier clinical trial of a product candidate do not necessarily predict final results and the results may not be repeated in later clinical trials. Because of the uncertainty of whether the accumulated preclinical evidence (PK, pharmacodynamic, safety and / or other factors) or early clinical results will be observed in later clinical trials, we can make no assurances regarding the likely results from our future clinical trials or the impact of those results on our business. For example, we initiated our FORWARD study, a Phase 3 pivotal trial of fostamatinib in patients with wAIHA in March 2019, completed the enrollment in November 2021 and completed the treatment period for the last patient under the trial in April 2022. In June 2022, we announced top- line efficacy and safety data results of our FORWARD study, and the results of the trial did not demonstrate statistical significance in the primary efficacy endpoint of durable hemoglobin response in the overall study population. We conducted an in- depth analysis of these data to better understand differences in patient characteristics and outcomes and submitted these findings to the FDA. In October 2022, we announced that we received guidance from the FDA' s review of these findings. Based on the result of the trial and the guidance from the FDA, we ~~did~~ **43did** not file an sNDA for this indication. Further, we ~~have~~ **may experience errors in the analysis of our clinical trial results. For example, we conducted** our Phase 3 clinical trial to evaluate safety and efficacy of fostamatinib in hospitalized COVID- 19 patients **,** which we launched in November 2020 **and** ~~. In July 2022, we~~ completed the enrollment on this trial ~~, and on~~ **in July 2022. We previously announced in** November ~~1,~~ 2022 ~~, we announced~~ the top- line results ~~of the clinical trial. The trial approached but~~ did not meet statistical significance in the primary efficacy endpoint. ~~All prespecified secondary~~ **Upon further analysis, we discovered an error by the biostatistical CRO in the application of a statistical stratification factor. After correcting for this statistical error, the primary** ~~endpoints~~ **endpoint** ~~in the trial numerically favored fostamatinib over placebo, including mortality, time to sustained recovery, change in ordinal scale assessment, and number~~ of ~~days in~~ the ~~ICU~~ **study was met** . ~~We are evaluating~~ **However, given** the ~~opportunity~~ **end of the federal COVID- 19 PHE in May 2023,** and ~~discussing next steps with~~ **based on feedback from** the FDA **, DOD and other advisors regarding the program' s regulatory requirements, costs, timeline and potential for success, we decided not to submit** ~~and~~ **an EUA** ~~in collaboration with our~~ **or sNDA** ~~partner, the US Department of Defense~~ . If the results of our clinical trials fail to meet the primary efficacy endpoints, or otherwise do not ultimately meet the requirements for an NDA approval by the FDA, the commercial prospects of our business may be harmed, our ability to generate product revenues may be delayed or eliminated or we may be forced to undertake other strategic alternatives that are in our shareholders' best interests, including cost reduction measures. If we are unable to obtain adequate financing or engage in a strategic transaction on commercially reasonable terms or at all, we may be required to implement further cost reduction strategies which could significantly impact activities related to our commercial efforts and / or research and development of our future product candidates, and could significantly harm our business, financial condition and results of operations. In addition, these cost reduction strategies could cause us to further curtail our operations or take other actions that would adversely impact our shareholders. **We are** ~~41We may be~~ subject ~~, directly or indirectly,~~ to federal and state healthcare fraud and abuse laws, false claims laws and other federal and state healthcare laws, and the failure to comply with such laws could result in substantial penalties. Our employees, independent contractors, consultants, principal investigators, ~~contract research organizations (~~ CROs ~~)~~, commercial partners and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements. Our business operations and current and future arrangements with investigators, healthcare professionals, consultants, third- party ~~payers~~ **payors** and customers, may expose us to broadly applicable federal, state and foreign fraud and abuse and other healthcare laws and regulations including anti- kickback and false claims laws, data privacy and security laws, and transparency reporting laws. These laws may constrain the business or financial arrangements and relationships through which we conduct our operations, including how we research, market, sell and distribute any product for which we have obtained regulatory approval, or for which we obtain regulatory approval in the future. In particular, the promotion, sales and marketing of healthcare items and services, as well as certain business arrangements in the healthcare industry, are subject to extensive laws and regulations intended to prevent fraud, misconduct, bribery kickbacks, self- dealing and other abusive or inappropriate practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, including promoting off- label uses of our products, **certain** commission compensation, certain customer incentive programs, certain patient support offerings, and other business arrangements generally. Activities subject to these laws also involve the improper use or misrepresentation of information obtained in the course of patient recruitment for clinical trials, creating fraudulent data in our preclinical studies or clinical trials or illegal misappropriation of drug product, which could result in regulatory sanctions and cause serious harm to our reputation. See " Part I, Item 1, Business – Government Regulation – Healthcare and Privacy Law and Regulation and Healthcare Reform " of this Annual Report on Form 10- K, for more information on the healthcare laws and regulations that may affect our ability to operate. We are also exposed to the risk of fraud, misconduct or other illegal activity by our employees,

independent contractors, consultants, principal investigators, CROs, commercial partners and vendors. Misconduct by these parties could include intentional, reckless and / or negligent conduct that fails to: comply with the laws of the FDA and other similar foreign regulatory bodies; provide true, complete and accurate information to the FDA and other similar foreign regulatory bodies; comply with manufacturing standards we have established; comply with federal and state data privacy, security, fraud and abuse and other healthcare laws and regulations in the US and similar foreign fraudulent misconduct laws; or report financial information or data accurately or to disclose unauthorized activities to us. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent inappropriate conduct may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. ~~We~~ **44We** are also subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. Efforts to ensure that our business arrangements will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant civil, criminal and administrative penalties, damages, disgorgement, monetary fines, imprisonment, additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non- compliance with these laws, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. ~~42We~~ **We** are subject to stringent and evolving privacy and information security laws, regulations, rules, policies, and contractual obligations, and changes in such laws, regulations, rules, policies, contractual obligations and our actual or perceived failure to comply with such requirements could subject us to significant investigations, fines, penalties and claims, any of which may have a material adverse effect on our business, financial condition, results of operations or prospects. We are subject to, or affected by, various federal, state and foreign laws, rules, directives, and regulations, as well as regulatory guidance, policies and contractual obligations relating to privacy and information security, governing the acquisition, collection, access, use, disclosure, processing, modification, retention, storage, transfer, destruction, protection, and security (collectively, " processing ") of personal information and other sensitive information about individuals. The global privacy and information security landscape is evolving rapidly, and implementation standards and enforcement practices are likely to continue to develop for the foreseeable future and may result in conflicting or inconsistent compliance obligations. Legislators and regulators are increasingly adopting or amending privacy and information security laws, rules, directives, and regulations that may create uncertainty in our business, affect our or our collaborators', service providers' and contractors' ability to operate in certain jurisdictions or to process personal information, transfer data internationally, necessitate the acceptance of more onerous obligations in our contracts, result in enforcement actions, litigation or other 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 or our collaborators, service providers and contractors to comply with federal, state or foreign laws or regulations, our internal policies and procedures or our contracts governing the processing of personal information could result in negative publicity, diversion of management time and effort and proceedings against us by governmental entities or others. In many jurisdictions, enforcement actions, litigation, and other consequences for noncompliance with privacy and information security laws and regulations are rising. Compliance with applicable privacy and information security laws and regulations, as well as regulatory guidance, policies and contractual obligations, is a rigorous and time- intensive process, and we may be required to put in place additional mechanisms to ensure compliance with the new privacy and information security requirements. If we fail to comply with any such obligations, we may face significant investigations, fines, penalties and claims that could materially and adversely affect our business, financial condition, results of operations, ability to process personal information and income from certain business initiatives. In the US, these obligations include various federal, state, and local statutes, rules, and regulations relating to privacy and data security. The Federal Trade Commission (FTC) has authority under Section 5 of the FTC Act to regulate unfair or deceptive or practices, and has used this authority to initiate enforcement actions against companies that implement inadequate controls around privacy and information security in violation of their externally facing policies. The **FTC has recently brought several cases alleging violations of Section 5 of the FTC Act with respect to health information, and has proposed rulemaking on privacy and data security, including with respect to the Health Breach Notification Rule. The** US federal government has also enacted statutes to address privacy and information security issues impacting particular industries or activities, including the following laws and regulations: the Electronic Communications Privacy Act, the Computer Fraud and Abuse Act, the Health Insurance Portability and Accountability Act, the Health Information Technology for Economic and Clinical Health Act, the Telephone Consumer Protection Act, the CAN- SPAM Act, and other laws and regulations. In addition, state legislatures have enacted statutes to address privacy and information security issues, including the California Consumer Privacy Act of 2018 (the CCPA), and similar state laws such as Virginia' s Consumer Data Protection Act and the Colorado Privacy Act. For example, the CCPA **, as 45amended by the California Privacy Rights Act (CPRA) in 2020,** establishes a privacy framework applicable to for- profit entities that are doing business in California, including an expansive definition of personal information and data privacy rights for California residents, and authorizes potentially severe statutory damages and creates a private right of action for certain data security breaches. The CCPA also requires businesses subject to the law to provide ~~new~~ disclosures to California residents and to provide them with ~~expanded~~ rights with respect to their personal information, including the right to opt out of the sale of such information **. Moreover the CPRA, among other things, impose new requirements relating to data minimization and correction, and gives California residents additional rights over their personal information, including the right to opt-**

out of the use of their personal information in online behavioral advertising and to opt- out of certain types of consumer. The CPRA also provides for penalties for CPRA violations concerning California residents under the age of 16, and establishes a new California Privacy Protection Agency to implement and enforce the law . Although there are limited exemptions for clinical trial and other research- related data under the CCPA, the CCPA and other similar laws could impact our business depending on how it will be interpreted by the new California Privacy Protection Agency. As we expand our operations, the CCPA may increase our compliance costs and potential liability. **Additionally** ~~In addition~~ , ~~California voters approved the California~~ **Colorado, Connecticut, Utah and Virginia passed comprehensive state** ~~Privacy~~ **privacy laws** ~~Rights Act of 2020 (CPRA)~~ , which **became** ~~goes into effect~~ **effective** on **July 1, 2023, July 1, 2023, December 31, 2023, and** January 1, 2023 **, respectively** . ~~The CPRA~~ **Several states have also passed similar privacy laws that** will **become** ~~, among other things, give California residents the ability to limit the use of their sensitive information, opt out of certain types of profiling and automated processing activities, provide for penalties for CPRA violations concerning California residents under the age of 16, and establish a new California Privacy Protection Agency to implement and enforce the law. Additionally, Colorado and Virginia both signed privacy legislation, each of which go into effect~~ **effective** in ~~2023~~ **2024 or later** , **including Delaware, Indiana, Iowa, Montana, New Jersey, Oregon, Tennessee** and **Texas.** ~~multiple~~ **Multiple** other states and the federal government are considering enacting similar legislation. **Other states have passed state privacy laws to impose enhanced privacy and cybersecurity obligations for consumer health data, such as, the Washington My Health My Data Act and Nevada' s Consumer Health Data Privacy Law.** Many states also have in place data security laws requiring companies to maintain certain safeguards with respect to the ~~43processing~~ -- **processing** of personal information, and all states require companies to notify individuals or government regulators in the event of a data breach impacting such information. New privacy laws add additional complexity, requirements, restrictions and potential legal risk. Accordingly, compliance programs may require additional investment in resources, and could impact availability of previously useful data. Internationally, our operations abroad may also be subject to increased scrutiny or attention from foreign data protection authorities. For example, our clinical trial programs and research collaborations outside the US may implicate foreign data protection laws, including **those** in the European Economic Area, Switzerland, and / or the UK (collectively, Europe). Many jurisdictions have established or are in the process of establishing privacy and data security legal frameworks with which we, our collaborators, service providers, including our CROs, and contractors must comply. For example, ~~European~~ **in the EU, the collection, use, disclosure, transfer and other processing of personal** data ~~protection laws, including, without limitation, the General Data Protection Regulation (the EU GDPR), impose strict requirements for processing personal information~~ (i. e., data which identifies an individual or from which an individual is identifiable) **is governed by the EU General Data Protection Regulation 2016 / 679 (the EU GDPR), which came into direct effect in all EU Member States on and from May 25, 2018. The UK has implemented the EU GDPR as the UK GDPR which sits alongside the UK Data Protection Act 2018 (the UK GDPR, together with the EU GDPR, the GDPR). The GDPR has direct effect where an entity is established in the European Economic Area (EEA) or the UK (as applicable) and has extraterritorial effect** , including ~~clinical trial~~ **where an entity established outside of the EEA or the UK processes personal** data ~~and grant~~ **in relation to offering goods or services to** individuals ~~' various~~ **in the EEA and / or the UK or monitoring their behavior. The GDPR imposes obligations on controllers, including, among others: ● accountability and transparency requirements, requiring controllers to demonstrate and record compliance with the GDPR and to provide more detailed information to data subjects regarding processing of their personal data; ● requirements to process personal data lawfully including specific requirements for obtaining valid consent where consent is the lawful basis for processing; ● obligations to consider data protection when any new products or services are developed and designed (including e. g., to limit the amount of personal data processed); ● obligations to comply with** data protection rights **of data subjects including a** ~~(e. g., the~~ right **:** ~~to erasure of personal information). In turn, the EU GDPR and similar laws increase our obligations with respect to clinical trials conducted in Europe by expanding the definition of personal information to also include coded data and requiring~~ (i) ~~changes~~ **of access** to **, erasure of,** ~~informed consent practices and more detailed notices for~~ - **or rectification of personal data,** ~~clinical trial participants and investigators;~~ (ii) ~~consideration of data protection as any new products or services are developed, including~~ to **restriction** ~~limit the amount~~ of ~~personal information processed;~~ **processing or to withdraw consent to processing,** and (iii) ~~implementation of appropriate technical and organizational measures~~ to ~~safeguard~~ **object to processing or to ask for a copy of** personal ~~information~~ **data to be provided to a third party; and 46 ●** ~~and~~ - **an obligation** to report ~~certain~~ personal data breaches to **: (i)** the ~~relevant~~ **data** supervisory authority without undue delay (**and** ~~for the EU GDPR~~ no later than 72 hours **after discovering the personal data breach,** where feasible) **, unless the personal data breach is unlikely to result in a risk to the data subjects' rights and freedoms; and (ii) to affected data subjects, where the personal data breach is likely to result in a high risk to their rights and freedoms** . In **addition** ~~the event of non- compliance~~ , the EU GDPR **prohibits** ~~provides for robust regulatory enforcement and fines of up to € 20 million or 4 % of~~ the **international transfer** ~~annual global revenue, whichever is greater. In addition, the EU GDPR confers a private right~~ of **personal** ~~action on~~ data ~~subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies and obtain compensation for damages resulting~~ from ~~violations of~~ the ~~EU GDPR.~~ **EEA to jurisdictions that the** European **Commission does** ~~data protection laws, including the EU GDPR, generally also restrict the transfer of personal information from Europe to the US and most other countries that are~~ not ~~recognized~~ - **recognize** as having ~~" '~~ **'** adequate ~~" '~~ **'** data protection laws unless **a data** ~~the parties to the~~ transfer **mechanism** ~~have implemented specific safeguards to protect the transferred personal information. One of the primary safeguards allowing US companies to import personal information from Europe~~ has been ~~certification~~ **put in place or a derogation under the EU GDPR can be relied on. In July 2020, the Court of Justice of the EU (CJEU) in its Schrems II judgement limited how organizations could lawfully transfer personal data from the EEA** to **the US by invalidating** the EU- US Privacy Shield **for purposes** ~~and Swiss- US Privacy Shield frameworks administered by the US Department~~ of

international ~~Commerce. However, the Court of Justice of the European Union (CJEU) issued a decision in July 2020 invalidating the EU- US Privacy Shield framework as a data transfer~~ **transfers** ~~mechanism (Schrems II)~~ and imposing further restrictions on the use of standard contractual clauses (**EU** SCCs), including a requirement for companies to carry out a transfer privacy impact assessment ~~, which~~ **(TIAs). A TIA** , among other things, assesses laws governing access to personal ~~information~~ **data** in the recipient country and considers whether supplementary measures that provide privacy protections additional to those provided under ~~the~~ **EU** SCCs will need to be implemented to ensure an **'** essentially equivalent **'** level of data protection to that afforded in ~~Europe. Following that decision, the Swiss Federal Data Protection and Information Commissioner (FDPIC) took a similar view and considered that data transfers based on the Swiss- US Privacy Shield framework are no longer lawful (despite the fact that Schrems II is not directly applicable in Switzerland (unless the Swiss based company is subject to the EU GDPR) and the Swiss- US Privacy Shield has not been officially invalidated). Further, the EC published new EU SCCs in June 2022, which place onerous obligations on the contracting parties. At present, there~~ -- **the EEA** ~~are few, if any, viable alternatives to the SCCs~~ . **On** ~~However, on~~ October 7, 2022, ~~the~~ US President **Biden** introduced an Executive Order to facilitate a new Trans- Atlantic Data Privacy Framework **(DPF) and on July 10** ~~which will act as a successor to the invalidated Privacy Shield. On December 13~~ , ~~2022~~ **2023** , the ~~EC also published~~ **European Commission adopted** its ~~draft~~ **Final Implementing Decision granting the U. S.** adequacy **(Adequacy** ~~decision~~ **Decision) for EU** ~~to reflect its view that the new executive order and Trans-~~ **US transfers** ~~Atlantic Data Privacy Framework, is able to meet the concerns raised in Schrems II. If the draft adequacy decision is approved and implemented, the agreement will facilitate the transatlantic flow~~ of personal data ~~and provide additional safeguards~~ **for entities self- certified** to ~~data transfer mechanisms (including~~ **the DPF. Entities relying on** EU SCCs ~~and Binding Corporate Rules)~~ for ~~companies transferring~~ **transfers** ~~personal data from the EU~~ to the ~~US~~ **U** . ~~However, before parties~~ **S. are also able to** rely on the **analysis in** ~~new framework, there~~ -- **the Adequacy Decision as support** ~~are still legislative and regulatory steps that must be undertaken both in the US and in the EU. As such, any transfers by us or~~ **for** ~~our third~~ - **their TIA regarding** ~~- party vendors, collaborators or others of personal information from Europe to~~ the ~~US or elsewhere~~ **equivalence of U. S. national security safeguards and redress. This** may **have implications** ~~not comply with European data protection laws, may increase our exposure to European data protection laws' heightened sanctions~~ for **our** cross- border data ~~transfer restrictions~~ **flows and has and** may ~~restrict our clinical trial activities~~ in ~~Europe and may limit our ability to collaborate with CROs, service providers, contractors and other~~ -- **the future result in** ~~companies subject to European data protection laws. Loss of our ability to transfer personal information from Europe may also require us to increase~~ **increased compliance costs** ~~our data processing capabilities in those jurisdictions at significant expense. 44Following the UK' s departure from the EU (Brexit), the EU GDPR' s data protection obligations continue to apply to the UK in substantially unvaried form under the so- called " UK GDPR " (i. e., the EU GDPR as it continues to form part of law in the UK by virtue of section 3 of the European Union (Withdrawal) Act 2018, as amended (including by the various Data Protection, Privacy and Electronic Communications (Amendments etc.) (EU Exit) Regulations))~~ . The UK GDPR ~~exists alongside~~ **also imposes similar restrictions on transfers of personal data from** the UK ~~Data Protection Act 2018 that implements certain derogations in the UK GDPR into UK law. Under the UK GDPR, companies not established in the UK but that process personal information either in relation to the offering of goods or services to individuals in the UK, or to monitor their behavior will be subject to the UK GDPR, the requirements of which are (at this time) largely aligned with those under the EU GDPR, and as such, may lead to similar compliance and operational costs with potential fines of up to £ 17. 5 million or 4 % of global turnover. As a result, we are potentially exposed to two~~ - **to jurisdictions** ~~parallel data protection regimes, each of which authorizes fines and the potential for divergent enforcement actions. It should also be noted~~ that the UK Government **does not consider adequate, including the US. The UK Government has** published its own form of **the** EU SCCs, known as the International Data Transfer Agreement **and** ~~(IDTA) and~~ - **an** International Data Transfer Addendum ~~(UK Addendum)~~ to the new EU SCCs. The UK Information Commissioner' s Office ~~(ICO)~~ has also published its version of the **TIA** ~~transfer impact assessment~~ and ~~revised~~ guidance on international transfers, although entities may choose to adopt either the EU or UK style **TIA. Further, on September 21, 2023, the UK Secretary of State for Science, Innovation and Technology established a UK- US data bridge (i. e., a UK adequacy decision) and adopted UK regulations to implement the UK- U. S. data bridge (" UK Adequacy Regulations "). The UK Adequacy Regulations have now been passed in the UK Parliament, and personal data may be** ~~transfer~~ **transferred from the UK under the UK- U. S. data bridge through the UK extension to the DPF, from October 12, 2023 to organizations self- certified under the DPF. The GDPR imposes fines for serious breaches of up to the higher of 4 % of the organization' s annual worldwide turnover or € 20m (under the EU GDPR) or £ 17. 5m (under the UK GDPR). The GDPR identifies a list of points to consider when determining the level of fines for data supervisory authorities to impose (including the nature, gravity and duration of the infringement). Data subjects also have a right to compensation, as a result of an organization' s breach of the GDPR which has affected them, for financial or non- financial losses (e. g., distress). Privacy and data protection compliance has and may in the future require substantial amendments to our procedures and policies and the changes could adversely** impact **our business by increasing** ~~assessment. In terms of international~~ - **operational and compliance costs or impact business practices. Further, there is a risk that the amended policies and procedures will not be implemented correctly or that individuals within the business will not be fully compliant with the new procedures. If there are breaches of these measures, we could face significant litigation, government investigations, administrative and monetary sanctions as well as reputational damage which may have a material adverse effect on our operations, financial condition and prospects. There is a risk that we could be impacted by a cybersecurity incident that results in loss or unauthorized disclosure of personal** data ~~transfers between~~ **, potentially resulting in us facing harms similar to** ~~the~~ **those described above** ~~UK and US, it is understood that the UK and the US are negotiating an adequacy agreement~~ . Additionally, other countries outside of Europe have enacted or are considering enacting similar cross- border data transfer restrictions and laws requiring local data residency, with strict requirements and limitations

for processing personal information, which could increase the cost and complexity of delivering our services and operating our business. For example, Brazil enacted the General Data Protection Law, New Zealand enacted the New Zealand Privacy Act, China released its Personal Information Protection Law, which went into effect November 1, 2021, and Canada ~~introduced~~ **47introduced** the Digital Charter Implementation Act. As with the EU GDPR, these laws are broad and may increase our compliance burdens, including by mandating potentially burdensome documentation requirements and granting certain rights to individuals to control how we collect, use, disclose, retain, and process personal information about them. We publish privacy policies and other documentation regarding our collection, processing, use and disclosure of personal information and / or other confidential information. Although we endeavor to comply with our published policies and other documentation, we may at times fail to do so or may be perceived to have failed to do so. Moreover, despite our efforts, we may not be successful in achieving compliance if our employees, collaborators, contractors, service providers or vendors fail to act in accordance with our published policies and documentation. Such failures can subject us to potential foreign, local, state and federal action if they are found to be deceptive, unfair, or misrepresentative of our actual practices. Moreover, trial participants or research subjects about whom we or our partners obtain information, as well as the providers who share this information with us, may contractually limit our ability to use and disclose the information or exercise their right to do so under applicable privacy legislation. Claims that we have violated individuals' privacy rights or failed to comply with data protection laws or applicable privacy policies and documentation, even if we are not found liable, could be expensive and time- consuming to defend and could result in adverse publicity that could harm our business. In addition to data privacy requirements **, cybersecurity requirements are laid down in various laws in the EU and the UK, the key ones being: (i) the GDPR (as discussed in detail above), which requires controllers and processors to implement appropriate technical and organizational measures to safeguard personal data to a level of security appropriate to the data protection risk; and (ii) the UK Network and Information Systems Regulation 2018 (NIS Regulations), and the the EU Network and Information Systems Security 1 Directive (" NISD1 ") as implemented into EU Member State law (and as updated by the EU Network and Information Systems Security 2 Directive (NISD2)). The GDPR does not provide for a specific set of cybersecurity requirements or measures to be implemented, but rather requires a controller or processor to implement appropriate cyber and data security measures in accordance with the then- current risk, the state of the art, the costs of implementation and the nature, scope, context and purposes of the processing. The GDPR however does explicitly require that controllers notify personal data breaches, within the meaning of the GDPR, without undue delay and in any event within 72 hours after becoming aware of it, to the relevant data protection supervisory authority, unless the breach is unlikely to result in a risk to the rights and freedoms of individuals. In addition, controllers are required to notify the individuals concerned of any personal data breach, without undue delay, when the personal data breach is likely to result in a high risk to the rights and freedoms of individuals. Processors are required to notify the controller without undue delay after becoming aware of a personal data breach. In the UK, the NIS Regulations apply to ' operators of essential services' (OES) and ' relevant digital service providers' (RDSP) and it was announced in January 2022, that the NIS Regulations will be updated to also cover ' managed service providers' (MSP) and potentially other digital service providers. The NIS Regulations require that appropriate and proportionate technical and organizational measures are implemented to manage the risk of network and information systems, and impose requirements related to incident handling and notification in relation to incidents with significant disruptive effect. Under the NIS Regulations, the UK' s data protection supervisory authority, the Information Commissioner' s Office, may issue fines of up to £ 17 million and take other action following non-compliance. In the EU, the NISD1 applies to ' operators of essential services' (OES) and ' digital service providers' (DSP) and an updated version of NISD1 has been adopted and entered into force on January 17, 2023, called NISD2. The NISD2 will take full effect following implementation into national EU Member State law (i. e., by October 17, 2024). Under the NISD1, OESs and DSPs are required to implement appropriate and proportionate technical and organizational measures to manage the risk of network and information systems, and adhere to incident handling and notification requirements regarding incidents with significant disruptive effect. Importantly, under the NISD2, more stringent cybersecurity and incident reporting requirements are imposed on ' essential' and ' important' entities, which include ICT managed service providers (MSP), cloud service providers as well as entities carrying out research and development activities of medicinal products, and certain specific medical device manufacturers. Our entities may be in scope of the NISD2 where they qualify as a MSP, cloud provider, R & D entity and / or medical device manufacturer within the meaning of NISD2 and offer those services in the EU. 48The NISD2 empowers the EU Member States to define all rules regarding penalties applicable to infringements, provided that they are effective, proportionate, and dissuasive. NISD2 states that any maximum fine which national implementing law provides for should at least be set at € 10 million or 2 % of total worldwide turnover, whichever is higher, where essential entities are concerned. Other sanctions may include (i) a temporary suspension to provide services in the EU (by suspending relevant authorizations / certifications); (ii) an order to make public certain elements of the infringement and / or inform customers; and (iii) injunctions to immediately cease infringing conduct. Importantly, NISD2 also provides that senior members of staff can be held personally liable, and face administrative fines or be temporarily suspended from exercising managerial functions at the legal representative or chief executive officer level. In addition, the EU Critical Entities Resilience Directive (CER) entered into force on January 17, 2023 and will take full effect following implementation into national EU Member State law (i. e., by October 17, 2024 – coinciding with the NISD2). The CER is aimed at strengthening the resilience of ' critical infrastructure' against specific threats including cyber incidents, natural hazards, terrorist attacks, insider threats, and sabotage. The scope of CER includes entities designated as ' critical' under CER and includes (among other things) the health sector and the manufacturers of medical devices as ' essential services.' The CER imposes cybersecurity and resilience requirements in particular in relation to incidents with so- called ' significant**

disruptive effects' – which are incidents that are able to significantly impact the continuation of the critical infrastructure service offering in the EU. Requirements include to: (i) identify relevant risks that may significantly disrupt the provision of essential services (i. e., pursuant to a risk assessment); (ii) take appropriate and proportionate technical, security and organizational measures to ensure resilience (i. e., based on the outcome of the risk assessment); and (iii) notify disruptive incidents to the competent authorities within 24 hours after becoming aware of an incident. The CER is enforceable on a national EU Member State level by the competent authorities, and allows EU Member States to set penalties as long as they are effective, proportionate, and dissuasive. Our entities may be in scope of the CER where they qualify as critical entities within the meaning of CER. In the EU, a number of new laws related to digital data and AI have also recently entered into force, are expected to enter into force in the foreseeable future, or have been proposed and are being considered. We are still assessing the scope of application, impact, and risk of these recent EU laws on our business, and will continue to assess this moving forward, including for example: (i) the EU' s Data Act – expected to come into force in the first quarter to second quarter of 2024 – which seeks to, among other things regulate the use of, and access to, data generated through connected (or Internet- of- Things) devices and introduces a new means for public sector bodies to access, use and re- use private sector data; and (ii) the proposed European Health Data Space Regulation (EHDS) – expected to be agreed in the third quarter of 2024 – which seeks to, among other things, provide individuals with more control over their electronic health data (EHD), enable cross- border sharing of EHD between national EU healthcare systems and facilitate the sharing of EHD for secondary research purposes. The EU has also developed a standalone law to govern the offering and use of AI systems in the EU (the AI Act) which reached political agreement on December 8, 2023 and is expected to be adopted and enter into force during the first quarter to second quarter of 2024. The AI Act imposes regulatory requirements onto AI system providers, importers, distributors, and users of AI systems, in accordance with the level of risk involved with the AI system (" unacceptable ", " high ", " limited ", and " minimal " risk). Unacceptable- risk AI systems are banned from being offered and used in the EU, and high- risk AI systems (which include AI used as part of medical devices in certain instances) are subject to a set of regulatory requirements under the AI Act including to establish quality and post- marketing monitoring and risk assessment systems, requirements related to the training of AI systems and training data, and requirements related to human oversight. Limited- risk AI systems are subject mainly to transparency requirements only and minimal- risk AI systems are not subject to obligations under the AI Act. In the most recent iteration of the AI Act' s text, general- purpose AI systems have also been made subject to a number of requirements – mostly akin to the requirements that apply to high- risk AI systems under the AI Act. Currently, the AI Act is expected to enter into application (i. e. be enforceable) in a gradual manner – depending on the regulatory requirement in question, and ranging anywhere from 6 to 36 months following adoption and entry into force of the AI Act (i. e., between fourth quarter of 2024 to first quarter of 2027). Non- compliance with the AI Act may be subject to regulatory fines of up to 7 % of annual worldwide turnover. In parallel, the EU has proposed revisions to the EU Product Liability Directive and has introduced a new EU AI Liability Directive to facilitate claims for damages brought by EU users of AI systems. 49The UK has adopted a " soft law " approach to AI regulation meaning it has not adopted formal legislation to regulate AI but has adopted soft law guidelines in the form of a White Paper. Further , many jurisdictions impose mandatory clinical trial information obligations on sponsors. In the EU, such obligations arise under the Transparency Regulation No 1049 / 2001, EMA Policy 0043, EMA Policy 0070 and the Clinical Trials Regulation No 536 / 2014, all of which impose on sponsors the obligation to make publicly available certain information stemming from clinical studies. In the EU, the transparency framework provides EU- based parties the right to submit an access to documents request to the EMA for information included in the **MAA** ~~marketing authorization application~~ dossier for approved medicinal products. Only very limited information is exempted from disclosure, i. e. **,** commercially confidential information (which is construed increasingly narrowly) and protected personal data. It is possible for competitors to access and use this data in their own research and development programs anywhere in the world, once this data is in the public domain . On May 3, 2022,..... in this " Risk Factors " section . Enhanced governmental and public scrutiny over, or investigations or litigation involving, pharmaceutical manufacturer donations to patient assistance programs may require us to modify our programs and could negatively impact our business practices, harm our reputation, divert the attention of management and increase our expenses. To help patients afford our products, we have a manufacturer- sponsored patient assistance program that helps financially needy patients **in the US access our therapies** . This type of program has become the subject of enforcement scrutiny in recent years. For example, some pharmaceutical manufacturers have been named in ~~class action~~ lawsuits challenging the legality of their patient assistance programs under a variety of federal and state laws. In addition, certain state and federal enforcement authorities have pursued investigations and settlements and members of Congress have initiated inquiries about manufacturer- sponsored patient support programs, including, for example, manufacturer- sponsored patient assistance programs, co- payment assistance programs, and manufacturer contributions to independent charitable patient assistance programs. Moreover, the **DHHS** ~~Department of Health and Human Services~~ , Office of the Inspector General ~~recently~~ **continues to** ~~published~~ -- **publish** ~~an~~ advisory ~~opinion~~ **opinions and other agency guidance** ~~(OIG Ad Op. No. 22- 19) that, while binding only~~ on the ~~requestor~~ **topic** of ~~the opinion~~ **patient assistance** , **which** reflects the government' s continued scrutiny of manufacturer ~~financial contributions to~~ **sponsored or supported** patient assistance programs ~~conducted through third parties, including charitable organizations~~ . Numerous organizations, including pharmaceutical manufacturers, have been subject to ongoing litigation, enforcement activities and settlements related to their patient support programs and certain of these organizations have entered into, or have otherwise agreed to, significant civil settlements with applicable enforcement authorities. It is possible that future legislation may be proposed that would establish requirements or restrictions with respect to these programs and / or support that would affect pharmaceutical manufacturers. Our patient assistance program could become the target of similar inquiries, litigation, enforcement, and / or legislative proposals. If we are deemed not to have complied with

laws or regulations in the operation of, or our interactions with, these programs, we could be subject to damages, fines, penalties or other criminal, civil or administrative sanctions or enforcement actions. We cannot ensure that our compliance controls, policies and procedures will be sufficient to protect against acts of our employees, business partners or vendors that may violate the laws or regulations of the jurisdictions in which we operate. A government investigation could negatively impact our business practices, harm our reputation, divert the attention of management and increase our expenses. ~~47If~~ **If** manufacturers obtain approval for generic versions of our products, or of products with which we compete, our business may be harmed. Under the FDCA, the FDA can approve an ANDA for a generic version of a branded drug without the ANDA applicant undertaking the clinical testing necessary to obtain approval to market a new drug. Generally, in place of such clinical studies, an ANDA applicant usually needs only to submit data demonstrating that its product has the same active ingredient (s), strength, dosage form and route of administration and that it is bioequivalent to the branded product. In September 2019, the FDA published product- specific bioequivalence guidance on fostamatinib disodium to let potential ANDA applicants understand the data FDA would expect to see for approval of a generic version of our products. The FDCA requires that an applicant for approval of a generic form of a branded drug certify either that its generic product does not infringe any of the patents listed by the owner of the branded drug in the **FDA' s Approved Drug Products with Therapeutic Equivalence Evaluations (referred to as the "** Orange Book **")** or that those patents are not enforceable. This process is known as a paragraph IV challenge. Upon notice of a paragraph IV challenge, a patent ~~owner~~ **50owner** has 45 days to bring a patent infringement suit in federal district court against the company seeking ANDA approval of a product covered by one of the owner' s patents. If this type of suit is commenced, the FDCA provides a 30- month stay on the FDA' s approval of the competitor' s application. If the litigation is resolved in favor of the ANDA applicant or the challenged patent expires during the 30- month stay period, the stay is lifted, and the FDA may thereafter approve the application based on the standards for approval of ANDAs. Once an ANDA is approved by the FDA, the generic manufacturer may market and sell the generic form of the branded drug in competition with the branded medicine. The ANDA process can result in generic competition if the patents at issue are not upheld or if the generic competitor is found not to infringe the owner' s patents. If this were to occur with respect to our products or products with which it competes, our business would be harmed ~~. We have a number of patents listed in the Orange Book, the last of which is expected to expire in July 2032~~ . In June 2022, we received a notice letter regarding an ANDA submitted to the FDA by Annora, requesting approval to market a generic version of TAVALISSE. The notice letter included a Paragraph IV certification with respect to our US Patent Nos. 7, 449, 458; 8, 263, 122; 8, 652, 492; 8, 771, 648 and 8, 951, 504, which are listed in the Orange Book. The notice letter asserts that these patents will not be infringed by Annora' s proposed product, are invalid and / or are unenforceable. Annora' s notice letter does not provide a Paragraph IV certification against our other patents listed in the Orange Book. On July 25, 2022, we filed a lawsuit in the US District Court for the District of New Jersey against Annora and its affiliates, Hetero Labs Ltd., and Hetero USA, Inc., for infringement of our US patents identified in Annora' s Paragraph IV certification. On September 21, 2022, Annora and its affiliates answered and counterclaimed for declaratory judgment of non- infringement and invalidity of the' 458,' 122,' 492,' 648, and' 504 patents. We filed an answer to Annora' s counterclaims on October 12, 2022. **Annora served invalidity and non- infringement contentions on December 31, 2022. We filed an answer to Annora' s invalidity and non- infringement contentions in March 2023. Litigation continues, and no trial date is currently set.** We intend to vigorously enforce and defend our intellectual property related to TAVALISSE. We cannot be assured that such lawsuit will prevent the introduction of a generic version of TAVALISSE for any particular length of time, or at all. If an ANDA from Annora or any other generic manufacturer is approved, and a generic version of TAVALISSE is introduced, whether following the expiration of our patents, the invalidation of our patents as a result of any litigation, or the determination that the proposed generic product does not infringe on our patents, our sales of TAVALISSE would be adversely affected. In addition, we cannot predict what additional ANDAs could be filed by Annora or other potential generic competitors requesting approval to market generic forms of ~~fostamatinib~~ **our products** , which would require us to incur significant additional expense and result in distraction for our management team, and if approved, result in significant decreases in the revenue derived from sales of our marketed products and thereby materially harm our business and financial condition. Unforeseen safety issues could emerge with our products that could require us to change the prescribing information to add warnings, limit use of the product, and / or result in litigation. Any of these events could have a negative impact on our business. Discovery of unforeseen safety problems or increased focus on a known problem could impact our ability to commercialize our products and could result in restrictions on its permissible uses, including withdrawal of the medicine from the market. ~~48If~~ **If** we or others identify additional undesirable side effects caused by our products after approval: ● regulatory authorities may require the addition of labeling statements, specific warnings, contraindications, or field alerts to physicians and pharmacies; ● regulatory authorities may withdraw their approval of the product and require us to take our approved drugs off the market **or suspend their commercialization until the identified issues have been satisfactorily addressed** ; ● we may be required to change the way the product is administered, conduct additional clinical trials, change the labeling of the product, or implement a Risk Evaluation and Mitigation Strategy **(** ~~, or~~ REMS **)** ; ● we may have **additional** limitations on how we promote our drugs; **51** ● third- party ~~payers~~ **payors** may limit coverage or reimbursement for our products; ● sales of our products may decrease significantly; ● we may be subject to litigation or product liability claims; and ● our reputation may suffer. Any of these events could prevent us from achieving or maintaining market acceptance of our products and could substantially increase our operating costs and expenses, which in turn could delay or prevent us from generating significant revenue from sale of our products. Side effects and toxicities associated with our products, as well as the warnings, precautions and requirements listed in the prescribing information for our products, could affect the willingness of physicians to prescribe, and patients to utilize, our products and thus harm commercial sales of our products. ~~The~~ **For example, for REZLIDHIA, the** FDA approved label ~~for REZLIDHIA~~ contains a boxed warning describing the risk of differentiation syndrome, which can be fatal, in patients receiving ~~REZLIDHIA~~ **the drug** . This and other restrictions could limit the commercial success of ~~REZLIDHIA~~ **the product** . If a safety issue emerges post- approval, we may

become subject to costly product liability litigation by our customers, their patients or ~~payers~~ **payors** . Product liability claims could divert management' s attention from our core business, be expensive to defend, and result in sizable damage awards against us that may not be covered by insurance. If we cannot successfully defend ourselves against claims that our products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in: ● decreased demand for any product candidates or products that we may develop; ● the inability to commercialize any products that we may develop; ● injury to our reputation and significant negative media attention; ● withdrawal of patients from clinical studies or cancellation of studies; ● significant costs to defend the related litigation; ● substantial monetary awards to patients; and ● loss of revenue. We currently hold $ 10. 0 million in product liability insurance coverage, which may not be adequate to cover all liabilities that we may incur. Insurance coverage is increasingly expensive. We may not be able to obtain insurance coverage at a reasonable cost or in amounts adequate to satisfy any liability or associated costs that may arise in the future. These events could harm our business and results of operations and cause our stock price to decline. ~~49If secondary use (among private companies and regulators to enable scientific research).Whilst the regulation is currently under discussions among the EU legislators,the text is expected to be finalized by the end of 2023 and for the EHDS to become applicable in 2025.This will impose new obligations,but also create opportunities,for entities engaged in health- related research to share and access health data on a scale much larger than 45what is foreseen under current applicable transparency provisions.~~ Our business could be materially and adversely affected by pandemics as a result of their potential impacts on our sales force and commercialization efforts,supply chain,regulatory,clinical development and corporate development activities and other business operations,in addition to the impact of a global economic slowdown.Pandemics may result in extended travel and other restrictions in order to reduce the spread of diseases.Government measures taken in response to pandemics could have a significant impact,both direct and indirect,on our business and commerce,as significant reductions in business related activities may occur,supply chains may be disrupted,and manufacturing and clinical development activities may be curtailed or suspended.For example, ~~since~~ **during** the COVID- 19 pandemic ~~was declared~~ ,we ~~have~~ observed reduced patient- doctor interactions and our representatives ~~have~~ had fewer visits with health care providers,which ~~has~~ negatively affected our product sales ~~and may continue to negatively affect our product sales in the future~~ .Physicians with practices severely impacted by the COVID- 19 pandemic, **or a pandemic occurring in the future,** and who currently prescribe our products,may eventually decide to close their independent practices and join a larger medical organization ~~with~~ **52with** a practice that does not prescribe our products.Additionally, **a pandemic,including COVID- 19 or any resurgence thereof,may impact** commercial- related activities,such as our marketing programs,speaker bureaus,and market access initiatives ~~were~~ **which may be required to be** conducted virtually,delayed or cancelled **,all of which occurred** as a result of the COVID- 19 pandemic. ~~We~~ **During the COVID- 19 pandemic,we** had to deploy resources to enable our field- based employees to continue to engage with health care providers in hybrid virtual and in- person interactions **,which may be required in the event a pandemic occurs in the future** .With respect to clinical development,in response to the COVID- 19 pandemic,we **took** ~~have taken,and may continue to take,~~ measures to implement remote and virtual approaches,including remote patient monitoring where possible and working with our investigators for appropriate care of these patients in a safe manner. ~~We have a number~~ **Due to the effects** of ~~ongoing clinical trials,including our clinical studies in~~ COVID **- 19 pandemic,we experienced a** ~~and IRAK 1 / 4 inhibitor program.A~~ number of our clinical trial investigators ~~have~~ **either** paused,postponed or delayed new patient enrollment and restricted site visits of existing patients enrolled. **In** ~~Although some sites have resumed patient screening,~~ the ~~progress is slow~~ **event that a global pandemic** , ~~and~~ **or a resurgence of the COVID- 19 pandemic,occurs in the future,** we **may need** ~~continue to experience delays in new patient enrollment.We are continuing~~ to make decisions **on a** country- by- country **basis** to minimize risk to the patients and clinical trial sites.We **may** also rely heavily on our clinical trial investigators to inform us of the best course of action with respect to resuming enrollment / screening,considering the ability of sites to ensure patient safety or data integrity ~~.Patients already enrolled in our studies continue to receive study drugs,and we remain focused on supporting our sites in providing care for these patients and providing continued investigational drug supply~~ .We experienced slower than anticipated enrollment in some of our clinical trials **due to adverse effects of COVID- 19 pandemic** ,and in the future,we may experience adverse ~~impact~~ **impacts of a global** ~~that the COVID- 19~~ pandemic ~~may have~~ on our clinical trials,including the timing thereof,or our ability to continue to treat patients enrolled in our trials,enroll and assess new patients,supply study drugs and obtain complete data points in accordance with study protocol.Pandemics may cause significant disruption in the supply chain for our commercial products.We ~~currently~~ rely on third parties to,among other things,manufacture and ship our commercial product,raw materials and product supply for our clinical trials,perform quality testing and supply other goods and services to help manage our commercial activities,our clinical trials and our operations in the ordinary course of business.While we have engaged actively with various elements of our supply chain and distribution channel,including our customers,contract manufacturers,and logistics and transportation provider to meet demand for our products and to remain informed of any challenges within our supply chain,we may face disruptions to our supply chain and operations,and associated delays in the manufacturing and supply of our products.Such supply disruptions would adversely impact our ability to generate sales of and revenues from our products and our business,financial condition,results of operations and growth prospects could be adversely affected.Pandemics may affect our collaboration and licensing partners for the commercialization of ~~fostamatinib~~ **our products** globally,as well as our ability to advance our various clinical stage programs.We cannot predict the impact of such disruptions on our partners' ability to advance commercialization of ~~fostamatinib~~ **our products** in the market and the timing of enrollment and completion of various clinical trials being conducted by our collaboration partners. ~~46Health~~ -- **Health** regulatory agencies globally may experience prolonged disruptions in their operations as a result of pandemics.For example,in response to the COVID- 19 pandemic,the FDA delayed inspections and evaluations of certain drug manufacturing facilities and clinical research sites We cannot predict whether,and when,health regulatory agencies will decide to pause or resume inspections due to pandemics.Any de- prioritization of our clinical trials or delay in regulatory review resulting from such disruptions could materially affect the completion of our clinical trials.In

addition,as seen in the COVID- 19 pandemic,pandemics could result in a significant disruption of global financial markets.We could experience an inability to access additional capital or an impact on liquidity,which could in the future negatively affect our capacity for certain corporate development transactions or our ability to make other important,opportunistic investments,or we may not be able to meet the requirements under our Credit and Security Agreement (Credit Agreement) with MidCap Financial Trust (MidCap) ~~in order for us to access the funds remaining under such Credit Agreement~~ .While we expect pandemics to adversely affect our business,financial condition,results of operations and growth prospects in the future periods,the extent of the impact on our ability to generate sales of and revenues from our approved products,our ability to continue to secure new collaborations and support existing collaboration efforts with our partners,our clinical development and regulatory efforts,our corporate development objectives and the **value of and market for our common stock,will depend on future circumstances that are highly uncertain and cannot be predicted with confidence at this time,such as the ultimate duration and severity of pandemics,travel restrictions,quarantines,social distancing and business closure requirements in the US and other countries,and the effectiveness of actions taken globally to contain and treat diseases.To the extent 53pandemics adversely affect our business and results of operations,it may also have the effect of heightening many of the other risks and uncertainties described elsewhere in this " Risk Factors " section.If** we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the US, we could be subject to additional rebate or discount requirements, fines, sanctions and exposure under other laws which could have an adverse effect on our business, results of operations and financial condition. We participate in the Medicaid Drug Rebate Program, as administered by the CMS, the 340B Drug Pricing Program, **as administered by the Health Resources and Services Administration,** and other federal and state government drug pricing programs in the US, and we may participate in additional government pricing programs in the future. These programs generally require us to pay rebates or otherwise provide discounts to government ~~payers~~ **payors** in connection with drugs that are dispensed to beneficiaries / recipients of these programs. In some cases, such as with the Medicaid Drug Rebate Program, the rebates are based on pricing metrics that we report on a monthly and quarterly basis to the government agencies that administer the programs. Pricing requirements and rebate / discount calculations are complex, vary among products and programs, and are often subject to interpretation by governmental or regulatory agencies and the courts. The requirements of these programs, including, by way of example, their respective terms and scope, change frequently. Responding to current and future changes may increase our costs, and the complexity of compliance will be time consuming. Invoicing for rebates is provided in arrears, and there is frequently a time lag of up to several months between the sales to which rebate notices relate and our receipt of those notices, which further complicates our ability to accurately estimate and accrue for rebates related to the Medicaid program as implemented by individual states. Thus, there can be no assurance that we will be able to identify all factors that may cause our discount and rebate payment obligations to vary from period to period, and our actual results may differ significantly from our estimated allowances for discounts and rebates. Changes in estimates and assumptions may have an adverse effect on our business, results of operations and financial condition. In addition, the **DHHS,** Office of Inspector General ~~of HHS~~ and other ~~Congressional~~ **governmental** enforcement and administrative bodies have ~~recently~~ increased their focus on pricing requirements for products, including, but not limited to the methodologies used by manufacturers to calculate average manufacturer price ~~(AMP)~~ and best price ~~(BP)~~ for compliance with reporting requirements under the Medicaid Drug Rebate Program. We are liable for errors associated with our submission of pricing data and for any overcharging of government ~~payers~~ **payors** . 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. Any required refunds to the US government or response to a government investigation or enforcement action would be expensive and time consuming and could have an adverse effect on our business, results of operations and financial condition. In addition, in the event that CMS were to terminate our rebate agreement, no federal payments would be available under Medicaid for our covered outpatient drugs or under Medicare Part B for any of our products that may be reimbursed under Part B. **Finally, we may be affected by developments relating to the 340B Drug Pricing Program. Recently, multiple manufacturers have implemented policies to reduce diversion and inappropriate claims for discounts and rebates by contract pharmacies affiliated with 340B-eligible entities. The DHHS has sent several of these manufacturers letters claiming that the policies violate the 340B statue and referring the manufacturers for potential enforcement action. Manufacturers have challenged these letters in federal court, and the U. S. Court of Appeals for the Third Circuit has ruled in favor of several manufacturers; other challenges are still pending. Further, Arkansas and Louisiana recently enacted laws requiring manufacturers to ship 340B drugs to certain contract pharmacies and imposing penalties on manufacturers that do not comply. Both laws have been challenged in federal court. Other states are considering similar laws. It is unclear how this pending litigation, recent and proposed legislation, or future administrative action relating to the 340B program will impact our business.** ~~Even~~ **54Even** for those product candidates that have or may receive regulatory approval, they may fail to achieve the degree of market acceptance by physicians, patients, ~~healthcare~~ **third- party** payors and others in the medical community necessary for commercial success, in which case we may not generate significant revenues or become profitable. For our product candidates that have or may receive regulatory approval, they may nonetheless fail to gain sufficient market acceptance by physicians, hospital administrators, patients, ~~healthcare~~ **third- party** payors and others in the medical community. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including the following: ● relative convenience and ease of administration; ● the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies; ● the willingness of physicians to change their current treatment practices **; ● any additional support that may be required to administer the treatment to patients** ; ● the willingness of hospitals and hospital systems to include our product candidates as treatment options; ● demonstration of efficacy and safety in clinical trials; ● the prevalence and severity of any side effects; ~~50~~ ● the ability to offer product candidates for sale at competitive prices; ● the price we charge for our product candidates; ● the strength of marketing and distribution support; and

● the availability of third- party coverage and adequate reimbursement and the willingness of patients to pay out- of- pocket in the absence of such coverage and adequate reimbursement. Efforts to educate the physicians, patients, ~~healthcare~~ **third- party** payors and others in the medical community on the benefits of our product candidates may require significant resources and may not be successful. If any of our product candidates are approved ~~, if at all~~, but do not achieve an adequate level of acceptance, we may not generate significant product revenue and we may not become profitable on a sustained basis. We will need additional capital in the future to sufficiently fund our operations and research. We have consumed substantial amounts of capital to date as we continue our research and development activities, including preclinical studies and clinical trials and for the commercialization of our products. We may seek another collaborator or licensee in the future for further clinical development and commercialization of ~~fostamatinib~~ **our products**, as well as our other clinical programs, which we may not be able to obtain on commercially reasonable terms or at all. We believe that our existing capital resources will be sufficient to support our current and projected funding requirements, including the continued commercialization of our products through at least the next 12 months. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. Because of the numerous risks and uncertainties associated with commercial launch, the development of our product candidates and other research and development activities, we are unable to estimate with certainty our future product revenues, our revenues from our current and future collaborative partners, the amounts of increased capital outlays and operating expenditures associated with our current and anticipated clinical trials and other research and development activities. We will continue to need additional capital and the amount of future capital needed will depend largely on the success of our commercialization of our products, and the success of our internally developed programs as they proceed in later and more expensive clinical trials, including any additional clinical trials that we may decide to conduct with respect to ~~fostamatinib~~ **our products**. While we intend to opportunistically seek access to additional funds through public or private ~~equity~~ **55equity** offerings or debt financings, we do not know whether additional financing will be available when needed, or that, if available, we will obtain financing on reasonable terms. Our ability to raise additional capital, including our ability to secure new collaborations and continue to support existing collaboration efforts with our partners, may also be adversely impacted by potential worsening global economic conditions and the recent disruptions to, and volatility in, the credit and financial markets in the US and worldwide resulting from the COVID- 19 pandemic and the ~~conflict in~~ **global tensions arising from** the **Russia-** Ukraine **war and the Hamas- Israel war**. Unless and until we are able to generate a sufficient amount of product, royalty or milestone revenue, which may never occur, we expect to finance future cash needs through public and / or private offerings of equity securities, debt financings or collaboration and licensing arrangements, as well as through proceeds from the exercise of stock options and interest income earned on the investment of our cash balances and short- term investments. To the extent we raise additional capital by issuing equity securities in the future, our stockholders could at that time experience substantial dilution. In addition, we have a significant number of stock options outstanding. To the extent that outstanding stock options have been or may be exercised or other shares issued, our stockholders may experience further dilution. Further, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. Our credit facility with MidCap includes certain covenants that may restrict our business, and any other debt financing that we are able to obtain in the future may involve operating covenants that restrict our business. To the extent that we raise additional funds through any new collaboration and licensing arrangements, we may be required to refund certain payments made to us, relinquish some rights to our technologies or product candidates or grant licenses on terms that are not favorable to us. ~~51We~~ **We** have indebtedness in the form of a term loan pursuant to the Credit Agreement ~~(as defined below)~~ with MidCap, which could adversely affect our financial condition and our ability to respond to changes in our business. Further, if we are unable to satisfy certain conditions of the Credit Agreement, we will be unable to draw down the remainder of the facility. We entered into ~~the~~ **a** Credit Agreement with MidCap on September 27, 2019, amended on March 29, 2021, February 11, 2022, and July 27, 2022 **. The Credit Agreement provides for a $ 60. 0 million term loan credit facility. As of December 31, 2023, the outstanding principal balance of the loan was $ 60. 0 million, and no remaining funds were available under the term loan credit facility**. Under the Credit Agreement, we are required to repay amounts due when there is an event of default for the term loans that results in the principal, premium, if any, and interest, if any, becoming due prior to the maturity date for the term loans. The Credit Agreement also contains a number of other affirmative and restrictive covenants. See " Note ~~9~~ **10** – Debt " to our " Notes to Financial Statements " contained in " Part II, Item 8, Financial Statements and Supplementary Data " of this Annual Report on Form 10- K for additional details of the Credit Agreement. These and other terms in the Credit Agreement have to be monitored closely for compliance and could restrict our ability to grow our business or enter into transactions that we believe would be beneficial to our business. Our business may not generate cash flow from operations in the future sufficient to service our debt and support our growth strategies. If we are unable to generate such cash flow, we may be required to adopt one or more alternatives, such as restructuring our debt or obtaining additional equity capital on terms that may be onerous or highly dilutive. Our ability to refinance our indebtedness will depend on the capital markets and our financial condition at such time. We may not be able to engage in any of these activities or engage in these activities on desirable terms, which could result in a default on our current debt obligations. In addition, we cannot be sure that additional financing will be available when required or, if available, will be on terms satisfactory to us. Further, even if we are able to obtain additional financing, we may be required to use such proceeds to repay a portion of our debt. Our indebtedness may have other adverse effects, such as: ● our vulnerability to adverse general economic conditions and heightened competitive pressures; ● dedication of a portion of our cash flow from operations to interest payments, limiting the availability of cash for other operational purposes; ● limited flexibility in planning for, or reacting to, changes in our business and industry; and ● our inability to obtain additional financing in the future. Our Credit Agreement with MidCap contains a mandatory prepayment provision that gives MidCap and / or its ~~agent~~ **56agent** the right to demand payment of the outstanding principal and additional interest and fees in the event of default. We may not have enough available cash or

be able to obtain financing at the time we are required to repay the term loan with additional interest and fees prior to maturity. ~~The Credit Agreement provides for a $ 60. 0 million term loan credit facility. As of December 31, 2022, the outstanding principal balance of the loan was $ 40. 0 million, and the facility gives us the ability to access an additional $ 20. 0 million aggregate principal amount of term loan at our option through March 31, 2023, subject to the satisfaction of applicable funding conditions which include minimum net revenue and compliance with financial covenants set forth in the Credit Agreement. If we are unable to satisfy these or other required conditions, we would not be able to draw down the remaining tranches of financing and may not be able to obtain alternative financing on commercially reasonable terms or at all, which could adversely impact our business.~~ We rely and may continue to rely on two distribution facilities for the sale of our products and potential sale of any of our product candidates. Our distribution operations for the sale of our products are currently concentrated in two distribution centers owned by a third- party logistics provider. Additionally, our distribution operations, if and when we launch any of our product candidates in the future, may also be concentrated in such distribution centers owned by a third- party logistics provider. Any errors in inventory level management and unforeseen inventory shortage could adversely affect our business. In addition, any significant disruption in the operation of the facility due to natural disaster or severe weather, or events such as fire, accidents, power outages, system failures, or other unforeseen causes, could devalue or damage a significant portion of our inventories and could adversely affect our product distribution and sales until such time as we ~~52could~~ -- **could** secure an alternative facility. Further, climate change may increase both the frequency and severity of extreme weather conditions and natural disasters, which may affect our business operations. If we encounter difficulties with any of our distribution facilities, whether due to the potential future impacts of **a global** ~~the COVID- 19~~ pandemic (including as a result of disruptions of global shipping and the transport of products) or otherwise, or other problems or disasters arise, we cannot ensure that critical systems and operations will be restored in a timely manner or at all, and this would have an adverse effect on our business. In addition, growth could require us to further expand our current facility, which could affect us adversely in ways that we cannot predict. Forecasting potential sales for any of our product candidates will be difficult, and if our projections are inaccurate, our business may be harmed, and our stock price may be adversely affected. Our business planning requires us to forecast or make assumptions regarding product demand and revenues for any of our product candidates if they are approved despite numerous uncertainties. These uncertainties may be increased if we rely on our collaborators or other third parties to conduct commercial activities in certain geographies and provide us with accurate and timely information. Actual results may differ materially from projected results for various reasons, including the following, as well as risks identified in other risk factors: ● the efficacy and safety of any of our product candidates, including as relative to marketed products and product candidates in development by third parties; ● pricing (including discounting or other promotions), reimbursement, product returns or recalls, competition, labeling, adverse events and other items that impact commercialization; ● the rate of adoption in the particular market, including fluctuations in demand for various reasons; ● potential future impacts, if any, due to **a global** ~~the COVID- 19~~ pandemic; ● lack of patient and physician familiarity with the drug; ● lack of patient use and physician prescribing history; ● lack of commercialization experience with the drug; ● actual sales to patients may significantly differ from expectations based on sales to wholesalers; and ● uncertainty relating to when the drug may become commercially available to patients and rate of adoption in other territories. We expect that our revenues from sales of any of our ~~product~~ **products** ~~candidates~~ will continue to be based in part on estimates, judgment and accounting policies. Any incorrect estimates or disagreements with regulators or others regarding such estimates or accounting policies may result in changes to our guidance, projections or previously reported results **. We make estimates for provisions for sales discounts, returns and allowances. Our estimates are based on available customer and payor data received from the specialty pharmacies and distributors, as well as third party market research data. In 57part, our estimates are dependent on our distribution channel and payor mix. If actual results in the future vary from our estimates, we adjust these estimates, which would affect our net product revenue and earnings in the period such variances become known** . Expected and actual product sales and quarterly and other results may greatly fluctuate, including in the near- term, and such fluctuations can adversely affect the price of our common stock, perceptions of our ability to forecast demand and revenues, and our ability to maintain and fund our operations. We do not and will not have access to all information regarding fostamatinib and product candidates we licensed to Lilly, Kissei, Grifols, Medison and Knight. We do not and will not have access to all information regarding fostamatinib and other product candidates, including potentially material information about commercialization plans, medical information strategies, clinical trial design and execution, safety reports from clinical trials, safety reports, regulatory affairs, process development, manufacturing and other areas known by Lilly, Kissei, Grifols, Medison and Knight. In addition, we have confidentiality obligations under our respective agreements with Lilly, Kissei, Grifols, Medison and Knight. Thus, our ability to keep our shareholders informed about the status of fostamatinib and other product candidates will be limited by the degree to which Lilly, Kissei, Grifols, Medison and / or Knight keep us informed and allows us to disclose such information to the public. If Lilly, Kissei, Grifols, Medison and / or Knight fail to keep us informed about commercialization efforts related to fostamatinib, or the status of the clinical development or regulatory approval pathway of other product candidates ~~53licensed~~ -- **licensed** to them, we may make operational and / or investment decisions that we would not have made had we been fully informed, which may adversely affect our business and operations. Our future funding requirements will depend on many uncertain factors. Our future funding requirements will depend upon many factors, many of which are beyond our control, including, but not limited to: ● the costs to commercialize our products in the US, or any other future product candidates, if any such candidate receives regulatory approval for commercial sale; ● the progress and success of our clinical trials and preclinical activities (including studies and manufacture of materials) of our product candidates conducted by us; ● **our ability to secure patent and regulatory protection; ● our ability to secure a favorable price or a positive HTA assessment; ●** potential future impacts, if any, of **a global** ~~the evolving COVID- 19~~ pandemic; ● the costs and timing of regulatory filings and approvals by us and our collaborators; ● the progress of research and development programs carried out by us and our collaborative partners; ● any changes in the breadth of our

research and development programs; ● the ability to achieve the events identified in our collaborative agreements that may trigger payments to us from our collaboration partners; ● our ability to acquire or license other technologies or compounds that we may seek to pursue; ● our ability to manage our growth; ● competing technological and market developments; ● the costs and timing of obtaining, enforcing and defending our patent and other intellectual property rights; ~~and~~ **and58** ● expenses associated with any unforeseen litigation, including any arbitration and securities class action lawsuits. Insufficient funds may require us to delay, scale back or eliminate some or all of our commercial efforts and / or research and development programs, to reduce personnel and operating expenses, to lose rights under existing licenses or to relinquish greater or all rights to product candidates at an earlier stage of development or on less favorable terms than we would otherwise choose or may adversely affect our ability to operate as a going concern. Our success as a company is uncertain due to our history of operating losses and the uncertainty of any future profitability. For the year ended December 31, ~~2022~~ **2023** , we recognized loss from operations of $ ~~55~~ **20** . ~~6~~ **5** million primarily due to higher operating and non- operating expenses, partly offset by our net product sales and collaboration revenues. We have historically incurred losses from operations each year since we were incorporated in June 1996 other than in fiscal year 2010, due in large part to the significant research and development expenditures required to identify and validate new product candidates and pursue our development efforts, and the costs of our ongoing commercial efforts for our products. We expect to continue to incur losses from operations, at least in the next 12 months, and there can be no assurance that we will generate annual operating income in the foreseeable future. Currently, our potential sources of revenues are our sales of our products, upfront payments, research and development contingent payments and royalty payments pursuant to our collaboration arrangements, which may never materialize if our collaborators do not achieve certain events or generate net sales to which these contingent payments are dependent on. If our future drug candidates fail or do not gain regulatory approval, or if our drugs do not achieve sustainable market acceptance, we may not be profitable. As of December 31, ~~2022~~ **2023** , we had an accumulated deficit of approximately $ 1. 4 billion. The extent of our ~~54future~~ **future** losses or profitability, if any ~~, especially due to the COVID- 19 pandemic~~ , is highly uncertain. If our corporate collaborations or license agreements are unsuccessful, or if we fail to form new corporate collaborations or license agreements, our research and development efforts could be delayed. Our strategy depends upon the formation and sustainability of multiple collaborative arrangements and license agreements with third parties now and in the future. We rely on these arrangements for not only financial resources, but also for expertise we need now and in the future relating to clinical trials, manufacturing, sales and marketing, and for licenses to technology rights. To date, we have entered into several such arrangements with corporate collaborators; however, we do not know if these collaborations or additional collaborations with third parties, if any, will dedicate sufficient resources or if any development or commercialization efforts by third parties will be successful. In addition, our corporate collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a drug candidate or development program. Should a collaborative partner fail to develop or commercialize a compound or product to which it has rights from us for any reason, including corporate restructuring, such failure might delay our ongoing research and development efforts, because we might not receive any future payments, and we would not receive any royalties associated with such compound or product. We may seek another collaborator or licensee in the future for clinical development and commercialization of ~~fostamatinib~~ **our products** , as well as our other clinical programs, which we may not be able to obtain on commercially reasonable terms or at all. If we are unable to form new collaborations or enter into new license agreements, our research and development efforts could be delayed. In addition, the continuation of some of our partnered drug discovery and development programs may be dependent on the periodic renewal of our corporate collaborations. Each of our collaborations could be terminated by the other party at any time, and we may not be able to renew these collaborations on acceptable terms, if at all, or negotiate additional corporate collaborations on acceptable terms, if at all. If these collaborations terminate or are not renewed, any resultant loss of revenues from these collaborations or loss of the resources and expertise of our collaborative partners could adversely affect our business. Conflicts also might arise with collaborative partners concerning proprietary rights to particular compounds. While our existing collaborative agreements typically provide that we retain milestone payments, royalty rights and / or revenue sharing with respect to drugs developed from certain compounds or derivative compounds, any such payments or royalty rights may be at reduced rates, and disputes may arise over the application of payment provisions or derivative payment provisions to such drugs, and we may not be successful in such disputes. For example, in September 2018, BerGenBio served us with a notice of arbitration seeking declaratory relief related to the interpretation of provisions ~~under~~ **59under** our June 2011 license agreement, particularly as they relate to the rights and obligations of the parties in the event of the license or sale of a product in the program by BerGenBio and / or the sale of BerGenBio to a third party. The arbitration panel dismissed four of the six declarations sought by BerGenBio, and we thereafter consented to one of the remaining declarations requested by BerGenBio. On February 27, 2019, the arbitration panel issued a determination granting the declaration sought by BerGenBio on the remaining issue, and held that in the event of a sale of shares by BerGenBio' s shareholders where there is no monetary benefit to BerGenBio, we would not be entitled to a portion of the proceeds from such a sale. In this circumstance where the revenue share provision is not triggered, the milestone and royalty payment provisions remain in effect. While we do not believe that the determination will have an adverse effect on our operations, cash flows or financial condition, we can make no assurance regarding any such impact. Additionally, the management teams of our collaborators may change for various reasons including due to being acquired. Different management teams or an acquiring company of our collaborators may have different priorities which may have adverse results on the collaboration with us. We are also a party to various license agreements that give us rights to use specified technologies in our research and development processes. The agreements pursuant to which we have in- licensed technology permit our licensors to terminate the agreements under certain circumstances. If we are not able to continue to license these and future technologies on commercially reasonable terms, our product development and research may be delayed or otherwise adversely affected. ~~55If~~ **If** conflicts arise between our collaborators or advisors and us, any of them may act in their self- interest, which may be adverse to our stockholders' interests. If conflicts arise between us and our corporate

collaborators or scientific advisors, the other party may act in its self- interest and not in the interest of our stockholders. Some of our corporate collaborators are conducting multiple product development efforts within each disease area that is the subject of the collaboration with us or may be acquired or merged with a company having a competing program. In some of our collaborations, we have agreed not to conduct, independently or with any third party, any research that is competitive with the research conducted under our collaborations. Our collaborators, however, may develop, either alone or with others, products in related fields that are competitive with the products or potential products that are the subject of these collaborations. Competing products, either developed by our collaborators or to which our collaborators have rights, may result in their withdrawal of support for our product candidates. If any of our corporate collaborators were to breach or terminate its agreement with us or otherwise fail to conduct the collaborative activities successfully and in a timely manner, the preclinical or clinical development or commercialization of the affected product candidates or research programs could be delayed or terminated. We generally do not control the amount and timing of resources that our corporate collaborators devote to our programs or potential products. We do not know whether current or future collaborative partners, if any, might pursue alternative technologies or develop alternative products either on their own or in collaboration with others, including our competitors, as a means for developing treatments for the diseases targeted by collaborative arrangements with us. Our success is dependent on intellectual property rights held by us and third parties, and our interest in such rights is complex and uncertain. Our success will depend to a large part on our own, our licensees' and our licensors' ability to obtain and defend patents for each party' s respective technologies and the compounds and other products, if any, resulting from the application of such technologies. For example, fostamatinib is covered as a composition of matter in a US issued patent that has an expected expiration date of September 2031 **(including the patent term extension granted on December 21, 2023) and olutasidenib is covered as a composition of matter in a US issued patent that has an expected expiration date of December 2036** , after taking into account patent term ~~adjustment and~~ extension rules. In the future, our patent position might be highly uncertain and involve complex legal and factual questions **, and the cost to defend may also be significant** . For example, we may be involved in post- grant proceedings before the US Patent and Trademark Office. Post- grant proceedings are complex and expensive legal proceedings and there is no assurance we will be successful in any such proceedings. A post- grant proceeding could result in our losing our patent rights and / or our freedom to operate and / or require us to pay significant royalties. Additionally, third parties may challenge the validity, enforceability or scope of our issued patents, which may result in such patents being narrowed, ~~invalidated~~ **60invalidated** or held unenforceable through interference, opposition or invalidity proceedings before the US Patent and Trademark Office or non- US patent offices. Any successful opposition to our patents could deprive us of exclusive rights necessary for the successful commercialization of ~~fostamatinib~~ **our products** or our other product candidates. Oppositions could also be filed to complementary patents, such as formulations, methods of manufacture and methods of use, that are intended to extend the patent life of the overall portfolio beyond the patent life covering the composition of matter. A successful opposition to any such complementary patent could impact our ability to extend the life of the overall portfolio beyond that of the related composition of matter patent. An adverse outcome may allow third parties to use our intellectual property without a license and / or allow third parties to introduce generic and other competing products, any of which would negatively impact our business. For example, in June 2022, we received a notice letter from Annora advising that it has filed an ANDA with the FDA for a generic version of TAVALISSE and asserting that certain patents related to TAVALISSE that are listed in the Orange Book will not be infringed by Annora' s proposed product, are invalid and / or are unenforceable. In July 2022, we filed a lawsuit in the US District Court for the District of New Jersey against Annora and its subsidiaries for infringement of those US patents. In September 2022, Annora and its subsidiaries answered and counterclaimed for declaratory judgment of non- infringement and invalidity of those patents. We filed an answer to Annora' s counterclaims on October 12, 2022. **Annora served invalidity and non- infringement contentions on December 31, 2022. We filed an answer to Annora' s invalidity and non- infringement contentions in March 2023. Litigation continues, and no trial date is currently set.** We intend to vigorously enforce and defend our intellectual property rights related to TAVALISSE. Should Annora or any other third parties receive FDA approval of an ANDA for a generic version of fostamatinib or a 505 (b) (2) NDA with respect to fostamatinib, and if our patents covering fostamatinib were held to be invalid (or if such competing generic versions of fostamatinib were found to not infringe our patents), then they could introduce generic versions of ~~56fostamatinib~~ -- **fostamatinib** or other such 505 (b) (2) products before our patents expire, and the resulting competition would negatively affect our business, financial condition and results of operations. Please also see the risk factor entitled, " If manufacturers obtain approval for generic versions of our products, or of products with which we compete, our business may be harmed. " **In the future, there might be other claims that are subject to substantial uncertainties and unascertainable damages or other remedies, and the cost to defend may also be significant.** Additional uncertainty may result because no consistent policy regarding the breadth of legal claims allowed in biotechnology patents has emerged to date. Accordingly, we cannot predict the breadth of claims allowed in our or other companies' patents. Because the degree of future protection for our proprietary rights is uncertain, we cannot assure ~~you~~ that: ● we were the first to make the inventions covered by each of our pending patent applications; ● we were the first to file patent applications for these inventions; ● others will not independently develop similar or alternative technologies or duplicate any of our technologies; ● any of our pending patent applications will result in issued patents; ● any patents issued to us or our collaborators will provide a basis for commercially viable products or will provide us with any competitive advantages or will not be challenged by third parties; ● we will develop additional proprietary technologies that are patentable; ● we will obtain a ~~supplemental~~ **supplementary** protection certificate that will extend the protection afforded by the patent to the product with a marketing authorization; or ● the patents of others will not have a negative effect on our ability to do business. We rely on trade secrets to protect technology where we believe patent protection is not appropriate or obtainable; however, trade secrets are difficult to protect. While we require employees, collaborators and consultants to enter into confidentiality agreements, we may not be able to adequately protect our trade secrets or other proprietary ~~information~~ **61information** in the event of any

unauthorized use or disclosure or the lawful development by others of such information. We are a party to certain in- license agreements that are important to our business, and we generally do not control the prosecution of in- licensed technology. Accordingly, we are unable to exercise the same degree of control over this intellectual property as we exercise over our internally developed technology. Moreover, some of our academic institution licensors, research collaborators and scientific advisors have rights to publish data and information in which we have rights. If we cannot maintain the confidentiality of our technology and other confidential information in connection with our collaborations, our ability to receive patent protection or protect our proprietary information may otherwise be impaired. In addition, some of the technology we have licensed relies on patented inventions developed using US government resources. The US government retains certain rights, as defined by law, in such patents, and may choose to exercise such rights. Certain of our in- licenses may be terminated if we fail to meet specified obligations. If we fail to meet such obligations and any of our licensors exercise their termination rights, we could lose our rights under those agreements. If we lose any of our rights, it may adversely affect the way we conduct our business. In addition, because certain of our licenses are sublicenses, the actions of our licensors may affect our rights under those licenses. If a dispute arises regarding the infringement or misappropriation of the proprietary rights of others, such dispute could be costly and result in delays in our research and development activities, partnering and commercialization activities. Our success will depend, in part, on our ability to operate without infringing or misappropriating the proprietary rights of others. There are many issued patents and patent applications filed by third parties relating to products or processes that are similar or identical to our licensors or ours, and others may be filed in the future. There may also be ~~57copyrights~~ **copyrights** or trademarks that third parties hold. There can be no assurance that our activities, or those of our licensors, will not violate intellectual property rights of others. We believe that there may be significant litigation in the industry regarding patent and other intellectual property rights, and we do not know if our collaborators or we would be successful in any such litigation. Any legal action against our collaborators or us claiming damages or seeking to enjoin commercial activities relating to the affected products, our methods or processes could: ● require our collaborators or us to obtain a license to continue to use, manufacture or market the affected products, methods or processes, which may not be available on commercially reasonable terms, if at all; ● prevent us from using the subject matter claimed in the patents held by others; ● subject us to potential liability for damages; ● consume a substantial portion of our managerial and financial resources; and ● result in litigation or administrative proceedings that may be costly, whether we win or lose. Our effective tax rate may fluctuate, and we may incur obligations in tax jurisdictions in excess of accrued amounts. We are subject to taxation in numerous US states and territories. As a result, our effective tax rate is derived from a combination of applicable tax rates in the various places that we operate. In preparing our financial statements, we estimate the amount of tax that will become payable in each of such places. Nevertheless, our effective tax rate may be different than experienced in the past due to numerous factors, including passage of the newly enacted federal income tax law, changes in the mix of our profitability from state to state, the results of examinations and audits of our tax filings, our inability to secure or sustain acceptable agreements with tax authorities, changes in accounting for income taxes and changes in tax laws. Any of these factors could cause us to experience an effective tax rate significantly different from previous periods or our current expectations and may result in tax obligations in excess of amounts accrued in our financial statements. ~~Our~~ **62Our** ability to use net operating losses (NOLs) and certain other tax attributes is uncertain and may be limited. Our ability to use our federal and state NOLs to offset potential future taxable income and related income taxes that would otherwise be due is dependent upon our generation of future taxable income before the expiration dates of the NOLs, and we cannot predict with certainty when, or whether, we will generate sufficient taxable income to use all of our NOLs. Federal NOLs generated prior to 2018 will continue to be governed by the NOL carryforward rules as they existed prior to the adoption of the Tax Cuts and Jobs Act (Tax Act), which means that generally they will expire 20 years after they were generated if not used prior thereto. Many states have similar laws. Accordingly, our federal and state NOLs could expire unused and be unavailable to offset future income tax liabilities. Under the Tax Act as modified by the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), federal NOLs incurred in tax years beginning after December 31, 2017 and before January 1, 2021 may be carried back to each of the five tax years preceding such loss, and NOLs arising in tax years beginning after December 31, 2020 may not be carried back. Moreover, federal NOLs generated in tax years ending after December 31, 2017 may be carried forward indefinitely, but the deductibility of such federal NOLs may be limited to 80 % of current year taxable income for tax years beginning after January 1, 2021. Under A. B. 85, our California NOL carryforwards are suspended for tax years 2020, 2021, and 2022, but the period to use these carryovers was extended. Further, the Tax Act requires the taxpayers to capitalize Research and Experimental (R & E) expenditures under Section 174 of the Internal Revenue Code, as amended (Code), effective for taxable years beginning after December 31, 2021, which will reduce our NOLs beginning in 2022. R & E expenditures attributable to US- based research must be amortized over a period of 5 years and R & E expenditures attributable to research conducted outside of the US must be amortized over a period of 15 years. In addition, utilization of NOLs to offset potential future taxable income and related income taxes that would otherwise be due is subject to annual limitations under the " ownership change " provisions of Sections 382 and 383 of the Code and similar state provisions, which may result in the expiration of NOLs before future utilization. In general, under the Code, if a corporation undergoes an " ownership change, " generally defined as a greater than 50 % change (by value) in its equity ownership over a three- year period, the corporation' s ability to use its pre- change NOLs and other pre- ~~58change~~ **change** tax attributes (such as research and development credit carryforwards) to offset its post- change taxable income or taxes may be limited. Our equity offerings and other changes in our stock ownership, some of which are outside of our control, may have resulted or could in the future result in an ownership change. Although we have completed studies to provide reasonable assurance that an ownership change limitation would not apply, we cannot be certain that a taxing authority would reach the same conclusion. If, after a review or audit, an ownership change limitation were to apply, utilization of our domestic NOLs and tax credit carryforwards could be limited in future periods and a portion of the carryforwards could expire before being available to reduce future income tax liabilities. Moreover, our ability to utilize our NOLs is conditioned upon us

achieving profitability and generating US federal taxable income. Because we expect to be dependent upon collaborative and license agreements, we might not meet our strategic objectives. Our ability to generate revenue in the near term depends on the timing of recognition of certain upfront payments, achievement of certain payment triggering events with our existing collaboration agreements and our ability to enter into additional collaborative agreements with third parties. Our ability to enter into new collaborations and the revenue, if any, that may be recognized under these collaborations is highly uncertain. If we are unable to enter into one or more new collaborations, our business prospects could be harmed, which could have an immediate adverse effect on our ability to continue to develop our compounds and on the trading price of our stock. Our ability to enter into a collaboration may be dependent on many factors, such as the results of our clinical trials, competitive factors and the fit of one of our programs with another company' s risk tolerance, including toward regulatory issues, patent portfolio, clinical pipeline, the stage of the available data, particularly if it is early, overall corporate goals and financial position. To date, a portion of our revenues have been related to the research or transition phase of each of our collaborative agreements. Such revenues are for specified periods, and the impact of such revenues on our results of operations is at least partially offset by corresponding research costs. Following the completion of the research or transition phase of each collaborative agreement, additional revenues may come only from payments triggered by milestones and / or the achievement of other contingent events, and royalties, which may not be paid, if at all, until certain conditions are met. This risk is heightened due to the fact that unsuccessful research efforts may preclude us from ~~receiving~~ **63receiving** any contingent payments under these agreements. Our receipt of revenues from collaborative arrangements is also significantly affected by the timing of efforts expended by us and our collaborators and the timing of lead compound identification. We have received payments from our **current** collaborations ~~with~~ **including** Lilly, Grifols, Kissei, Medison, **Knight** ~~Aclaris, Celgene, BMS, AZ~~, BerGenBio, **and** ~~Janssen Pharmaceutica N. V., a division of Johnson & Johnson, Novartis Pharma A. G.,~~ Daiichi ~~, Merck & Co., Inc., Merck Serono and Pfizer~~. Under ~~many~~ **several** agreements, future payments may not be earned until the collaborator has advanced product candidates into clinical testing, which may never occur or may not occur until sometime well into the future. If we are not able to generate revenue under our collaborations when and in accordance with our expectations or the expectations of industry analysts, this failure could harm our business and have an immediate adverse effect on the trading price of our common stock. Our business requires us to generate meaningful revenue from royalties and licensing agreements. To date, we have not recognized material amount of revenue from royalties for the commercial sale of drugs, and we do not know when we will be able to generate such meaningful revenue in the future. Securities class action lawsuits or other litigation could result in substantial damages and may divert management' s time and attention from our business. We have been subject to class action lawsuits in the past and we may be subject to lawsuits in the future, such as those that might occur if there was to be a change in our corporate strategy. These and other lawsuits are subject to inherent uncertainties, and the actual costs to be incurred relating to the lawsuit will depend upon many unknown factors. The outcome of litigation is necessarily uncertain, and we could be forced to expend significant resources in the defense of such suits, and we may not prevail. Monitoring and defending against legal actions is time- consuming for our management and detracts from our ability to fully focus our internal resources on our business activities. In addition, we may incur substantial legal fees and costs in connection with any such litigation. We have not established any reserves for any potential liability relating to any such potential lawsuits. It is possible that we could, in the future, incur judgments or enter into settlements of claims for monetary damages. A decision adverse to our interests on any such ~~59actions~~ -- **actions** could result in the payment of substantial damages, or possibly fines, and could have an adverse effect on our cash flow, results of operations and financial position. If our competitors develop technologies that are more effective than ours, our commercial opportunity will be reduced or eliminated. The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. Many of the drugs that we are attempting to discover will be competing with existing therapies. In addition, a number of companies are pursuing the development of pharmaceuticals that target the same diseases and conditions that we are targeting. For example, the commercialization of new pharmaceutical products is highly competitive, and we face substantial competition with respect to our products in which there are existing therapies and drug candidates in development for the treatment of hematologic disorders and cancer that may be alternative therapies to our products. Many of our competitors, including a number of large pharmaceutical companies that compete directly with us, have significantly greater financial resources and expertise commercializing approved products than we do. Also, many of our competitors are large pharmaceutical companies that will have a greater ability to reduce prices for their competing drugs in an effort to gain market share and undermine the value proposition that we might otherwise be able to offer to ~~payers~~ **payors** . We face, and will continue to face, intense competition from pharmaceutical and biotechnology companies, as well as from academic and research institutions and government agencies, both in the US and abroad. Some of these competitors are pursuing the development of pharmaceuticals that target the same diseases and conditions as our research programs. Our competitors including fully integrated pharmaceutical companies have extensive drug discovery efforts and are developing novel small- molecule pharmaceuticals. We also face significant competition from organizations that are pursuing the same or similar technologies, including the discovery of targets that are useful in compound screening, as the technologies used by us in our drug discovery efforts. Competition may also arise from: ● new or better methods of target identification or validation; ● generic versions of our products or of products with which we compete; **64** ● other drug development technologies and methods of preventing or reducing the incidence of disease; ● new small molecules; or ● other classes of therapeutic agents. Our competitors or their collaborative partners may utilize discovery technologies and techniques or partner with collaborators in order to develop products more rapidly or successfully than we or our collaborators are able to do. Many of our competitors, particularly large pharmaceutical companies, have substantially greater financial, technical and human resources and larger research and development staffs than we do. 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 and may establish exclusive collaborative or licensing relationships with our competitors. We believe that our ability to compete is dependent, in part, upon our ability to create,

maintain and license scientifically- advanced technology and upon our and our collaborators' ability to develop and commercialize pharmaceutical products based on this technology, as well as our ability to attract and retain qualified personnel, obtain patent protection or otherwise develop proprietary technology or processes, secure effective market access by ensuring competitive pricing and reimbursement in territories of interest, and secure sufficient capital resources for the expected substantial time period between technological conception and commercial sales of products based upon our technology. The failure by any of our collaborators or us in any of those areas may prevent the successful commercialization of our potential drug targets. Many of our competitors, either alone or together with their collaborative partners, have significantly greater experience than we do in: ~~60~~ ● identifying and validating targets; ● screening compounds against targets; and ● undertaking preclinical testing and clinical trials. Accordingly, our competitors may succeed in obtaining patent protection, identifying or validating new targets or discovering new drug compounds before we do. Our competitors might develop technologies and drugs that are more effective or less costly than any that are being developed by us or that would render our technology and product candidates obsolete and noncompetitive. In addition, our competitors may succeed in obtaining the approval of the FDA or other regulatory agencies for product candidates more rapidly. Companies that complete clinical trials, obtain required regulatory agency approvals and commence commercial sale of their drugs before us may achieve a significant competitive advantage, including certain patent and FDA marketing exclusivity rights that would delay or prevent our ability to market certain products. Any drugs resulting from our research and development efforts, or from our joint efforts with our existing or future collaborative partners, might not be able to compete successfully with competitors' existing or future products or obtain regulatory approval in the US or elsewhere. We face and will continue to face intense competition from other companies for collaborative arrangements with pharmaceutical and biotechnology companies, for establishing relationships with academic and research institutions and for licenses to additional technologies. These competitors, either alone or with their collaborative partners, may succeed in developing technologies or products that are more effective than ours. Our ability to compete successfully will depend, in part, on our ability to: ● identify and validate targets; ● discover candidate drug compounds that interact with the targets we identify in a safe and efficacious way; ● attract and retain scientific and product development personnel; **65** ● recruit subjects into our clinical trials; ● obtain and maintain required regulatory approvals; ● obtain patent or other proprietary protection for our new drug compounds and technologies; ● **obtain access to manufacturing resources of the sufficient standard and scale; ●** enter commercialization agreements for our new drug compounds; and ● obtain and maintain appropriate reimbursement price and positive recommendations by HTA bodies. Our stock price may be volatile, and our stockholders' investment in our common stock could decline in value. The market prices for our common stock and the securities of other biotechnology companies have been highly volatile and may continue to be highly volatile in the future. The following factors, in addition to other risk factors described in this section, may have a significant impact on the market price of our common stock: ● the progress and success of our clinical trials and preclinical activities (including studies and manufacture of materials) of our product candidates conducted by us; ● our ability to continue to sell our products in the US; ● our ability to enter into partnering opportunities across our pipeline; ● the receipt or failure to receive the additional funding necessary to conduct our business; ● selling of our common stock by large stockholders; ~~61~~ ● presentations of detailed clinical trial data at medical and scientific conferences and investor perception thereof; ● announcements of technological innovations or new commercial products by our competitors or us; ● the announcement of regulatory applications, such as Annora' s ANDA, seeking approval of generic versions of our marketed products; ● developments concerning proprietary rights, including patents; ● developments concerning our collaborations; ● publicity regarding actual or potential medical results relating to products under development by our competitors or us; ● regulatory developments in the US and foreign countries; ● changes in the structure of healthcare payment systems; ● litigation or arbitration; ● economic and other external factors or other disaster or crisis; and ● period- to- period fluctuations in financial results. ~~If~~ **66If** we fail to continue to meet the listing standards of Nasdaq, our common stock may be delisted, which could have a material adverse effect on the liquidity of our common stock. Our common stock is currently listed on the Nasdaq Global Market. The Nasdaq Stock Market LLC **(Nasdaq)** has requirements that a company must meet in order to remain listed on Nasdaq. In particular, Nasdaq rules require us to maintain a minimum bid price of $ 1. 00 per share of our common stock (the " Bid Price Requirement "). If the closing bid price of our common stock falls below $ 1. 00 per share for 30 consecutive trading days or we do not meet other listing requirements, we would fail to be in compliance with Nasdaq listing standards. There can be no assurance that we will continue to meet the **Bid** ~~minimum bid price~~ **Price** ~~requirement~~ **Requirement** , or any other requirement in the future. On November 22, 2022, we received a deficiency letter from the Listing Qualifications Department of ~~the~~ Nasdaq ~~Stock Market LLC~~ notifying us that, for the last 30 consecutive business days, the bid price for our common stock **had** closed below ~~the Bid Price Requirement. We were provided a period of 180 calendar days, or until May 22, 2023 (the " Compliance Date "), to regain compliance with~~ the Bid Price Requirement. On January 5, 2023, we received notification from the Listing Qualifications Department of ~~the~~ Nasdaq ~~Stock Market LLC~~ that we ~~have~~ **had** regained compliance with the Bid Price Requirement because the closing bid price of our common stock closed at $ 1. 00 or more for over 10 consecutive business days from December 13, 2022 to January 4, 2023. ~~While~~ **On November 27, 2023, we again received a deficiency letter from the Listing Qualifications Department of Nasdaq notifying us that, for the last 30 consecutive business days, the bid price for our common stock had closed below the Bid Price Requirement. On December 12, 2023, we received notification from the Listing Qualifications Department of Nasdaq that we had regained our compliance with the Bid Price Requirement because the closing bid price of our common stock closed at $ 1. 00 or more for over 10 consecutive business days from November 28, 2023 to December 11, 2023. Although** we have regained compliance, the Nasdaq ~~Stock Market LLC~~ may in the future initiate the delisting process with a notification letter if we were to again fall out of compliance. If we were to receive such a notification, we would be afforded a grace period of 180 calendar days to regain compliance with the **Bid** ~~minimum bid price~~ **Price** ~~requirement~~ **Requirement** . In order to regain compliance, shares of our common stock would need to maintain a minimum closing bid price of at least $ 1. 00 per share for a minimum of 10

consecutive trading days. ~~In addition~~ **We would be required to notify Nasdaq of our intent to cure the minimum bid price deficiency, which may include, if necessary, seeking stockholder approval to implement a reverse stock split. Any reverse stock split may not be approved by our stockholders, or if approved the market price per share of our common stock after the reverse stock split may not remain unchanged or increase in proportion to the reduction in the number of common stock outstanding before the reverse stock split. Additionally** , we may be unable to meet other applicable Nasdaq listing requirements, including maintaining minimum levels of stockholders' equity or market values of our common stock in which case, our common stock could be delisted. If our common stock were to be delisted, the liquidity of our common stock would be adversely affected and the market price of our common stock could decrease. ~~62The~~ -- **The** withdrawal of the UK from the EU may adversely impact our ability to obtain regulatory approvals of our product candidates in the UK ~~and the EU~~ , result in restrictions or imposition of taxes and duties for importing our product candidates into the UK ~~and the EU~~ , and may require us to incur additional expenses in order to develop, manufacture and commercialize our product candidates in the UK ~~and the EU~~ . Following the result of a referendum in 2016, the UK left the EU on January 31, 2020, commonly referred to as Brexit. Pursuant to the formal withdrawal arrangements agreed between the UK and the EU, the UK was subject to a transition period until December 31, 2020, or the Transition Period, during which EU rules continued to apply. A trade and cooperation agreement (Trade Agreement) that outlines the future trading relationship between the UK and the EU was agreed to in December 2020 and has been approved by each EU member state and the UK. Since a significant proportion of the regulatory framework in the UK applicable to our business and our product candidates is derived from EU directives and regulations, Brexit has had, and will continue to have, a material impact upon the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the UK or the EU. Great Britain (made up of England, Scotland, and Wales) is no longer covered by the EEA' s procedures for the grant of marketing authorizations (Northern Ireland will be covered by such procedures). **The UK Government and the EU recently adopted a new agreement, the " Windsor Framework " which will 67replace the Northern Ireland Protocol. According to the Windsor Framework, medicinal products intended for the UK market including Northern Ireland will be authorized by the MHRA, and will bear a " UK only " label. This means that Medicinal products placed on the market in Northern Ireland will no longer need to be compliant with EU law. These new measures will be implemented from January 1, 2025.** A separate marketing authorization will be required to market drugs in Great Britain. **The** ~~It is currently unclear whether the Medicines and Healthcare Products Regulatory Agency, or~~ MHRA ~~, in~~ **has launched** the ~~UK is sufficiently prepared to handle the increased volume of~~ **Innovative Licensing and Access Pathway, or ILAP, a new accelerated assessment procedure for** marketing authorization applications ~~that~~ **facilitating the interaction with pricing authorities and HTA bodies and aiming to enable companies to enter the UK market faster. On January 1st 2024, the MHRA launched a new International Recognition Procedure for Great Britain (England, Scotland and Wales) marketing authorization applications whereby the MHRA will, when considering such applications, recognize the approval of medicines by trusted reference regulators in Australia, Canada, Switzerland, Singapore, Japan, United States and EU following** ~~it~~ **its own abbreviated assessment** ~~is likely to receive~~ . Any delay in obtaining, or an inability to obtain, any marketing approvals would delay or prevent us from commercializing our product candidates in the UK or the EU and restrict our ability to generate revenue and achieve and sustain profitability. While the Trade Agreement provides for the tariff- free trade of medicinal products between the UK and the EU, there may be additional non- tariff costs to such trade which did not exist prior to the end of the Transition Period. Further, should the UK diverge from the EU from a regulatory perspective in relation to medicinal products, tariffs could be put into place in the future. We could therefore, both now and in the future, face significant additional expenses (when compared to the position prior to the end of the Transition Period) to operate our business, which could significantly and materially harm or delay our ability to generate revenues or achieve profitability of our business. Any further changes in international trade, tariff and import / export regulations as a result of Brexit or otherwise may impose unexpected duty costs or other non- tariff barriers on us. These developments, or the perception that any of them could occur, may significantly reduce global trade and, in particular, trade between the impacted nations and the UK. It is also possible that Brexit may negatively affect our ability to attract and retain employees, particularly those from the EU. Orphan designation in Great Britain following Brexit is granted on an essentially identical basis as in the EU but is based on the prevalence of the condition in Great Britain. It is therefore possible that conditions that are currently designated as orphan conditions in Great Britain will no longer be, and conditions that are not currently designated as orphan conditions in the EU will be designated as such in Great Britain. **In April 2023, the European Commission adopted a wide ranging proposal for a new Directive and a new Regulation. If made into law, this proposal will revise and replace the existing general pharmaceutical legislation. This change will likely result in significant changes to the pharmaceutical industry. In particular, it is expected that the new Directive and Regulations will, if made into law, affect the duration of the period of regulatory protection afforded to medicinal products including regulatory data protection (also called " data exclusivity "), marketing exclusivity afforded to orphan medicinal products, as well as the conditions of eligibility to the orphan designation.** If product liability lawsuits are successfully brought against us, we may incur substantial liabilities and may be required to limit commercialization of our products. The testing and marketing of medical products and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, health care providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our products. We carry product liability insurance that is limited in scope and amount and may not be adequate to fully protect us against product liability claims. If and when we obtain marketing approval for our product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. Our inability to obtain sufficient product liability insurance at an acceptable cost to

protect against potential product liability claims could prevent or inhibit the commercialization of pharmaceutical products we develop, alone or with corporate collaborators. We, or our corporate collaborators, might not be able to obtain insurance at a reasonable cost, if at all. While under various circumstances we are entitled to be indemnified against losses by our corporate collaborators, indemnification may not be available or adequate should any claim arise. ~~63We~~ **68We** depend on various scientific consultants and advisors for the success and continuation of our research and development efforts. We work extensively with various scientific consultants and advisors. The potential success of our drug discovery and development programs depends, in part, on continued collaborations with certain of these consultants and advisors. We, and various members of our management and research staff, rely on certain of these consultants and advisors for expertise in our research, regulatory and clinical efforts. Our scientific advisors are not our employees and may have commitments to, or consulting or advisory contracts with, other entities that may limit their availability to us. We do not know if we will be able to maintain such consulting agreements or that such scientific advisors will not enter into consulting arrangements with competing pharmaceutical or biotechnology companies, any of which may have a detrimental impact on our research objectives and could have an adverse effect on our business, financial condition and results of operations. While we have a strong compliance process in place to ensure we are complying with all requirements of law, our consulting or advisory contracts with our scientific consultants and advisors may be scrutinized under the Anti- Kickback Statute, the UK Bribery Act 2010, and other similar national and state- level legislation, which prohibit, among other things, companies from offering or paying anything of value as remuneration for ordering, purchasing, or recommending the ordering or purchasing of pharmaceutical and biological products that may be paid for, in whole or in part, by Medicare, Medicaid, or another federal healthcare program. Although there are several statutory exceptions and regulatory safe harbors that may protect these arrangements from prosecution or regulatory sanctions, our consulting and advising contracts may be subject to scrutiny if they do not fit squarely within an available exception or safe harbor. If we use biological and hazardous materials in a manner that causes injury or violates laws, we may be liable for damages, penalties or fines. Our research and development activities involve the controlled use of potentially harmful biological materials as well as hazardous materials, chemicals, animals, and various radioactive compounds. We cannot completely eliminate the risk of accidental contamination or injury from the use, storage, handling or disposal of these animals and materials. In the event of contamination or injury, we could be held liable for damages that result or for penalties or fines that may be imposed, and such liability could exceed our resources. We are also subject to federal, state and local laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products. The cost of compliance with, or any potential violation of, these laws and regulations could be significant. Our information technology systems, or those used by our CROs or other contractors or consultants, may fail or suffer other breakdowns, cyber- attacks, or information security breaches. We are ~~increasingly~~ dependent upon information technology systems, infrastructure, and data to operate our business **. While we believe our cybersecurity measures are adequate** , ~~particularly during the COVID- 19 pandemic~~ **our cybersecurity risk management, strategy and governance may be found to be inadequate that could harm our business** . We ~~also~~ rely on third **-** party vendors and their information technology systems. Despite the implementation of security measures, our recovery systems, security protocols, network protection mechanisms and other security measures and those of our CROs and other contractors and consultants are vulnerable to compromise from natural disasters; terrorism; war; telecommunication and electric failures; traditional computer hackers; malicious code (such as computer viruses or worms); employee error, theft or misuse; denial- of- service attacks; cyber- attacks by sophisticated nation- state and nation- state supported actors including ransomware; or other system disruptions. We receive, generate and store significant and increasing volumes of personal (including health), confidential and proprietary information. There can be no assurance that we, or our collaborators, CROs, third- party vendors, contractors and consultants will be successful in efforts to detect, prevent, protect against or fully recover systems or data from all **breakdowns** ~~break- downs~~ , service interruptions, attacks or breaches. Any breakdown, cyber- attack or information security breach could result in a disruption of our drug development programs or other aspects of our business. For example, the loss of clinical trial data from completed or ongoing clinical trials for a product candidate could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of personal, confidential or proprietary information, we could incur liability, incur significant remediation or litigation costs, result in product development delays, disrupt key business operations, cause loss of revenue and divert attention of management and key information technology resources. ~~64Hackers~~ **69Hackers** and data thieves are increasingly sophisticated and operate large- scale and complex automated attacks, including on companies within the healthcare industry. As the cyber- threat landscape evolves, these threats are likely growing in frequency, sophistication and intensity and are increasingly difficult to detect. The costs of maintaining or upgrading our cyber- security systems at the level necessary to keep up with our expanding operations and prevent against potential attacks are increasing. Cyber threats may be generic, or they may be targeted against our information systems. Our network and storage applications and those of our contract manufacturing organizations, collaborators, contractors, CROs or vendors may be subject to unauthorized access or processing by hackers or breached due to operator or other human error, theft, malfeasance or other system disruptions. We may be unable to anticipate or immediately detect information security incidents and the damage caused by such incidents. These data breaches and any unauthorized access, processing or disclosure of our information or intellectual property could compromise our intellectual property and expose our sensitive business information. Such attacks, such as in the case of a ransomware attack, also may interfere with our ability to continue to operate and may result in delays and shortcomings due to an attack that may encrypt our or our service providers' or partners' systems unusable. Additionally, because our services involve the processing of personal information and other sensitive information about individuals we are subject to various laws, regulations, industry standards, and contractual requirements related to such processing. Any event that leads to unauthorized access, processing or disclosure of personal information, including personal information regarding our clinical trial participants or employees, could

harm our reputation and business, compel us to comply with federal and / or state breach notification laws and foreign law equivalents, subject us to investigations and mandatory corrective action, and otherwise subject us to liability under laws, regulations or contracts that protect the privacy and security of personal information, which could disrupt our business, damage our reputation with our stakeholders, result in increased costs or loss of revenue, lead to negative publicity or result in significant financial exposure. The CCPA, in particular, includes a private right of action for California consumers whose personal information is impacted by a data security incident resulting from a company' s failure to maintain reasonable security procedures, and hence may result in civil litigation in the event of a security breach impacting such information. In addition, legislators and regulators in the US have enacted and are proposing new and more robust privacy and cybersecurity laws and regulations in response to increasing broad- based cyberattacks, including the CCPA and New York SHIELD Act **. Notably, on July 26, 2023, the SEC adopted a final rule on cybersecurity risk management, strategy, governance and incident disclosure (the " SEC Cyber Rule "). The SEC Cyber Rule requires public companies to make current disclosures about material cybersecurity incidents as well as annual disclosures of material information about their cybersecurity risk management, strategy and governance. The SEC Cyber Rule became effective on September 5, 2023** . New data security laws add additional complexity, requirements, restrictions and potential legal risk, and compliance programs may require additional investment in resources, and could impact strategies and availability of previously useful data. The costs to respond to a security breach and / or to mitigate any identified security vulnerabilities could be significant, our efforts to address these issues may not be successful, and these issues could result in interruptions, delays, negative publicity, loss of customer trust, and other harms to our business and competitive position. Remediation of any potential security breach may involve significant time, resources, and expenses. We could be required to fundamentally change our business activities and practices in response to a security breach and our systems or networks may be perceived as less desirable, which could negatively affect our business and damage our reputation. A security breach may cause us to breach our contracts with third parties. Our agreements with relevant stakeholders such as collaborators may require us to use legally required, industry- standard or reasonable measures to safeguard personal information. A security breach could lead to claims by relevant stakeholders that we have failed to comply with such contractual obligations, or require us to cooperate with these stakeholders in their own compliance efforts related to the security breach. In addition, any non- compliance with our data privacy obligations in our contracts or our inability to flow down such obligations from relevant stakeholders to our vendors may cause us to breach our contracts. As a result, we could be subject to legal action or the relevant stakeholders could end their relationships with us. There can be no assurance that the limitations of liability in our contracts would be enforceable or adequate or would otherwise protect us from liabilities or damages. We may not have adequate insurance coverage for security incidents or breaches. The successful assertion of one or more large claims against us that exceeds our available insurance coverage, or results in changes to our insurance policies (including premium increases or the imposition of large deductible or co- insurance requirements), could have an ~~adverse~~ **70adverse** effect on our business. In addition, we cannot be sure that our existing insurance coverage will continue to be available on acceptable terms or that our insurers will not deny coverage as to any future claim. ~~65Future~~ -- **Future** equity issuances or a sale of a substantial number of shares of our common stock may cause the price of our common stock to decline. Because we will continue to need additional capital in the future to continue to expand our business and our research and development activities, among other things, we may conduct additional equity offerings. For example, on August 3, 2021, a new automatic shelf registration statement was filed by us ~~,~~ as a well- known seasoned issuer (WKSI). The automatic shelf registration statement was filed to register, among other securities, the sale of up to a maximum aggregate offering price of $ 100. 0 million of shares of our common stock that may be issued and sold from time to time under our Open Market Sale Agreement with Jefferies LLC ~~.~~ (Jefferies), and a base prospectus which covers the offering, issuance, and sale by us of the securities identified above from time to time in one or more offerings. On March 1, 2022, we filed a post- effective amendment to the automatic shelf registration statement immediately after filing our Annual Report Form 10- K for the year ended December 31, 2021 because we no longer qualified as a WKSI upon filing of such Annual Report. The post- effective amendment was declared effective on May 3, 2022. The post- effective amendment registers, among other securities, a base prospectus which covers the offering, issuance, and sale by us of up to $ 250. 0 million in the aggregate of the securities identified from time to time in one or more offerings, which include the $ 100. 0 million of shares of our common stock that may be offered, issued and sold under the Open Market Sale Agreement. We may also in the future enter into underwriting or sales agreements with financial institutions for the offer and sale of any combination of common stock, preferred stock, debt securities and warrants in one or more offerings. If we or our stockholders sell, or if it is perceived that we or they will sell, substantial amounts of our common stock in the public market, the market price of our common stock could fall. A decline in the market price of our common stock could make it more difficult for us to sell equity or equity- related securities in the future at a time and price that we deem appropriate. In addition, future sales by us of our common stock may be dilutive to existing stockholders. Furthermore, if we obtain funds through a credit facility or through the issuance of debt or preferred securities, these securities would likely have rights senior to the rights of our common stockholders, which could impair the value of our common stock. Risks Related to Clinical Development and Regulatory ApprovalEnacted or future legislation, and / or potentially unfavorable pricing regulations or other healthcare reform initiatives, may increase the difficulty and cost for us to obtain regulatory approval of our product candidates and / or commercialize ~~fostamatinib~~ **our products** or our product candidates, once approved, and affect the prices we may set or obtain. The regulations that govern, among other things, regulatory approvals, coverage, pricing and reimbursement for new drug products vary widely from country to country. In the US and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay regulatory approval of our product candidates, restrict or regulate post- approval activities and affect our ability to successfully sell ~~fostamatinib~~ **our products,** or any product candidates for which we obtain regulatory approval in the future. In particular, in March 2010, the Affordable Care Act was enacted, which substantially changed the way health care is financed by both governmental and private

insurers, and continues to significantly impact the US pharmaceutical industry. On June 17, 2021, the US Supreme Court dismissed the most recent judicial challenge to the Affordable Care Act brought by several states without specifically ruling on the constitutionality of the law. ~~Prior to the Supreme Court' s decision, President Biden issued an executive order that instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the Affordable Care Act.~~ It is unclear how future actions before the Supreme Court, other such litigation, and the healthcare reform measures of the Biden administration will impact the Affordable Care Act and our business. There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. We cannot predict the initiatives that may be adopted in the future. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce the costs of healthcare and / or impose price controls may adversely affect, for example: ~~66~~ ● the demand for ~~fostamatinib~~ **our products,** or our product candidates, if we obtain regulatory approval; **71** ● our ability to set a price that we believe is fair for our products; ● our ability to generate revenue and achieve or maintain profitability; ● the level of taxes that we are required to pay; and ● the availability of capital. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors, which may adversely affect our future profitability. In the US, the EU and other potentially significant markets for our current and future products, government authorities and third-party payors are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which has resulted in lower average selling prices. In the US, there have been several ~~recent~~ Congressional inquiries and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer- sponsored patient assistance programs, and reform government program reimbursement methodologies for drugs. On March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which, among other changes, eliminates the statutory Medicaid drug rebate cap, currently set at 100 % of a drug' s average manufacture price, for single source and innovator multiple source drugs, beginning January 1, 2024. The American Rescue Plan Act also temporarily increased premium tax credit assistance for individuals eligible for subsidies under the ~~ACA~~ **Affordable Care Act** for 2021 and 2022 and removed the 400 % federal poverty level limit that otherwise applies for purposes of eligibility to receive premium tax credits. ~~The~~ IRA extended this increased tax credit assistance and removal of the 400 % federal poverty limit through 2025. Additionally, **beginning in April 2013,** the ~~temporary suspension~~ **Budget Control Act** of ~~the~~ **2011 created an automatic reduction of Medicare payments to providers of up to** 2 % **. As a result** ~~reduction in Medicare payments to providers that was instituted in the wake~~ of the COVID- 19 pandemic ~~expired on July~~ **, this reduction was temporarily suspended from May** 1, **2020 through March 31,** 2022, with ~~the~~ **subsequent reductions to 1 % from April 1, 2022 until June 30, 2022. The** 2 % reduction ~~set to~~ **was then reinstated and has been in effect since July 1, 2022, and will** remain in effect ~~until~~ **through the first six months of fiscal year** ~~2031~~ **2032 sequestration order,** unless additional Congressional action is taken. Moreover, on June 16, 2022, the Federal Trade Commission issued a policy statement stating its ~~intension~~ **intent** to increase enforcement scrutiny of " exclusionary rebates " to PBMs and other intermediaries that " foreclose competition. " On August 16, 2022, President Biden signed into law the IRA, which, among other reforms, allows Medicare to: beginning in 2026, establish a " maximum fair price " for ~~certain~~ **a fixed number of** pharmaceutical and biological products covered under Medicare Parts B and D **following a price negotiation with CMS** ; beginning in 2023, penalize drug companies that raise prices for products covered under Medicare Parts B and D faster than inflation; and beginning in 2025 **,** impose new ~~discounts~~ **discount** obligations on pharmaceutical and biological manufacturers for products covered under Medicare Part D. **CMS has recently taken steps to implement the IRA. First, on June 9, 2023, CMS released a list of 43 Medicare Part B products that had an adjusted coinsurance rate based on the inflationary rebate provisions of the IRA for the time period of July 1, 2023 to September 30, 2023. Additionally, on June 30, 2023, CMS issued guidance detailing the requirements and parameters of the first round of price negotiations for products subject to the " maximum fair price " provision. On August 29, 2023, CMS released the initial list of ten drugs subject to price negotiations. This negotiation process will occur during 2023 and 2024 and result in maximum prices that will be effective beginning in 2026. None of our products were listed among the first ten products slated for the program as announced on August 29, 2023. On November 17, 2023, CMS released guidance outlining the methodology for identifying certain manufacturers eligible to participate in a phase- in period where discounts on applicable products will be lower than those required by the Medicare Part D Manufacturer Discount Program. Most recently, on December 14, 2023, CMS released a list of 48 Medicare Part B products that had adjusted coinsurance rates based on the inflationary rebate provisions of the IRA for the time period of January 1, 2024 to March 31, 2024 and also issued revised guidance for manufacturers in the Medicare Part B and D drug discount programs. While it remains to be seen how the drug pricing provisions imposed by the IRA will affect the broader pharmaceutical industry, several pharmaceutical manufacturers and other industry stakeholders have challenged the law, including through lawsuits brought against the DHHS, the Secretary of the DHHS, CMS, and the CMS Administrator challenging the constitutionality and administrative implementation of the IRA' s drug price negotiation provisions.** ~~The~~ **72The** Biden administration has also taken executive action to address drug pricing and other healthcare policy changes. For example, ~~in response to a July 9, 2021 Executive Order from President Biden that included several prescription drug initiatives, on September 9, 2021, the Department of Health and Human Services issued a Comprehensive Plan for Addressing High Drug Prices that identified potential legislative policies and administrative tools that Congress and the agency can pursue in order to make drug prices more affordable and equitable, improve and promote competition throughout the prescription drug industry, and foster scientific innovation. Additionally,~~ on September 12, 2022, President Biden issued an Executive Order to promote biotechnology and biomanufacturing innovation. The Order noted several

methods through which the Biden Administration would support the advancement of biotechnology and biomanufacturing in healthcare, and instructed the **DHHS** ~~Department of Health and Human Service~~ to submit, within 180 days of the Order, a report assessing how to use biotechnology and biomanufacturing to achieve medical breakthroughs, reduce the overall burden of disease, and improve health outcomes. On October 14, 2022, President Biden issued an Executive Order on Lowering Prescription Drug Costs for Americans which instructed the Secretary of the **DHHS** ~~Department of Health and Human Services~~ to consider whether to select for testing by the CMS Innovation Center new health care payment and delivery models that would lower drug costs and promote access to innovative drug therapies for beneficiaries enrolled in the Medicare and Medicaid programs. ~~The Executive Order further directed the Secretary of the Department of Health and Human Services to submit, within 90 days after the date of the Executive Order, a report regarding any models that may lead to lower cost- sharing for commonly used drugs and support value- based payment that promotes high- quality care.~~ On February 14, 2023, the **DHHS** ~~Department of Health and Human Services~~ issued a report in response to the October 14, 2022, Executive Order, ~~67which --~~ **which** , among other things, selects three potential drug affordability and accessibility models to be tested by the CMS Innovation Center. Specifically, the report addresses: (1) a model that would allow Part D Sponsors to establish a " high- value drug list " setting the maximum co- payment amount for certain common generic drugs at $ 2; (2) a Medicaid- focused model that would establish a partnership between CMS, manufacturers, and state Medicaid agencies that would result in multi- state outcomes- based agreements for certain cell and gene therapy drugs; and (3) a model that would adjust Medicare Part B payment amounts for Accelerated Approval Program drugs to advance the developments of novel treatments. **Other proposed administrative actions may affect our government pricing responsibilities. For example, CMS has issued proposals to amend the existing Medicaid Drug Rebate Program regulations. In addition, there are pending legal and legislative developments relating to the 340B Drug Pricing Program, including ongoing litigation challenging federal enforcement actions against manufacturers and recently introduced and enacted state legislation.** It remains to be seen how these drug pricing initiatives will affect the broader pharmaceutical industry. At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing. Specifically, several U. S. states and localities have enacted legislation requiring pharmaceutical companies to establish marketing compliance programs, file periodic reports, and / or make periodic public disclosures on sales, marketing, pricing, clinical trials, and other activities. Other state laws prohibit certain marketing- related activities including the provision of gifts, meals or other items to certain healthcare providers, and restrict the ability of manufacturers to offer co- pay support to patients for certain prescription drugs. ~~In addition, several~~ **Several** ~~recently passed~~ state laws require disclosures related to state agencies and / or commercial purchasers with respect to ~~certain~~ price increases **and new product launches** that exceed ~~a~~ certain ~~level~~ **thresholds** as identified in the relevant statutes. **Another emerging trend at the state level is the establishment of prescription drug affordability boards, some of which will prospectively permit certain states to establish upper payment limits for drugs that the state has determined to be " high- cost. "** Some of these laws and regulations contain ambiguous requirements that government officials have not yet clarified. Given the lack of clarity in the laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent federal and state laws and regulations. Furthermore, the increased emphasis on managed healthcare in the US and on country and regional pricing and reimbursement controls in the EU and the UK will put additional pressure on product pricing, reimbursement and usage, which may adversely affect our sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid ~~and~~ **,** healthcare reform, pharmaceutical reimbursement policies and pricing in general. Legislative and regulatory proposals have been made to expand post- approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot predict the likelihood, nature, or extent of health reform initiatives that may arise from future legislation or administrative action. However, we expect these initiatives to increase pressure on drug pricing. Further, certain broader legislation that is not targeted to the health care industry may nonetheless adversely affect our profitability. If we or any third parties we may engage are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or such third parties are not able to maintain regulatory compliance, our product candidates may lose any regulatory approval that may have been obtained and we may not achieve or sustain profitability. ~~See~~ **73See** " Part I, Item 1 – Business – Government Regulation – Healthcare Reform " of this Annual Report on Form 10- K ~~for the year ended December 31, 2022~~ . Regulatory approval for any approved product is limited by the FDA, the EC and other regulators to those specific indications and conditions for which clinical safety and efficacy have been demonstrated, and we may incur significant liability if it is determined that we are promoting the " off- label " use of our products or any of our future product candidates if approved. Any regulatory approval is limited to those specific diseases, indications and patient populations for which a product is deemed to be safe and effective by the FDA, the EC and other regulators. For example, the FDA- approved label for TAVALISSE is only approved for use in adults with ITP who have had an insufficient response to other treatments and for REZLIDHIA is only approved for use in adult patients with R / R AML with a susceptible IDH1 mutation as detected by an FDA- approved test. In addition to the FDA approval required for new formulations, any new indication for an approved product also requires FDA approval. If we are not able to obtain FDA approval for any desired future indications for our products and product candidates, our ability to effectively market and sell our products may be reduced and our business may be adversely affected. ~~68While --~~ **While** physicians may choose to prescribe drugs for uses that are not described in the product' s labeling and for uses that differ from those tested in clinical studies and approved by the regulatory authorities, our ability to promote the products is limited to those indications and patient populations that are specifically approved by the FDA. These " off- label " uses are common across medical specialties and may constitute an appropriate treatment for some patients in varied circumstances. We have implemented compliance and monitoring policies and procedures, including a process for internal review of promotional materials, to deter the promotion of our products for off- label uses. We cannot guarantee that these compliance activities will prevent or timely detect off- label promotion by sales

representatives or other personnel in their communications with health care professionals, patients and others, particularly if these activities are concealed from us. Regulatory authorities in the US generally do not regulate the behavior of physicians in their choice of treatments. Regulatory authorities do, however, restrict communications by pharmaceutical companies on the subject of off- label use. If our promotional activities fail to comply with the FDA' s or other competent national authority' s regulations or guidelines, we may be subject to warnings from, or enforcement action by, these regulatory authorities. In addition, our failure to follow FDA rules and guidelines relating to promotion and advertising may cause the FDA to issue warning letters or untitled letters, suspend or withdraw an approved product from the market, require a recall or institute fines, which could result in the disgorgement of money, operating restrictions, injunctions or civil or criminal enforcement, and other consequences, any of which could harm our business. Notwithstanding the regulatory restrictions on off- label promotion, the FDA and other regulatory authorities allow companies to engage in truthful, non- misleading and non- promotional scientific exchange concerning their products. We engage in medical education activities and communicate with investigators and potential investigators regarding our clinical trials. If the FDA or other regulatory or enforcement authorities determine that our communications regarding our marketed product are not in compliance with the relevant regulatory requirements and that we have improperly promoted off- label uses, or that our communications regarding our investigational products are not in compliance with the relevant regulatory requirements and that we have improperly engaged in pre- approval promotion, we may be subject to significant liability, including civil and administrative remedies as well as criminal sanctions. Delays in clinical testing could result in increased costs to us. We may not be able to initiate or continue clinical studies or trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these clinical trials as required by the FDA or other regulatory authorities, whether due to the impacts of **a global** ~~the COVID- 19~~ pandemic, **global tensions arising from** the Russian- Ukrainian ~~conflict~~ **war and Hamas- Israel war** or otherwise. Even if we are able to enroll a sufficient number of patients in our clinical trials, if the pace of enrollment is slower than we expect, the development costs for our product candidates may increase and the completion of our clinical trials may be delayed, or our clinical trials could become too expensive to complete. Significant delays in clinical testing could negatively impact our product development costs and timing. Our estimates regarding timing are based on a number of assumptions, including assumptions based on past experience with ~~our~~ **74our** other clinical programs. If we are unable to enroll the patients in these trials at the projected rate, the completion of the clinical program could be delayed and the costs of conducting the program could increase, either of which could harm our business. Clinical trials can be delayed for a variety of reasons, including delays in obtaining regulatory approval to commence a study, delays from scaling up of a study, delays in reaching agreement on acceptable clinical trial agreement terms with prospective clinical sites, delays in obtaining institutional review board approval to conduct a study at a prospective clinical site or delays in recruiting subjects to participate in a study. In addition, we typically rely on third- party clinical investigators to conduct our clinical trials and other third- party organizations to oversee the operations of such trials and to perform data collection and analysis. The clinical investigators are not our employees, and we cannot control the amount or timing of resources that they devote to our programs. Failure of the third- party organizations to meet their obligations, whether due to the potential future impacts of **a global** ~~the COVID- 19~~ pandemic, **the global tensions arising from** the Russian- Ukrainian ~~conflict~~ **war and Hamas- Israel war** or otherwise, could adversely affect clinical development of our products. As a result, we may face additional delaying factors outside our control if these parties do not perform their obligations in a timely fashion. For example, any number of those issues could arise with our clinical trials causing a delay. Delays of this sort could occur for the reasons identified above or other reasons. If we have delays in conducting the clinical trials or obtaining regulatory approvals, our product development costs will increase. For example, we may need to make additional payments to third- party investigators and organizations to retain their services or we may need to pay recruitment incentives. If the delays are significant, our financial results and the commercial prospects for our product candidates will be harmed, and our ability ~~69to~~ **to** become profitable will be delayed. Moreover, these third- party investigators and organizations may also have relationships with other commercial entities, some of which may compete with us. If these third- party investigators and organizations assist our competitors at our expense, it could harm our competitive position. Due to the ~~evolving~~ effects of the COVID- 19 pandemic, for several of our development programs, we ~~had~~ experienced ~~and may continue to experience~~ disruption or delay in our ability to enroll and assess patients, maintain patient enrollment, supply study ~~drug~~ **drugs** , report trial results, or interact with regulators, ethics committees or other important agencies due to limitations in employee resources or otherwise. In addition, **in the event that a global pandemic occurs in the future,** some patients **in our clinical trial** may not be able or willing to comply with clinical trial protocols if quarantines impede patient movement or interrupt healthcare services. Similarly, our ability to recruit and retain patients and principal investigators and site staff ~~who, as healthcare providers,~~ may **be** ~~have heightened exposure to COVID- 19 may~~ adversely **affected** ~~impact our clinical trial operations. In light of the evolving effects of the COVID- 19 pandemic, we had taken measures to implement remote and virtual approaches to clinical development, including remote patient monitoring where possible, and~~ if **a global** ~~the COVID- 19~~ pandemic continues and persists for an extended period of time, **and** we ~~could~~ **may** experience significant disruptions to our clinical development timelines, which would adversely affect our business, financial condition, results of operations and growth prospects **in the future** . We have conducted in the past and are currently conducting **or may conduct in the future** clinical trials in the US and outside **the** US including Ukraine ~~and ,~~ Russia **and Israel** . Recent actions taken by the Russian Federation in Ukraine and surrounding areas have destabilized the region and caused the adoption of comprehensive sanctions by, among others, the EU, the US and the UK, which restrict a wide range of trade and financial dealings with Russia and Russian persons, as well as certain regions in Ukraine **. Also, the recent global tensions arising from the Hamas- Israel war may result in disruptions in the broader global economic environment** . Further, some patients may not be able to comply with clinical trial protocols if the conflict impedes patient movement or interrupts healthcare services. In addition, clinical trial site initiation and patient enrollment may be delayed, and we may not be able to access sites for initiation and monitoring in regions affected by the Russian- Ukrainian ~~conflict~~ **war or the Hamas-**

Israel war including due to the prioritization of hospital resources away from clinical trials or as a result of **warfare, violence,** government- imposed curfews, **or events** ~~warfare, violence~~ or other governmental actions ~~or events~~ that restrict movement. We could also experience disruptions in our supply chain or limits our ability to obtain sufficient materials for our drug products in certain regions ~~. We may not be able to obtain an EUA for fostamatinib for the treatment of hospitalized patients with COVID- 19, and, even if we do, absent sNDA approval for that indication, such EUA would be revoked when the COVID- 19 emergency terminates. Based on the results of the NIH / NHLBI- sponsored Phase 2 trial, in May 2021, we filed an EUA for the use of fostamatinib for the treatment of hospitalized patients with COVID- 19. In August 2021, the FDA informed us that the clinical data submitted from the NIH / NHLBI- sponsored Phase 2 trial of fostamatinib to treat hospitalized patients suffering from COVID- 19 was insufficient for EUA. In July 2022, we completed enrollment with 280 patients in our pivotal FOCUS Phase 3 clinical trial evaluating fostamatinib in high- risk patients hospitalized with COVID- 19. The trial had originally targeted a total of 308 patients; however, we determined the trial would be sufficiently powered with 280 patients to potentially provide a clinically meaningful result and determine the efficacy and safety of fostamatinib in hospitalized COVID- 19 patients. On November 1, 2022, we announced the top- line results of the clinical trial. The trial approached but did not meet statistical significance in the primary efficacy endpoint. All prespecified secondary endpoints in the trial numerically favored fostamatinib over placebo, including mortality, time to sustained recovery, change in ordinal scale assessment, and number of days in the ICU. We are evaluating the opportunity and discussing next steps with the FDA and in collaboration with our partner, the US Department of Defense. Section 564 of the FDCA (21 U. S. C. § 360bbb- 3) allows the FDA to authorize the shipment of drugs, biological products, or medical devices that either lack required approval, licensure, or clearance (unapproved products), or are approved but are to be used for unapproved ways to diagnose, treat, or prevent serious diseases or conditions in the event of an emergency declaration by the HHS Secretary. On February 4, 2020, then- HHS Secretary Alex M. Azar II determined that a public health emergency exists for COVID- 19 and declared that it justifies the authorization of emergency use of in vitro diagnostics for COVID- 19, pursuant to Section 564 of the FDCA. On March 2, 2020, March 24, 2020, and March 27, 2020, Secretary Azar issued corresponding declarations for personal respiratory protective devices; for medical devices, including alternative products used as medical devices; and, for drugs and biological products. The determination and these declarations were published in the Federal 70Register on February 7, 2020, March 10, 2020, March 27, 2020, and April 1, 2020, respectively. While the emergency determination and declarations are effective, the FDA may authorize the use of an unapproved product or an unapproved use of an approved product if it concludes that: • an agent referred to in the emergency declaration could cause a serious or life- threatening disease or condition; • it is reasonable to believe that the authorized product may be effective in diagnosing, treating, or preventing that disease or condition or a serious or life- threatening disease or condition caused by an approved product or a product marketed under an EUA; • the known and potential benefits of the authorized product, when used for that disease or condition, outweigh known and potential risks, taking into consideration the material threat of agents identified in the emergency declaration; • there is no adequate, approved, and available alternative to the authorized product for diagnosing, preventing, or treating the relevant disease or condition; • any other criteria prescribed by the FDA is satisfied. Medical products that are granted an EUA are only permitted to commercialize their products under the terms and conditions provided in the authorization. The FDCA authorizes FDA to impose such conditions on an EUA as may be necessary to protect the public health. Consequently, postmarketing requirements will vary across EUAs. In addition, FDA has, on occasion, waived requirements for drugs marketed under an EUA. Generally, EUAs for unapproved products or unapproved uses of approved products require that manufacturers distribute factsheets for healthcare providers, addressing significant known and potential benefits and risk, and the extent to which benefits and risks are unknown, and the fact that FDA has authorized emergency use; and, distribution of factsheets for recipients of the product, addressing significant known and potential benefits and risk, and the extent to which benefits and risks are unknown, the option to accept or refuse the product, the consequences of refusing, available alternatives and the fact that FDA has authorized emergency use. Generally, EUAs for unapproved products and, per FDA' s discretion, EUAs for unapproved uses of approved products, include requirements for adverse event monitoring and reporting, and other recordkeeping and reporting requirements. Note, however, that approved products are already subject to equivalent requirements. In addition, the FDA may include various requirements in an EUA as a matter of discretion as deemed necessary to protect the public health, including restrictions on which entities may distribute the product, and how to perform distribution (including requiring that distribution be limited to government entities), restrictions on who may administer the product, requirements for collection and analysis of safety and effectiveness data, waivers of cGMP, and restrictions applicable to prescription drugs or restricted devices (including advertising and promotion restrictions). The FDA may revoke an EUA when it is determined that the underlying health emergency no longer exists or warrants such authorization, if the conditions for the issuance of the EUA are no longer met, or if other circumstances make revocation appropriate to protect the public health or safety. We cannot predict how long, if ever, an EUA would remain in place. It is difficult to predict when the determination and declaration will be revoked or ended, which will impact the marketing of products under existing EUAs and the availability of new EUAs based on the determination and declaration. For example, in January 2023, Congress proposed legislation that would end other COVID- 19- related emergency declarations, if passed, and the White House has issued a statement that those declarations will end on May 11, 2023. FDA officials have stated that this will not impact FDA' s ability to authorize treatments for emergency use, such that existing EUAs will remain in effect and the agency may continue to issue new EUAs going forward when criteria for issuance are met. This is nonetheless subject to change. 71We cannot predict with certainty whether the result of our trial will be sufficient for submission of a second application for an EUA for fostamatinib, and we cannot predict whether FDA will grant an EUA for fostamatinib based on the trial data. We also cannot predict how long, if ever, an EUA would remain in place. Our COVID- 19 product candidate may not successfully protect against variants of the SARS- CoV- 2 virus. As the SARS- CoV- 2 virus continues to evolve, new strains of the virus or those that are already in circulation may prove more transmissible or cause more severe forms of COVID- 19 disease than the predominant strains to date. There is~~

~~a risk that any product candidates we develop will not be as effective against variant strains of the SARS- CoV- 2 virus expressing variants of the spike protein, particularly strains with mutations in the receptor binding domain and N- terminal domain. Such failure could lead to significant reputational harm, in addition to adversely affecting our financial results~~ . Public perception of the risk- benefit balance for our COVID- 19 product candidates may be affected by adverse events in clinical trials involving our product candidate or other COVID- 19 treatments. Negative perception of the efficacy, safety, or tolerability of any investigational medicines that we develop, or of other products similar to products we are developing, such as fostamatinib for the treatment of COVID- 19, could adversely affect our ability to conduct our business, advance our investigational medicines, or obtain regulatory approvals. ~~Adverse~~ **75Adverse** events in clinical trials of our investigational medicines or in clinical trials of others developing similar products, including other COVID- 19 treatments, could result in a decrease in the perceived benefit of one or more of our programs, increased regulatory scrutiny, decreased confidence by patients and clinical trial collaborators in our investigational medicines, and less demand for any product that we may develop. If and when they are used in clinical trials, our developmental candidates and investigational medicines could result in a greater quantity of reportable adverse events, including suspected unexpected serious adverse reactions, other reportable negative clinical outcomes, manufacturing reportable events or material clinical events that could lead to clinical delay or hold by the FDA or applicable regulatory authority or other clinical delays, any of which could negatively impact the perception of one or more of our programs, as well as our business as a whole. In addition, responses by US, state, or foreign governments to negative public perception may result in new legislation or regulations that could limit our ability to develop any investigational medicines or commercialize any approved products, obtain or maintain regulatory approval, or otherwise achieve profitability. More restrictive statutory regimes, government regulations, or negative public opinion would have an adverse effect on our business, financial condition, results of operations, and prospects and may delay or impair the development of our investigational medicines and commercialization of any approved products or demand for any products we may develop. We lack the capability to manufacture compounds for clinical development, and we rely on and intend to continue relying on third parties for commercial supply, manufacturing and distribution if any of our product candidates which receive regulatory approval and we may be unable to obtain required material or product in a timely manner, at an acceptable cost or at a quality level required to receive regulatory approval. We currently do not have the manufacturing capabilities or experience necessary to produce our products or any product candidates for clinical trials ~~, including fostamatinib in our ongoing clinical trials for certain indications~~ . We currently use one active pharmaceutical ingredient manufacturer and one finished goods manufacturer for each of our products. We do not currently have, nor do we plan to acquire the infrastructure or capability to supply, manufacture or distribute preclinical, clinical or commercial quantities of drug substances or products. For each clinical trial of our unpartnered product candidates, we rely on third- party manufacturers for the active pharmaceutical ingredients, as well as various manufacturers to manufacture starting components, excipients and formulated drug products. Our ability to develop our product candidates, and our ability to commercially supply our products will depend, in part, on our ability to successfully obtain the active pharmaceutical ingredients and other substances and materials used in our product candidates from third parties and to have finished products manufactured by third parties in accordance with regulatory requirements and in sufficient quantities for preclinical and clinical testing and commercialization. If we fail to develop and maintain supply relationships with these third parties, we may be unable to continue to develop or commercialize our product candidates. ~~72We~~ **We** rely and will continue to rely on certain third parties, including those located outside the US, as our limited source of the materials they supply or the finished products they manufacture. The drug substances and other materials used in our product candidates are currently available only from one or a limited number of suppliers or manufacturers and certain of our finished product candidates are manufactured by one or a limited number of contract manufacturers. Any of these existing suppliers or manufacturers may: ● fail to supply us with product on a timely basis or in the requested amount due to unexpected damage to or destruction of facilities or equipment or otherwise; ● fail to increase manufacturing capacity and produce drug product and components in larger quantities and at higher yields in a timely or cost- effective manner, or at all, to sufficiently meet our commercial needs; ● be unable to meet our production demands due to issues related to their reliance on sole- source suppliers and manufacturers; ● supply us with product that fails to meet regulatory requirements; ● become unavailable through business interruption or financial insolvency; ● lose regulatory status as an approved source; ● be unable or unwilling to renew current supply agreements when such agreements expire on a timely basis, ~~on~~ **76on** acceptable terms or at all; or ● discontinue production or manufacturing of necessary drug substances or products. Our current and anticipated future dependence upon these third- party manufacturers may adversely affect our ability to develop and commercialize product candidates on a timely and competitive basis, which could have an adverse effect on sales, results of operations and financial condition. If we were required to transfer manufacturing processes to other third- party manufacturers and we were able to identify an alternative manufacturer, we would still need to satisfy various regulatory requirements. Satisfaction of these requirements could cause us to experience significant delays in receiving an adequate supply of our products and products in development and could be costly. Moreover, we may not be able to transfer processes that are proprietary to the manufacturer, if any. These manufacturers may not be able to produce material on a timely basis or manufacture material at the quality level or in the quantity required to meet our development timelines and applicable regulatory requirements and may also experience a shortage in qualified personnel ~~, including due to the impacts of the COVID- 19 pandemic~~ . Our third- party manufacturers import certain materials from China to produce our products. The tensions between the US and China have led to a series of tariffs and sanctions being imposed by the US on imports from China mainland, as well as other business restrictions. Such tensions could adversely impact us and our third-party manufacturers. We may not be able to maintain or renew our existing third- party manufacturing arrangements, or enter into new arrangements, on acceptable terms, or at all. Our third- party manufacturers could terminate or decline to renew our manufacturing arrangements based on their own business priorities, at a time that is costly or inconvenient for us. If we are unable to contract for the production of materials in sufficient quantity and of sufficient quality on acceptable terms, our planned

clinical trials may be significantly delayed. Manufacturing delays could postpone the filing of our **investigational new drug (** IND **)** applications and / or the initiation or completion of clinical trials that we have currently planned or may plan in the future. Drug manufacturers are subject to ongoing periodic unannounced inspection by the FDA, the Drug Enforcement Administration, the European Medicines Agency, national competent authorities in the EU and UK and other federal and state government and regulatory agencies to ensure strict compliance with cGMP and other government regulations and corresponding foreign standards. We do not have control over third- party manufacturers' compliance with these regulations and standards and they may not be able to comply. Switching manufacturers may be difficult because the number of potential manufacturers is limited. It may be difficult or impossible for us to find a replacement manufacturer quickly on acceptable terms, or at all. Additionally, if we are required to enter into new supply arrangements, we may not be able to obtain approval from the FDA of any alternate supplier in a timely manner, or at all, which could delay or prevent the clinical development and commercialization of any related product candidates. Failure of our third- party manufacturers or us to comply with applicable regulations, whether due to the impacts of **a global** ~~the 73COVID- 19~~ pandemic or otherwise, could result in sanctions being imposed on us, including fines, civil penalties, delays in or failure to grant marketing approval of our product candidates, injunctions, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of products and compounds, operating restrictions and criminal prosecutions, warning or similar letters or civil, criminal or administrative sanctions against us, any of which could adversely affect our business. Any product for which we have obtained regulatory approval, or for which we obtain approval in the future, is subject to, or will be subject to, extensive ongoing regulatory requirements by the FDA, EMA **, MHRA** and other comparable regulatory authorities, and if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, we may be subject to penalties, we may be unable to generate revenue from the sale of such products, our potential for generating positive cash flow will be diminished, and the capital necessary to fund our operations will be increased. ~~In April 2018, the FDA approved TAVALISSE for the treatment of adult patients with chronic ITP who have had insufficient response to previous treatment. In December 2022, the FDA approved REZLIDHIA for the treatment of adult patients with R / R AML with a susceptible IDH1 mutation as detected by an FDA- approved test.~~ We commercialize **our products** ~~TAVALISSE and REZLIDHIA~~ in the US and we have entered into commercialization agreements with third parties to commercialize fostamatinib outside the US. Any product for which we have obtained regulatory approval, or for which we obtain regulatory approval in the future, along with the manufacturing processes and practices, post- approval clinical research, product labeling, advertising and promotional activities for such product, are subject to continual requirements of, and review by, the FDA, the EMA and other comparable international regulatory authorities. These requirements include submissions of safety and other post- marketing information and reports, registration and listing requirements, ~~current good manufacturing practices (~~ cGMP ~~)~~ requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians, import and ~~export~~ **77export** requirements and recordkeeping. If we or our suppliers encounter manufacturing, quality or compliance difficulties with respect to our products or any of our product candidates, when and if approved, whether due to the impacts of **a global** ~~the COVID- 19~~ pandemic (including as a result of disruptions of global shipping and the transport of products) or otherwise, we may be unable to obtain or maintain regulatory approval or meet commercial demand for such products, which could adversely affect our business, financial conditions, results of operations and growth prospects. 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 labeling. Thus, we will not be able to promote any products we develop for indications or uses for which they are not approved. In addition, the FDA often requires post- marketing testing and surveillance to monitor the effects of products. The FDA, the EMA and other comparable international regulatory agencies may condition approval of our product candidates on the completion of such post- marketing clinical studies. These post- marketing studies may suggest that a product causes undesirable side effects or may present a risk to the patient. Additionally, the FDA may require ~~Risk Evaluation and Mitigation Strategies (~~ REMS ~~)~~ to help ensure that the benefits of the drug outweigh its risks. A REMS may be required to include various elements, such as a medication guide or patient package insert, a communication plan to educate healthcare providers of the drug' s risks, limitations on who may prescribe or dispense the drug, requirements that patients enroll in a registry or undergo certain health evaluations or other measures that the FDA deems necessary to ensure the safe use of the drug. Discovery after approval of previously unknown problems with any of our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in actions such as: ● restrictions on our ability to conduct clinical trials, including full or partial clinical holds on ongoing or planned trials ; ● restrictions on product manufacturing processes; ● restrictions on the marketing of a product; ● restrictions on product distribution; ~~74~~ ● requirements to conduct post- marketing clinical trials; ● untitled or warning letters or other adverse publicity; ● withdrawal of products from the market; ● refusal to approve pending applications or supplements to approved applications that we submit; ● recall of products; ● refusal to permit the import or export of our products; ● product seizure; ● fines, restitution or disgorgement of profits or revenue; ● refusal to allow us to enter into supply contracts, including government contracts; ● injunctions; or ● imposition of civil or criminal penalties. If such regulatory actions are taken, the value of our company and our operating results will be adversely affected. Additionally, if the FDA, the EMA or any other comparable international regulatory agency withdraws its approval of a product that is or may be approved, we will be unable to generate revenue from the sale of that product in the relevant jurisdiction, our potential for generating positive cash flow will be diminished and the capital necessary to fund our operations will be increased. Accordingly, we continue to expend significant time, money and effort in all areas ~~of~~ **78of** regulatory compliance, including manufacturing, production, product surveillance, post- marketing studies and quality control. If any of our third- party contractors fail to perform their responsibilities to comply with FDA rules and regulations, the marketing and sales of our products could be delayed and we may be subject to enforcement action, which could decrease our revenues. Conducting our business requires us to manage relationships with third- party contractors. As a result, our success depends partially on the

success of these third parties in performing their responsibilities to comply with FDA rules and regulations. Although we pre-qualify our contractors and we believe that they are fully capable of performing their contractual obligations, we cannot directly control the adequacy and timeliness of the resources and expertise that they apply to these activities. If any of our partners or contractors fail to perform their obligations in an adequate and timely manner, or fail to comply with the FDA' s rules and regulations, then the marketing and sales of our products could be delayed. The FDA may also take enforcement actions against us based on compliance issues identified with our contractors. If any of these events occur, we may incur significant liabilities, which could decrease our revenues. For example, sales and medical science liaison or MSL personnel, including contractors, must comply with FDA requirements for the advertisement and promotion of products. ~~Fast track designation by the FDA may not actually lead to a faster development or regulatory review or approval process and does not assure FDA approval of our product candidates. If a product candidate is intended for the treatment of a serious or life- threatening condition and the product candidate demonstrates the potential to address unmet medical need for this condition, the sponsor may apply for FDA fast track designation. Fast track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a fast track product has opportunities for more frequent interactions with the review team during product development, and the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor 75pays any required user fees upon submission of the first section of the NDA. However, fast track designation does not change the standards for approval and does not ensure that the product candidate will receive marketing approval or that approval will be granted within any particular timeframe. As a result, while the FDA has granted fast track designation to fostamatinib for the treatment of wAIHA and / or we may seek and receive fast track designation for our future product candidates, we may not experience a faster development process, review or approval compared to conventional FDA procedures. In addition, the FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program. Fast track designation alone does not guarantee qualification for the FDA' s priority review procedures.~~ If we are unable to obtain regulatory approval to market products in the US and foreign jurisdictions, we will not be permitted to commercialize products we or our collaborative partners may develop. We cannot predict whether regulatory clearance will be obtained for any product that we, or our collaborative partners, hope to develop. Satisfaction of regulatory requirements typically takes many years, is dependent upon the type, complexity and novelty of the product and requires the expenditure of substantial resources. Of particular significance to us are the requirements relating to research and development and testing. Before commencing clinical trials in humans in the US, we, or our collaborative partners, will need to submit and receive approval from the FDA of an IND application. Clinical trials are subject to oversight by institutional review boards and the FDA and: ● must be conducted in conformance with the FDA' s good clinical practices and other applicable regulations; ● must meet requirements for institutional review board oversight; ● must meet requirements for informed consent; ● are subject to continuing FDA and regulatory oversight; ● may require large numbers of test subjects; and ● may be suspended by us, our collaborators or the FDA at any time if it is believed that the subjects participating in these trials are being exposed to unacceptable health risks or if the FDA finds deficiencies in the IND or the conduct of these trials. While we have stated that we intend to file additional INDs for future product candidates, this is only a statement of intent, and we may not be able to do so because we may not be able to identify potential product candidates. In addition, the FDA may not approve any IND we or our collaborative partners may submit in a timely manner, or at all. Before receiving FDA approval to market a product, we must demonstrate with substantial clinical evidence that the product is safe and effective in the patient population and the indication that will be treated. Data obtained from preclinical and clinical activities are susceptible to varying interpretations that could delay, limit or prevent regulatory approvals. In addition, delays or rejections may be encountered based upon additional government regulation from future legislation or administrative action or changes in FDA policy during the period of product development, clinical trials and FDA regulatory review. Failure to comply with applicable FDA or other applicable regulatory requirements may result in criminal prosecution, civil penalties, recall or seizure of products, total or partial suspension of production or ~~injunction~~ **79injunction**, adverse publicity, as well as other regulatory action against our potential products or us. Additionally, we have limited experience in conducting and managing the clinical trials necessary to obtain regulatory approval. If regulatory approval of a product is granted, this approval will be limited to those indications or disease states and conditions for which the product is demonstrated through clinical trials to be safe and efficacious. We cannot assure ~~you~~ that any compound developed by us, alone or with others, will prove to be safe and efficacious in clinical trials and will meet all of the applicable regulatory requirements needed to receive marketing approval. Outside the US, our ability, or that of our collaborative partners, to market a product is contingent upon receiving a marketing authorization from the appropriate regulatory authorities. This foreign regulatory approval process typically ~~76includes~~ -- **includes** all of the risks and costs associated with FDA approval described above and may also include additional risks and costs, such as the risk that such foreign regulatory authorities, which often have different regulatory and clinical trial requirements, interpretations and guidance from the FDA, may require additional clinical trials or results for approval of a product candidate, any of which could result in delays, significant additional costs or failure to obtain such regulatory approval. There can be no assurance, however, that we or our collaborative partners will not have to provide additional information or analysis, or conduct additional clinical trials, before receiving approval to market product candidates. We may be unable to expand our product..... stage clinical trial, be shown to have ~~inadequate efficacy, harmful side effects, suboptimal pharmaceutical profiles or other characteristics suggesting that they are unlikely to be commercially viable products. Apart from our internal discovery efforts, our strategy to expand our development pipeline is also dependent on our ability to successfully identify and acquire or in- license relevant product candidates. In July 2022, we entered into a license and transition services agreement with Forma for~~ an ~~exclusive license to develop, manufacture and commercialize olutasidenib, Forma' s proprietary inhibitor of mIDH1, for any uses worldwide, including for the treatment of AML and other malignancies. Forma submitted an~~

~~NDA for olutasidenib to the FDA with PDUFA action date for the application of February 15, 2023. On December 1, 2022, the FDA approved REZLIDHIA (olutasidenib) capsules for the treatment of adult patients with R / R AML with a susceptible IDH1 mutations as detected by and FDA- approved test. REZLIDHIA is our second commercial product and is highly synergistic with our existing hematology- oncology focused commercial and medical affairs infrastructure. The in- licensing and acquisition of product candidates is a highly competitive area, and many other companies are pursuing the same or similar product candidates to those that we may consider attractive. In particular, larger companies with more well- established and diverse revenue streams may have a competitive advantage over us due to their size, financial resources and more extensive clinical development and commercialization capabilities. Furthermore, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We may also be unable to in- license or acquire additional relevant product candidates on acceptable terms that would allow us to realize an appropriate return on our investment. If we are unable to develop suitable product candidates through internal discovery efforts, whether due to the impacts of the COVID- 19 pandemic or otherwise, or if we are unable to successfully obtain rights to additional suitable product candidates, our business and prospects for growth could suffer. Even if we succeed in our efforts to obtain rights to suitable product candidates, the competitive business environment may result in higher acquisition or licensing costs, and our investment in these potential products will remain subject to the inherent risks associated with the development and commercialization of new medicines. In certain circumstances, we may also be reliant on the licensor for the continued development of the in- licensed technology and their efforts to safeguard their underlying intellectual property. With respect to acquisitions, we may not be able to integrate the target company successfully into our existing business, maintain the key business relationships of the target, or retain key personnel of an acquired business. Furthermore, we could assume unknown or contingent liabilities or incur unanticipated expenses. Any acquisitions or investments made by us also could result in our spending significant amounts, issuing dilutive securities, assuming or incurring significant debt obligations and contingent liabilities, incurring large one- time expenses and acquiring intangible assets that could result in significant future amortization expense and significant write- offs, any of which could harm our operating results. 77We have obtained~~ orphan drug designation from the FDA for fostamatinib for the treatment of ITP and wAIHA **, and for olutasidenib for the treatment of AML** , but we may not be able to obtain **additional** ~~or maintain~~ orphan drug ~~designation~~ **designations in the future, or maintain the orphan drug designations** or exclusivity for ~~fostamatinib~~ **the approved drugs** for the treatment of **respective indications** ~~ITP, wAIHA or our other product candidates~~ , or we may be unable to maintain the benefits associated with orphan drug ~~designation~~ **designations** , including the potential for market exclusivity. We have ~~obtained~~ **an** orphan drug designation in the US for fostamatinib for the treatment of ITP and wAIHA **, and for olutasidenib for the treatment of AML. Also, pralsetinib has orphan drug designations in the US for the treatment of adult patients with metastatic RET fusion- positive NSCLC as detected by an FDA- approved test, for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion- positive thyroid cancer who require systemic therapy and who are radioactive iodine- refractory (if radioactive iodine is appropriate), and for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET- mutant medullary thyroid carcinoma who require systemic therapy** . We may seek orphan drug designation for other product candidates in the future. Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug or biologic intended to treat a rare disease or condition, which is defined as one occurring in a patient population of fewer than 200, 000 in the US, or a patient population greater than 200, 000 in the US where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the US. In the US, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user- fee waivers. In addition, if a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications, including a full NDA, to market the same drug for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or where the manufacturer is unable to assure sufficient product quantity. At this time, we do not have nor will we seek to apply for orphan drug designation in the EU or the UK in the foreseeable future. We cannot assure ~~you~~ that any future application for orphan drug designation with respect to any other product candidate will be granted. If we are unable to obtain orphan drug designation with respect to other product candidates in the US, we will not be eligible to obtain the period of market exclusivity that could result from orphan drug designation or be afforded the financial incentives associated with orphan drug designation. Even though we have received orphan drug designation for fostamatinib for the treatment of ITP and wAIHA in the US, we may not be the first to obtain marketing approval for the orphan- designated indication due to the uncertainties associated with developing pharmaceutical products or we might not maintain our orphan drug designation. In addition, exclusive marketing rights in the US for fostamatinib for the treatment of ITP, wAIHA or any future product candidate may be limited if we seek approval for an indication broader than the orphan- designated indication or may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties can be approved for the same condition. Even after an orphan product is approved, ~~the~~ **80the** FDA can subsequently approve the same drug with the same active moiety for the same condition if the FDA concludes that the later drug is safer, more effective, or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process. In addition, Congress is considering updates to the orphan drug provisions of the FDCA in response to a recent 11th Circuit decision. Any changes to the orphan drug provisions could change our opportunities for, or likelihood of success in obtaining, orphan drug exclusivity and would materially adversely affect our business, financial condition, results of operations, cash flows and prospects. Risks Related to CommercializationOur prospects are highly dependent on our

commercial products. To the extent that the commercial success of our products in the US is diminished or is not commercially successful, our business, financial condition and results of operations may be adversely affected, and the price of our common stock may decline ~~. TAVALISSE is our first drug that has been approved for sale in the US and Europe for patients with chronic ITP. REZLIDHIA is our second drug product which was recently approved by the FDA for the treatment of adult patients with R / R- AML with susceptible IDH1 mutations as detected by an FDA- approved test, and began its commercialization in December 2022~~ . We are focusing a significant portion of our activities and resources on our products, and we believe our prospects are highly dependent on, and a significant portion of the value of our company relates to, our ability to sustain successful commercialization of our products in the US. We have also entered into exclusive commercialization agreements with third parties to commercialize fostamatinib outside the US, and we plan to further enter partnership with existing or other third parties to commercialize **our products** ~~fostamatinib and olutasidenib~~ outside the ~~78US~~ **US** in the future. Sustained successful commercialization of our products is subject to many risks and uncertainties, including the impact of **a global** ~~the COVID- 19~~ pandemic on the successful commercialization in the US, as well as the successful commercialization efforts for our products through our collaborative partners. There are numerous examples of unsuccessful product launches and failures to meet high expectations of market potential, including by pharmaceutical companies with more experience and resources than us. ~~As we continue to build out our commercial team, there~~ **There** are many factors that could cause the commercialization of our products to be unsuccessful, including a number of factors that are outside our control. The commercial success of our products depends on the extent to which patients and physicians accept and adopt our products to treat the related diseases. We also do not know how physicians, patients and payors will respond to our future price increases of our products. Physicians may not prescribe our products and patients may be unwilling to use our products if coverage is not provided or reimbursement is inadequate to cover a significant portion of the cost. Our products compete, and may in the future compete, with currently existing therapies, including generic drugs, and products currently under development. Our competitors, particularly large pharmaceutical companies, may deploy more resources to market, sell and distribute their products. If our efforts are not appropriately resourced to adequately promote our products, the commercial potential of our sales may be diminished. Additionally, any negative development for ~~fostamatinib~~ **our products** in clinical development in additional indications ~~, such as in the clinical trials of fostamatinib in COVID- 19 patients,~~ may adversely impact the **commercialization** ~~commercial results~~ and potential of fostamatinib. Thus, significant uncertainty remains regarding the commercial potential of ~~fostamatinib~~ **our products** . Market acceptance of ~~fostamatinib~~ **our products** will depend on a number of factors, including: ● the timing of market introduction of the product as well as competitive products; ● the clinical indications for which the product is approved; ● acceptance by physicians, the medical community and patients of the product as a safe and effective treatment; ● potential future impacts, if any, due to the ~~evolving~~ effects of **a global** ~~the COVID- 19~~ pandemic and **the global tensions arising from** the Russian-Ukrainian ~~conflict~~ **war and Hamas- Israel war** ; ● the ability to distinguish safety and efficacy from existing, less expensive generic alternative therapies, if any; **81** ● the convenience of prescribing, administrating and initiating patients on the product and the length of time the patient is on the product; ● the potential and perceived value and advantages of the product over alternative treatments; ● the cost of treatment in relation to alternative treatments, including any similar generic treatments; ● pricing and the availability of coverage and adequate reimbursement by third- party payors and government authorities; ● a positive HTA ~~assessment~~ concluding that the product is cost- effective and the HTA bodies issuing a positive recommendation for the use of the product as a first or second line of treatment for the granted therapeutic indication; ● the prevalence and severity of adverse side effects; and ● the effectiveness of sales and marketing efforts. ~~79If~~ **If** we are unable to sustain anticipated level of sales growth from our products, or if we fail to achieve anticipated product royalties and collaboration milestones, we may need to reduce our operating expenses, access other sources of cash or otherwise modify our business plans, which could have a negative impact on our business, financial condition and results of operations. For example, during 2021, we experienced lower than anticipated sales of our products due to continuing impacts of physician and patient access issues created by the COVID- 19 pandemic. From time to time, our net product sales are negatively impacted by the decrease in level of inventories remaining at our distribution channels. We also may not be successful entering into arrangements with third parties to sell and market one or more of our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, including Kissei' s development and commercialization of fostamatinib in all indications in Japan, China, Taiwan, and the Republic of Korea, Grifols' commercialization of fostamatinib in Europe and Turkey, Medison for future commercialization of fostamatinib in Canada and Israel, and Knight for commercialization of fostamatinib in Latin America. As a consequence of our license agreements with Kissei, Grifols, Medison and Knight, we rely heavily upon their regulatory, commercial, medical affairs, market access and other expertise and resources for commercialization of fostamatinib in their respective territories outside of the US. We cannot control the amount of resources that our partners dedicate to the commercialization of fostamatinib, and our ability to generate revenues from the commercialization of fostamatinib by our partners depends on their ability to achieve market acceptance of fostamatinib in its approved indications in their respective territories. Furthermore, foreign sales of fostamatinib by our partners could be adversely affected by the imposition of governmental controls, political and economic instability, outbreaks of pandemic diseases, such as the COVID- 19 pandemic, trade restrictions or barriers and changes in tariffs and escalating global trade and political tensions. For example, the COVID- 19 pandemic has resulted in increased travel restrictions and extended shutdowns of certain businesses in the US and around the world. If our collaborators are unable to successfully complete clinical trials, delay commercialization of fostamatinib or do not invest the resources necessary to successfully commercialize fostamatinib in international territories where it has been approved, this could reduce the amount of revenue we are due to receive under these license agreements, resulting in harm to our business and operations. If we do not establish and maintain sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates. Even if we, or any of our collaborative partners, are able to continue to commercialize our products or

any product candidate that we, or they, develop, the product may become subject to unfavorable pricing regulations, third- party payor reimbursement practices or labeling restrictions, all of which may vary from country to country and any of which could harm our business. The commercial success of any product for which we have obtained regulatory approval, or for which we obtain regulatory approval in the future will depend substantially on the extent to which the costs of our product or product ~~candidates~~ **82candidates** are or will be paid by third- party payors, including government health care programs and private health insurers. There is a significant trend in the health care industry by public and private ~~payers~~ **payors** to contain or reduce their costs, including by taking the following steps, among others: decreasing the portion of costs ~~payers~~ **payors** will cover, ceasing to provide full payment for certain products depending on outcomes, and / or not covering certain products at all. If ~~payers~~ **payors** implement any of the foregoing with respect to our products, it would have an adverse impact on our revenue and results of operations. If coverage is not available, or reimbursement is limited, we, or any of our collaborative partners, may not be able to successfully commercialize our products or any of our product candidates in some jurisdictions. Even if coverage is provided, the approved reimbursement amount may not be at a rate that covers our costs, including research, development, manufacture, sale and distribution. In the US, no uniform policy of coverage and reimbursement for products exists among third- party payors; therefore, coverage and reimbursement levels for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time consuming and costly process that may require us to provide scientific, clinical or other support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. There is significant uncertainty related to third- party payor coverage and reimbursement of newly approved drugs. Marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. ~~80Some~~ -- **Some** countries require approval of the sale price of a drug before it can be marketed, which could delay market entry (or, if pricing is not approved, we may be unable to sell at all in a country where we have received regulatory approval for a product. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some countries, the proposed pricing for a drug must be approved before it may be lawfully marketed). In addition, authorities in some countries impose additional obligations, such as HTAs, which assess the performance of a drug in comparison with its cost. The outcome of HTA assessments is judged on a national basis and some ~~payers~~ **payors** may not reimburse the use of our products or may reduce the rate of reimbursement for our products and as a result, revenue from such products may decrease. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we, or any of our collaborative partners, might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenues we are able to generate from the sale of the product in that country. In particular, we cannot predict to what extent the ~~evolving~~ effects of **a global** ~~the COVID- 19~~ pandemic, depending on its scale and duration, may ~~continue to~~ disrupt global healthcare systems and access to our products or result in a widespread loss of individual health insurance coverage due to unemployment, a shift from commercial payor coverage to government payor coverage, or an increase in demand for patient assistance and / or free drug programs, any of which would adversely affect access to and demand for our products and our net sales. Adverse pricing limitations may also hinder our ability or the ability of any future collaborators to recoup our or their investment in one or more product candidates, even if our product candidates obtain marketing approval. Further, even if favorable coverage and reimbursement status is attained for one or more products for which we or our collaborative partners receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future. Patients who are provided medical treatment for their conditions generally rely on third- party payors to reimburse all or part of the costs associated with their treatment. Therefore, our ability, and the ability of any of our collaborative partners, to successfully commercialize our products or any of our product candidates will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from third- party payors. Additionally, the labeling ultimately approved for any of our product candidates for which we have or may obtain regulatory approval may include restrictions on their uses and may be subject to ongoing FDA or international regulatory authority requirements governing the labeling, packaging, storage, distribution, safety surveillance, advertising, promotion, record- keeping and reporting of safety and other post- market information. If we or any of our collaborative partners do not timely obtain or comply with the labeling approval by the FDA or international regulatory authorities on any of our product candidates, it may delay or inhibit our ability to successfully commercialize our products and generate revenues. ~~If~~ **83If** we are unable to successfully market and distribute our products and retain experienced commercial personnel, our business will be substantially harmed. We **continuously** ~~currently have limited experience in marketing and selling pharmaceutical products. As a result, we will be required to~~ expend significant time and resources to maintain a sales force that is credible and compliant with applicable laws in marketing our products. In addition, we must continually train our sales force to ensure that an appropriate and compliant message about our products is being delivered. If we are unable to effectively train our sales force and equip them with compliant and effective materials, including medical and sales literature to help them appropriately inform and educate health care providers regarding the potential benefits and proper administration of our products, our efforts to successfully commercialize our products could be put in jeopardy, which would negatively impact our ability to generate product revenues. We have established our distribution, sales, marketing and market access capabilities, all of which will be necessary to successfully commercialize our products. As a result, we will be required to expend significant time and resources to market, sell, and distribute our products to hematologists and ~~hematologists~~ **hematologist** - oncologists. There is no guarantee that the marketing strategies we have developed, or the distribution, sales, marketing and market access capabilities that we have developed will be successful. Particularly, we are dependent on third- party logistics, specialty pharmacies and distribution partners in the distribution of our products. If they are unable to perform effectively or if they do not provide efficient distribution of the medicine to patients, our business may be harmed ~~. In addition, we 81actively participate in medical conferences and exhibits, such as the ASCO and ASH Annual~~

~~Meeting & Exposition that are significant opportunities for us to educate physicians and key opinion leaders about our products. ASCO was held in Chicago, Illinois as well as virtually in June 2022, and ASH was held in New Orleans, Louisiana as well as virtually in December 2022. In the future, other key conferences may be held live, virtually, postponed or cancelled. Such disruptions may prevent us from effectively educating the prescribing physicians and key opinion leaders about our products which would negatively impact utilization of our products and our results of operations and growth prospects could be adversely affected~~ . Maintaining our sales, marketing, market access and product distribution capabilities requires significant resources, and there are numerous risks involved with managing our commercial team, including our potential inability to successfully train, retain and incentivize adequate numbers of qualified and effective sales and marketing personnel. We are also competing for talent with numerous commercial and pre- commercial- stage oncology- focused biotechnology companies seeking to build out their commercial organizations, as well as other large pharmaceutical organizations that have extensive, well- funded and more experienced sales and marketing operations, and we may be unable to maintain or adequately scale our commercial organization as a result of such competition. If we cannot maintain effective sales, marketing, market access and product distribution capabilities, ~~whether as a result of the COVID- 19 pandemic or otherwise,~~ we may be unable to realize the commercial potential of our products. Also, to the extent that the commercial opportunities for our products grow over time, we may not properly judge the requisite size and experience of our current commercialization teams or the level of distribution necessary to market and sell our products, which could have an adverse impact on our business, financial condition and results of operations. We may not be able to successfully develop or commercialize our product candidates if problems arise in the clinical testing and approval process. The activities associated with the research, development and commercialization of ~~fostamatinib~~ **our products** and other product candidates in our pipeline must undergo extensive clinical trials, which can take many years and require substantial expenditures, subject to extensive regulation by the FDA and other regulatory agencies in the US and by comparable authorities in other countries. The process of obtaining regulatory approvals in the US and other foreign jurisdictions is expensive, and lengthy, if approval is obtained at all. Our clinical trials may fail to produce results satisfactory to the FDA or regulatory authorities in other jurisdictions. The regulatory process also requires preclinical testing, and data obtained from preclinical and clinical activities are susceptible to varying interpretations. The FDA has substantial discretion in the approval process and may refuse to approve any NDA or sNDA and decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. Varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent regulatory approval of ~~fostamatinib~~ **our products** for any individual, additional indications. For example, in June 2022, we announced that the top- line results from our Phase 3 trial in wAIHA did not demonstrate statistical significance in the primary efficacy endpoint of durable hemoglobin response in the overall study population. While we conducted an in- depth analysis of these data to better understand differences in patient characteristics and outcomes and submitted these findings to the FDA, in October 2022, we announced that we received guidance from the FDA' s of these findings. Based on the result of the trial and the guidance from the FDA, we did not file an sNDA for wAIHA. **It** ~~Due to the evolving effects of COVID- 19 pandemic, it~~ is also possible that we could experience delays in the timing of our interactions with regulatory authorities due to absenteeism by governmental employees or the diversion of regulatory authority efforts and attention to approval of other therapeutics **,** ~~or other activities related to COVID- 19~~ or other public health emergencies **including a global pandemic** , which could delay or limit our ~~ability~~ **84ability** to make planned regulatory submissions or develop and commercialize our product candidates on anticipated timelines. In addition, delays or rejections may be encountered based upon changes in regulatory policy for product approval during the period of product development and regulatory agency review, which may cause delays in the approval or rejection of an application for ~~fostamatinib~~ **our products** or for our other product candidates. Commercialization of our product candidates depends upon successful completion of extensive preclinical studies and clinical trials to demonstrate their safety and efficacy for humans. Preclinical testing and clinical development are long, expensive and uncertain processes. ~~82In~~ **In** connection with clinical trials of our product candidates, we may face the following risks among others: ● the product candidate may not prove to be effective; ● the product candidate may cause harmful side effects; ● the clinical results may not replicate the results of earlier, smaller trials; ● we or third parties with whom we collaborate, may be significantly impacted by **force majeure events** ~~the evolving impacts of the COVID- 19 pandemic~~ ; ● we, or the FDA or similar foreign regulatory authorities, may delay, terminate or suspend the trials; ● our results may not be statistically significant; ● patient recruitment and enrollment may be slower than expected; ● patients may drop out of the trials or otherwise not enroll; and ● regulatory and clinical trial requirements, interpretations or guidance may change. We do not know whether we will be permitted to undertake clinical trials of potential products beyond the trials already concluded and the trials currently in process. It will take us or our collaborative partners several years to complete any such testing, and failure can occur at any stage of testing. Interim results of trials do not necessarily predict final results, and acceptable results in early trials may not be repeated in later trials. A number of companies in the pharmaceutical industry, including biotechnology companies, have suffered significant setbacks in advanced clinical trials, even after achieving promising results in earlier trials. ~~General~~ **Further, evolving FDA standards may cause additional setbacks. In 2023, FDA published guidance documents and a final rule which all concern clinical trial requirements. In June 2023, FDA published a draft guidance, E6 (R3) Good Clinical Practice, which seeks to unify standards for clinical trial data for the International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use member countries and regions. In August 2023, FDA published a guidance document, Informed Consent, Guidance for IRBs, Clinical Investigators, and Sponsors, which supersedes past guidance and finalizes draft guidance on informed consent. Further, in December 2023, FDA published a final rule, Institutional Review Board Waiver or Alteration of Informed Consent for Minimal** Risk **Clinical Investigations, which allows exceptions from informed consent requirements when a clinical investigation poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of human subjects. Alterations to clinical trial requirements may affect recruitment and retention of patients and may**

hinder or delay a clinical trial. Further, changes to data requirements may cause FDA or comparable foreign regulatory authorities to disagree with data from preclinical studies or clinical trials, and may require further studies. Changes to trial requirements or trial data may increase costs and delay product development. 85General Risk FactorsGlobal economic conditions could adversely impact our business. Deterioration in the macroeconomic economy could lead to losses or defaults by our customers or suppliers, which in turn, could have a material adverse effect on our current and / or projected business operations and results of operations and financial condition. The global financial markets and economy are currently, and have from time to time experienced extreme volatility and disruptions, including severely diminished liquidity and credit availability, rising interest and inflation rates, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. Any significant deterioration in the US economy would likely affect the operation of our business and ability to raise capital. In addition, US debt ceiling and budget deficit concerns have increased the possibility of additional credit- rating downgrades and economic slowdowns, or a recession in the US. Although US lawmakers passed legislation to raise the federal debt ceiling on multiple occasions, ratings agencies have lowered or threatened to lower the long- term sovereign credit rating on the US. The impact of this or any further downgrades to the US government' s sovereign credit rating or its perceived creditworthiness could adversely affect the US and global financial markets and economic conditions. The global financial markets and economy may also be adversely affected by the current or anticipated impact of military conflict, including the ongoing Russian- Ukrainian war, and the Hamas- Israel war, terrorism or other geopolitical events. Sanctions imposed by the US and other countries in response to such conflicts, including the Russian- Ukrainian war and the Hamas- Israel war, may also adversely impact the financial markets and the global economy, and any economic countermeasures by the affected countries or others could exacerbate market and economic instability. The US government has indicated its intent to alter its approach to international trade policy and in some cases to renegotiate, or potentially terminate, certain existing bilateral or multi- lateral trade agreements and treaties with foreign countries. In addition, the US government has initiated or is considering imposing tariffs on certain foreign goods. Related to this action, certain foreign governments, including China, have instituted or are considering imposing tariffs on certain US goods. It remains unclear what the US Administration or foreign governments will or will not do with respect to tariffs or other international trade agreements and policies. A trade war or other governmental action related to tariffs or international trade agreements or policies has the potential to disrupt our research activities, affect our suppliers and / or the US or global economy or certain sectors thereof and, thus, could adversely impact our businesses. Bank failures or other events affecting financial institutions could adversely impact our liquidity and other business. Financial institutions have recently experienced, and may experience in the future, industry instability and failures which have led to disruptions in access to bank deposits or lending commitments. In 2023, the closures of Silicon Valley Bank (SVB) and Signature Bank and their placement into receivership with the Federal Deposit Insurance Corporation (FDIC), as well as the FDIC' s seizure and sale of First Republic Bank, created bank- specific and broader financial institution liquidity risk and concerns. On March 12, 2023, federal regulators announced that the FDIC would complete its resolution of SVB in a manner that fully protects all depositors. On March 27, 2023, First Citizens Bank (FCB) announced that it has entered into an agreement with FDIC to purchase all of the asset and liabilities of SVB. Customers of SVB automatically become customers of FCB following the acquisition. We maintain a depository relationship with SVB / FCB and other banking institutions. All of our cash deposits are accessible to us, and we do not anticipate any losses with respect to such funds. Since the March 2023 financial institution failure, there has been a heightened risk and greater focus on the potential failures of other banks in the future. If these banks fail in the future, we may not be able to immediately (or ever) recover our cash in excess of the FDIC insured limits which would adversely impact our operating liquidity and could negatively impact our operations, results of operations and financial performance. Although we believe our exposure is limited, if in the future any of the financial institutions that we maintain depository or lending relationships were to be placed into receivership, we may be unable to access such funds to meet our working capital requirements. In addition, if any of our customers, suppliers or other parties with whom we conduct business are unable to access funds, such parties' ability to pay their obligations to us or to enter into new commercial arrangements requiring additional payments to us could be adversely affected. Although 86we assess our banking and customer relationships as we believe necessary or appropriate, our access to funding sources and other credit arrangements in amounts adequate to finance or capitalize our current and projected future business operations could be significantly impacted by factors that affect us, the financial institutions with which we have credit agreement or arrangements directly, or the financial services industry or economy in general. ~~FactorsShareholder -------~~ **Shareholder** activism **and private securities- related litigation** could cause material disruption to our business. Publicly traded companies have increasingly become subject to campaigns by our stakeholders, including investors, and more recently regulatory organizations advocating corporate actions such as actions related to ~~environment, social and governance (~~ESG ~~)~~ matters, impacts of climate change, financial restructuring, increased borrowing, dividends, share repurchases and even sales of assets or the entire company. Responding to proxy contests and other actions by such activist investors or others in the future could be costly and time- consuming, disrupt our operations and divert the attention of our Board of Directors and senior management from the pursuit of our business strategies, which could adversely affect our results of operations and financial condition **. There' s a growing emphasis from select investors, regulators, and other stakeholders on corporate responsibility, particularly regarding ESG factors. Some investors and advocacy groups utilize these factors to shape investment strategies, potentially opting out of investing in our company if they perceive our corporate responsibility policies as insufficient. Third- party providers offering corporate responsibility ratings and reports have surged to meet rising investor demand, with numerous organizations evaluating companies on ESG matters, and these evaluations receive widespread attention. A low ESG or sustainability rating from such providers**

could lead certain investors to overlook our common stock in favor of competitors. Institutional investors, in particular, use these ratings to compare companies, and any perceived lag in our ESG efforts might prompt voting decisions or other actions to hold our board accountable. Furthermore, evolving assessment criteria for corporate responsibility practices may raise expectations, compelling us to undertake costly initiatives to meet new standards. Failure to meet these evolving criteria could reinforce the perception of inadequate corporate responsibility policies. Non- compliance could also lead to reputational damage if our procedures or standards fall short of stakeholder expectations. Securities-related class action lawsuits and / or derivative lawsuits have often been brought against companies, including biotechnology and biopharmaceutical companies, that experience volatility in the market price of their securities. It is possible that such lawsuit will be filed, or allegations from stockholders with this matter. Such lawsuits and any other related lawsuits are subject to inherent uncertainties, and the actual defense and disposition costs will depend upon many unknown factors. The outcome of such lawsuits is necessarily uncertain. We could be forced to expend significant resources in the defense of the pending lawsuits and any additional lawsuits, and we may not prevail . Anti- takeover provisions in our charter documents and under Delaware law may make an acquisition of us, which may be beneficial to our stockholders, more difficult. Provisions of our amended and restated certificate of incorporation and bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us, even if doing so would benefit our stockholders. These provisions: ● establish that members of the board of directors may be removed only for cause upon the affirmative vote of stockholders owning a majority of our capital stock; ● authorize the issuance of " blank check " preferred stock that could be issued by our board of directors to increase the number of outstanding shares and thwart a takeover attempt; ● limit who may call a special meeting of stockholders; ● prohibit stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders; ~~83~~ ● establish advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted upon at stockholder meetings; **87** ● provide for a board of directors with staggered terms; and ● provide that the authorized number of directors may be changed only by a resolution of our board of directors. In addition, Section 203 of the Delaware General Corporation Law (DGCL), which imposes certain restrictions relating to transactions with major stockholders, may discourage, delay or prevent a third party from acquiring us. Our bylaws designate a state or federal court located within the State of Delaware as the sole and exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our current or former directors, officers, stockholders, or other employees. Our bylaws provide that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware shall be the sole and exclusive forum for (i) any derivative action or proceeding brought on behalf of us under Delaware law, (ii) any action asserting a claim of breach of a fiduciary duty ~~owed~~ by any current or former director, officer, or other employee of ~~the Company~~ **ours that is owed** to us or our stockholders, (iii) any action asserting a claim against us or any of our directors, officers, or other employees arising pursuant to any provision of the DGCL or our amended and restated certificate of incorporation and bylaws (as either may be amended from time to time), (iv) any action asserting a claim against us governed by the internal affairs doctrine, or (v) any other action asserting an " internal corporate claim, " as defined under Section 115 of the DGCL. The forgoing provisions do not apply to any claims arising under the Securities Act and, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States will be the sole and exclusive forum for resolving any action asserting a claim arising under the Securities Act. These choice of forum provisions may limit a stockholder' s ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our current or former directors, officers, or other employees, which may discourage lawsuits with respect to such claims. There is uncertainty as to whether a court would enforce such provisions, and the enforceability of similar choice of forum provisions in other companies' charter documents has been challenged in legal proceedings. It is possible that a court could find these types of provisions to be inapplicable or unenforceable, and if a court were to find the choice of forum provision to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could harm our business, results of operations, and financial condition. Increasing use of social media could give rise to liability and may harm our business. We and our employees are increasingly utilizing social media tools and our website as a means of communication. Despite our efforts to monitor evolving social media communication guidelines and comply with applicable laws, regulations and national and EU codes of conduct, there is risk that the unauthorized use of social media by us or our employees to communicate about our products or business, sharing of publications in unintended audiences in other jurisdictions, or any inadvertent promotional activity or disclosure of material, nonpublic information through these means, may cause us to be found in violation of applicable laws and regulations, which may give rise to liability and result in harm to our business. In addition, there is also risk of inappropriate disclosure of sensitive information, which could result in significant legal and financial exposure and reputational damages that could potentially have an adverse impact on our business, financial condition and results of operations. Furthermore, negative posts or comments about us or our products on social media could seriously damage our reputation, brand image and goodwill. Our **future success depends on our ability** ~~research and development efforts will be seriously jeopardized if we are unable~~ to attract and retain key employees and relationships. ~~Our success~~ **We are highly** ~~depends~~ **dependent** on the **commercial** ~~continued contributions of our principal management and scientific personnel and on our ability to develop and maintain important relationships with leading academic institutions~~ , ~~scientists and companies in the face of intense competition for such personnel. In particular, our~~ research ~~programs depend on our 84ability to attract and retain highly skilled chemists, other scientists,~~ and development, ~~regulatory and~~ clinical ~~personnel. If we lose the services of any of our key personnel~~ , **business** ~~our research and~~ development ~~efforts could be seriously and adversely affected. Our employees can terminate their employment with us at any time. Global economic conditions could adversely impact our business. The US government has indicated its intent to alter its approach to international trade policy and in some cases to renegotiate~~ , ~~or potentially terminate, certain existing bilateral or multi- lateral trade agreements and treaties~~

with foreign countries. In addition, the US government has initiated or is considering imposing tariffs on certain foreign goods. Related to this action, certain foreign governments, including China, have instituted or are considering imposing tariffs on certain US goods. It remains unclear what the US Administration or foreign governments will or will not do with respect to tariffs or other international trade agreements and policies. A trade war or other governmental action related to tariffs or international trade agreements or policies has the potential to disrupt our research activities, affect our suppliers and / or the US economy or certain sectors thereof and, thus, could adversely impact our businesses. The transition away from the London Interbank Offered Rate (LIBOR) could affect the value of certain short- term investments. The UK' s Financial Conduct Authority (FCA), which regulates LIBOR, has announced plans to phase out the use of LIBOR discontinued as a floating rate benchmark. The date of discontinuation will vary depending on the LIBOR currency and tenor. The FCA has announced that, after specified dates, LIBOR settings will cease to be provided by any administrator or will no longer be representative. Those dates are: (i) June 30, 2023, in the case of the principal US dollar LIBOR tenors (overnight and one, three, six and 12 month s); and (ii) December 31, 2021, in all other cases (i. e., one- week and two- month US dollar LIBOR and all tenors of non- US dollar LIBOR). LIBOR has been the principal floating rate benchmark in the financial markets, and **legal expertise** its discontinuation has affected and will continue to affect the financial markets generally and may also affect our operations specifically. The FCA and certain US regulators have stated that, despite expected publication of US dollar LIBOR through June 30, 2023, no new contracts using US dollar LIBOR should be entered into after December 31, 2021. Regulators have also stated that, for certain purposes, market participants should transition away from US. dollar LIBOR sooner. Regulatory authorities and legislative bodies have taken other actions related to the LIBOR discontinuation and are expected to continue to do so. There is no assurance as to the consequences of any such statements and other actions. Although the foregoing reflects the likely timing of the LIBOR discontinuation and certain consequences, there is no assurance that LIBOR, of any particular currency or **our executive officers** tenor, will continue to be published until any particular date or in any particular form, and there is no assurance regarding the consequences of the LIBOR discontinuation. We have certain short- term investments which include financial instruments subject to LIBOR. Our debt facility with MidCap was subject to LIBOR prior to the Third Amendment to the Credit Agreement entered in July 2022, whereby the interest rate benchmark was changed from LIBOR to Secured Overnight Financing Rate (SOFR) (as defined in the amended Credit Agreement). There remains uncertainty regarding the future utilization of LIBOR and the nature of any replacement rate, and any potential effects of the transition away from LIBOR on certain instruments into which we may enter in the future are not known. The transition process may involve, among other things, increased volatility or illiquidity in markets for instruments that currently rely on LIBOR. The transition may also result in reductions in the value of certain instruments or the effectiveness of related transactions such as hedges, increased borrowing costs, uncertainty under applicable documentation, or difficult and costly consent processes. Any such effects of the transition away from LIBOR, as well as **the** other unforeseen effects, result in expenses, **principal members of our management. We expect to continue hiring and retaining qualified personnel which is critical to our success. Replacing key employees and executive officers may be** difficulties --- **difficult** , complications **and may take an extended period of time because of the limited number of individuals in** or **our industry** delays in connection with **the breadth of skills** future financing efforts, which could have an **and** adverse impact **experience required to successfully develop, gain regulatory approval of and commercialize drugs. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel** on our business, financial condition **acceptable terms given the competition among numerous pharmaceutical** and **88** results of operations. 85