Risk Factors Comparison 2024-03-27 to 2023-03-02 Form: 10-K

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

We operate in a dynamic and rapidly changing business environment that involves multiple risks and substantial uncertainty. The following discussion addresses risks and uncertainties that could cause, or contribute to causing, actual results to differ from expectations in material ways. In evaluating our business, investors should carefully consider the risks described below in addition to the other information set forth in this Annual Report on Form 10- K, or Annual Report, including the Management' s Discussion and Analysis of Financial Condition and Results of Operations section and the consolidated financial statements and related notes. These risks, some of which have occurred and any of which may occur in the future, can have a material adverse effect on our business, financial condition, results of operations or the price of our publicly traded securities. The risks described below are not the only risks we face. Additional risks and uncertainties not currently known to us, or that we currently deem to be immaterial, may occur or become material in the future and adversely affect our business, reputation, financial condition, results of operations or the price of our publicly traded securities. Therefore, historical operating results, financial and business performance, events and trends are often not a reliable indicator of future operating results, financial and business performance, events or trends. If any of the following risks occurs, our business, financial condition, and results of operations and future growth prospects could be materially and adversely affected. Risks Related to Our Financial Position and Need for Additional Capital We have incurred significant losses since inception, expect to incur significant ~~and increasing~~ losses for at least the next several years, and may never achieve or maintain profitability. We have incurred significant annual net operating losses in every year since our inception. We expect to continue to incur significant ~~and increasing~~ net operating losses for at least the next several years. Our net losses were $ **164** ~~94. 7 million, $ 86~~ . 6 million ~~,~~ and $ ~~84~~ **94** . ~~0~~ **7** million for the years ended December 31, **2023 and** 2022 ~~, 2021 and 2020~~ , respectively. As of December 31, ~~2022~~ **2023** , we had an accumulated deficit of $ ~~558~~ **722** . ~~2~~ **8** million. We have not generated any revenues from product sales, have not completed the development of any product candidate and may never have a product candidate approved for commercialization. We have financed our operations to date primarily through the ~~sale~~ **issuance** of equity securities **, through license and collaboration agreements, and through our credit facility with Oxford Finance LLC, or Oxford** . We have devoted substantially all of our financial resources and efforts to research and development and general and administrative expense to support such research and development. Our net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity and working capital. We anticipate that our future funding requirements, both short- term and long- term, will depend on many factors and will increase substantially if and as we: • continue our planned clinical development activities with respect to tamibarotene ~~, SY- 2101 and SY- 5609~~ ; • develop and seek approval of companion diagnostic tests for use in identifying patients who may benefit from treatment with **tamibarotene** ~~our~~ **or** ~~products and~~ **any future** product candidates ~~; • initiate and continue research, preclinical and clinical development efforts for our research and preclinical programs~~ ; • seek to identify and develop additional product candidates, which may involve entering into collaborations, licensing agreements or other arrangements; • acquire or in- license other product candidates or technologies; • seek regulatory and marketing approvals for **tamibarotene** ~~our~~ **or any future** product candidates that successfully complete clinical trials, if any; • establish sales, marketing, distribution and other commercial infrastructure ~~in the future~~ to commercialize ~~various~~ **tamibarotene or other** products for which we may obtain marketing approval, if any; • become obligated to make milestone payments upon the successful completion of specified development and commercialization activities; • require the manufacture of larger quantities of product candidates for clinical development and, potentially, commercialization; • maintain, expand and protect our intellectual property portfolio; and • hire and retain additional personnel and add operational, financial and management information systems, including personnel and systems to support our product development and commercialization efforts. Our ability to become and remain profitable depends on our ability to generate revenue. We do not expect to generate significant revenue unless and until we are, or any collaborator is, able to obtain marketing approval for, and successfully commercialize, **tamibarotene** ~~one or more of our~~ **or any future** product candidates. Successful commercialization will require achievement of key milestones, including initiating and successfully completing clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling products for which marketing approval has been obtained, satisfying any post- marketing requirements and obtaining reimbursement for our products from private insurance or government payors. Because of the uncertainties and risks associated with these activities, we are unable to accurately predict the timing and amount of revenues, and if or when we might achieve profitability. We may never succeed in these activities and, even if we do, or any collaborators do, we may never generate revenues that are large enough for us to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our pipeline of product candidates or continue our operations and cause a decline in the value of our common stock. We will need substantial additional funding to execute our operating plan, and if we are unable to raise capital, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts. Developing pharmaceutical products, including conducting ~~preclinical studies and~~ clinical trials, is a time consuming, expensive and uncertain process. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we may be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts. We believe that our cash ~~,~~ **and** cash equivalents

~~and marketable securities~~ as of December 31, ~~2022~~ **2023** will enable us to fund our planned operating expense and capital expenditure requirements into the second quarter of 2025. Our estimate as to how long we expect our existing cash ~~,~~ **and** cash equivalents ~~, and marketable securities~~ to be able to continue to fund our operations is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. In any event, our existing cash ~~,~~ **and** cash equivalents ~~and marketable securities~~ will not be sufficient to fund all of the efforts that we plan to undertake or to fund the completion of development of all of our product candidates. Our future funding requirements will depend on many factors, including those discussed above under " We have incurred significant losses since inception, expect to incur significant ~~and increasing~~ losses for at least the next several years, and may never achieve or maintain profitability. " Our future funding requirements may also depend on: • ~~whether a drug candidate will be nominated to enter into investigational new drug application- enabling studies under our sickle cell disease collaboration with GBT, whether GBT will exercise its option to exclusively license intellectual property arising from the collaboration, whether and when any option exercise fees, milestone payments or royalties under the collaboration agreement with GBT will ever be paid, and whether we exercise our U. S. co- promotion option under the GBT agreement; • whether our target discovery collaboration with Incyte will yield any validated targets, whether Incyte will exercise any of its options to exclusively license intellectual property directed to such targets, and whether and when any of the target validation fees, option exercise fees, milestone payments or royalties under the collaboration agreement with Incyte will ever be paid; •~~ the costs of precommercial activities related to ~~our~~ **tamibarotene and any future** product candidates, including any physician education programs relating to selecting and treating genomically defined patient populations; • the timing and amount of milestone and other payments due to TMRC Co. Ltd., or TMRC, associated with the development, manufacture and commercialization of tamibarotene; • the timing and amount of milestone payments due to ~~Orsenix~~ **Qiagen Manchester Limited** , ~~LLC~~ **or Qiagen** , associated with the **development and commercialization of a companion diagnostic test for use with tamibarotene; and • the timing and amount of milestone payments due to Orsenix, LLC, or Orsenix, associated with any potential further** development and commercialization of SY- 2101 **in** ~~; and •~~ the **future** ~~timing and amount of milestone payments due to Qiagen Manchester Limited associated with the development and commercialization of a companion diagnostic test for use with tamibarotene~~ . Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and stock price. Global credit and financial markets have experienced extreme volatility and disruptions in the past several years, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability, including most recently in connection with the impacts of COVID- 19, disruptions impacting global supply, the conflict between Russia and Ukraine and related sanctions against Russia **, conflict in the Middle East** , increasing inflation rates and interest rate changes. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, or do not improve, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive. Furthermore, our stock price may decline due in part to the volatility of the stock market and the general economic downturn. Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates. We expect our expenses to remain high in connection with our planned operations. To the extent that we raise additional capital through the sale of common stock, convertible securities or other equity securities, as we did through **underwritten offerings of our common stock in December 2023 and January 2021 and in** a private placement of our securities in September 2022, the ownership interests of our existing stockholders may be substantially diluted, and the terms of these securities could include liquidation or other preferences and anti- dilution protections that could adversely affect our stockholders' rights. In addition, debt financing, such as our term loan facility with Oxford ~~that we entered into in February 2020~~ , has created fixed payment obligations and imposed restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures, creating liens, redeeming stock or declaring dividends, that could adversely impact our ability to conduct our business. In addition, securing financing could require a substantial amount of time and attention from our management and may divert a disproportionate amount of their attention away from day- to- day activities, which may adversely affect our management' s ability to oversee the development of our product candidates. If we raise additional funds through collaborations or marketing, distribution or licensing arrangements with third parties, ~~such as our collaboration agreement with GBT,~~ we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. In this regard, we ~~recently announced that we~~ are seeking ~~a partnership~~ **out- licensing opportunities** for the clinical development of SY- 5609 ~~, and that we are seeking partnerships for our oncology discovery programs, including our CDK12 program~~ . However, we cannot provide assurance that ~~these~~ **such a** ~~transactions~~ **transaction** will be consummated, or that sufficient additional capital to support ~~the~~ further development ~~of SY- 5609 or of our oncology discovery programs~~ can be obtained or will be obtained on favorable terms. The terms of our Loan and Security Agreement place restrictions on our operating and financial flexibility. In February 2020, we entered into a Loan and Security Agreement with Oxford, which is secured by substantially all of our currently owned or later acquired personal property other than our intellectual property (but including the right to payments and proceeds of intellectual property), which is subject to a negative pledge. We refer to the Loan and Security Agreement with Oxford as the Loan Agreement. We borrowed $ 20. 0 million upon execution of the Loan Agreement and borrowed an additional $ 20. 0 million term loan advance in December 2020. One additional term loan advance

of $ 20. 0 million remains available under the Loan Agreement, subject to certain terms and conditions, including the achievement of certain milestones. On July 3, 2022, we entered into an amendment to the Loan Agreement, or the Loan Amendment, pursuant to which Oxford, in its capacity as lender and agent, has agreed to modify the Loan Agreement in order to, among other things, (i) extend the interest only period from March 1, 2023 to March 1, 2024 and extend the maturity date from February 1, 2025 to February 1, 2026, and (ii) upon the achievement of certain milestones and subject to the payment of certain fees, further extend the interest only period to September 1, 2024 and maturity date to August 1, 2026. The Loan Agreement, as amended by the Loan Amendment, contains representations and warranties, affirmative and negative covenants applicable to us and our subsidiaries and events of default, as more fully described in the Loan Agreement ~~and Loan Amendment~~ **, as amended** . In particular, the Loan Agreement also includes events of default, the occurrence and during the continuation of which provide Oxford, as collateral agent, with the right to exercise remedies against us and the collateral securing the loans under the Loan Agreement, including foreclosure against our property securing the Loan Agreement, including our cash, potentially requiring us to renegotiate our agreement on terms less favorable to us, or to immediately cease operations. Further, if we are liquidated, the lenders' right to repayment would be senior to the rights of the holders of our common stock to receive any proceeds from the liquidation. Oxford could declare a default upon the occurrence of any event that they interpret as a material adverse change as defined under the Loan Agreement, thereby requiring us to repay the loan immediately or to attempt to reverse the declaration of default through negotiation or litigation. Any declaration by Oxford of an event of default could significantly harm our business and prospects and could cause the price of our common stock to decline. Risks Related to the ~~Discovery,~~ Development and Commercialization of Product Candidates Our approach to the discovery and development..... for medicines we may successfully commercialize. In the near term, we are dependent on the success of tamibarotene ~~, SY- 2101 and SY- 5609~~ . If we are unable to ~~initiate or~~ complete the clinical development of, obtain marketing approval for **,** or successfully commercialize tamibarotene, ~~SY- 2101 or SY- 5609,~~ either alone or with a collaborator, or if we experience significant delays in doing so, our business ~~could~~ **will** be substantially harmed. We currently have no products approved for sale and are **focusing** ~~investing a significant portion of~~ our efforts and financial resources ~~in~~ **towards** the development of tamibarotene ~~, SY- 2101 and SY- 5609~~ . Our ability to generate product revenue will depend heavily on the successful clinical development and eventual commercialization of ~~our current and any future product candidates, such as~~ tamibarotene ~~, SY- 2101 and SY- 5609~~ . We, and any collaborators, are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining marketing approval from the FDA. Foreign regulatory authorities, such as the **European Medicines Agency, or** EMA, impose similar requirements in foreign jurisdictions. Before obtaining marketing approval from regulatory authorities for the sale of **tamibarotene** ~~our~~ **or any future** product candidates, we must ~~complete preclinical development and then~~ conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical trials of a ~~new~~ product candidate require the activation of clinical trial sites and the enrollment of a sufficient number of patients, including patients who are suffering from the disease the product candidate is intended to treat and who meet other eligibility criteria. Our anticipated time to data in our clinical trials and the quantity of data to be presented from these trials is and will continue to be subject to our continued ability to activate clinical trial sites, recruit eligible patients, and the satisfaction by patients of other eligibility criteria for participation in the trial. In the case of tamibarotene, our time to data is also dependent on the prevalence of patients who overexpress the RARA biomarker and the impact of new product approvals in the AML and MDS fields. The rate of site activations and patient enrollment in the trial is difficult to predict, and we have experienced slower- than- anticipated site activations in our SELECT- MDS- 1 trial as we expanded the study global footprint. There can be no assurance that we will enroll or have data from our clinical trials when we anticipate **. Further, we may experience delays in initiating or completing clinical trials and preparing for regulatory submissions, particularly if there are changes in or the enactment of additional statutes, promulgation of regulations or issuance of guidance during preclinical or clinical development. For example, in December 2022, with the passage of Food and Drug Omnibus Reform Act, Congress required sponsors to develop and submit a diversity action plan for each Phase 3 clinical trial or any other " pivotal study " of a new drug or biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late- stage clinical trials of FDA regulated products** . Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. The clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of product development. Moreover, we, or any collaborators, may experience any of a number of possible unforeseen adverse events in connection with clinical trials, many of which are beyond our control, including: • we, or our collaborators, may fail to demonstrate efficacy in a clinical trial or across a broad population of patients; • it is possible that, even if one or more of our product candidates has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. For example, many compounds that initially showed promise in earlier stage testing have later been found to cause side effects that prevented further development of the compound; • our product candidates may have undesirable side effects or other unexpected characteristics or otherwise expose participants to unacceptable health risks, causing us, our collaborators or our investigators, regulators or institutional review boards or the data safety monitoring board for such trial to halt, delay, interrupt, suspend or terminate the trials or cause us, or any collaborators, to abandon development or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk- benefit perspective; • if our product candidates have undesirable side effects, it could result in a more restrictive label, or it could result in the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities; • clinical trials of our product candidates may produce negative or inconclusive results, and we, or our

collaborators, may decide, or regulators may require us, to conduct additional clinical trials, including testing in more subjects, or abandon product development programs; • regulators or institutional review boards may not authorize us, our collaborators or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site; • we or our collaborators may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites; • the number of patients required for clinical trials of our product candidates may be larger than we anticipate; • enrollment in these clinical trials, which may be particularly challenging for some of the diseases we target, may be slower than we anticipate; • or participants may drop out of these clinical trials at a higher rate than we anticipate; • third- party contractors used by us or our collaborators may fail to comply with regulatory requirements or meet their contractual obligations in a timely manner, or at all; • significant ~~preclinical study or~~ clinical trial delays could shorten any periods during which we, or any collaborators, may have the exclusive right to commercialize our product candidates or allow our competitors, or the competitors of any collaborators, to bring products to market before we, or any collaborators, do; • the cost of clinical trials of our product candidates may be greater than anticipated; and • the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate. In addition, we are conducting our SELECT- MDS- 1 **and SELECT- AML- 1** clinical ~~trial~~ **trials** in foreign countries and may conduct other clinical trials outside the United States in the future. We do not have employees or significant operational capabilities located outside of the United States, and we rely on third parties, such as contract research organizations, or CROs, to conduct our clinical trials in foreign countries. Conducting clinical trials in foreign countries presents additional risks that may delay completion of our clinical trials. These risks include the failure of enrolled patients in foreign countries to adhere to clinical protocols as a result of differences in healthcare services or cultural customs, managing additional administrative burdens associated with foreign regulatory schemes, as well as political and economic risks relevant to such foreign countries. **In addition, conducting clinical trials in non- U. S. countries, as we may do for our product candidates, may present additional risks that may delay completion of our clinical trials. For example, on January 31, 2022, the new Clinical Trials Regulation (EU) No 536 / 2014 became applicable in the European Union, or EU, and replaced the prior Clinical Trials Directive 2001 / 20 / EC. The new regulation aims at simplifying and streamlining the authorization, conduct and transparency of clinical trials in the EU. Under the new coordinated procedure for the approval of clinical trials, the sponsor of a clinical trial to be conducted in more than one Member State of the European Union, or EU Member State, will only be required to submit a single application for approval. The submission will be made through the Clinical Trials Information System, a new clinical trials portal overseen by the EMA and available to clinical trial sponsors, competent authorities of the EU Member States and the public. We have not previously secured authorization to conduct clinical studies in the EU pursuant to this new regulation and, accordingly, there is a risk that we may be delayed in commencing such studies.** Our failure to successfully ~~begin and~~ complete clinical trials of **tamibarotene** ~~our~~ **or any future** product candidates ~~, including tamibarotene, SY- 2101 and SY- 5609~~ , and to demonstrate the efficacy and safety necessary to obtain regulatory approval to market **such** ~~any of our~~ product candidates **,** could result in additional costs to us, or any collaborators, would impair our ability to generate revenue from product sales, regulatory and commercialization milestones and royalties and would significantly harm our business **.Our approach to the development of tamibarotene** is novel and unproven,and we do not know whether we will be able to **recognize** ~~develop any products of~~ commercial value **from tamibarotene** .We are ~~primarily~~ **currently** focused on **the** ~~developing~~ **development** ~~medicines for the treatment~~ of ~~hematologic malignancies.Tamibarotene~~ **tamibarotene** , **which** ~~our lead product candidate,~~ is being evaluated in genomically defined patients whose diseases have not been adequately addressed to date by **existing** ~~other genomics~~ approaches.While we believe that targeting **the** ~~this genomically defined~~ patient population **that overexpresses RARA** may potentially lead to a higher likelihood of clinical success,our approach is both novel and unproven,and our efforts may not result in the development of **a** commercially viable ~~medicines~~ **medicine** .We may also be incorrect about the effects of **tamibarotene** ~~our product candidates~~ on the diseases of ~~genomically defined patient~~ **patients** ~~populations~~ **that overexpress RARA** ,which may limit the utility of our approach or the perception of the utility of our approach.For example,we have not yet succeeded and may never succeed in demonstrating efficacy and safety for **tamibarotene** ~~our current~~ or any ~~future~~ **other** product candidates in a pivotal clinical trial or in obtaining marketing approval thereafter.Furthermore,our estimates of ~~genomically defined~~ patient populations **with RARA overexpression** available for study and treatment may be lower than expected,which could adversely affect our ability to conduct **our** clinical trials **of tamibarotene** and may also adversely affect the size of any market for ~~medicines~~ **tamibarotene that** we may successfully commercialize . Adverse events or undesirable side effects caused by, or other unexpected properties of, product candidates that we develop may be identified during development and could delay or prevent their marketing approval or limit their use. Side effects from product candidates undergoing clinical evaluation may be unpredictable. Tamibarotene has been observed to be associated with adverse events, such as mild or moderate dry skin, skin rash, headache and bone pain, as well as retinoic acid syndrome and elevated levels of cholesterol, lipids, liver function enzymes and white blood cells, which were severe in certain cases. Furthermore, retinoids such as tamibarotene may cause birth defects and therefore may carry a warning on their label. Other examples of retinoids, a class of chemical compounds that are related to vitamin A, include all trans retinoic acid (also known as ATRA), Retin- A, retinol (found in over- the- counter skin creams), isotretinoin and bexarotene. ~~Additionally, SY- 5609 has been observed to be associated with adverse events such as nausea, diarrhea, thrombocytopenia, fatigue and anemia. Furthermore, we have limited experience administering SY- 2101 to humans, so the safety profile it will demonstrate in human clinical trials remains uncertain.~~ We cannot predict at this time whether the combination of **tamibarotene** ~~our~~ **or any future** product candidates with another product, or with any premedication administered to mitigate potential side effects, will be well tolerated by patients in clinical studies or that any unexpected adverse events or undesirable side effects will not occur. If any of our product candidates is associated with adverse events or undesirable side effects or has properties that are unexpected, we, or any collaborators, may need to abandon development or limit development of that product candidate to certain uses or

subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk- benefit perspective. Failure to successfully **develop,** validate, ~~develop and~~ obtain regulatory approval for **, and commercialize** companion diagnostics could harm our **commercialization** ~~drug development~~ strategy. **If** ~~As one of the key elements of our development strategy,~~ we ~~seek~~ **are to succeed in obtaining regulatory approval for a companion diagnostic** to identify genomically defined subsets of patients ~~within a disease category who may derive benefit from the product candidates we are developing. In collaboration~~ with ~~partners~~ **AML or MDS using our RARA biomarker** , we ~~plan~~ **will need** to **demonstrate to regulatory authorities that RARA biomarker selection is associated with a response to tamibarotene. We do not** develop companion diagnostics **internally and thus we will be dependent on the sustained cooperation and effort of third- party collaborators in developing, obtaining approval for, and commercializing a companion diagnostic** to ~~help us to more accurately~~ identify patients ~~within~~ -- **with** ~~a particular subset~~ **RARA overexpression. In March 2022** , ~~both during~~ **we entered into a Master Collaboration Agreement and associated project work plan with Qiagen, pursuant to which Qiagen has agreed to develop and commercialize a companion diagnostic for this biomarker. Any delay** ~~our~~ **or failure by us, Qiagen, or any future collaborators to develop, validate, obtain regulatory approval for, or commercialize companion diagnostics could harm our drug development strategy by delaying or preventing approval of tamibarotene or any future product candidates, delaying the commercialization of such product candidates, or diminishing the likelihood of achieving the commercial potential for such product candidates. We and our collaborators may encounter difficulties in developing and validating companion diagnostics, including issues relating to selectivity / specificity, analytical validation, reproducibility, or** clinical ~~trials and~~ **validation. In addition, Qiagen or any future collaborators may encounter production difficulties that could constrain the supply of the companion diagnostics. In addition, Qiagen or any future collaborators may decide to discontinue selling or manufacturing the companion diagnostic that we anticipate using** in connection with **tamibarotene** ~~the commercialization of our~~ **or any future** product candidates ~~that we are developing~~ **due to lack of commercial viability, or** ~~or~~ **our relationship with such collaborator** may **otherwise terminate. We may not be able to enter into arrangements with another provider to obtain supplies of an alternative diagnostic test for use** in **connection with such product candidates or do so on commercially reasonable terms. Any of** ~~the~~ **these challenges could adversely affect and / or delay the development and commercialization of the companion diagnostic and tamibarotene or any** future ~~develop~~ **product candidate** . **In addition,** ~~Companion~~ **companion** diagnostics are subject to regulation by the FDA and comparable foreign regulatory authorities as medical devices and require separate regulatory approval prior to commercialization. While ~~our~~ **tamibarotene and any future** drug candidates will have their marketing applications reviewed by FDA' s Center for Drug Evaluation and Research, ~~or CDER,~~ companion diagnostics require separate marketing applications under the primary jurisdiction of FDA' s Center for Devices and Radiological Health ~~, or CDRH~~ . This parallel jurisdiction and separate marketing applications could result in coordination issues, require additional time and effort, or result in delays or failure to obtain marketing approval for either the companion diagnostic or related drug indications. ~~We materially impaired.In August 2014~~ **Foreign regulatory authorities may also require clinical trials to demonstrate the safety and efficacy of companion diagnostics** , **which would require separate regulatory clearance or approval prior to commercialization in** ~~the~~ **those countries.The companion diagnostic** ~~FDA issued final guidance clarifying the requirements that will apply to~~ approval ~~of~~ **process can impact the** therapeutic ~~products~~ **product** ~~and~~ **approval process** in **several ways** ~~vitro companion diagnostics~~ .According to ~~the~~ **FDA** guidance,if the FDA determines that a companion diagnostic device is essential to **ensuring** the safe and effective use of a novel therapeutic product or **new** indication,the FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic is not also approved or cleared for that indication. **Additional regulations apply to companion diagnostics that are used to make critical treatment decisions.For example,the FDA has stated that a companion diagnostic used to determine patient selection will be considered a significant risk device requiring an investigational device exemption.If any companion diagnostic that we develop,whether alone or with a collaborator such as Qiagen,does not comply with these requirements,we would not be able to proceed with our planned trial of the applicable product candidate in these patient populations.Further,** ~~Under~~ **under** the Federal Food,Drug,and Cosmetic Act,or FDCA, ~~companion diagnostics are regulated as medical devices and~~ the FDA has generally required companion diagnostics intended to select the patients who will respond to cancer treatment to obtain premarket approval,or a PMA.Consequently, ~~we anticipate that~~ certain of our companion diagnostics may require us or our collaborators to obtain a PMA ~~.For example,we expect that the FDA will require a PMA for the companion diagnostic being developed by Qiagen for use with tamibarotene to identify genomically defined subsets of patients with AML or MDS using our RARA biomarker~~ .The PMA process,including the gathering of clinical and preclinical data and the submission to and review by the FDA,involves a rigorous premarket review during which the sponsor must prepare and provide the FDA with reasonable assurance of the device ~~'~~ **'** s safety and effectiveness and information about the device and its components regarding,among other things,device design,manufacturing and labeling.PMA ~~approval~~ is not guaranteed and may take considerable time,and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time- consuming to generate and that can substantially delay approval.As a result,if we or our collaborators are required by the FDA to obtain approval of a companion diagnostic for a candidate therapeutic product,and we or our collaborators ~~do not obtain or there are delays in obtaining FDA approval of a diagnostic device,we may not be able to effectively commercialize the product candidate and our ability to generate revenue will be materially impaired.In its August 2014 guidance,the FDA also indicated that companion diagnostics used to make treatment decisions in clinical trials of a therapeutic~~ do not ~~develop~~ **obtain, or there are delays in obtaining, FDA approval of a diagnostic device, we may not be able to effectively commercialize the product candidate and our ability to generate revenue will be materially impaired. We may also face challenges related to the commercialization of** companion diagnostics **. Any delays** ~~internally and thus we will be dependent on the sustained cooperation and effort of one or~~

~~more third- party collaborators in developing, obtaining approval for~~ **or** ~~, and commercializing~~ **failures related to** ~~these~~ -- **the companion diagnostics. We and our collaborators may encounter difficulties in developing development and obtaining approval for the companion diagnostics** , ~~including issues relating to selectivity / specificity, analytical~~ validation ~~, reproducibility, or clinical validation. For~~ - **or** ~~example, if we are to succeed in obtaining~~ regulatory approval **processes described above could delay the commercialization of tamibarotene** ~~for~~ - **or any future product candidate. In addition** ~~a companion diagnostic to identify genomically defined subsets of patients with AML or MDS using our RARA biomarker~~ , **while** we **believe** ~~will need to demonstrate to regulatory authorities~~ that ~~RARA biomarker selection~~ **the adoption of screening and treatment into clinical practice guidelines** is **important for payer access** ~~associated with a response to tamibarotene. In March 2022~~ , **reimbursement, utilization in medical practice** ~~we entered into a Master Collaboration Agreement~~ and ~~associated project work plan with~~ **commercial success, we and** Qiagen ~~, pursuant to which Qiagen will develop and commercialize a companion diagnostic for this biomarker. Any delay or failure by us, Qiagen,~~ or any future collaborators ~~to develop or obtain regulatory approval of the companion diagnostics could delay or prevent approval of our product candidates, delay the commercialization of our product candidates, or diminish the likelihood of achieving the commercial potential for our product candidates. In addition, Qiagen or any future collaborators may encounter production difficulties that could constrain the supply of the companion diagnostics, and both they and we~~ may have difficulties gaining acceptance of the use of the companion ~~diagnostics~~ - **diagnostic** in the clinical community. If such companion diagnostics fail to gain market acceptance, it would have an adverse effect on our ability to derive ~~revenues~~ - **revenue** from sales, if any, of **tamibarotene** ~~our products. In addition, Qiagen~~ or any **future** ~~other companion diagnostic collaborator with whom we contract may decide not to commercialize or to discontinue selling or manufacturing the companion diagnostic that we anticipate using in connection with development and commercialization of our~~ product candidates ~~,~~ **that are approved** ~~or~~ **for commercial sale** ~~our relationship with such collaborator may otherwise terminate~~ . ~~We may not~~ **As a result, our business, results of operations and financial condition could** be **materially harmed** ~~able to enter into arrangements with another provider to obtain supplies of an alternative diagnostic test for use in connection with the development and commercialization of our product candidates or do so on commercially reasonable terms, which could adversely affect and / or delay the development or commercialization of our product candidates~~ . If we, or any collaborators, experience delays or difficulties in the enrollment of patients in clinical trials, our or their receipt of necessary regulatory approvals could be delayed or prevented. We, or any collaborators, may not be able to initiate or continue clinical trials for **tamibarotene** ~~our current product candidates~~ or any future product candidates that we, or any collaborators, may develop if we, or they, are unable to locate and enroll a sufficient number of eligible patients to participate in clinical trials. Patient enrollment is a significant factor in the timing of clinical trials, and is affected by many factors, including the size and nature of the patient population, the severity of the disease under investigation, and the availability of approved or investigational therapeutics for the relevant disease, the proximity of patients to clinical sites, the eligibility criteria for and design of the trial, efforts to facilitate timely enrollment, competing clinical trials, clinicians ~~'~~ **'** and patients ~~'~~ **'** perceptions as to the potential advantages and risks of the drug being studied in relation to other available therapies, and actual or threatened public health emergencies and outbreaks of disease (including, for example, the COVID- 19 pandemic). In addition, patients that enroll may subsequently be dropped from the clinical trial due to having misrepresented their eligibility to participate or due to non- compliance with clinical trial protocol, resulting in the need to increase the enrollment size for the clinical trial or extend the clinical trial ~~'~~ **'** s duration. In particular, ~~we intend to enrich certain of~~ our clinical trials **of tamibarotene are enrolling patients** with **RARA overexpression, which** patients **we believe are** most likely to respond to **tamibarotene** ~~our product candidates~~ . ~~Genomically defined diseases~~ **Our estimates as to the prevalence of RARA overexpression in the patient populations we are targeting** may **prove to be incorrect** , **and the** ~~however, have~~ relatively low prevalence ~~and~~ **of RARA overexpression may make** it ~~may be~~ difficult for us or third parties with whom we collaborate to identify patients for our trials, which may lead to delays in enrollment for our trials. ~~We intend to develop, or engage third parties such as Qiagen to develop, companion diagnostics for use in our clinical trials, but we or such third parties may not be successful in developing such companion diagnostics, furthering the difficulty in identifying genomically defined subsets of patients for our clinical trials.~~ Moreover, in light of the recent approval of new products for the treatment of AML, there is substantial competition for patients to be enrolled in clinical trials for this disease. Our inability, or the inability of any collaborators, to enroll a sufficient number of patients for our, or their, clinical trials could result in significant delays or may require us or them to abandon one or more clinical trials altogether. Enrollment delays in our, or their, clinical trials may result in increased development costs for **tamibarotene** ~~our~~ - **or any future** product candidates, delay or halt the development of and approval processes for ~~our~~ **such** product candidates and jeopardize our, or any collaborators', ability to commence sales of and generate revenues from ~~our~~ **such** product candidates, which could cause the value of our company to decline and limit our ability to obtain additional financing, if needed. Results of preclinical studies and early clinical trials may not be predictive of results of future or late- stage clinical trials. We cannot assure you that we will be able to replicate in human clinical trials the results we observed in earlier studies. Moreover, the outcome of preclinical studies and early clinical trials may not be predictive of the success of later or late- stage clinical trials, and interim results of clinical trials do not necessarily predict success in future clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late- stage clinical trials after achieving positive results in earlier development, and we could face similar setbacks **in our clinical trials involving tamibarotene or in any future clinical trials involving other product candidates** . In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. If we fail to receive positive results in clinical trials of **tamibarotene** ~~our~~ - **or** ~~product~~ **any future** candidates, the development timeline and regulatory approval and commercialization prospects for **such** ~~our most advanced~~ product candidates, and, correspondingly, our

business and financial prospects would be negatively impacted. We have never obtained marketing approval for a product candidate and we may be unable to obtain, or may be delayed in obtaining, marketing approval for **tamibarotene** ~~our current product candidates~~ or any future product candidates that we, or any collaborators, may develop. We have never obtained marketing approval for a product candidate. It is possible that the FDA may refuse to accept for substantive review any new drug applications, or NDAs, that we submit for **tamibarotene** ~~our~~ **or any future** product candidates **,** or may conclude after review of our data that our application is insufficient to obtain marketing approval of ~~our~~ **such** product candidates. If the FDA does not accept or approve our NDAs for **tamibarotene or** any **future** ~~of our~~ product candidates, it may require that we conduct additional clinical trials, preclinical studies or manufacturing validation studies and submit that data before it will reconsider our applications. Depending on the extent of these or any other FDA- required trials or studies, approval of any NDA or application that we submit may be delayed by several years, or may require us to expend more resources than we have available. It is also possible that additional trials or studies, if performed and completed, may not be considered sufficient by the FDA to approve our NDAs. In addition, our development ~~programs~~ **program for tamibarotene** ~~contemplate~~ **contemplates** the development of **a** companion ~~diagnostics~~ **diagnostic** by **Qiagen,** our third- party ~~collaborators~~ **collaborator** ~~, such as Qiagen~~. Companion diagnostics are subject to regulation as medical devices and must themselves be approved for marketing by the FDA or certain other foreign regulatory agencies before we may commercialize our product candidates. Any delay in obtaining, or an inability to obtain, marketing approvals would prevent us from commercializing ~~our~~ **tamibarotene, any future** product candidates **,** or any companion diagnostics, **and from** generating revenues and achieving and sustaining profitability. If any of these outcomes occur, we may be forced to abandon our development efforts for ~~our~~ **such** product candidates, which could significantly harm our business. Even if any product candidates that we, or any collaborators, may develop receive marketing approval, we or others may later discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, which could compromise our ability, or that of any collaborators, to market the product. Clinical trials of tamibarotene ~~, SY- 2101 or SY- 5609~~ or any future product candidates that we, or any collaborators, may develop will be conducted in carefully defined subsets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials, or those of any collaborators, may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If, following approval of a product candidate, we, or others, discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, we could be subject to the withdrawal of prior regulatory approvals and / or the imposition of additional regulatory requirements, restrictions on manufacturing, labelling and marketing, and product recalls. In addition, we our any collaborators could be sued and held liable for harm caused to patients and could become subject to fines, injunctions or the imposition of civil or criminal penalties. Any of these events could harm our reputation, business and operations and could negatively impact our stock price. Even if **tamibarotene** ~~our current product candidates,~~ or any future product candidate that we, or any collaborators, may develop receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, 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. We have never commercialized a product, and even if **tamibarotene** ~~one of our~~ **or any future** product ~~candidates~~ **candidate** is approved by the appropriate regulatory authorities for marketing and sale, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third- party payors and others in the medical community. Physicians are often reluctant to switch their patients from existing therapies even when new and potentially more effective or convenient treatments enter the market. Further, patients often acclimate to the therapy that they are currently taking and do not want to switch unless their physicians recommend switching products or they are required to switch therapies due to lack of reimbursement for existing therapies. Efforts to educate the medical community and third- party payors on the benefits of ~~our~~ **tamibarotene and any future** product candidates may require significant resources and may not be successful. If any **such** ~~of our~~ product ~~candidates~~ **candidate** is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues and we may not become profitable. The degree of market acceptance of ~~our~~ **any** product candidates, if approved for commercial sale, will depend on a number of factors, including the efficacy and safety of the product, the potential advantages of the product compared to competitive therapies, the prevalence and severity of any side effects, whether the product is designated under physician treatment guidelines as a first-, second- or third-line therapy, our ability, or the ability of any collaborators, to offer the product for sale at competitive prices, the product' s convenience and ease of administration compared to alternative treatments, the willingness of the target patient population to try, and of physicians to prescribe, the product, limitations or warnings, including distribution or use restrictions, contained in the product' s approved labeling, the strength of sales, marketing and distribution support, changes in the standard of care for the targeted indications for the product; and the availability and amount of coverage and reimbursement from government payors, managed care plans and other third- party payors. We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success. Because we have limited financial resources, we intend to focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of both their potential for marketing approval and commercialization. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential. In this regard, we announced in November 2022 that we have elected to seek a partnership for the further development of SY- 5609. **Further, in October 2023, we announced a strategic realignment to prioritize key development and pre- launch activities to advance tamibarotene for the treatment of newly diagnosed HR- MDS and newly diagnosed AML, and to stop further investment in the clinical development of SY- 2101.** Our ~~resource allocation decisions~~ **decision to cease development of SY- 2101 and SY- 5609 and to allocate our resources towards the development of tamibarotene** may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on ~~current and~~ **tamibarotene or any** future ~~research and~~ development programs

and product candidates for specific indications may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to the product candidate. If we are unable to establish sales ~~, marketing~~ and distribution capabilities or enter into sales ~~, marketing~~ and distribution arrangements with third parties, we may not be successful in commercializing any product candidates if approved. We **are planning our distribution, dispensing, commercial operations, and sales infrastructure strategy for a commercial launch of tamibarotene in the United States, subject to receiving marketing approval. We intend to build a focused and specialized sales and marketing organization in the United States to sell tamibarotene. We are building a marketing and commercial organization to create and implement marketing strategies for the anticipated commercial launch of tamibarotene and to oversee and support our sales force. We** do not have a sales ~~, marketing~~ or distribution infrastructure and have no experience in the sale ~~, marketing~~ or distribution of pharmaceutical products. To achieve commercial success for any approved product, we must either develop a sales and marketing organization or outsource these functions to third parties. We plan to build focused **and specialized** capabilities to commercialize **tamibarotene** ~~development programs~~ for ~~certain~~ **the HR- MDS and AML** indications **,** where we believe that ~~the~~ medical specialists ~~for the indications~~ are sufficiently concentrated to allow us to effectively promote the product with a targeted sales team. The development of sales, marketing and distribution capabilities ~~will require~~ **requires** substantial resources, **is** ~~will be~~ time consuming and could delay any product launch. If the commercial launch of ~~a~~ **tamibarotene or any future** product candidate for which we recruit a sales force and establish marketing and distribution capabilities is delayed or does not occur for any reason, we could have prematurely or unnecessarily incurred these commercialization costs. This may be costly, and our investment could be lost if we cannot retain or reposition our sales and marketing personnel. In addition, we may not be able to hire or retain a sales force that is sufficient in size or has adequate expertise in the medical markets that we plan to target. If we are unable to establish or retain a sales force and marketing and distribution capabilities, our operating results may be adversely affected. If a potential partner has development or commercialization expertise that we believe is particularly relevant to one of our products, then we may seek to collaborate with that potential partner even if we believe we could otherwise develop and commercialize the product independently. In certain indications, we plan to seek to enter into collaborations that we believe may contribute to our ability to advance development and ultimately commercialize our product candidates. We also intend to seek to enter into collaborations where we believe that realizing the full commercial value of our development programs will require access to broader geographic markets or the pursuit of broader patient populations or indications. **To that end, we intend to seek a partner to commercialize tamibarotene in the territories outside the United States.** As a result of entering into **any such** ~~arrangements~~ **arrangement** with **a** third ~~parties~~ **party** to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues may be lower, perhaps substantially lower, than if we were to directly market and sell products in those markets. Furthermore, we may be unsuccessful in entering into the necessary arrangements with third parties or may be unable to do so on terms that are favorable to us. In addition, we may have little or no control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales, marketing and distribution capabilities, either on our own or in collaboration with third parties, we will not be successful in commercializing **tamibarotene or** any **future** ~~of our~~ product candidates that **may** receive marketing approval. We face substantial competition, which may result in others ~~discovering,~~ developing or commercializing products before or more successfully than we do. We expect that we, and any collaborators, will face significant competition from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide with respect to any of our product candidates that we, or any collaborators, may seek to develop or commercialize in the future. Specifically, there are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of product candidates for the treatment of the key indications ~~of~~ **targeted in** our ~~most advanced programs~~ **clinical trials involving tamibarotene** . For example, we are aware of several new drugs approved by the FDA since 2018 for the treatment of newly diagnosed unfit AML or patient subsets within newly diagnosed unfit AML (including ivosidenib, venetoclax, and glasdegib), and one new drug approved by the FDA in 2020 for the treatment of MDS or patient subsets within MDS (decitabine / cedazuridine). Tamibarotene may also face competition from other agents currently in clinical development for AML and MDS, including those in late- stage development from ~~Gilead Sciences, Inc., Abbvie~~ **AbbVie** Inc., Roche Holding AG, **Taiho Oncology** ~~Novartis AG, Astex Pharmaceuticals~~ , Inc. **,** and Pfizer Inc ~~. SY- 2101 may face competition from Trisenox ® or any of the generic forms of Trisenox, an IV ATO product approved by the FDA for the treatment of APL. We are also aware of a traditional Chinese medicine (TCM)- based formulation of oral arsenic commercially available in China. In addition, we are aware of an oral formulation of ATO in clinical development by Phebra Pty Ltd, or Phebra, an Australian based specialty pharmaceutical group. Phebra has entered into an agreement with Medsenic SAS, a European biopharmaceutical company, for the investigation of their oral ATO compound for the treatment of autoimmune diseases. We are also aware of an oral formulation of ATO being studied in an academic setting in Hong Kong. In addition, we are aware of selective CDK7 inhibitors being developed in early clinical trials by Carrick Therapeutics Ltd., Exelixis, Inc. and Qurient Co. Ltd., as well as other selective CDK7 inhibitor programs that we believe are in preclinical development from Yungjin Pharma Co., Ltd., The Translational Genomics Research Institute, Applied Pharmaceutical Science, Inc. and Kirilys Therapeutics, Inc., and a collaboration between Exscientia Ltd. and GT Apeiron Therapeutics Ltd. focused on developing novel cyclin- dependent kinase, or CDK, inhibitors, including selective CDK7 inhibitors. SY- 5609 may face competition from these CDK7 inhibitors. There is also significant competition from products with mechanisms other than CDK7 inhibition in pancreatic cancer and BRAF- mutant colorectal cancer, the disease areas where we are currently focusing our development of SY- 5609~~ . Our competitors may succeed in developing, acquiring or licensing technologies and products that are more effective, have fewer side effects or

more tolerable side effects, have greater ease of access, or are less costly than any product candidates that we are currently developing or that we may develop, which could render our product candidates obsolete and noncompetitive. ~~Our competitors may develop and commercialize products that are safer or more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we, or any collaborators, may develop.~~ For example, the evolving standard of care for the treatment of patients with AML and the response rates and duration of response seen with approved and investigational agents in this disease may result in a longer and more complex clinical development path for tamibarotene, which in turn will impact the potential return on investments in clinical trials of tamibarotene. Our competitors also may obtain FDA or other marketing approval for their products before we, or any collaborators, are able to obtain approval for ours, which could result in our competitors establishing a strong market position before we, or any collaborators, are able to enter the market. Many of our existing and potential future competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining marketing approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early- stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, the development of our product candidates. Even if we, or any collaborators, are able to commercialize any product candidate that we, or they, develop, the product may become subject to unfavorable pricing regulations, third- party payor reimbursement practices or healthcare reform initiatives, any of which could harm our business. The commercial success of **tamibarotene** ~~our~~ **or any future** product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of ~~our~~ **such** product candidates will be paid by third- party payors, including government health care programs and private health insurers. If coverage is not available, or reimbursement is limited, we, or any collaborators, may not be able to successfully commercialize ~~our~~ **such** product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us, or any collaborators, to establish or maintain pricing sufficient to realize a sufficient return on our or their investments. In the United States, no uniform policy of coverage and reimbursement for products exists among third- party payors and 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 and clinical 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. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we, or any collaborators, 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. Adverse pricing limitations may hinder our ability or the ability of any collaborators to recoup our or their investment in ~~one~~ **tamibarotene** or ~~more~~ **any future** product candidates, even if ~~our~~ **such** product candidates obtain marketing approval. 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 collaborators, to successfully commercialize **tamibarotene or** any **future** ~~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. Third- party payors decide which medications they will cover and establish reimbursement levels. The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. Government authorities and other third- party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability or that of any collaborators to sell our product candidates profitably. These payors may not view our products, if any, as cost- effective, and coverage and reimbursement may not be available to our customers, or those of any collaborators, or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost- control initiatives could cause us, or any collaborators, to decrease the price we, or they, might establish for products, which could result in lower than anticipated product revenues. If the prices for our products, if any, decrease or if governmental and other third- party payors do not provide coverage or adequate reimbursement, our prospects for revenue and profitability will suffer. There may also be delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Reimbursement rates may vary, by way of example, according to the use of the product and the clinical setting in which it is used. Reimbursement rates may also be based on reimbursement levels already set for lower cost drugs or may be incorporated into existing payments for other services. In addition, increasingly, third- party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government- funded and private payors for **tamibarotene or** any **future** ~~of our~~ product candidates for which we, or any collaborator, obtain marketing approval could significantly harm our operating results, our ability to raise capital needed to commercialize products and our overall financial condition. Product liability

lawsuits against us could divert our resources, cause us to incur substantial liabilities and limit commercialization of any products that we may develop. We ~~will~~ face an inherent risk of product liability claims as a result of the clinical testing of ~~our~~ **tamibarotene and any future** product candidates **,** despite obtaining appropriate informed consents from our clinical trial participants. We will face an even greater risk if we or any collaborators commercially sell any product that we may or they may develop. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of **tamibarotene** ~~our~~ **or any future** product candidates. Regardless of the merits or eventual outcome, liability claims may result in, among other consequences, decreased demand for ~~our~~ **such** product candidates or products that we may develop, injury to our reputation and significant negative media attention, withdrawal of clinical trial participants, significant costs to defend resulting litigation, substantial monetary awards to trial participants or patients, loss of revenue, reduced resources of our management to pursue our business strategy, and the inability to commercialize any products that we may develop. Although we maintain clinical trial liability insurance coverage in the amount of up to $ 10. 0 million in the aggregate, this insurance may not fully cover potential liabilities that we may incur. The cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial. We will need to increase our insurance coverage if and when we commercialize any product that receives marketing approval. In addition, insurance coverage is becoming increasingly expensive. If we are unable to obtain or maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of **tamibarotene** ~~our~~ **or any future** product candidates, which could harm our business, financial condition, results of operations and prospects. If the FDA or comparable foreign regulatory authorities approve generic versions of any of our products that receive marketing approval, or such authorities do not grant our products appropriate periods of data exclusivity before approving generic versions of our products, the sales of our products could be adversely affected. Once an NDA is approved, the product covered thereby becomes a" reference- listed drug" in the FDA' s publication," Approved Drug Products with Therapeutic Equivalence Evaluations," or the Orange Book. Manufacturers may seek approval of generic versions of reference- listed drugs through submission of abbreviated new drug applications, or ANDAs, in the United States. In support of an ANDA, a generic manufacturer need not conduct clinical trials. Rather, the applicant generally must show that its product has the same active ingredient (s), dosage form, strength, route of administration and conditions of use or labeling as the reference- listed drug and that the generic version is bioequivalent to the reference- listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the reference- listed drug and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference- listed drug may be typically lost to the generic product. The FDA may not approve an ANDA for a generic product until any applicable period of non- patent exclusivity for the reference- listed drug has expired. The FDCA provides a period of five years of non- patent exclusivity for a new drug containing a new chemical entity, or NCE. Specifically, in cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the reference- listed drug is either invalid or will not be infringed by the generic product, in which case the applicant may submit its application four years following approval of the reference- listed drug. Because the composition of matter patent for tamibarotene has expired and our license rights to tamibarotene from TMRC are limited to human cancer indications, it is possible that another applicant could obtain approval for a similar product from the FDA before us, in which case our NDA for tamibarotene would not be eligible for NCE exclusivity. See" — Risks Related to Our Intellectual Property — We do not have composition of matter patent protection with respect to tamibarotene or the active pharmaceutical ingredient of SY- 2101." If any product we develop does not receive five years of NCE exclusivity, the FDA may approve generic versions of such product three years after its date of approval, subject to the requirement that the ANDA applicant certifies to any patents listed for our products in the Orange Book. Manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if we still have patent protection for our product. Competition that our products may face from generic versions of our products could negatively impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on our investments in those product candidates. Risks Related to Our Dependence on Third Parties We rely on third parties to conduct our clinical trials and certain aspects of our research ~~and preclinical testing~~, and those third parties may not perform satisfactorily, including by failing to meet deadlines for the completion of such trials ~~,~~ **or** research ~~or testing~~. We currently rely and expect to continue to rely on third parties such as consultants, clinical investigators, CROs, clinical data management organizations, medical institutions and other similar entities, to complete certain aspects of our ~~preclinical testing and~~ clinical trials and provide services in connection with such clinical trials. Any third parties on which we currently rely or may in the future rely may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it could delay our product development activities. We additionally rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of **tamibarotene** ~~our~~ **or any future** product candidates or commercialization of our medicines, producing additional losses and depriving us of potential product revenue. Our reliance on these third parties for research and development activities will reduce our control over these activities, but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as good clinical practices, for conducting, recording and reporting the results of clinical trials to

assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government- sponsored database, ClinicalTrials. gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions. Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for **tamibarotene** ~~our~~ **or any future** product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our medicines. We currently depend on third- party manufacturers to produce our ~~preclinical and~~ clinical drug supplies and we intend to rely upon third- party manufacturers to produce commercial supplies of any approved product candidates. We do not have any manufacturing facilities. We currently rely, and expect to continue to rely, on third- party manufacturers for the manufacture of ~~our~~ **tamibarotene and any future** product candidates for ~~preclinical and~~ clinical testing and for commercial supply of any of ~~these~~ **such** product candidates for which we or our collaborators obtain marketing approval. We have engaged, and expect to continue engaging, third- party suppliers and manufacturers in China and India. Natural disasters such as earthquakes, tsunamis, power shortages or outages, floods or monsoons, public health crises such as ~~the~~ COVID- 19 ~~pandemic~~ or other pandemics or epidemics, political crises such as terrorism, war, political insecurity or other conflict, or other events outside of our control could adversely affect the ability of these third parties to perform their obligations as expected. We also do not currently have a long- term supply agreement with any third- party manufacturers. We may be unable to establish any agreements with third- party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third- party manufacturers, we face risks such as the possible breach of the agreement by the third party or termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient to us. We also face risks associated with reliance on third parties for regulatory compliance, quality assurance, and safety and pharmacovigilance reporting. Third- party manufacturers may not be able to comply with current good manufacturing practices, or cGMP, regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third- party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or medicines, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our medicines and harm our business and results of operations. Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply of bulk drug substance or drug product. If any one of our current contract manufacturers cannot perform as agreed, we may be required to replace that manufacturer. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement. We currently depend on a third- party manufacturer to develop and validate the clinical trial assay being used to select patients with our proprietary RARA biomarker, and if this assay does not perform as designed, our clinical trials of tamibarotene may be adversely affected. We are currently conducting SELECT- MDS- 1, a Phase 3 clinical trial evaluating tamibarotene in combination with azacitidine in HR- MDS patients who have been prospectively selected using our proprietary RARA biomarker, and SELECT- AML- 1, a randomized Phase 2 clinical trial evaluating tamibarotene in combination with venetoclax and azacitidine in newly diagnosed patients with AML who are positive for RARA overexpression and are not suitable candidates for standard intensive chemotherapy. We collaborate with a third party with respect to the clinical trial assay being used to select patients with the RARA biomarker for inclusion in these trials. The FDA has approved an investigational device exemption for the assay being used to select patients with the RARA biomarker, and we used this assay in our earlier Phase 2 trial evaluating the safety and efficacy of tamibarotene in certain AML and MDS patient populations. Based on data from over 175 patients screened in our clinical trials, we believe approximately 50 % of MDS patients and approximately 30 % of AML patients are positive for RARA overexpression. Our ability to continue to prospectively select patients who overexpress RARA for SELECT- MDS- 1 and SELECT- AML- 1 depends on the ability of this clinical trial assay to identify suitable patients for these clinical trials. If this assay does not perform as designed, it could adversely affect our estimated timelines to enroll patients, or adversely impact the results of these trials, which could significantly harm our business and commercial prospects. **Failure of Qiagen to successfully develop or commercialize a companion diagnostic test for use with tamibarotene to identify patients with RARA overexpression could harm our ability to commercialize tamibarotene. We do not plan to internally develop a commercial companion diagnostic test to identify patients with RARA overexpression and, as a result, we will be dependent on the efforts of Qiagen to successfully develop and commercialize this test. Qiagen may not perform its obligations as expected or as required under our agreement with Qiagen, may encounter production difficulties that could constrain the supply of the companion diagnostic test, may have difficulties gaining acceptance of the use of the companion diagnostic test in the clinical community, may not pursue commercialization of the companion diagnostic test even if they receive any required regulatory approvals, may elect not to continue the development of the companion diagnostic test based on changes in its strategic focus or available funding, or external factors such as an acquisition, that divert resources or create competing priorities, may not commit sufficient resources to the marketing and distribution of the companion diagnostic test, and may terminate their relationship with us. If the companion diagnostic test that is developed for use with tamibarotene fails to gain market acceptance, our ability to derive revenues from sales from tamibarotene would be harmed. If Qiagen or any other third parties we engage fail to commercialize the companion diagnostic test, we may not be able to enter into arrangements with another diagnostic company to obtain supplies of an alternative test for use with tamibarotene or do so on commercially reasonable terms, which could adversely affect and / or delay commercial launch and cause us to fail to realize the full commercial potential of tamibarotene.** To the extent that we enter into collaborations with third parties

for the development and commercialization of any product candidates, our prospects with respect to those product candidates will depend in significant part on the success of those collaborations. We expect to enter into collaborations for the development and commercialization of one or more product candidates we may develop ~~, as we have with GBT to develop novel therapies for sickle cell disease and beta thalassemia and with Incyte to identify new drug targets in the field of myeloproliferative neoplasms~~ . To the extent we enter into such collaborations, we will have limited control over the amount and timing of resources that our collaborators will dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on any collaborators' abilities to successfully perform the functions assigned to them in these arrangements. In addition, collaborators may have the right to abandon research or development projects and terminate applicable agreements, including funding obligations, prior to or upon the expiration of the agreed upon terms. Collaborations involving our product candidates pose a number of risks, including the following: • collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations; • collaborators may not perform their obligations as expected; • collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs, based on clinical trial results, changes in the collaborators' strategic focus or available funding or external factors, such as an acquisition, that divert resources or create competing priorities; • collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing; • collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates; • a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products; • disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time consuming and expensive; • collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation; • collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; • ~~our~~ collaboration agreements **may** ~~with GBT and Incyte~~ contain ~~, and any collaboration agreement that we enter into in the future may contain,~~ restrictions on our ability to enter into potential collaborations, to conduct research or development in certain fields, or to otherwise develop specified product candidates; • there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential collaborators; and • collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates. Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If any collaborator of ours is involved in a business combination, it could decide to delay, diminish or terminate the development or commercialization of any product candidate licensed to it by us. We are currently seeking, and we expect to continue to seek ~~,~~ to establish additional collaborations and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans. **If** ~~We are currently seeking, and we expect to continue to seek, to establish one or more additional collaborators for the development and commercialization of one or more of our product candidates or to validate targets. For example, we are seeking partnership opportunities for our SY- 5609 clinical program and for our oncology discovery programs. Likely collaborators may include large and mid- size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. In addition, if~~ we are able to obtain marketing approval for **tamibarotene or any future** product candidates from foreign regulatory authorities, we intend to enter into strategic relationships with international biotechnology or pharmaceutical companies for the commercialization of such product candidates outside of the United States. **In addition, we may seek to establish one or more additional collaborators for the development and commercialization of any future product candidates. Likely collaborators may include large and mid- size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies.** We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator' s resources and expertise, the terms and conditions of the proposed collaboration, and the proposed collaborator' s evaluation of a number of factors. Those factors may include the potential differentiation of our product candidates from competing product candidates, design or results of clinical trials, the likelihood of approval by the FDA or comparable foreign regulatory authorities and the regulatory pathway for any such approval, the potential market for the product candidate, the costs and complexities of manufacturing and delivering the product to patients and the potential of competing products. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available for collaboration and whether such a collaboration could be more attractive than the one with us for our product candidate. We may not be able to negotiate new collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate ~~, such as SY-5609 or our oncology discovery programs~~ , reduce or delay our development program or one or more of our other development programs, delay our potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we fail to comply with our obligations under our existing and any future intellectual property licenses with third parties, we could lose license rights that are important to our business. We are party to several license agreements under which we license patent rights and other intellectual property related to our business, including the TMRC license agreement, pursuant to which we were granted a license under specified patent rights, data, regulatory filings and other intellectual property primarily for the North American

and European development and commercialization of tamibarotene for the treatment of human cancer indications. We may enter into additional license agreements in the future. Our license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with our obligations under these licenses, our licensors may have the right to terminate these license agreements, in which event we might not be able to market any product that is covered by these agreements, or our licensors may convert the license to a non-exclusive license, which could adversely affect the value of the product candidate being developed under the license agreement. Termination of these license agreements or reduction or elimination of our licensed rights may also result in our having to negotiate new or reinstated licenses with less favorable terms. We own certain patents and patent applications with claims directed to specific methods of using tamibarotene and we expect to have marketing exclusivity from the FDA and EMA for a period of no less than five and ten years, respectively, because tamibarotene has not been approved in these markets. Composition of matter patent protection in the United States and elsewhere covering tamibarotene has expired, however. In addition, **we may in the future pursue further development of SY- 2101, and** we do not have composition of matter patent protection for arsenic trioxide, the active pharmaceutical ingredient of SY- 2101. We may be limited in our ability to list our method patents in the FDA' s Orange Book if the use of our products, consistent with its FDA- approved label, would not fall within the scope of our patent claims. Also, our competitors may be able to offer and sell products so long as these competitors do not infringe any other patents that we (or third parties) hold, including patents with claims directed to the manufacture of tamibarotene and / or method of use patents, or to the formulation of SY- 2101 drug product and / or methods of manufacture of SY- 2101. In general, method of use patents are more difficult to enforce than composition of matter patents because, for example, of the risks that the FDA may approve alternative uses of the subject compounds not covered by the method of use, formulation or manufacturing method patents, and others may engage in off- label sale or use of the subject compounds. Physicians are permitted to prescribe an approved product for uses that are not described in the product' s labeling. Although off- label prescriptions may infringe our method of use patents, the practice is common across medical specialties and such infringement is difficult to prevent or prosecute. FDA approval of uses of a generic version of tamibarotene or SY- 2101 that are not covered by our patents would limit our ability to generate revenue from the sale of such ~~product~~ **products** ~~candidates~~, if approved for commercial sale. In addition, any off- label use of a generic version of tamibarotene would limit our ability to generate revenue from the sale of tamibarotene, if approved for commercial sale. Our intellectual property licenses with third parties may be subject to disagreements over contract interpretations, which could narrow the scope of our rights to the relevant intellectual property or technology or increase our financial or other obligations to our licensors. The agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could harm our business, financial condition, results of operations and prospects. We may not be successful in obtaining or maintaining necessary rights to current or future product candidates through acquisitions and in- licenses. We currently have rights to certain intellectual property, through ownership or licenses from third parties, to develop and commercialize tamibarotene for human cancers in North and South America and Europe, Israel, Russia and Australia, and for SY- 2101 and SY- 5609 for all potential uses in North America and major markets in Europe and elsewhere. Because our programs may require the use of proprietary rights by third parties, the growth of our business likely will depend, in part, on our ability to acquire, in- license or use these proprietary rights. We may be unable to acquire or in- license from third parties any intellectual property rights directed to compositions, methods of use, or processes that we identify as necessary for any product candidates. The licensing or acquisition of third- party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third- party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third- party intellectual property rights on terms that would allow us to make an appropriate return on our investment. ~~We sometimes collaborate with non- profit and academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution' s rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us or we may decide not to execute such option if we believe such license is not necessary to pursue our program. If we are unable or opt not to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.~~ If we are unable to successfully obtain rights to required third- party intellectual property rights or maintain the existing intellectual property rights we have, we may be required to expend significant time and resources to redesign **tamibarotene** ~~our~~ **or any future** product candidates or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected product candidate, which could harm our business significantly. We depend upon our license with TMRC, and we may not be able to maintain that license. We have entered into a standby license with TMRC and Toko Pharmaceuticals Ind. Co. Ltd., or Toko, providing that if at any time the license agreement between Toko and TMRC relating to the tamibarotene rights that TMRC has licensed to us terminates or otherwise ceases to be in effect for any reason, Toko will grant directly to us such rights and licenses with respect to tamibarotene as are necessary for us to continue to develop tamibarotene. If the TMRC license agreement terminates and this standby license terminates, then we may lose rights to tamibarotene that may be necessary to the development and commercialization of tamibarotene, which could have a material adverse impact on our business. If we are unable to obtain and maintain sufficient patent protection for **tamibarotene or** any

future product candidates, or if the scope of the patent protection is not sufficiently broad, our competitors could develop and commercialize products similar or identical to ours, and our ability to successfully commercialize ~~our~~ **such** product candidates may be adversely affected. Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to ~~our~~ **tamibarotene and any future** proprietary product candidates. If we do not adequately protect our intellectual property, our competitors may be able to erode or negate any competitive advantage we may have, which could harm our business and ability to achieve profitability. To protect our proprietary position, we file patent applications in the United States and abroad related to ~~our novel~~ **tamibarotene and other potential** product candidates that are important to our business. We also license or purchase patent applications filed by others. The patent application and approval processes are expensive and time consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. Agreements through which we license patent rights may not give us control over patent prosecution or maintenance, so that we may not be able to control which claims or arguments are presented and may not be able to secure, maintain, or successfully enforce necessary or desirable patent protection from those patent rights. We have not had and do not have primary control over patent prosecution and maintenance for certain of the patents and patent applications we license, and therefore cannot guarantee that these patents and applications will be prosecuted in a manner consistent with the best interests of our business. We cannot be certain that patent prosecution and maintenance activities by our licensors have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents. We, or any partners, collaborators or licensees, may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection for them. Therefore, we may miss potential opportunities to strengthen our patent position. It is possible that defects of form in the preparation or filing of our patents or patent applications may exist, or may arise in the future, for example with respect to proper priority claims, inventorship, claim scope or patent term adjustments. If we or our partners, collaborators, licensees, or licensors, whether current or future, fail to establish, maintain or protect such patents and other intellectual property rights, such rights may be reduced or eliminated. If our partners, collaborators, licensees or licensors, are not fully cooperative or disagree with us as to the prosecution, maintenance or enforcement of any patent rights, such patent rights could be compromised. If there are material defects in the form, preparation, prosecution, or enforcement of our patents or patent applications, such patents may be invalid and / or unenforceable, and such applications may never result in valid, enforceable patents. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business. The patent position of biotechnology and pharmaceutical companies generally is highly uncertain. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the United States or in many foreign jurisdictions. In addition, the determination of patent rights with respect to pharmaceutical compounds commonly involves complex legal and factual questions, which has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent except that, prior to March 16, 2013 in the United States, the first to invent was entitled to the patent. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases, not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. Similarly, we cannot be certain that parties from whom we do or may license or purchase patent rights were the first to make relevant claimed inventions, or were the first to file for patent protection for them. If third parties have filed patent applications on inventions claimed in our patents or applications on or before March 15, 2013, an interference proceeding in the United States can be initiated by such third parties to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. If third parties have filed such applications after March 15, 2013, a derivation proceeding in the United States can be initiated by such third parties to determine whether our invention was derived from theirs. Moreover, because the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, our patents or pending patent applications may be challenged in the courts or patent offices in the United States and abroad. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found. If such prior art exists, it may be used to invalidate a patent, or may prevent a patent from issuing from a pending patent application. For example, such patent filings may be subject to a third-party pre- issuance submission of prior art to the USPTO or to other patent offices around the world. Alternately or additionally, we may become involved in post- grant review procedures, oppositions, derivations, proceedings, reexaminations, inter partes review or interference proceedings, in the United States or elsewhere, challenging patents or patent applications in which we have rights, including patents on which we rely to protect our business. An adverse determination in any such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. Pending and future patent applications may not result in patents being issued which protect our business, in whole or in part, or which effectively prevent others from commercializing competitive products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, the laws of foreign countries may not protect our rights to the same extent or in the same manner as the laws of the United States. Issued patents that we have or may obtain or license may not provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us

with any competitive advantage. Our competitors may be able to circumvent our patents by developing similar or alternative technologies or products in a non- infringing manner. Our competitors may also seek approval to market their own products similar to or otherwise competitive with our products. Alternatively, our competitors may seek to market generic versions of any approved products by submitting ANDAs to the FDA in which they claim that patents owned or licensed by us are invalid, unenforceable or not infringed. In these circumstances, we may need to defend or assert our patents, or both, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid or unenforceable, or that our competitors are competing in a non- infringing manner. Thus, even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives. Pursuant to the terms of some of our license agreements with third parties, some of our third-party licensors have the right, but not the obligation, in certain circumstances to control enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents. Even if we are permitted to pursue such enforcement or defense, we will require the cooperation of our licensors, and cannot guarantee that we would receive it and on what terms. We cannot be certain that our licensors will allocate sufficient resources or prioritize their or our enforcement of such patents or defense of such claims to protect our interests in the licensed patents. If we cannot obtain patent protection, or enforce existing or future patents against third parties, our competitive position and our financial condition could suffer. If we are unable to protect the confidentiality of our trade secrets, the value of our technology could be materially adversely affected and our business would be harmed. In addition to the protection afforded by patents, we may also rely on trade secret protection. We seek to protect these trade secrets, in part, by entering into non- disclosure and confidentiality agreements with parties who have access to them, such as our employees, consultants, independent contractors, advisors, contract manufacturers, suppliers and other third parties. We also enter into confidentiality and invention or patent assignment agreements with employees and certain consultants. Any party with whom we have executed such an agreement may breach that agreement and disclose our proprietary information, including any information we hold in confidence or as a trade secret, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated confidential information or a trade secret is difficult, expensive and time consuming, and the outcome is unpredictable. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret. Further, if any of our confidential information or trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent such third party, or those to whom they communicate such technology or information, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our business and competitive position could be harmed. We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful. Competitors may infringe our patents, trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both. In any patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent' s claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving one or more of our patents could limit our ability to assert those patents against those parties or other competitors and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks. Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could adversely affect the price of shares of our common stock. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings. If we are sued for infringing intellectual property rights of third parties, such litigation could be costly and time consuming and could prevent or delay us from developing or commercializing **tamibarotene** ~~our~~ **or any future** product candidates. Our commercial success depends, in part, on our ability to develop, manufacture, market and sell ~~our~~ **tamibarotene and any future** product candidates without infringing the intellectual property and other proprietary rights of third parties. Third parties may have U. S. and non-U. S. issued patents and pending patent applications relating to compounds and methods of use for the treatment of the disease indications for which we are developing ~~our~~ **tamibarotene and any future** product candidates. If any third- party patents or patent applications are found to cover ~~our~~ **such** product candidates or their methods of use, we may not be free to manufacture or market ~~our~~ **such** product candidates as planned without obtaining a license, which may not be available on commercially reasonable terms, or at all. There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, litigation or other adversarial proceedings regarding

intellectual property rights with respect to **tamibarotene** ~~our~~ **or any future** product candidates, including interference proceedings before the USPTO. There may be third- party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of ~~our~~ **such** product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that ~~our~~ **such** product candidates may be accused of infringing. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Accordingly, third parties may assert infringement claims against us based on existing or future intellectual property rights. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The pharmaceutical and biotechnology industries have produced a significant number of patents, and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of use. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we were sued for patent infringement, we would need to demonstrate that ~~our~~ **such** product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Proving invalidity is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could significantly harm our business and operating results. In addition, we may not have sufficient resources to bring these actions to a successful conclusion. If we are found to infringe a third party' s intellectual property rights, we could be forced, including by court order, to cease developing, manufacturing or commercializing the infringing product candidate or product. Alternatively, we may be required to obtain a license from such third party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing product candidate or product. It is possible, however, that we would be unable to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non- exclusive, thereby giving our competitors access to the same technologies licensed to us. Alternatively, or additionally, it could include terms that impede or destroy our ability to compete successfully in the commercial marketplace. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing **tamibarotene** ~~our~~ **or any future** product candidates or force us to cease some of our business operations, which could harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business. Changes to the patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products. As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Patent reform legislation in the United States, including the Leahy- Smith America Invents Act, or the America Invents Act, could increase those uncertainties and costs. The America Invents Act was signed into law on September 16, 2011, and many of the substantive changes became effective on March 16, 2013. The America Invents Act reforms United States patent law in part by changing the U. S. patent system from a" first to invent" system to a" first inventor to file" system, expanding the definition of prior art, and developing a post- grant review system. This legislation changes United States patent law in a way that may weaken our ability to obtain patent protection in the United States for those applications filed after March 16, 2013. Further, the America Invents Act created new procedures to challenge the validity of issued patents in the United States, including post- grant review and inter partes review proceedings, which some third parties have been using to cause the cancellation of selected or all claims of issued patents of competitors. For a patent with an effective filing date of March 16, 2013 or later, a petition for post- grant review can be filed by a third party in a nine- month window from issuance of the patent. A petition for inter partes review can be filed immediately following the issuance of a patent if the patent has an effective filing date prior to March 16, 2013. A petition for inter partes review can be filed after the nine- month period for filing a post- grant review petition has expired for a patent with an effective filing date of March 16, 2013 or later. Post- grant review proceedings can be brought on any ground of invalidity, whereas inter partes review proceedings can only raise an invalidity challenge based on published prior art and patents. These adversarial actions at the USPTO review patent claims without the presumption of validity afforded to U. S. patents in lawsuits in U. S. federal courts and use a lower burden of proof than used in litigation in U. S. federal courts. Therefore, it is generally considered easier for a competitor or third party to have a U. S. patent invalidated in a USPTO post- grant review or inter partes review proceeding than invalidated in a litigation in a U. S. federal court. If any of our patents are challenged by a third party in such a USPTO proceeding, there is no guarantee that we or our licensors or collaborators will be successful in defending the patent, which would result in a loss of the challenged patent right to us. In addition, the USPTO continues to modify its guidelines regarding subject matter eligibility, a process that began with decisions rendered in Association for Molecular Pathology v. Myriad Genetics, Inc.; BRCA1- & BRCA2- Based Hereditary Cancer Test Patent Litigation; and Promega Corp. v. Life Technologies Corp. Those court decisions have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents once obtained. Depending on future actions by the U. S. Congress, the U. S. courts, the USPTO and the relevant law- making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. We may not be able to enforce our intellectual property rights throughout the world. Filing, prosecuting and defending patents on **tamibarotene** ~~our~~ **or any future** product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be

less extensive than those in the United States. The requirements for patentability may differ in certain countries, particularly in developing countries; thus, even in countries where we do pursue patent protection, there can be no assurance that any patents will issue with claims that cover our products. Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. Additionally, laws of some countries outside of the United States and Europe do not afford intellectual property protection to the same extent as the laws of the United States and Europe. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, including India, China and other countries, do not favor the enforcement of patents and other intellectual property rights. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our inventions in certain countries outside the United States and Europe. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop and market their own products and, further, may export otherwise infringing products to territories where we have patent protection, if our ability to enforce our patents to stop infringing activities is inadequate. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. Further, a decree was adopted by the Russian government in March 2022 allowing Russian companies and individuals to exploit inventions owned by patent holders from the United States without consent or compensation. Consequently, we would not be able to prevent third parties from practicing our inventions in Russia or from selling or importing products made using our inventions in and into Russia. Agreements through which we license patent rights may not give us sufficient rights to permit us to pursue enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents (or control of enforcement or defense) of such patent rights in all relevant jurisdictions as requirements may vary. Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business. Moreover, such proceedings could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Furthermore, while we intend to protect our intellectual property rights in major markets for our products, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our products. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate. Patent terms may be inadequate to protect our competitive position on our products for an adequate amount of time. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. We expect to seek extensions of patent terms in the United States and, if available, in other countries where we are prosecuting patents. In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984 permits a patent term extension of up to five years beyond the normal expiration of the patent, which is limited to the approved indication (or any additional indications approved during the period of extension). The applicable authorities, including the FDA and the USPTO in the United States, and any equivalent regulatory authority in other countries, may not agree, however, with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case. We may be subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property or claiming ownership of what we regard as our own intellectual property. Many of our employees and our licensors' employees, including our senior management, were previously employed at universities or at other biotechnology or pharmaceutical companies, some of which may be competitors or potential competitors. Some of these employees, including each member of our senior management, executed proprietary rights, non- disclosure and non- competition agreements, or similar agreements, in connection with such previous employment. Although we try to ensure that our employees do not use the proprietary information or know- how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such third party. Litigation may be necessary to defend against such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel or sustain damages. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products. Such a license may not be available on commercially reasonable terms or at all. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management. In addition, while we typically require our employees, consultants, contractors and vendors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own, which may result in claims by or against us related to the ownership of such intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our senior management and scientific personnel. Obtaining and maintaining patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non- compliance with these requirements. Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and applications are required to be paid to the USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and applications. The USPTO and various non- U. S. governmental patent agencies require compliance with a

number of procedural, documentary, fee payment and other similar provisions during the patent application process and after a patent has issued. There are situations in which non- compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Risks Related to Regulatory Approval and Marketing of ~~Our~~ **Tamibarotene or Any Future** Product Candidates and Other Legal Compliance Matters Even if we complete the necessary ~~preclinical studies and~~ clinical trials, the regulatory approval process is expensive, time consuming and uncertain and may prevent us or any collaborators from obtaining approvals for the commercialization of **tamibarotene** ~~some or all of our~~ **or any future** product candidates. As a result, we cannot predict when or if, and in which territories, we, or any collaborators, will obtain marketing approval to commercialize a product candidate. The research, testing, manufacturing, labeling, approval, selling, marketing, promotion and distribution of products are subject to extensive regulation by the FDA and comparable foreign regulatory authorities. We, and any collaborators, are not permitted to market ~~our~~ **any** product candidates in the United States or in other countries until we, or they, receive approval of an NDA from the FDA or marketing approval from applicable regulatory authorities outside the United States. ~~Our~~ **Tamibarotene and any future** product candidates ~~are in various stages of development and~~ are subject to the risks of failure inherent in drug development. We have not submitted an application for or received marketing approval for any ~~of our~~ product candidates in the United States or in any other jurisdiction. We have limited experience in conducting and managing the clinical trials necessary to obtain marketing approvals, including FDA approval of an NDA. The process of obtaining marketing approvals, both in the United States and abroad, is lengthy, expensive and uncertain. It may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information, including manufacturing information, to regulatory authorities for each therapeutic indication to establish the product candidate' s safety and efficacy. The FDA or other regulatory authorities may determine that **tamibarotene** ~~our~~ **or any future** product candidates are not safe and effective, only moderately effective or have undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use. Moreover, the FDA or other regulatory authorities may fail to approve the **commercial companion diagnostic that Qiagen is developing to identify patients with RARA overexpression or any other** companion diagnostics **that** we ~~contemplate~~ **may** ~~developing~~ **develop** with partners **in the future** . Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable. In addition, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we, or any collaborators, ultimately obtain may be limited or subject to restrictions or post- approval commitments that render the approved product not commercially viable. Any delay in obtaining or failure to obtain required approvals could negatively affect our ability or that of any collaborators to generate revenue from ~~the particular~~ **tamibarotene or any future** product candidate, which likely would result in significant harm to our financial position and adversely impact our stock price. If we are required by the FDA..... or commercialization of our product candidates. Failure to obtain marketing approval in foreign jurisdictions would prevent **tamibarotene** ~~our~~ **or any future** product candidates from being marketed abroad. Any approval we are granted for ~~our~~ **a** product ~~candidates~~ **candidate** in the United States would not assure approval of ~~our~~ **that** product ~~candidates~~ **candidate** in foreign jurisdictions. In order to market and sell our products in the European Union and other foreign jurisdictions, we, and any collaborators, must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The marketing approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, a product must be approved for reimbursement before the product can be approved for sale in that country. We, and any collaborators, may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may file for marketing approvals but not receive necessary approvals to commercialize our products in any market. In many countries outside the United States, a product candidate must also be approved for reimbursement before it can be sold in that country. In some cases, the price that we intend to charge for our products, if approved, is also subject to approval. Obtaining non- U. S. regulatory approvals and compliance with non- U. S. regulatory requirements could result in significant delays, difficulties and costs for us and any collaborators and could delay or prevent the introduction of **tamibarotene** ~~our~~ **or any future** product candidates in certain countries. In addition, if we or any collaborators fail to obtain the non- U. S. approvals required to market ~~our~~ **such** product candidates outside the United States or if we or any collaborators fail to comply with applicable non- U. S. regulatory requirements, our target market will be reduced and our ability to realize the full market potential of ~~our~~ **such** product candidates will be harmed and our business, financial condition, results of operations and prospects may be adversely affected. ~~Additionally~~ **Further** , we could face heightened risks with respect to ~~seeking~~ **obtaining** marketing ~~approval~~ **authorization** in the ~~United Kingdom~~ **U. K.** as a result of the ~~recent~~ withdrawal of the ~~United Kingdom~~ **U. K.** from the **EU** ~~European Union~~ , commonly referred to as Brexit. **The U. K.** ~~Effective January 1, 2021, the United Kingdom~~ is no longer part of the European Single Market and **EU** ~~European Union~~ Customs Union. As of January 1, 2021, the Medicines and Healthcare ~~Products~~ **products** Regulatory Agency, or ~~the~~ MHRA, became responsible for supervising medicines and medical devices in Great Britain, comprising

England, Scotland and Wales under domestic law, whereas ~~Northern Ireland will continue to be subject to European Union rules~~ under **the terms of** the Northern Ireland Protocol **, Northern Ireland is currently subject to EU rules** . The ~~MHRA will rely on~~ **U. K. and EU have however agreed to** the **Windsor Framework which fundamentally changes** ~~Human Medicines Regulations 2012 (SI 2012 / 1916) (as amended), or~~ the ~~HMR, as~~ **existing system under** the ~~basis for~~ **Northern Ireland Protocol, including with respect to the** ~~regulating~~ **regulation** ~~medicines. The HMR has been incorporated into the domestic law~~ of ~~the body of European Union law instruments governing~~ medicinal products ~~that pre- existed prior to~~ **in the U. K. Once implemented, the changes introduced by the Windsor Framework will see the MHRA be responsible for approving all medicinal products destined for the U. K. market (i. e., Great Britain and Northern Ireland), and the EMA will no longer have any role in approving medicinal products destined for Northern Ireland. In addition, foreign regulatory authorities may change** ~~the~~ **their** ~~United Kingdom~~ **approval policies and new regulations may be enacted. For instance, the EU pharmaceutical legislation is currently undergoing a complete review process, in the context of the Pharmaceutical Strategy for Europe initiative, launched by the European Commission in November 2020. The European Commission** ~~'s withdrawal from~~ **proposal for revision of several legislative instruments related to medicinal products (potentially reducing the duration of regulatory data protection, revising the eligibility for expedited pathways, etc.) was published on April 26, 2023. The proposed revisions remain to be agreed and adopted by** the European ~~Union~~ **Parliament and European Council and the proposals may therefore be substantially revised before adoption, which is not anticipated before early 2026** . ~~Since~~ **The revisions may however have** a significant ~~proportion of~~ **impact on** the ~~regulatory framework for~~ pharmaceutical **industry** ~~products in the U. K. covering the quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from EU directives and regulations, Brexit may have a material impact upon the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the U. K. For example, the U. K. is no longer covered by the centralized procedures for obtaining EU- wide marketing authorization from the EMA, and a separate marketing authorization will be required to market our product candidates in the U. K. Until December 31, 2023, it is possible for the MHRA to rely on a decision taken by the European Commission on the approval of a new marketing authorization via the centralized procedure. Any delay in obtaining, or an~~ **and** ~~inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may force us to restrict or delay efforts to seek regulatory approval in the United Kingdom for our product candidates, which could significantly and materially harm~~ our business **in the long term** . We expect that we will be subject to additional risks in commercializing any of our product candidates that receive marketing approval outside the United States, including tariffs, trade barriers and regulatory requirements; economic weakness, including inflation, or political instability in particular foreign economies and markets (such as the ongoing conflict between Ukraine and Russia); compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country; and workforce uncertainty in countries where labor unrest is more common than in the United States. We **are conducting and intend to continue conducting certain of our clinical trials globally. However, the FDA and other foreign equivalents may not accept data from such trials, in which case our development plans will be delayed, which could materially harm our business. We are conducting and intend to continue conducting certain of our clinical trials globally. The acceptance by the FDA or other regulatory authorities of study data from clinical trials conducted outside their jurisdiction may be subject to certain conditions or may not be accepted at all. In cases where data from foreign clinical trials are intended to serve as the sole basis for marketing approval in the United States, the FDA will generally not approve the application on the basis of foreign data alone unless (i) the data are applicable to the U. S. population and U. S. medical practice; (ii) the trials were performed by clinical investigators of recognized competence and pursuant to good clinical practices, or GCP, regulations; and (iii) the data may be considered valid without the need for an on- site inspection by the FDA, or if the FDA considers such inspection to be necessary, the FDA is able to validate the data through an on- site inspection or other appropriate means. In addition, even where the foreign study data are not intended to serve as the sole basis for approval, the FDA will not accept the data as support for an application for marketing approval unless the study is well- designed and well- conducted in accordance with GCP requirements and the FDA is able to validate the data from the study through an onsite inspection if deemed necessary. Many foreign regulatory authorities have similar approval requirements. In addition, such foreign trials would be subject to the applicable local laws of the foreign jurisdictions where the trials are conducted. There can be no assurance that the FDA or any comparable foreign regulatory authority will accept data from trials conducted outside of the United States or the applicable jurisdiction. If the FDA or any comparable foreign regulatory authority does not accept such data, it would result in the need for additional trials, which could be costly and time- consuming, and which may result in current or future product candidates that we may develop not receiving approval for commercialization in the applicable jurisdiction. Conducting clinical trials outside the United States also exposes us to additional risks, including risks associated with: • additional foreign regulatory requirements; • foreign exchange fluctuations; • compliance with foreign manufacturing, customs, shipment and storage requirements; • cultural differences in medical practice and clinical research; • diminished protection of intellectual property in some countries; and • interruptions or delays in our trials resulting from geopolitical events, such as war or terrorism. We** , or any collaborators, may not be able to obtain orphan drug designation or orphan drug exclusivity for ~~our~~ **any future** product candidates and, even if we do, that exclusivity may not prevent the FDA or the EMA from approving competing products. Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200, 000 individuals annually in the United States. Generally, a product with orphan drug designation only becomes

entitled to orphan drug exclusivity if it receives the first marketing approval for the indication for which it has such designation, in which case the FDA or the EMA will be precluded from approving another marketing application for the same product for that indication for the applicable exclusivity period. The applicable exclusivity period is seven years in the United States and ten years in Europe. The European exclusivity period can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. We have obtained orphan drug designation for tamibarotene for the treatment of MDS in the United States, and for the treatment of AML in the United States and in Europe. In addition, the EMA has issued a positive opinion on our application for orphan drug designation for tamibarotene for the treatment of MDS in Europe. ~~SY- 2101 has also received orphan drug designation for the treatment of APL in the United States and for the treatment of AML in Europe, and SY- 5609 has received orphan drug designation for the treatment of pancreatic cancer in the United States.~~ In the future, we or any collaborators may seek orphan drug designations for tamibarotene ~~, SY- 2101 or SY- 5609~~ in other indications or territories or for other product candidates and may be unable to obtain such designations. Even if we do secure such designations and orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition. Further, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer, to be more effective or to make a major contribution to patient care. Finally, orphan drug exclusivity may be lost if the FDA or the EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition. The FDA and Congress may further reevaluate the Orphan Drug Act and its regulations and policies. This may be particularly true in light of a decision from the Court of Appeals for the 11th Circuit in September 2021 finding that, for the purpose of determining the scope of exclusivity, the term " same disease or condition " means the designated " rare disease or condition " and could not be interpreted by the Agency to mean the " indication or use. " Although there have been legislative proposals to overrule this decision, they have not been enacted into law. On January 23, 2023, the FDA announced that, in matters beyond the scope of the court' s order, the FDA will continue to apply its existing regulations tying orphan- drug exclusivity to the uses or indications for which the orphan drug was approved. We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted. Any product candidate for which we or our collaborators obtain marketing approval is subject to ongoing regulation and could be subject to restrictions or withdrawal from the market, and we may be subject to substantial penalties if we fail to comply with regulatory requirements, when and if **tamibarotene or** any **future** ~~of our~~ product candidates are approved. Any product candidate for which we or our collaborators obtain marketing approval will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post- marketing information and reports, registration and listing requirements, cGMP requirements relating to quality control and manufacturing, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping. In addition, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for costly post- marketing testing and surveillance to monitor the safety or efficacy of the medicine, including the requirement to implement a risk evaluation and mitigation strategy. Accordingly, if we receive marketing approval for **tamibarotene** ~~one or more of our~~ **or any future** product candidates, we would continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we fail to comply with these requirements, we could have the marketing approvals for our products withdrawn by regulatory authorities and our ability to market any products could be limited, which could adversely affect our ability to achieve or sustain profitability ~~. We and our collaborators must also comply with requirements concerning advertising and promotion for any of our product candidates for which we obtain marketing approval. Promotional communications with respect to prescription products 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 September 2021, the FDA published final regulations which describe the types of evidence that the FDA will consider in determining the intended use of a drug or biologic. Moreover, with passage of the Pre- Approval Information Exchange Act, or PIE Act, in December 2022, sponsors of products that have not been approved may proactively communicate to payors certain information about products in development to help expedite patient access upon product approval. Nonetheless, the FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post- approval marketing and promotion of products to ensure that they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. Violations of the FDCA and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription products may lead to investigations and enforcement actions alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws~~ . Failure to comply with regulatory requirements, may yield various results, including: • restrictions on such products, manufacturers or manufacturing processes; • restrictions on the labeling or marketing of a product; • restrictions on distribution or use of a product; • requirements to conduct post- marketing studies or clinical trials; • warning letters or untitled letters; • withdrawal of the products from the market; • refusal to approve pending applications or supplements to approved applications that we submit; • recall of products; • damage to relationships with collaborators; • unfavorable press coverage and damage to our reputation; • fines, restitution or disgorgement of profits or revenues; • suspension or withdrawal of marketing approvals; • refusal to permit the import or export of our products; • product seizure; • injunctions or the imposition of civil or criminal penalties; and • litigation involving patients using our products. Non- compliance with EU requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly,

failure to comply with the EU' s requirements regarding the protection of personal information can also lead to significant penalties and sanctions. **The FDA, EMA and other regulatory authorities actively enforce the laws and regulations prohibiting the promotion of off- label uses. If tamibarotene or any future product candidates are approved and we are found to have improperly promoted off- label uses of those products, we may become subject to significant liability. The FDA, EMA and other regulatory authorities strictly regulate the promotional claims that may be made about prescription products, such as tamibarotene or any future product candidate, if approved. In particular, a product may not be promoted in the United States for uses that are not approved by the FDA as reflected in the product' s approved labelling, or in other jurisdictions for uses that differ from the labelling or uses approved by the applicable regulatory authorities. While physicians may prescribe products for off- label uses, the FDA, EMA and other regulatory authorities actively enforce laws and regulations that prohibit the promotion of off- label uses by companies, including promotional communications made by companies' sales force with respect to off- label uses that are not consistent with the approved labelling, and a company that is found to have improperly promoted off- label uses may be subject to significant civil, criminal and administrative penalties. 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 communications concerning their products in certain circumstances. For example, in October 2023, the FDA published draft guidance outlining the agency' s non- binding policies governing the distribution of scientific information on unapproved uses to healthcare providers. This draft guidance calls for such communications to be truthful, non-misleading, factual, and unbiased and include all information necessary for healthcare providers to interpret the strengths and weaknesses and validity and utility of the information about the unapproved use. In addition, under some relatively recent guidance from the FDA and the Pre- Approval Information Exchange Act, signed into law as part of the Consolidated Appropriations Act of 2023, companies may also promote information that is consistent with the prescribing information and proactively speak to formulary committee members of payors regarding data for an unapproved drug or unapproved uses of an approved drug. We may engage in these discussions and communicate with healthcare providers, payors and other constituencies in compliance with all applicable laws, regulatory guidance and industry best practices. We will need to carefully navigate the FDA' s various regulations, guidance and policies, along with recently enacted legislation, to ensure compliance with restrictions governing promotion of our products. If we are found to have promoted such off- label uses, we may become subject to significant liability. The U. S. federal government has levied large civil and criminal fines against companies for alleged improper promotion of off- label use and has enjoined several companies from engaging in off- label promotion. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. If we cannot successfully manage the promotion of tamibarotene or any future product candidates, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.** We may seek certain designations for ~~our~~ product candidates, including Breakthrough Therapy and Fast Track designations, but we might not receive such designations, and even if we do, such designations may not lead to a faster development or regulatory review or approval process. We may seek certain designations for ~~one or more of our~~ product candidates that could expedite review and approval by the FDA. A Breakthrough Therapy product is defined as a product that is intended, alone or in combination with one or more other products, to treat a serious condition, and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For products that have been designated as Breakthrough Therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Products designated as Breakthrough Therapies by the FDA may also be eligible for priority review if supported by clinical data at the time the NDA is submitted to the FDA. The FDA may also 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 it demonstrates the potential to address unmet medical needs for such a disease or condition. For example, the FDA has granted Fast Track designation to tamibarotene for the treatment of HR- MDS. 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. Designation as a Breakthrough Therapy or Fast Track is within the discretion of the FDA. Accordingly, even if we believe that **a** ~~one of our~~ product ~~candidates~~ **candidate** meets the criteria for these designations, the FDA may disagree and instead determine not to make such designation. Further, even though we have received Fast Track designation for tamibarotene for the treatment of HR-MDS, and even if we receive Breakthrough Therapy or Fast Track designation for ~~one or more of our other~~ **another** product ~~candidates~~ **candidate** , the receipt of such designations may not result in a faster development or regulatory review or approval process compared to products considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, the FDA may later decide that tamibarotene or one or more of our ~~other~~ **future** product candidates no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. Inadequate funding for the FDA, the SEC and other government agencies, including from government shut downs, or other disruptions to these agencies' operations, could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business. The ability of the FDA to review and approve new products can be affected by a variety of factors,

including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory and policy changes. Average review times at the agency have fluctuated in recent years as a result. Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates to be reviewed and / or approved by necessary government agencies, which would adversely affect our business. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable. ~~Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates to be reviewed and / or approved by necessary government agencies, which would adversely affect our business.~~ For example, over the last several years the U. S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. **During the COVID- 19 pandemic, a number of companies announced receipt of complete response letters due to the FDA' s inability to complete required inspections for their applications. In the event of a similar public health emergency in the future, the FDA may not be able to continue its current pace and review timelines could be extended. Regulatory authorities outside the United States facing similar circumstances may adopt similar restrictions or other policy measures in response to a similar public health emergency and may experience delays in their regulatory activities.** If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations. ~~Separately, in response to the COVID- 19 pandemic in 2020 and 2021, a number of companies announced receipt of complete response letters due to the FDA' s inability to complete required inspections for their applications. As of May 26, 2021, the FDA noted it was continuing to ensure timely reviews of applications for medical products during the ongoing COVID- 19 pandemic in line with its user fee performance goals and conducting mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. However, the FDA may not be able to continue its current pace and review timelines could be extended; therefore, the FDA may be unable to complete such required inspections during the review period. Regulatory authorities outside the U. S. may adopt similar restrictions or other policy measures in response to the COVID- 19 pandemic and may experience delays in their regulatory activities.~~ Current and future legislation may result in more rigorous coverage and reimbursement criteria for product candidates, which could increase the difficulty and cost for us and any collaborators to obtain marketing approval of **tamibarotene** ~~our~~ **or any future** product candidates. In the United States and foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of **tamibarotene** ~~our~~ **or any future** product candidates, restrict or regulate post- approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval. In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the ACA. In addition, other legislative changes have been proposed and adopted since the ACA 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. These changes included aggregate reductions to Medicare payments to providers of up to 2 % per fiscal year which went into effect in April 2013 and will remain in effect through 2031 under the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for **tamibarotene or** any **future** ~~of our~~ product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. **Indeed, under current legislation, the actual reductions in Medicare payments may vary up to 4 %. The Consolidated Appropriations Act, which was signed into law by President Biden in December 2022, made several changes to sequestration of the Medicare program. Section 1001 of the Consolidated Appropriations Act delays the 4 % Statutory Pay- As- You- Go Act of 2010 (PAYGO) sequester for two years, through the end of calendar year 2024. Triggered by enactment of the American Rescue Plan Act of 2021, the 4 % cut to the Medicare program would have taken effect in January 2023. The Consolidated Appropriations Act' s health care offset title includes Section 4163, which extends the 2 % Budget Control Act of 2011 Medicare sequester for six months into fiscal year 2032 and lowers the payment reduction percentages in fiscal years 2030 and 2031.** Since enactment of the ACA, there have been and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act, or TCJA, in 2017, Congress repealed the " individual mandate. " The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. ~~Further~~ **On June 17** ~~on December 14, 2018~~ **2021** ~~a U. S. District Court judge in~~ the ~~Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the ACA are invalid as well. The~~ U. S. Supreme Court ~~heard this case~~ **dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling** on ~~November 10, 2020 and on June 17, 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge~~ the constitutionality of the ACA. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results. The Trump administration also took executive actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals,

healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care, and consider actions that will protect and strengthen that access. Under this Order, federal agencies are directed to re- examine: policies that undermine protections for people with pre- existing conditions, including complications related to COVID- 19; demonstrations and waivers under Medicaid and the ACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the ACA; and policies that reduce affordability of coverage or financial assistance, including for dependents. **Current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any collaborators, may receive for any approved products. If reimbursement of our products is unavailable or limited in scope or amount, our business could be materially harmed. Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition.** The TCJA, as amended by the CARES Act, additionally contains changes in tax law that could adversely affect our business or financial condition. The TCJA contains significant changes to corporate taxation, including a reduction of the corporate tax rate from a top marginal rate of 35 % to a flat rate of 21 %, **and** ~~the limitation of the tax deduction for net interest expense to 30 % of adjusted taxable income (except for certain small businesses),~~ the limitation of the deduction for net operating losses to 80 % of current year taxable income ~~and elimination of net operating loss carrybacks, in each case,~~ for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely **). In addition,** ~~and such net operating losses arising in taxable years~~ beginning **in** ~~before January 1, 2021~~ **2022** ~~are generally eligible~~ **, the TCJA eliminates the option** to ~~be carried back up~~ **deduct research and development expenditures currently and requires corporations** to **capitalize and amortize them over** five years **or 15 years (for expenditures attributable to foreign research**) ~~, one- time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, the elimination of U. S. tax on foreign earnings (subject to certain important exceptions), the allowance of immediate deductions for certain new investments instead of deductions for depreciation expense over time, and the modification or repeal of many business deductions and credits~~ . In addition to the CARES Act, as part of Congress' **s** response to the COVID- 19 pandemic, economic relief legislation **was** ~~has been~~ enacted in 2020 and 2021 containing tax provisions. **The IRA also introduced new tax provisions, including a one percent excise tax imposed on certain stock repurchases by publicly traded companies. The one percent excise tax generally applies to any acquisition of stock by the publicly traded company (or certain of its affiliates) from a stockholder of the company in exchange for money or other property (other than stock of the company itself), subject to a de minimis exception. Thus, the excise tax could apply to certain transactions that are not traditional stock repurchases.** Regulatory guidance under the TCJA **, the IRA,** and such additional legislation is and continues to be forthcoming, and such guidance could ultimately increase or lessen the impact of these laws on our business and financial condition. **In** ~~Also, as a result of the changes in the U. S. presidential administration and control of the U. S. Senate, additional~~ - **addition** ~~tax legislation may be enacted; any~~ **, it is uncertain if and to what extent various states will conform to the TCJA, the IRA and** such additional legislation ~~could have an impact on us. Current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any collaborators, may receive for any approved products. If reimbursement of our products is unavailable or limited in scope or amount, our business could be materially harmed~~ . Current and future legislation designed to reduce prescription drug costs may affect the prices we and any collaborators may obtain for **tamibarotene** ~~our~~ - **or any future** product candidates. The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. There have been several recent U. S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, and reduce the costs of pharmaceuticals under Medicare and Medicaid. In 2020, President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician- administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, on December 29, 2021, CMS issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence- based care. In addition, in October 2020, **the Department of Health and Human Services, or** HHS **,** and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program ~~, or SIP~~ , to import certain prescription drugs from Canada into the United States. ~~The final rule is currently~~ **That regulation was challenged in a lawsuit by** the ~~subject~~ **Pharmaceutical Research and Manufacturers** of ~~ongoing litigation~~ **America, or PhRMA** , but ~~at least six~~ **the case was dismissed by a federal district court in February 2023 after the court found that PhRMA did not have standing to sue HHS. Nine** states (~~Vermont,~~ Colorado, Florida, Maine **, New Hampshire** , New Mexico, **North Dakota, Texas, Vermont** and **Wisconsin** ~~New Hampshire~~) have passed laws allowing for the importation of drugs from Canada ~~with~~ **. Certain of** ~~the~~ **these** ~~intent of developing SIPs for review~~ **states have submitted Section 804 Importation Program proposals** and **are awaiting FDA** approval ~~by~~ **. On January 5, 2024,** the FDA **approved Florida' s plan for Canadian drug importation** . Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point- of- sale, as well as a ~~new~~ safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. ~~The~~ **Pursuant to court order, the removal and addition of the aforementioned safe**

harbors were delayed and recent legislation imposed a moratorium on implementation of the rule ~~was delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation, and was subsequently delayed~~ until January 1, 2026 ~~by the Infrastructure Investment and Jobs Act~~ **. The IRA further delayed implementation of this rule to January 1, 2032** . More recently, on August 16, 2022, the IRA was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of ~~the Department of Health and Human Services (~~ HHS ~~)~~ to implement many of these provisions through guidance, as opposed to regulation, for the initial years. Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single- source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high- cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Nonetheless, since CMS may establish a maximum price for these products in price negotiations, we would be fully at risk of government action if our products are the subject of Medicare price negotiations. Moreover, given the risk that could be the case, these provisions of the IRA may also further heighten the risk that we would not be able to achieve the expected return on our drug products or full value of our patents protecting our products if prices are set after such products have been on the market for nine years. Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated " maximum fair price " under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out- of- pocket drug costs at an estimated $ 4, 000 a year in 2024 and, thereafter beginning in 2025, at $ 2, 000 a year. **On June 6, 2023, Merck & Co. filed a lawsuit against HHS and CMS asserting that, among other things, the IRA' s Drug Price Negotiation Program for Medicare constitutes an uncompensated taking in violation of the Fifth Amendment of the Constitution. Subsequently, a number of other parties, including the U. S. Chamber of Commerce, Bristol Myers Squibb Company, PhRMA, Astellas, Novo Nordisk, Janssen Pharmaceuticals, Novartis, AstraZeneca and Boehringer Ingelheim, also filed lawsuits in various courts with similar constitutional claims against HHS and CMS. We expect that litigation involving these and other provisions of the IRA will continue, with unpredictable and uncertain results.** At the state level, legislatures are increasingly passing legislation and implementing 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. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for **tamibarotene** ~~our~~ **or any future** product candidates or additional pricing pressures. Finally, outside the United States, in some nations, including those of the EU, the pricing of prescription pharmaceuticals is subject to governmental control and access. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we, or our collaborators may be required to conduct a clinical trial that compares the cost- effectiveness of our product to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be materially harmed. We may be subject to certain healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, fines, disgorgement, exclusion from participation in government healthcare programs, curtailment or restricting of our operations, and diminished profits and future earnings. Healthcare providers, third- party payors and others will play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. Our future arrangements with healthcare providers and third- party payors will expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we obtain marketing approval. Potentially applicable U. S. federal and state healthcare laws and regulations include the following: Anti- Kickback Statute. The federal Anti- Kickback Statute prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, 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 under federal healthcare programs such as Medicare and Medicaid; False Claims Laws. The federal false claims laws, including the civil False Claims Act, impose criminal and civil penalties, including those from civil whistleblower or qui tam actions against individuals or entities for knowingly presenting, or causing to be presented to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government; HIPAA. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing or attempting to execute a scheme to defraud any healthcare benefit program; HIPAA and HITECH.

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or ~~the~~ HITECH ~~Act~~, also imposes obligations on certain types of individuals and entities, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. While these provisions likely will not apply to us directly, they will apply to many of our partners and other entities assisting with our clinical trials and future activities, and therefore may impact our relationships with these entities and related costs; False Statements Statute. The federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services; Transparency Requirements. The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid, or the Children' s Health Insurance Program, with specific exceptions, to report annually to **HHS** ~~the U. S. Department of Health and Human Services~~ information related to payments and other transfers of value, including ownership and investment interests, to physicians and their family members; and Analogous State and Foreign Laws. Analogous state laws and regulations, such as state anti- kickback and false claims laws, and transparency laws, may apply to sales or marketing arrangements, and claims involving healthcare items or services reimbursed by non- governmental third party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry' s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, in addition to requiring drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures ~~. Many state laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. Foreign laws also govern the privacy and security of health information in many circumstances~~ . Efforts to ensure that our business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, disgorgement, contractual damages, and reputational harm, any of which could substantially disrupt our operations. If any of the physicians or other providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. Compliance with global privacy and data security requirements could result in additional costs and liabilities to us or inhibit our ability to collect and process data globally, and the failure to comply with such requirements could subject us to significant fines and penalties, which may have a material adverse effect on our business, financial condition or results of operations. We are subject to data privacy and protection laws and regulations that apply to the collection, transmission, storage and use of personally identifying information, which among other things, impose certain requirements relating to the privacy, security and transmission of personal information, including comprehensive regulatory systems in the U. S., EU and United Kingdom. The legislative and regulatory landscape for privacy and data protection continues to evolve in jurisdictions worldwide, and there has been an increasing focus on privacy and data protection issues with the potential to affect our business. Failure to comply with any of these laws and regulations could result in enforcement action against us, including fines, claims for damages by affected individuals, damage to our reputation and loss of goodwill, any of which could have a material adverse effect on our business, financial condition, results of operations or prospects. There are numerous U. S. federal and state laws and regulations related to the privacy and security of personal information. In particular, regulations promulgated pursuant to HIPAA establish privacy and security standards that limit the use and disclosure of individually identifiable health information, or protected health information, and require the implementation of administrative, physical and technological safeguards to protect the privacy of protected health information and ensure the confidentiality, integrity and availability of electronic protected health information. Determining whether protected health information has been handled in compliance with applicable privacy standards and our contractual obligations can be complex and may be subject to changing interpretation. These obligations may be applicable to some or all of our business activities now or in the future. If we are unable to properly protect the privacy and security of protected health information, we could be found to have breached our contracts. Further, if we fail to comply with applicable privacy laws, including applicable HIPAA privacy and security standards, we could face civil and criminal penalties. HHS enforcement activity can result in financial liability and reputational harm, and responses to such enforcement activity can consume significant internal resources. In addition, state attorneys general are authorized to bring civil actions seeking either injunctions or damages in response to violations that threaten the privacy of state residents. We cannot be sure how these regulations will be interpreted, enforced or applied to our operations. In addition to the risks associated with enforcement activities and potential contractual liabilities, our ongoing efforts to comply with evolving laws and regulations at the federal and state level may be costly and require ongoing modifications to our policies, procedures and systems. **States also are passing privacy laws that may impact our business operations.** In 2018, California passed into law the California Consumer Privacy Act, or the CCPA, which took effect on January 1, 2020 and imposed many requirements on businesses that process the personal information of California residents. Many of the CCPA' s requirements are similar to those found in the General Data Protection Regulation, or the GDPR, including requiring businesses to provide notice to data subjects regarding the information collected about them and how such information is used and shared, and providing data subjects the right to request access to such personal information and, in certain cases, request the erasure of such personal information. The CCPA also affords California residents the right to opt- out of " sales " of their personal information. The CCPA contains significant penalties for companies that violate its requirements. In November 2020, California voters passed a ballot initiative for the California Privacy Rights Act, or the CPRA, which went into effect on January 1, 2023 and significantly

expanded the CCPA to incorporate additional GDPR- like provisions including requiring that the use, retention, and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA also created a new enforcement agency – the California Privacy Protection Agency – whose sole responsibility is to enforce the CPRA, which will further increase compliance risk. The provisions in the CPRA may apply to some of our business activities. **These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products.** In addition **to California** , **eleven** other states, ~~including Virginia, Colorado, Utah, and Connecticut already~~ have passed ~~state~~ **comprehensive** privacy laws **similar to the CCPA and CPRA** . **These** ~~Virginia' s privacy law~~ **laws** ~~also went into~~ **are either in** effect **or** ~~on January 1, 2023, and the laws in the other three states~~ will go into effect ~~later in~~ **sometime before the end of 2026. Like the CCPA and CPRA,** ~~the~~ **these** ~~year~~ **laws create obligations related to the processing of personal information, as well as special obligations for the processing of " sensitive " data, which includes health data in some cases. Some of the provisions of these laws may apply to our business activities. There are also states that are strongly considering or have already passed comprehensive privacy laws during the 2024 legislative sessions that will go into effect in 2025 and beyond** . Other states will be considering ~~these~~ **similar** laws in the future, and Congress has also been debating passing a federal privacy law **. There are also states that are specifically regulating health information that may affect our business. For example, the State of Washington passed the My Health My Data Act in 2023 which specifically regulated health information that is not otherwise regulated by the HIPAA rules, and the law also has a private right of action, which further increases the relevant compliance risk. Connecticut and Nevada have also passed similar laws regulating consumer health data, and more states are considering such legislation in 2024** . These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products. Similar to the laws in the U. S., there are significant privacy and data security laws that apply in Europe and other countries. The collection, use, disclosure, transfer, or other processing of personal data, including personal health data, regarding individuals who are located in the European Economic Area, or the EEA, and the processing of personal data that takes place in the EEA, is regulated by the GDPR, which went into effect in May 2018 and which imposes obligations on companies that operate in our industry with respect to the processing of personal data and the cross- border transfer of such data. The GDPR imposes onerous accountability obligations requiring data controllers and processors to maintain a record of their data processing and policies. If our or our partners' or service providers' privacy or data security measures fail to comply with the GDPR requirements, we may be subject to litigation, regulatory investigations, enforcement notices requiring us to change the way we use personal data and / or fines of up to 20 million Euros or up to 4 % of the total worldwide annual turnover of the preceding financial year, whichever is higher, as well as compensation claims by affected individuals, negative publicity, reputational harm and a potential loss of business and goodwill. The GDPR places restrictions on the cross- border transfer of personal data from the EU to countries that have not been found by the EC to offer adequate data protection legislation, such as the U. S. There are ongoing concerns about the ability of companies to transfer personal data from the EU to other countries. In July 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU- U. S. Privacy Shield, one of the mechanisms used to legitimize the transfer of personal data from the EEA to the U. S. The CJEU decision also drew into question the long- term viability of an alternative means of data transfer, the standard contractual clauses, for transfers of personal data from the EEA to the U. S. While we were not self- certified under the Privacy Shield, this CJEU decision may lead to increased scrutiny on data transfers from the EEA to the U. S. generally and increase our costs of compliance with data privacy legislation as well as our costs of negotiating appropriate privacy and security agreements with our vendors and business partners. ~~Additionally~~ **Following the CJEU decision** , in October 2022, President ~~Joe~~ Biden signed an executive order to implement the EU- U. S. Data Privacy Framework, which would serve as a replacement to the EU- US Privacy Shield. The ~~EC~~ **European Union** initiated the process to adopt an adequacy decision for the EU- ~~US~~ **U. S.** Data Privacy Framework in December 2022 **,** ~~. It is unclear if~~ and ~~when~~ the **European Commission adopted the adequacy decision in July 2023. The adequacy decision permits U. S. companies who self- certify to the EU- U. S. Data Privacy** ~~framework~~ **Framework to rely on it as a valid data transfer mechanism for data transfers from the European Union to the United States. However, some privacy advocacy groups have already suggested that they** will be ~~finalized and whether it will be~~ **challenging the EU- U. S. Data Privacy Framework. If these** ~~challenged~~ **challenges** ~~in court~~ **are successful, they may not only impact the EU- U. S. Data Privacy Framework, but also further limit the viability of the standard contractual clauses and other data transfer mechanisms** . The uncertainty around this issue ~~may further~~ **has the potential to** impact our business ~~operations in the EU~~ . Following the withdrawal of the U. K. from the EU, the U. K. Data Protection Act 2018 applies to the processing of personal data that takes place in the ~~UK~~ **U. K.** and includes parallel obligations to those set forth by GDPR. In relation to data transfers, both the U. K. and the EU have determined, through separate " adequacy " decisions, that data transfers between the two jurisdictions are in compliance with the U. K. Data Protection Act and the GDPR, respectively. **The U. K. and the U. S. have also agreed to a U. S.- U. K. " Data Bridge, " which functions similarly to the EU- U. S. Data Privacy Framework and provides an additional legal mechanism for companies to transfer data from the U. K. to the United States. In addition to the U. K., Switzerland is also in the process of approving an adequacy decision in relation to the Swiss- U. S. Data Privacy Framework (which would function similarly to the EU- U. S. Data Privacy Framework and the U. S.- U. K. Data Bridge in relation to data transfers from Switzerland to the United States).** Any changes or updates to these **developments** ~~adequacy decisions~~ have the potential to impact our business. Beyond GDPR, there are privacy and data security laws in a growing number of countries around the world. While many loosely follow GDPR as a model, other laws contain different or conflicting provisions. These laws will impact our ability to conduct our business activities, including both our clinical trials and the sale and distribution of commercial products, through increased compliance costs, costs associated

with contracting and potential enforcement actions. While we continue to address the implications of the recent changes to data privacy regulations, data privacy remains an evolving landscape at both the domestic and international level, with new regulations coming into effect and continued legal challenges, and our efforts to comply with the evolving data protection rules may be unsuccessful. It is possible that these laws may be interpreted and applied in a manner that is inconsistent with our practices. We must devote significant resources to understanding and complying with this changing landscape. Failure to comply with laws regarding data protection would expose us to risk of enforcement actions taken by data protection authorities in the EEA and elsewhere and carries with it the potential for significant penalties if we are found to be non- compliant. Similarly, failure to comply with federal and state laws in the U. S. regarding privacy and security of personal information could expose us to penalties under such laws. Any such failure to comply with data protection and privacy laws could result in government-imposed fines or orders requiring that we change our practices, claims for damages or other liabilities, regulatory investigations and enforcement action, litigation and significant costs for remediation, any of which could adversely affect our business. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our business, financial condition, results of operations or prospects. We are subject to U. S. and foreign anti- corruption and anti- money laundering laws with respect to our operations and non- compliance with such laws can subject us to criminal and / or civil liability and harm our business. We are subject to the U. S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, the U. S. domestic bribery statute contained in 18 U. S. C. § 201, the U. S. Travel Act, the USA PATRIOT Act, and possibly other state and national anti- bribery and anti- money laundering laws in countries in which we conduct activities. Anti- corruption laws are interpreted broadly and prohibit companies and their employees, agents, third- party intermediaries, joint venture partners and collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or benefits to recipients in the public or private sector. We may have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. In addition, we may engage third party intermediaries to promote our clinical research activities abroad and / or to obtain necessary permits, licenses, and other regulatory approvals. We can be held liable for the corrupt or other illegal activities of these third- party intermediaries, our employees, representatives, contractors, partners, and agents, even if we do not explicitly authorize or have actual knowledge of such activities. We have adopted a Code of Business Conduct and Ethics that mandates compliance with the FCPA and other anti- corruption laws applicable to our business throughout the world. We cannot assure you, however, that our employees and third- party intermediaries will comply with this code or such anti- corruption laws. Noncompliance with anti- corruption and anti- money laundering laws could subject us to whistleblower complaints, investigations, sanctions, settlements, prosecution, other enforcement actions, disgorgement of profits, significant fines, damages, other civil and criminal penalties or injunctions, suspension and / or debarment from contracting with certain persons, the loss of export privileges, reputational harm, adverse media coverage, and other collateral consequences. If any subpoenas, investigations, or other enforcement actions are launched, or governmental or other sanctions are imposed, or if we do not prevail in any possible civil or criminal litigation, our business, results of operations and financial condition could be materially harmed. In addition, responding to any action will likely result in a materially significant diversion of management' s attention and resources and significant defense and compliance costs and other professional fees. In certain cases, enforcement authorities may even cause us to appoint an independent compliance monitor which can result in added costs and administrative burdens. We are subject to governmental export and import controls that could impair our ability to compete in international markets due to licensing requirements and subject us to liability if we are not in compliance with applicable laws. Our products and solutions are subject to export control and import laws and regulations, including the U. S. Export Administration Regulations, U. S. Customs regulations, and various economic and trade sanctions regulations administered by the U. S. Treasury Department' s Office of Foreign Assets Controls. Exports of our products and solutions outside of the United States must be made in compliance with these laws and regulations. If we fail to comply with these laws and regulations, we and certain of our employees could be subject to substantial civil or criminal penalties, including the possible loss of export or import privileges; fines, which may be imposed on us and responsible employees or managers; and, in extreme cases, the incarceration of responsible employees or managers. In addition, changes in our products or solutions or changes in applicable export or import laws and regulations may create delays in the introduction, provision, or sale of our products and solutions in international markets, prevent customers from using our products and solutions or, in some cases, prevent the export or import of our products and solutions to certain countries, governments or persons altogether. Any limitation on our ability to export, provide, or sell our products and solutions could adversely affect our business, financial condition and results of operations. If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business. We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. From time to time and in the future, our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials, and may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and waste products, we cannot completely eliminate the risk of contamination or injury resulting from these materials. In the event of contamination or injury resulting from the use or disposal of our hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations. We maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, but this insurance may not provide adequate coverage against potential liabilities. We do not, however, maintain insurance for environmental liability or toxic tort claims that may be asserted against us. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. Current or future environmental laws and regulations may impair our research, development or production efforts.

In addition, failure to comply with these laws and regulations may result in substantial fines, penalties or other sanctions. Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations. Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. The most recent global financial crisis caused extreme volatility and disruptions in the capital and credit markets, and it is unclear what impact the decision by the United Kingdom to leave the European Union will have on the global economy. A severe or prolonged economic downturn, such as the most recent global financial crisis, could result in a variety of risks to our business, including weakened demand for **tamibarotene** ~~our~~ **or any future** product candidates and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could strain our suppliers, possibly resulting in supply disruption, or cause delays in payments for our services by third- party payors or our collaborators. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business. Our internal computer systems, or those of any collaborators or contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs. Despite the implementation of security measures and certain data recovery measures, our internal computer systems and those of our current and any collaborators and other contractors or consultants are vulnerable to damage from cyber- attacks, computer viruses, unauthorized access, sabotage, natural disasters, terrorism, war and telecommunication and electrical failures. We have experienced, and may experience in the future, security breaches of our information technology systems. Any system failure, accident or security breach that causes interruptions in our operations, for us or those third parties with which we contract, could result in a material disruption of our product development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions, in addition to possibly requiring substantial expenditures of resources to remedy. For example, the loss of clinical trial data from an ongoing, completed or future clinical trial 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 results in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we may incur liabilities, our competitive position could be harmed and the further development and commercialization of **tamibarotene** ~~our~~ **or any future** product candidates may be delayed. In addition, we may not have adequate insurance coverage to provide compensation for any losses associated with such events. We could be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in the information systems and networks of our company, including personal information of our employees. In addition, outside parties have attempted, and may in the future attempt, to penetrate our systems or those of our vendors or fraudulently induce our employees or employees of our vendors to disclose sensitive information to gain access to our data. Like other companies, we may experience threats to our data and systems, including malicious codes and viruses, and other cyber- attacks. The number and complexity of these threats continue to increase over time. If a material breach of our security or that of our vendors occurs, the market perception of the effectiveness of our security measures could be harmed, we could lose business and our reputation and credibility could be damaged. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks. Although we develop and maintain systems and controls designed to prevent these events from occurring, and we have a process to identify and mitigate threats, the development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become more sophisticated. Moreover, **our ability to oversee and identify risks from cybersecurity threats associated with the use of third- party service providers is limited.** ~~despite~~ **Despite** our efforts, the possibility of these events occurring **to our internal computer systems or to those of the third parties on which we rely** cannot be eliminated entirely **. Additionally, the risk of cyber- attacks or other privacy or data security incidents may be heightened as a result of our moving increasingly towards a remote working environment as a result of public health outbreaks, which may be less secure and more susceptible to hacking attacks** . Our employees, independent contractors, CROs, consultants, commercial partners, vendors, and principal investigators may engage in misconduct or other improper activities, including non- compliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation. We are exposed to the risk of fraud or other misconduct by our employees, independent contractors, CROs, consultants, commercial partners, vendors and principal investigators, including intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards we have established, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately or disclose unauthorized activities to us. Misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions. Risks Related to Our Business Operations, Employee Matters and Managing Growth Public health epidemics or outbreaks, including COVID- 19, have had, and may continue to have, an adverse impact on our business. Public health crises such as pandemics, epidemics and outbreaks could adversely impact our business. For example, COVID- 19 has impacted, and it or another public health epidemic or outbreak may impact in the future, our operations and those of our third- party partners. The ultimate impact of any such public health epidemic or outbreak will depend on future developments which are highly uncertain and cannot be predicted with confidence, including the scope, severity, duration and any recurrence of such pandemic,

actions taken to contain the pandemic or mitigate its impact, the direct and indirect economic effects of the pandemic and containment measures, the effectiveness of vaccination and booster vaccination campaigns, work from home and return- to- work arrangements, compliance with governmental measures in connection with such pandemic, among others. Such pandemic or a similar public health epidemic or outbreak could adversely impact our ability to conduct clinical trials and our business generally and could have a material adverse impact on our operations and financial condition and results. In addition, a recession, depression or other sustained adverse market event resulting from ~~the~~ COVID- 19 ~~pandemic~~ or a similar public health epidemic or outbreak could materially and adversely affect our business and the value of our common stock. Our future success depends on our ability to attract and retain key management and scientists, development, medical and commercial staff, consultants and advisors. Our ability to compete in the biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on the pharmaceutical research and development and business development expertise of **Conley Chee** ~~Nancy Simonian, M. D.~~, our president and chief executive officer; ~~Conley Chee, our chief commercial officer;~~ Jason Haas, our chief financial officer; ~~Eric R. Olson, Ph. D., our chief scientific officer;~~ Gerald E. Quirk, Esq., our chief legal officer **and head of business development**; David A. Roth, M. D., our chief medical officer; and Kristin Stephens, our chief development officer. Each ~~member~~ of our ~~management team is~~ **executive officers are** employed" at will," meaning any of them may terminate his or her employment with us at any time with or without notice and for any reason or no reason. We also rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our industry has experienced a high rate of turnover of management, scientific, clinical, medical and commercial personnel in recent years. If we lose one or more of our executive officers or other key employees, our ability to implement our business strategy successfully could be seriously harmed. Replacing executive officers or other key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain marketing approval of and commercialize products successfully. We face intense competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities, governmental entities and other research institutions, many of which have substantially greater resources with which to attract and reward qualified individuals than we do. In addition, due to the risks associated with developing a new class of medicine, we may face additional challenges in attracting and retaining employees. If we are unable to continue to attract and retain highly qualified personnel, our ability to develop and commercialize **tamibarotene** ~~our~~ **or any future** product candidates will be limited. We expect to expand our organization, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations. ~~We~~ **If we receive marketing approval for tamibarotene, we** expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of ~~clinical development, drug manufacturing, regulatory affairs and~~ sales, marketing and distribution. To manage these growth activities, we must continue to implement and improve our managerial, operational and financial systems ~~, expand our facilities~~ and ~~continue to~~ recruit and train additional qualified personnel. Our management may need to devote a significant amount of its attention to managing these growth activities. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion ~~or relocation~~ of our operations, retain key employees, or identify, recruit and train additional qualified personnel. Our inability to manage the expansion ~~or relocation~~ of our operations effectively may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could also require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If we are unable to effectively manage our expected growth, our expenses may increase more than expected, our ability to generate revenues could be reduced and we may not be able to implement our business strategy, including the successful commercialization of **tamibarotene** ~~our~~ **or any future** product candidates. We may engage in acquisitions that could disrupt our business, cause dilution to our stockholders or reduce our financial resources. In the future, we may enter into transactions to acquire other businesses, products or technologies ~~. Because we have not made any acquisitions to date, our ability to do so successfully is unproven~~. If we do identify suitable candidates, we may not be able to make such acquisitions on favorable terms, or at all. Any acquisitions we make may not strengthen our competitive position, and these transactions may be viewed negatively by customers or investors. We may decide to incur debt in connection with an acquisition or issue our common stock or other equity securities to the stockholders of the acquired company **, as we did in connection with our acquisition of Tyme Technologies, Inc. in 2022**, which would reduce the percentage ownership of our existing stockholders. We could incur losses resulting from undiscovered liabilities of the acquired business that are not covered by the indemnification we may obtain from the seller. In addition, we may not be able to successfully integrate the acquired personnel, technologies and operations into our existing business in an effective, timely and non- disruptive manner. Acquisitions may also divert management attention from day- to- day responsibilities, increase our expenses and reduce our cash available for operations and other uses. We cannot predict the number, timing or size of future acquisitions or the effect that any such transactions might have on our operating results. Our operations or those of the third parties upon whom we depend might be affected by the occurrence of a catastrophic event, such as a terrorist attack, war or other armed conflict, geopolitical tensions or trade wars, pandemic or natural disaster. We depend on our employees, consultants, CROs, as well as regulatory agencies and other parties, for the continued operation of our business. Despite any precautions that we or any third parties on whom we depend take for catastrophic events, including terrorist attacks, wars or other armed conflicts, geopolitical tensions or trade wars, pandemics or natural disasters, these events could result in significant disruptions to our research and development, manufacturing, preclinical studies, clinical trials, and, ultimately, if approved, the commercialization of **tamibarotene** ~~our~~ **or any other future** products. Long- term disruptions in the infrastructure caused by these types of events, such as natural disasters, which are increasing in frequency due to the impacts of climate change, the outbreak of wars or other armed conflicts,

the escalation of hostilities, geopolitical tensions or trade wars, acts of terrorism or " acts of God, " particularly involving geographies in which we or third parties on whom we depend have offices, manufacturing or clinical trial sites, could adversely affect our businesses. We cannot be certain what the overall impact of such events will be on our business or on the business of any third parties on whom we depend. Although we carry business interruption insurance policies and typically have provisions in our contracts that protect us in certain events, our coverage might not include or be adequate to compensate us for all losses that may occur. Any catastrophic event affecting us, our CROs, regulatory agencies or other parties with which we are engaged could have a material adverse effect on our operations and financial performance. Risks Related to Our Common Stock The price of our common stock is likely to be highly volatile, which could result in substantial losses for our stockholders. Our stock price is likely to be highly volatile. The stock market in general and the market for smaller pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may lose some or all of your investment. The market price for our common stock may be influenced by many factors, including: • the timing and results of clinical trials of tamibarotene **or any future product candidates** ~~, SY- 2101 and SY- 5609~~ ; • the success of existing or new competitive products or technologies; • regulatory actions with respect to **tamibarotene** ~~our~~ **or any future** product candidates or our competitors' products and product candidates; • announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments; • commencement or termination of collaborations for our research or development programs; • failure or discontinuation of any of our development programs; • results of clinical trials of product candidates of our competitors; • regulatory or legal developments in the United States and other countries; • developments or disputes concerning patent applications, issued patents or other proprietary rights; • the recruitment or departure of key personnel; • the level of expenses related to any of our product candidates or clinical development programs; • the results of our efforts to develop additional product candidates or products; • actual or anticipated changes in estimates as to financial results or development timelines or recommendations by securities analysts; • announcement or expectation of additional financing efforts; • sales of our common stock by us, our insiders or other stockholders; • variations in our financial results or those of companies that are perceived to be similar to us; • changes in estimates or recommendations by securities analysts, if any, that cover our stock; • changes in the structure of healthcare payment systems; • market conditions in the pharmaceutical and biotechnology sectors; • general economic, industry and market conditions; • actual or threatened public health emergencies and outbreaks of disease (including, for example, ~~the~~ COVID- 19 ~~pandemic~~); and • the other factors described in this " Risk Factors " section and elsewhere in this Annual Report. In the past, companies that have experienced volatility in the market price of their stock have been subject to an increased incidence of securities class action litigation. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management' s attention and resources, which could harm our business. We may also face other material adverse consequences due to volatility or a sustained decrease in the price of our common stock, such as negative publicity, a decreased ability to obtain additional financing, diminished investor and / or employee confidence, and the loss of business development opportunities, some or all of which may contribute to a further decline in our stock price. We must maintain effective internal control over financial reporting, and if we are unable to do so, the accuracy and timeliness of our financial reporting may be adversely affected, which could have a material adverse effect on our business and stock price. We must maintain effective internal control over financial reporting in order to accurately and timely report our results of operations and financial condition. In addition, as a public company, the Sarbanes- Oxley Act of 2002, or the Sarbanes- Oxley Act, requires, among other things, that we assess the effectiveness of our disclosure controls and procedures quarterly and the effectiveness of our internal control over financial reporting at the end of each fiscal year. The rules governing the standards that must be met for our management to assess our internal control over financial reporting pursuant to Section 404 of the Sarbanes- Oxley Act are complex and require significant documentation, testing and possible remediation. These standards require that our audit committee be advised and regularly updated on management' s review of internal control over financial reporting. Our management may not be able to effectively and timely implement controls and procedures that comply with the increased regulatory compliance and reporting requirements that are applicable to us as a public company. If we fail to staff our accounting and finance function adequately or maintain internal control over financial reporting adequate to meet the demands that are placed upon us as a public company, including the requirements of the Sarbanes- Oxley Act, our business and reputation may be harmed and our stock price may decline. We might not be able to utilize a significant portion of our net operating loss carryforwards and research and development tax credit carryforwards. As of December 31, ~~2022~~ **2023** , we had federal and state net operating loss carryforwards of $ ~~300~~ **348** . ~~2~~ **7** million and $ ~~300~~ **349** . ~~2~~ **0** million, respectively, and federal and state research and development tax credit carryforwards of $ **10. 6 million and $** 1 ~~. 9 million and $ 0~~ . 5 million, respectively. These carryforwards could expire unused and be unavailable to offset future income tax liabilities. Our net operating loss carryforwards generated before 2018 will generally expire at various dates through 2037 and our research and development tax credit carryforwards will generally expire at various dates through ~~2042~~ **2043** . ~~The~~ **As described above in " Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition, " the** TCJA, as amended by the CARES Act, **includes** ~~contains significant~~ changes ~~with respect~~ to **U. S.** federal **tax rates and the rules governing** net operating loss carryforwards **that have significantly impacted our ability** ~~, including the limitation of the deduction for net operating loss carryforwards~~ to **utilize our** ~~80 % of current year taxable income and the elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such~~ net operating losses **to offset** ~~may be carried forward indefinitely and such net operating losses arising in~~ taxable **income in** ~~years beginning before January 1, 2021 are generally eligible to be carried back up to five years). Regulatory guidance under~~ the **future** ~~TCJA and the CARES Act is and continues to be forthcoming, and such guidance could further impact our ability to utilize our net operating loss carryforwards~~ . In addition, the net operating loss and tax credit carryforwards are subject to review

and possible adjustment by the Internal Revenue Service and state tax authorities. Furthermore, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, and corresponding provisions of state law, if a corporation undergoes an" ownership change," which is generally defined as a cumulative change in ownership of significant shareholders of greater than 50 %, by value, over a three- year period, the corporation' s ability to use its pre- change net operating loss carryforwards and research and development tax credit carryforwards to offset its post- change income may be limited. Our acquisition of Tyme Technologies, Inc. and concurrent private financing in September 2022 resulted in an ownership change for purposes of Section 382, and as a result our ability to use our historical net operating loss and tax credit carryforwards will be materially limited. Such limitation, or any adjustments to our carryforwards made by the Internal Revenue Service or state tax authorities, could harm our future operating results by effectively increasing our future tax obligations. We do not anticipate paying any cash dividends on our capital stock in the foreseeable future. Accordingly, stockholders must rely on capital appreciation, if any, for any return on their investment. We have never declared nor paid cash dividends on our capital stock. We currently plan to retain all of our future earnings, if any, to finance the operation, development and growth of our business. In addition, the terms of our term loan facility with Oxford precludes us from paying cash dividends to our stockholders without Oxford’ s consent. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future. Concentration of ownership of our common stock among our principal stockholders may prevent new investors from influencing significant corporate decisions. Our stockholders who own more than 5 % of our outstanding common stock and their affiliates, in the aggregate, beneficially own a significant portion of our common stock. As a result, if these stockholders were to choose to act together, they would be able to substantially influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would substantially influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of ownership control may: • delay, defer or prevent a change in control; • entrench our management or the board of directors; or • impede a merger, consolidation, takeover or other business combination involving us that other stockholders may desire. Provisions in our certificate of incorporation and bylaws and under Delaware law may prevent or frustrate attempts by our stockholders to change our management or hinder efforts to acquire a controlling interest in us. Provisions in our certificate of incorporation and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions: • establish a classified board of directors such that all members of the board are not elected at one time; • allow the authorized number of our directors to be changed only by resolution of our board of directors; • limit the manner in which stockholders can remove directors from the board; • establish advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted on at stockholder meetings; • require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent; • limit who may call a special meeting of stockholders; • authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a" poison pill" that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and • require the approval of the holders of at least 75 % of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our certificate of incorporation or bylaws. Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the General Corporation Law of the State of Delaware, which prohibits a person who owns in excess of 15 % of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15 % of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. This could discourage, delay or prevent someone from acquiring us or merging with us, whether or not it is desired by, or beneficial to, our stockholders. This could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock. If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline. The trading market for our common stock will likely depend in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. There can be no assurance that analysts will cover us, or provide favorable coverage. Securities or industry analysts may elect not to provide research coverage of our common stock, and such lack of research coverage may negatively impact the market price of our common stock. In the event we do have analyst coverage, if one or more analysts downgrade our stock or change their opinion of our stock, our share price would likely decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.