Risk Factors Comparison 2024-04-01 to 2023-03-22 Form: 10-K

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

Risks Relating to Our Business and Industry We are dependent on the success of our INTASYL technology platform, and our product candidates based on this platform, which is unproven and may never lead to approved and marketable products. Our efforts have been focused on the development of product candidates based on our INTASYL technology platform. We have invested, and we expect to continue to invest, significant financial resources and efforts developing our product candidates. Our ability to eventually generate revenue is highly dependent on the successful development, regulatory approval and commercialization of our INTASYL product candidates by us or by collaborative partners, which may not occur for the foreseeable future, if ever, and is highly uncertain and depends on a number of factors, many of which are beyond our control. Therefore, it is difficult to accurately predict challenges we may face with our product candidates as they move through the discovery, preclinical and clinical development stages. We will spend large amounts of money developing our INTASYL platform technology and may never succeed in obtaining regulatory approval. In addition, our research methodology may be unsuccessful in identifying product candidates and results from preclinical studies and clinical trials may not predict the results that will be obtained in later phase trials of our product candidates or our product candidates may interact with patients in unforeseen or harmful ways that may make it impractical or impossible to manufacture, receive regulatory approval or commercialize. If we are not successful in bringing an INTASYL product candidate to market, it could negatively impact our business and financial condition and we may not be able to identify and successfully implement an alternative product development strategy. Our product candidates are in an early stage of development and we may fail, experience significant delays, never advance clinical development or not be successful in our efforts to identify or discover additional product candidates, which may materially and adversely impact our business. Our success depends heavily on the successful development of our product candidates, which may never occur. Our product candidates, which are in early stages of development, could be delayed, not advance into the clinic, or unexpectedly fail at any stage of development. Our ability to identify, develop and commercialize product candidates is dependent on extensive preclinical and other non- clinical tests in order to support an IND ~~application~~ in the United States, or the equivalent with regulatory authorities in other jurisdictions **, if applicable** . These research programs to identify new product candidates require substantial financial and human resources, are difficult to design and can take many years to complete. We cannot be certain of the outcome of our research studies and clinical trials and the results from these studies and clinical trials may not predict the results that will be obtained in later stages of development and we may focus our efforts and resources on product candidates that may prove to be unsuccessful. There is no assurance that we will be able to successfully develop our product candidates, and we may forego opportunities with certain product candidates or for indications that later prove to have greater commercial potential. If we are not able to successfully develop our product candidates, we may be forced to abandon or delay our development efforts, which may materially and adversely affect our business, financial condition, and results of operations. Further, the FDA ~~, or equivalent foreign regulatory authority,~~ may not accept the results of our preclinical studies or clinical trials and may require us to complete additional studies or impose stricter approval conditions than we expect, which could impact the value of a particular program, the approvability or commercialization of the particular product candidate or product and our Company in general. Because of these factors, it is difficult to predict the time and cost of the development of our product candidates. Any delay or failure in obtaining required approvals may prevent us from completing our preclinical studies or clinical trials and could have a material adverse effect on our ability to initiate or commercialize ~~any~~ drug **or biologic** candidate on a timely basis, or at all. Additionally, preclinical studies and clinical trials are lengthy and expensive and if our cash resources become limited we may not be able to commence, continue or complete such preclinical studies or clinical trials. We are dependent on our collaboration ~~partners~~ **partner** for the successful development of our adoptive cell therapy product ~~candidates~~ **candidate** . We are dependent on third parties that have direct access to the patient or donor cells used in cell therapy and expect to depend on **our** third- party ~~collaborators~~ **collaborator** to support the clinical development of our ACT product ~~candidates~~ **candidate** . We have entered into a clinical **co- development** collaboration ~~development~~ agreement with AgonOx, Inc. ~~for the~~ **to conduct a Phase 1** clinical ~~development~~ **trial** of ~~our~~ **the evaluation of** PH- 762 ~~product candidate~~ **treated " double positive " tumor infiltrating lymphocytes** in ~~ACT~~ **patients with advanced melanoma** and ~~have entered into~~ other **advanced solid tumors** ~~research agreements with academic and industry collaborators, each of which is terminable by the relevant party at any time, subject to applicable notice periods~~ . The success of our ~~collaborations~~ **collaboration** depends upon the efforts of our collaboration ~~partners~~ **partner** , and their performance in achieving the development activities to the extent they are responsible under our collaboration ~~agreements~~ **agreement** . **Our** ~~Each of our partners~~ **partner** may not be successful in performing these activities, including completing the required preclinical studies and other information to be included in an IND application (or foreign equivalent), obtaining approval to initiate clinical trials, conducting the necessary clinical trials and arranging for the manufacturing or contract research organization (" CRO ") relationships and obtaining marketing authorization. Our ~~partners~~ **partner** ~~work~~ **works** with other companies, potentially including some of our competitors, their corporate objectives may not align with ours, and they may change their strategic focus or pursue alternative technologies. If our ~~collaborations~~ **collaboration** ~~are~~ **is** not successful or ~~a~~ **our** partner terminates our collaboration agreement, our business, financial condition, and results of operations could be materially and adversely affected. Further, we may not be successful in negotiating agreements with ~~these~~ **this** ~~collaborators~~ **collaborator** or with future collaborators for the development and commercialization of our ACT product candidates through collaborations such as joint development or licensing agreements. Our ability to successfully negotiate such agreements will

depend on, among other things, potential partners' evaluation of the superiority of our technology over competing technologies, the quality of preclinical data that we have generated, the perceived risks specific to developing our product candidates and our partners' own strategic and corporate objectives. If we fail to negotiate these agreements, we may not be able commence clinical trials with our ACT product candidates or we may be required to obtain licenses from cell therapy companies and our business, financial condition, and results of operations could be materially and adversely affected. If we experience delays or difficulties in identifying and enrolling ~~subjects~~ **patients** in clinical trials, it may lead to delays in generating clinical data and the receipt of necessary regulatory approvals. Clinical trials of a new drug **or biologic** candidate require the enrollment of a sufficient number of ~~subjects~~ **patients**, including ~~subjects~~ **patients** who are suffering from the disease or condition the drug **or biologic** candidate is intended to treat and who meet other eligibility criteria. Rates of ~~subject~~ **patient** enrollment are affected by many factors, and delays in ~~subject~~ **patient** enrollment can result in increased costs and longer development times, which could materially and adversely impact our business and financial condition. We may experience slower than expected ~~subject~~ **patient** enrollment ~~, including as a result of the coronavirus pandemic,~~ in our current or future clinical trials. In addition, clinical trials for drug **or biologic** candidates that treat the same indications as our product candidates may result in ~~subjects~~ **patients** who would otherwise be eligible for our clinical trials instead enrolling in clinical trials for other drug **or biologic** candidates. Topline data may not accurately reflect or may materially differ from the complete results of a clinical trial. From time to time, we may publicly disclose topline or interim data from our clinical trials based on a preliminary analysis of then- available data, of which the results, related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. Preliminary observations made in early stages of clinical trials are not necessarily indicative of results that will be obtained when full data sets are analyzed or in subsequent clinical trials. As a result, topline data may differ from future results from the same studies or different conclusions may qualify such results once additional data has been received and evaluated. Topline or interim data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data that we publicly disclose and should be viewed with caution until the complete data is available. If the topline data we report differs from future analysis of results, or if others, including regulatory authorities, disagree with the conclusions reached, our business, financial condition, and results of operations could be materially and adversely affected. We rely upon third- parties to conduct our clinical trials and other studies for our product candidates, and if they do not successfully fulfill their obligations, the development of our product candidates may be materially impacted. We ~~depend~~ **rely** upon third- party CROs, medical institutions, **collaborators,** clinical investigators, consultants and other third- parties to support and conduct our clinical trials and **we** rely on these third- party CROs for the execution of certain of our preclinical studies and expect to continue to do so. Because we rely on these third- parties, we cannot necessarily control the timing, quality of work or amount of resources that our contract partners will devote to these activities. We **, our collaborators,** and our CROs are responsible for ensuring that our clinical trials are conducted in accordance with applicable regulations and protocols. If we **, our collaborators,** or our CROs fail to comply with these applicable regulations, the FDA ~~, or equivalent foreign regulatory authority,~~ may not accept these data and may require us to complete additional preclinical studies and clinical trials, which could result in significant additional costs and delays to us. As we only control certain aspects of their activities, we cannot guarantee that these partners will fulfill their obligations to us under these arrangements. If these third- parties do not successfully carry out their responsibilities, as well as within a timely fashion, our clinical trials and preclinical studies may be delayed, unsuccessful or otherwise adversely affected. If we have to enter into alternative arrangements it may delay or adversely affect the development of our product candidates and our business operations. This could be difficult, costly or impossible, and our preclinical studies or clinical trials may need to be extended, delayed, terminated or repeated, and we may not be able to obtain regulatory approval in a timely fashion, or at all, for the applicable drug **or biologic** candidate, or to commercialize such drug **or biologic** candidate being tested in such studies or trials ~~. France adopted the General Data Protection Regulation, a data privacy regulation, and as we are conducting a clinical trial in France we are required to follow this law, which, if violated, could subject us to significant fines. The collection and use of personal health data and other personal information in the European Union is governed by the provisions of the GDPR, which came into force in May 2018 and related implementing laws in individual EU Member States. The GDPR imposes a number of strict obligations and restrictions on the ability to process (processing includes collection, analysis and transfer of) personal data of individuals within the EU and in the EEA, including health data from clinical trials and adverse event reporting. The GDPR also includes requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals prior to processing their personal data or personal health data, notification of data processing obligations to the national data protection authorities and the security and confidentiality of the personal data. EU Member States may also impose additional requirements in relation to health, genetic and biometric data through their national implementing legislation. Under the GDPR, personal data can only be transferred within the EU Member States and the three additional EEA countries (Norway, Iceland and Liechtenstein) that have adopted a national law implementing the GDPR. Appropriate safeguards are required to enable cross- border transfers of personal data from the EU and EEA Member States to a " third country " (a country outside the EU or EEA). This status has a number of significant practical consequences, in particular for international data transfers, competent supervisory authorities and enforcement of the GDPR. The GDPR prohibits the transfer of personal data to countries outside of the EU / EEA (including the United States) that are not considered by the EC to provide an adequate level of data protection, except if the data controller meets very specific requirements such as the use of standard contractual clauses (" SCCs "), issued by the EC. In this respect recent legal developments in Europe have created complexity and compliance uncertainty regarding certain transfers of personal data from the EU / EEA. For example, following the Schrems II decision of the Court of Justice of the EU on July 16, 2020, in which the Court invalidated the Privacy Shield under which personal data could be transferred from the EU / EEA to United States entities who had self- certified under the~~

~~Privacy Shield scheme, there is uncertainty as to the general permissibility of international data transfers under the GDPR. The Court did not invalidate the then current SCCs, but ruled that data exporters relying on these SCCs are required to verify, on a case- by- case basis, if the law of the third country ensures an adequate level of data protection that is essentially equivalent to that guaranteed in the EU / EEA. In light of the implications of this decision we may face difficulties regarding the transfer of personal data from the EU / EEA to third countries, such as the United States. However, on June 4, 2021 the EC issued a new set of SCCs for data transfers from controllers or processors in the EU / EEA to controllers or processors established outside the EU / EEA. These SCCs replace the old sets of SCCs that were adopted under the previous European Data Protection Directive 95 / 46. Since September 27, 2021, it is no longer possible to conclude contracts incorporating these previous versions of the SCCs. In addition, for contracts concluded before September 27, 2021, it is still possible to rely on the previous SCCs until the end of an additional 15 months transitional period (until December 27, 2022), provided that the processing operations which are the subject matter of the contract remain unchanged and reliance on previous SCCs ensures that the transfer is subject to appropriate safeguards. On November 11, 2021, the European Data Protection Board adopted recommendations on such appropriate safeguards that supplement transfer mechanisms. These recommendations aim to assist data exporters with their duty to identify and implement appropriate supplementary measures where they are needed to ensure an essentially equivalent level of protection to the personal data they transfer to third countries. Failure to comply with the requirements of the GDPR and the related national data protection laws of the EU Member States may result in significant monetary fines for noncompliance of up to € 20 million or 4 % of the annual global revenues of the noncompliant company, whichever is greater, other administrative penalties and a number of criminal offenses (punishable by uncapped fines) for organizations and in certain cases their directors and officers as well as civil liability claims from individuals whose personal data was processed. Data protection authorities from the different EU Member States may still implement certain variations, enforce the GDPR and national data protection laws differently, and introduce additional national regulations and guidelines, which adds to the complexity of processing personal data in the EU. Guidance developed at both EU level and at the national level in individual EU Member States concerning implementation and compliance practices are often updated or otherwise revised. Ensuring compliance with GDPR is time- intensive and may increase the cost of doing business, and failure to comply with these laws may have a material impact on our operations and financial condition. There is, moreover, a growing trend towards required public disclosure of clinical trial data in the EU which adds to the complexity of obligations relating to processing health data from clinical trials. Such public disclosure obligations are provided in the new EU Clinical Trials Regulation, EMA disclosure initiatives and voluntary commitments by industry. Failing to comply with these obligations could lead to government enforcement actions and significant penalties against us, harm to our reputation, and adversely impact our business and operating results. The uncertainty regarding the interplay between different regulatory frameworks, such as the Clinical Trials Regulation and the GDPR, further adds to the complexity that we face with regard to data protection regulation. On June 28, 2021 the European Commission adopted two adequacy decisions for the UK – one under the GDPR and the other for the Law Enforcement Directive. Personal data may now freely flow from the EU to the UK since the UK is deemed to have an adequate data protection level. Additionally, following the UK' s withdrawal from the EU and the EEA, companies also have to comply with the UK' s data protection laws (including the UK GDPR, which is based on the EU GDPR), the latter regime having the ability to separately fine up to the greater of £ 17. 5 million or 4 % of global turnover. The adequacy decisions include a ' sunset clause' which entails that the decisions will automatically expire four years after their entry into force~~ . A number of different factors could prevent us from advancing into clinical development, obtaining regulatory approval, and ultimately commercializing our product candidates on a timely basis, or at all. Before obtaining regulatory approval for the sale of any drug **or biologic** candidate, we must conduct extensive preclinical tests and successful clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Before human clinical trials may commence, we must submit to the FDA an IND ~~application, or foreign equivalent~~ . An IND ~~application~~ involves the completion of preclinical studies and the submission of the results, together with proposed clinical protocols, manufacturing information, analytical data and other data in the IND submission. The FDA may require us to complete additional preclinical studies or disagree with our clinical trial study design. Also, animal models may not exist for some of the disease areas we choose to develop our product candidates for. As a result, our clinical trials may be delayed or we may be required to incur more expense than we anticipated. Clinical trials require the review and oversight of IRBs, which approve and continually review clinical investigations and protect the rights and welfare of **patients** ~~human subjects~~ . Before our clinical trials can begin, we must also submit to the FDA a clinical protocol accompanied by the approval of the IRB at the institution (s) participating in the clinical trial. An inability or delay in obtaining IRB approval could prevent or delay the initiation and completion of our clinical trials, and the FDA may decide not to consider any data or information derived from a clinical investigation not subject to initial and continuing IRB review and approval. Preclinical studies and clinical trials are lengthy and expensive, and their outcome is highly uncertain. Historical failure rates are high due to a number of factors, such as safety and efficacy of drug **or biologic** candidates. We, our collaborators, the FDA, or an IRB may suspend clinical trials of a drug **or biologic** candidate at any time for various reasons, including if we or they believe the ~~subjects~~ **patients** participating in such trials are being exposed to unacceptable health risks. Among other reasons, adverse side effects of a drug **or biologic** candidate on ~~subjects~~ **patients** in a clinical trial could result in the FDA ~~or other regulatory authorities~~ suspending or terminating the clinical trial and refusing to approve a particular drug **or biologic** candidate for any or all indications of use ~~. We also are subject to numerous foreign regulatory requirements governing the conduct of clinical trials, manufacturing and marketing authorization, pricing and third- party reimbursement. The foreign regulatory approval process includes all of the risks associated with the FDA approval described above, as well as risks attributable to the satisfaction of local regulations in foreign jurisdictions. Approval by the FDA does not assure approval by regulatory authorities outside of the United States~~ . An additional number of factors could affect the timing, cost or outcome of our drug development efforts, including the following: · Delays in filing or acceptance of ~~initial drug applications~~ **INDs, NDAs, or BLA** for our product

candidates; · Difficulty in securing centers to conduct clinical trials; · Conditions imposed on us by the FDA ~~or comparable foreign authorities~~ regarding the scope or design of our clinical trials; · Problems in engaging IRBs to oversee trials or problems in obtaining or maintaining IRB approval of studies; · Difficulty in enrolling ~~subjects~~ **patients** in conformity with required protocols or projected timelines; · Third- party contractors failing to comply with regulatory requirements or to meet their contractual obligations to us in a timely manner; · Our drug **or biologic** candidates having unexpected and different chemical and pharmacological properties in humans than in laboratory testing and interacting with human biological systems in unforeseen, ineffective or harmful ways; · The need to suspend or terminate clinical trials **, for example,** if the participants are being exposed to unacceptable health risks; · Insufficient or inadequate supply or quality of our product candidates or other necessary materials necessary to conduct our clinical trials; · Effects of our product candidates not having the desired effects or including undesirable side effects or the product candidates having other unexpected characteristics; · The cost of our clinical trials being greater than we anticipate; · Negative or inconclusive results from our clinical trials or the clinical trials of others for similar product candidates or inability to generate statistically significant data confirming the efficacy of the product being tested; · Changes in the FDA' s requirements **or expectations** for testing during the course of that testing ~~; · The impact from the ongoing coronavirus pandemic~~ ; · Reallocation of our limited financial and other resources to other clinical programs; and · Adverse results obtained by other companies developing similar drugs. A failure of any preclinical study or clinical trial can occur at any stage of testing. Any delay or failure in obtaining required approvals may prevent us from completing our preclinical studies or clinical trials and could have a material adverse effect on our ability to initiate or commercialize any drug **or biologic** candidate on a timely basis, or at all. Additionally, preclinical studies and clinical trials are lengthy and expensive and if our cash resources become limited we may not be able to commence, continue or complete our clinical trials, which could have a material impact on our business, financial condition, and results of operations. We are subject to significant competition and may not be able to compete successfully. The biotechnology and pharmaceutical industries ~~have~~ **are** ~~intense~~ **intensely** ~~competition~~ **competitive** ~~and~~ **,** contain a high degree of risk and there are many other companies actively engaged in the discovery, development and commercialization of products that may compete with our product candidates. **Many** ~~We face a number~~ of **our** competitors ~~that~~ have substantially greater experience and greater research and development capabilities, staffing, financial, manufacturing, marketing, technical and other resources than us, and we may not be able to successfully compete with them. These companies include large and small pharmaceutical and biotechnology companies, academic institutions, government agencies and other private and public research organizations. In addition, even if we are successful in developing our product candidates, in order to compete successfully we may need to be first to market or to demonstrate that our products are superior to therapies based on different technologies. Some of our competitors may develop and commercialize products that are introduced to market earlier than our product candidates or on a more cost- effective basis. A number of our competitors have already commenced clinical testing of product candidates and may be more advanced than we are in the process of developing **such** ~~products~~ **product candidates** . If we are not first to market or are unable to demonstrate superiority, on a cost- effective basis or otherwise, any products for which we are able to obtain approval may not be successful. **We** ~~Our competitors~~ also **face competition** ~~compete with us in~~ acquiring technologies complementary to our INTASYL technology. ~~We~~ **Further, we** may face competition with respect to product efficacy and safety, ease of use and adaptability to modes of administration, acceptance by physicians, timing and scope of regulatory approvals, reimbursement coverage, price and patent position, including dominant patent positions of others. If we are not able to successfully obtain regulatory approval or commercialize our product candidates, we may not be able to establish market share and generate revenues from our technology. If we fail to attract, hire and retain qualified personnel, we may not be able to design, develop, market or sell our products or successfully manage our business. We have a small core management team and are particularly dependent on them. Accordingly, our business prospects are dependent on the principal members of our executive team, the loss of whose services could make it difficult for us to manage our business successfully and achieve our business objectives. While we have entered into an employment agreement with our Chief Executive Officer, ~~they~~ **he** could leave at any time, in addition to our other employees, who are all " at will " employees. Our ability to identify, attract, retain and integrate additional qualified key personnel is also critical to our success. Competition for skilled research, product development, regulatory and technical personnel is intense, and we may not be able to recruit and retain the personnel we need. The loss of the services of any key ~~research, product development, regulatory and technical~~ personnel, or our inability to hire new personnel with the requisite skills, could restrict our ability to develop our product candidates. We are subject to potential liabilities from clinical testing and future product liability claims. The use of our product candidates in clinical trials and, if any of our product candidates receive regulatory approval, the sale of our product candidates for commercial use expose us to the risk of product liability claims. Product liability claims may be brought against us by patients, healthcare providers, consumers or others who come into contact with our product candidates or approved products. We **have, and** will seek to obtain **,** clinical trial insurance for **current and any future** clinical trials that we conduct, as well as liability insurance for any products that we market. However, there is no assurance that we will be able to obtain insurance in the amounts we seek, or at all. We anticipate that licensees who develop our products will carry liability insurance covering the clinical testing of our product candidates and the marketing of those product candidates, if approved. There is no assurance, however, that any insurance maintained by us or our licensees will prove adequate in the event of a claim against us. If we cannot successfully defend against product liability claims, we could incur substantial liabilities. Even if claims asserted against us are unsuccessful, they may divert management' s attention from our operations and we may have to incur substantial costs to defend such claims. Any of these outcomes could materially impact our business and financial condition. We rely upon third parties for the manufacture of the clinical supply for our product candidates. We rely on third- party suppliers and manufacturers to provide us with the materials and services to manufacture our product candidates for certain preclinical studies and for our clinical trials, and we expect that we will continue to rely on third- party manufacturers for the supply of our product candidates in the future. We have limited in- house manufacturing capabilities

and resources, and we do not own or lease manufacturing facilities or have our own supply source for the required materials to manufacture our compounds. Further, we have limited ~~current good manufacturing practice (" cGMP ")~~ manufacturing capabilities and limited experience **scaling** ~~in scale-~~ up of clinical supply as our internal capabilities are limited to small- scale production of research material. Accordingly, we are dependent upon third- party suppliers and contract manufacturers to obtain supplies and manufacture our product candidates and we will need to either develop, contract for, or otherwise arrange for the necessary manufacturers for these supplies. There are a limited number of manufacturers that make oligonucleotides and we currently contract with multiple manufacturers for the supply of our product candidates to reduce the risk of supply interruption or availability. However, there is no assurance that our supply of our product candidates will not be limited, interrupted, of satisfactory quality or be available at acceptable prices. For example, constraints on the supply chain and availability of resources ~~due to the ongoing coronavirus pandemic~~ have resulted in delays and shortages at manufacturing facilities. While we have engaged with multiple manufacturers for the supply of our product candidates in order to mitigate the impact of the loss or delay of any one manufacturer, there can be no assurance that our efforts will be successful. If for any reason we are unable to obtain the clinical supply of our product candidates from our current manufacturers, we would have to seek to contract with another major manufacturer. If we or any of these manufacturers are unable or unwilling to increase its manufacturing capacity or if we are unable to establish alternative arrangements on a timely basis or on acceptable terms, the development and commercialization of such an approved product may be delayed or there may be a shortage in supply. Any inability to manufacture our product candidates or future approved drugs in sufficient quantities when needed would seriously harm our business. Approval of any of our product candidates will not occur unless the manufacturing facilities are in compliance with the FDA' s cGMP regulations ~~, or a foreign equivalent' s regulations,~~ in order to ensure that drug products are safe and that they consistently meet applicable requirements and specifications. These requirements are enforced by the FDA ~~and other regulatory authorities~~ through periodic inspections of the manufacturing facilities and can result in enforcement action, such as warning letters, fines and suspension of production if they are found to not be in compliance with the regulations. If our suppliers or manufacturers do not comply with the FDA ~~or foreign~~ regulations for our product candidates, we may experience delays in timing or supply, be forced to manufacture our product candidates ourselves or seek to contract with another supplier or manufacturer. If we are required to switch suppliers or manufacturers, we will be required to verify that the new supplier or manufacturer maintains facilities and processes in line with cGMP regulations, which may result in delays, additional expenses, and may have a material adverse effect on our ability to complete the development of our product candidates. Unstable market and economic conditions, including elevated and sustained inflation, may have serious adverse consequences on our business, financial condition and stock price. As has been widely reported, we are currently operating in a period of economic uncertainty and capital markets disruption, which has been significantly impacted by domestic and global monetary and fiscal policy, geopolitical instability, ~~an~~ ongoing military ~~conflict~~ **conflicts** ~~between Russia and Ukraine~~, and ~~historically~~ high domestic and global inflation ~~. In particular, the conflict in Ukraine has exacerbated market disruptions, including significant volatility in commodity prices, as well as supply chain interruptions, and has contributed to record inflation globally~~. The U. S. Federal Reserve and other central banks may be unable to contain inflation through more restrictive monetary policy and inflation may increase or continue for a prolonged period of time. Inflationary factors, such as increases in the cost of clinical supplies, interest rates, overhead costs and transportation costs may adversely affect our operating results. We continue to monitor these events and the potential impact on our business. Although we do not believe that inflation has had a material impact on our financial position or results of operations to date, we may be adversely affected in the future due to domestic and global monetary and fiscal policy, supply chain constraints, consequences associated with the coronavirus pandemic and the ongoing **military** ~~conflict~~ **conflicts** ~~between Russia and Ukraine~~, and such factors may lead to increases in the cost of manufacturing our product candidates and delays in initiating studies. In addition, global credit and financial markets have experienced extreme volatility and disruptions in the past several years and the foregoing factors have led to and may continue to cause diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, uncertainty about economic stability and increased inflation. 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~~ **financings** more difficult, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive these difficult economic times, which could directly affect our ability to attain our operating goals. **Our** ~~Natural disasters, epidemic or pandemic disease outbreaks, trade wars, political unrest or other events could disrupt our~~ business ~~or~~ **and** operations **would suffer in the event of computer system failures, cyberattacks or a deficiency in** ~~or~~ **our cybersecurity. Despite the implementation of security measures, our internal computer systems and** those of our ~~development partners, manufacturers, regulators or other~~ third **- party contractors and collaborators are vulnerable to damage from computer viruses** ~~parties with whom we conduct business now or in the future. A wide variety of events beyond our control~~ , ~~including~~ **unauthorized access,** natural disasters, ~~epidemic~~ **terrorism, war and telecommunication and electrical failures, cyberattacks or cyber- intrusions over the Internet, attachments to emails, persons inside** ~~or~~ **our** ~~pandemic disease outbreaks (such~~ **organization, or persons with access to systems inside our organization. The risk of a security breach or disruption, particularly through cyber- attacks or cyber intrusion, including by computer hackers, foreign governments, and cyber terrorists, has generally increased** as the **number** ~~coronavirus pandemic)~~ , ~~trade wars, political unrest or~~ **intensity and sophistication of attempted attacks and intrusions from around** ~~other~~ -- **the world have increased. Such an** ~~events~~ - **event** could ~~disrupt~~ **cause interruption of our operations. As part of** our business **, we and** ~~or~~

our ~~operations or those of our manufacturers, regulatory authorities, or other~~ third **- party contractors and collaborators maintain large amounts of confidential information, including non- public personal information on** ~~parties~~ **patients** ~~with whom we conduct business. These events may cause businesses~~ and ~~government agencies to be shut down, supply chains to be interrupted, slowed, or~~ **our employees** ~~rendered inoperable, and individuals to become ill, quarantined, or otherwise unable to work and / or travel due to health reasons or governmental restrictions~~ . ~~These limitations~~ **Breaches in security** could ~~negatively affect our business operations and continuity, and could negatively impact our development timelines and ability to timely perform basic business functions, including preparing and filing financial reports. If our operations or those of third parties with whom we have business are impaired or curtailed as a~~ result ~~of~~ **in** ~~these~~ -- **the loss** ~~events, the development and commercialization of our~~ **or misuse of this information** ~~products and product candidates could be impaired or halted~~ , which could **, in turn, result in potential regulatory actions or litigation, including material claims for damages, interruption to our operations, damage to our reputation or otherwise** have a material adverse ~~impact~~ **effect** on our business **, financial condition and operating results. We expect to have appropriate information security policies and systems in place in order to prevent unauthorized use or disclosure of confidential information, including non- public personal information, but there can be no assurance that such use or disclosure will not occur** . Risks Relating to Our Intellectual Property We may be involved in litigation to protect our patents and intellectual property rights and our ability to protect our patents and intellectual property rights is uncertain and may subject us to potential liabilities. We have filed patent applications, have pending patents that we have licensed and those that we own and expect to continue to file patent applications. We may also need to license patents and patent applications from research sponsored by us with third- parties. There is no assurance that these applications will result in any issued patents or that those patents would withstand possible legal challenges or protect our technologies from competition. The patent granting authorities have upheld stringent standards for the RNAi patents that have been prosecuted so far and, consequently, pending patents that we have licensed and those that we own may continue to experience long and difficult prosecution challenges and may ultimately issue with much narrower claims than those in the pending applications. In addition, others may challenge the patents or patent applications that we currently license or may license in the future or that we own and, as a result, these patents could be narrowed, invalidated or rendered unenforceable, which would negatively affect our ability to exclude others from using the technologies described in these patents. There is no assurance that these patents or other pending applications or issued patents we license or that we own will withstand possible legal challenges. Moreover, the laws of some foreign countries may not protect our proprietary rights to the same extent as do the laws of the United States. Our efforts to enforce and maintain our intellectual property rights may not be successful and may result in substantial costs and diversion of management and key employee' s time. If we are unable to defend our licensed or owned intellectual property, it may have a materially and adverse impact on our business, results of operations and financial condition. Third- parties may claim that we infringe their patents, which may result in substantial liabilities and prevent us from pursuing the development of our product candidates. Because the field we operate in is constantly changing and patent applications are still being processed by government patent offices around the world, there is a great deal of uncertainty about which patents will issue, when, to whom and with what claims. Although we are not aware of any blocking patents or other proprietary rights, it is likely that there will be significant litigation and other proceedings, such as interference and opposition proceedings in various patent offices, relating to patent rights in the field we operate. Further, many patents in the fields we are pursuing have already been exclusively licensed to third- parties, including our competitors. It is possible that we may become a party to such proceedings. If a claim should be brought against us and we are found to infringe the rights of others, we may be required to pay substantial damages, be forced to stop the development of product candidates affected by the claim, and / or establish licenses or similar arrangements. Furthermore, any such licenses may not be available when needed, on commercially reasonable terms or at all. Whether an infringement claim is successful or not, the cost of these proceedings may be significant and divert the attention of management and other key employees. As a result, we cannot be certain that our patents or those we license will not be challenged by others, which could have a material adverse effect on our business, results of operations and financial condition. We are dependent on the patents we own and the technologies we license, and if we fail to maintain our patents or lose the right to license such technologies, our ability to develop new products would be harmed. Our success depends upon our ability to obtain and maintain intellectual property protection for our product candidates. Any patents issued to us or our licensors may not provide us with any competitive advantages, and there is no assurance that the patents of others will not have an adverse effect on our ability to do business or to continue to develop our product candidates freely. Pending patents that we have licensed and those that we own may continue to experience long and difficult prosecution challenges and may ultimately issue with much narrower claims than those in the pending applications. Because of the extensive time required for development, testing, and regulatory review of a potential product, it is possible that, before any of our product candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thus reducing any advantage provided by the patent. Further, even if our rights are valid, enforceable and broad in scope, competitors may develop products based on technology that is not covered by our licenses or patents or patent applications that we own. If we are unable to derive value from our licensed or owned intellectual property, it may have a materially and adverse impact on our business, results of operations and financial condition. Third parties may hold or seek to obtain additional patents that could make it more difficult or impossible for us to develop products based on our technologies without obtaining a license to such patents, which licenses may not be available on attractive terms, or at all. If there is any dispute or issue of non- performance between us and the respective licensing partner regarding the rights or obligations under the license agreements, the ability to develop and commercialize the affected product candidate may be adversely affected. Moreover, if any of our existing licenses are terminated, the development of the product candidates contemplated by the licenses could be delayed or terminated and we may not be able to negotiate additional licenses on acceptable terms, if at all, which would have a material adverse effect on our business. To the extent that we are required and are able to obtain multiple licenses from third parties to develop or

commercialize a product candidate, the aggregate licensing fees and milestones and royalty payments made to these parties may materially reduce our economic returns or even cause us to abandon development or commercialization of a product candidate. Risks Relating to Our Financial Condition We will require substantial additional funds to complete our research and development activities. We have used substantial funds to develop our product candidates and will need to raise additional substantial funds to continue our drug development efforts and support our operations. Our future capital requirements and the period for which our existing resources are able to support our operations may vary significantly from what we expect. We anticipate that we will need to raise substantial amounts of money to fund a variety of future activities integral to the development of our business, which may include but is not limited to the following: · To conduct research and development to successfully develop our product candidates; · To obtain regulatory approval for our product candidates; · To file and prosecute patent applications and to defend and assess patents to protect our technologies; · To retain qualified employees, particularly in light of intense competition for qualified personnel; · To manufacture products ourselves or through third parties; · To market our products, either through building our own sales and distribution capabilities or relying on third parties; and · To acquire new technologies, licenses or products. We are dependent on obtaining funding from third parties, such as proceeds from the issuance of debt, sale of equity or strategic opportunities, in order to maintain our operations. We cannot assure you that additional financing will be available to us on acceptable terms, or at all. If we cannot, or are limited in the ability to, issue equity, incur debt or enter into strategic collaborations, we may be unable to fund the discovery and development of our product candidates or improve our technology. If we fail to obtain additional funding when needed, we may ultimately be unable to continue to develop and potentially commercialize our product candidates, and we may be forced to scale back or terminate our operations or seek to merge with or be acquired by another company. We have a history of net losses, and we expect to continue to incur net losses for the foreseeable future and may not achieve or maintain profitability. We have generated significant losses to date, have not generated any product revenue and may not generate product revenue in the foreseeable future, or ever. We expect to incur significant operating losses as we advance our product candidates through drug development and the regulatory process. Our ability to achieve profitability, if ever, will depend on, among other things, us or our collaborators, obtaining regulatory approvals and successfully commercializing our drug **or biologic** candidates. Even if we are able to successfully commercialize our drug **or biologic** candidates, we may not be able to achieve or sustain profitability, which could have a material adverse effect on our business, financial condition and results of operations. Future financing may be obtained through, and future development efforts may be paid for by, the issuance of debt or equity, which may have an adverse effect on our stockholders or may otherwise adversely affect our business. If we raise funds through the issuance of debt or equity, any debt securities or preferred stock issued will have rights, preferences and privileges senior to those of holders of our common stock in the event of a liquidation. In such event, there is a possibility that once all senior claims are settled, there may be no assets remaining to pay out to the holders of common stock. The terms of debt securities may also impose restrictions on our operations, which may include limiting our ability to incur additional indebtedness, to pay dividends on or repurchase our capital stock, or to make certain acquisitions or investments. In addition, we may be subject to covenants requiring us to satisfy certain financial tests and ratios, and our ability to satisfy such covenants may be affected by events outside of our control. If we raise funds through the issuance of additional equity, whether through private placements or public offerings, such an issuance would dilute current stockholders' ownership in us, perhaps substantially. The issuance of a significant amount of shares of common stock could cause the market price of our common stock to decline or become highly volatile. We expect to continue to incur significant research and development expenses, which may make it difficult for us to attain profitability, and may lead to uncertainty as to our ability to continue as a going concern. We expend substantial funds to develop our technologies, and additional substantial funds will be required for further research and development, including preclinical testing and clinical trials of any product candidates, and to manufacture and market any products that are approved for commercial sale. Because the successful development of our products is uncertain, we are unable to precisely estimate the actual funds we will require to develop and potentially commercialize them. In addition, we may not be able to generate enough revenue, even if we are able to commercialize any of our product candidates, to become profitable. Changes in our operating plans, our existing and anticipated working capital needs, the acceleration or modification of our expansion plans, increased expenses, potential acquisitions or other events will all affect our ability to continue as a going concern. **We have** ~~The Company has~~ limited cash resources, ~~has~~ **have** reported recurring losses from operations since inception **, negative operating cashflows** and ~~has~~ **have** not yet received product revenues. These factors raise substantial doubt regarding **our** ~~the Company' s~~ ability to continue as a going concern, and the Company' s current cash resources may not provide sufficient capital to fund operations for at least the next 12 months from the date of the release of ~~these~~ -- **the consolidated** financial statements **included elsewhere in this Annual Report** . The continuation of the Company as a going concern depends upon **our** ~~the Company' s~~ ability to raise additional capital through ~~an~~ equity ~~offering~~ **offerings** , debt ~~offering~~ **offerings and /** or strategic ~~opportunity~~ **opportunities** to fund ~~its~~ **our** operations. There can be no assurance that **we** ~~the Company~~ will be successful in accomplishing these plans in order to continue as a going concern. Any such inability to continue as a going concern may result in our common stockholders losing their entire investment. There is no guarantee that we will become profitable or secure additional financing. Our ability to utilize net operating loss carryforwards and other tax benefits may be limited. We have historically incurred net losses and may never achieve or sustain profitability. Under the Internal Revenue Code of 1986, as amended (the " Code "), a corporation is generally allowed a deduction for net operating losses carried forward from a prior taxable year. Under that provision, we can carryforward our net operating losses to offset our future taxable income, if any, until such net operating losses are used or expire. Net operating losses incurred in tax years beginning after December 31, 2017 may be carried forward indefinitely, but are limited to offset up to 80 % of future taxable income. Certain of our net operating loss carryforwards predating December 31, 2017 could expire unused before offsetting potential future income tax liabilities. Additionally, an ownership change, as defined by Section 382 and 383 of the Code, results from transactions increasing the ownership of certain stockholders or public groups

in the stock of a corporation by more than 50 % over a three- year period. Pursuant to Section 382 and 383 of the code, if the Company has experienced a change of control at any time since inception, utilization of the Company' s net operating loss or tax credit carryforwards then in existence would be subject to an annual limitation. Any limitation may result in expiration of a portion of the net operating loss or tax credit carryforwards before utilization. **We have** ~~During 2021, the Company~~ completed ~~an~~ **multiple** ~~assessment~~ **assessments** of the available net operating loss and tax credit carryforwards under ~~Section~~ **Sections** 382 and 383 **of the Code through the year ended December 31, 2023** and determined that **we** ~~the Company~~ underwent multiple ownership changes during the period from **inception to** ~~2012~~ - **2023** ~~to 2021~~. As a result, our net operating losses and tax credit carryforwards are subject to substantial annual limitations under ~~Section~~ **Sections** 382 and 383 **of the Code** due to these ownership changes. The Company has adjusted its net operating loss and tax credit carryforwards to address the impact of the ownership changes. **We** ~~The Company assesses~~ -- **assess** the need to conduct an ownership change analysis to determine whether any changes occurred in ownership that would limit net operating loss or tax credit carryforwards on an annual basis. We may experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurs and our ability to use our net operating loss and tax credit carryforwards is materially limited, it could harm our future operating results by effectively increasing our future tax obligations. Risks Relating to Our Securities The price of our common stock has been and may continue to be volatile. Our stock price has historically fluctuated widely and is likely to continue to be volatile. Because we are at an early stage of development and in the absence of product revenue as a measure of operating performance, we anticipate that the market price for our common stock may be influenced by, but not limited to, such factors as: · Announcements regarding the initiation or completion, and the results of preclinical studies and clinical trials of our product candidates; · Announcements regarding clinical trial results or development announcements concerning our competitors product candidates; · Regulatory or legal developments in the United States ~~and other countries~~ ; · The recruitment or departure of key personnel; · The issuance of competitive patents or disallowance or loss of our patent rights; · Our ability to raise additional capital and the terms on which additional capital is raised; · To acquire new technologies, licenses or products; ~~· Natural disasters and calamities, including the coronavirus pandemic;~~ and · General economic, industry and market conditions. The stock markets, in general, and the markets for drug delivery and pharmaceutical company stocks, in particular, have experienced extreme volatility, that has often been unrelated to the operating performance of **these** particular companies. These broad market fluctuations may adversely affect the trading price of our common stock and could result in the loss of all or part of your investment. In addition, the limited trading volume of our stock may contribute to its volatility. Moreover, if we are unable to trade above $ 1. 00 for a certain period of time, or fulfill the other continued listing standards, The Nasdaq Stock Market **(" Nasdaq ")** may delist our common stock. Delisting our common stock from Nasdaq would adversely affect our trading volume and would likely negatively impact our trading price. **We may not be able to regain compliance with the continued listing requirements of The Nasdaq Capital Market. On January 24, 2024, we received notice (the " Notification Letter ") from Nasdaq notifying us that we are not in compliance with the minimum bid price requirements set forth in Nasdaq Listing Rule 5550 (a) (2) for continued listing on The Nasdaq Capital Market. Nasdaq Listing Rule 5550 (a) (2) requires listed securities to maintain a minimum bid price of $ 1. 00 per share, and Listing Rule 5810 (c) (3) (A) provides that a failure to meet the minimum bid price requirement exists if the deficiency continues for a period of 30 consecutive business days. Based on the closing bid price of our common stock for the 30 consecutive business days prior to the date of the Notification Letter, we no longer meet the minimum bid price requirement. The Notification Letter does not impact our listing on The Nasdaq Capital Market at this time. The Notification Letter states that we have 180 calendar days, or until July 22, 2024, to regain compliance. To regain compliance, the bid price of our common stock must have a closing bid price of at least $ 1. 00 per share for a minimum of 10 consecutive business days at any time prior to July 22, 2024. In the event that we do not regain compliance by July 22, 2024, we may be eligible for additional time to reach compliance with the minimum bid price requirement. However, if we fail to regain compliance with the minimum bid price listing requirement or fail to maintain compliance with all other applicable continued listing requirements and Nasdaq determines to delist our common stock, the delisting could adversely impact us by, among other things, reducing the liquidity and market price of our common stock; reducing the number of investors willing to hold or acquire our common stock; limiting our ability to issue additional securities in the future; and limiting our ability to fund our operations.** Our Board of Directors has the authority to issue shares of " blank check " preferred stock and the terms of the preferred stock may reduce the value of our common stock. We are authorized to issue up to 10, 000, 000 shares of preferred stock in one or more series ~~and as of the year ended December 31, 2022 had one share of Series D Preferred Stock outstanding, which was subsequently redeemed in full in January 2023 and is no longer outstanding~~ . Our Board of Directors (the " Board ") may determine the terms of future preferred stock offerings without further action by our stockholders. The issuance of our preferred stock could affect the rights of existing stockholders or reduce the value of our outstanding preferred stock or common stock. In particular, rights granted to holders of certain series of preferred stock may include voting rights, preferences as to dividends and liquidation, conversion and redemption rights and restrictions on our ability to merge with or sell our assets to a third party. We may acquire other businesses or form joint ventures that may be unsuccessful and could dilute your ownership interest in the Company. As part of our business strategy, we may pursue future acquisitions of other complementary businesses and technology licensing arrangements. We also may pursue strategic alliances. We have limited experience with respect to acquiring other companies and with respect to the formation of collaborations, strategic alliances and joint ventures. We may not be able to integrate such acquisitions successfully into our existing business, and we could assume unknown or contingent liabilities. We also could experience adverse effects on our reported results of operations from acquisition related charges, amortization of acquired technology and other intangibles and impairment charges relating to write- offs of goodwill and other intangible assets from time to time following the acquisition. Integration of an acquired company requires management resources that otherwise would

be available for ongoing development of our existing business. We may not realize the anticipated benefits of any acquisition, technology license or strategic alliance. There is no assurance that we will be successful in developing such assets, and a failure to successfully develop such assets could diminish our prospects. To finance future acquisitions, we may choose to issue shares of our common stock or preferred stock as consideration, which would dilute current stockholders' ownership interest in us. Alternatively, it may be necessary for us to raise additional funds through public or private financings. Additional funds may not be available on terms that are favorable to us and, in the case of equity financings, may result in dilution to our stockholders. Any future acquisitions by us also could result in large and immediate write- offs, the incurrence of contingent liabilities or amortization of expenses related to acquired intangible assets, any of which could harm our operating results. Provisions of our certificate of incorporation and bylaws and Delaware law might discourage, delay or prevent a change of control of the Company or changes in our management and, as a result, depress the trading price of our common stock. Our certificate of incorporation and bylaws contain provisions that could discourage, delay or prevent a change of control of the Company or changes in our management that the stockholders of the Company may deem advantageous. These provisions: · Authorize the issuance of " blank check " preferred stock that our Board could issue to increase the number of outstanding shares and to discourage a takeover attempt; · Prohibit stockholder action by written consent, which requires all stockholder actions to be taken at a meeting of our stockholders; · Provide that the Board is expressly authorized to adopt, alter or repeal our bylaws; and · Establish advance notice requirements for nominations for election to our Board or for proposing matters that can be acted upon by stockholders at stockholder meetings. Although we believe these provisions collectively provide for an opportunity to receive higher bids by requiring potential acquirers to negotiate with our Board, they would apply even if the offer may be considered beneficial by some stockholders. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management team by making it more difficult for stockholders to replace members of our Board, which is responsible for appointing the members of our management. Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, 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. ITEM 1B. UNRESOLVED STAFF COMMENTS