UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

☑ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2016

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period from _____ to _____

Commission file number: 001-37772

PhaseRx, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**20-4690620**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification Number)**

410 W. Harrison Street, Suite 300
Seattle, Washington 98119
(Address of registrant's principal executive offices)

Registrant's telephone number, including area code: (206) 805-6300

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Name of each exchange on which registered**
Common Stock, $0.0001 par value	**The NASDAQ Capital Market**

Securities registered pursuant to Section 12(g) of the Act:
None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☑

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☑

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☑ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☑ No ☐

Indicate by a check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer	☐	Accelerated filer	☐
Non-accelerated filer	☐ (Do not check if a smaller reporting company)	Smaller reporting company	☑

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☑

As of March 24, 2017, 11,690,329 shares of the registrant's common stock, $0.0001 par value per share, were outstanding. The aggregate market value of the voting and non-voting common equity of the registrant held by non-affiliates, computed by reference to the closing sales price of such stock, as of June 30, 2016 was $28.1 million. (For purposes of determination of the aggregate market value, only directors, executive officers and 10% or greater shareholders have been deemed affiliates.)

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement on Schedule 14A to be furnished to stockholders in connection with its 2017 Annual Meeting of Stockholders, which shall be filed with the Securities and Exchange Commission within 120 days after the end of the fiscal year to which this Annual Report on Form 10-K relates, are incorporated by reference in Part III, Items 10-14 of this Annual Report on Form 10-K.

PHASERX, INC.
ANNUAL REPORT ON FORM 10-K

TABLE OF CONTENTS

PART I

Unless the context otherwise indicates, the terms "we," "us" and "our" as used in this Annual Report on Form 10-K refer to PhaseRx, Inc. and its directly and indirectly owned subsidiaries on a consolidated basis.

Cautionary Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K contains "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. All statements other than statements of historical facts contained in this Annual Report on Form 10-K, including statements regarding our future results of operations and financial position, business strategy, prospective products, product approvals, timing and likelihood of success, plans and objectives of management for future operations, and future results of current and anticipated products are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements.

In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "anticipate," "could," "intend," "target," "project," "contemplates," "believes," "estimates," "predicts," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this Annual Report on Form 10-K are only predictions. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our business, financial condition and results of operations. These forward-looking statements speak only as of the date of this Annual Report on Form 10-K and are based on information we have when those statements are made or our management's good faith belief as of that time with respect to future events, and are subject to risks and uncertainties that could cause actual performance or results to differ materially from those expressed in or suggested by the forward-looking statements. Important factors that could cause such differences include, but are not limited to:

- our history of recurring losses and negative cash flows from operating activities, significant future commitments and the uncertainty regarding the adequacy of our liquidity to pursue or complete our business objectives;
- our inability to carry out research, development and commercialization plans;
- our inability to manufacture our product candidates on a commercial scale on our own or in collaborations with third parties;
- our inability to complete preclinical testing and clinical trials as anticipated;
- our ability to adequately protect and enforce rights to intellectual property;
- difficulties in obtaining financing on commercially reasonable terms, or at all;
- intense competition in our industry, with competitors having substantially greater financial, technological, research and development, regulatory and clinical, manufacturing, marketing and sales, distribution and personnel resources than we do;
- entry of new competitors and products and potential technological obsolescence of our products;
- adverse market and economic conditions;
- loss of one or more key executives or scientists;
- difficulties in securing regulatory approval to market our product candidates; and
- our use of the proceeds from our initial public offering, or the IPO.

For a more detailed discussion of these and other that may affect our business and that could cause our actual results to differentiate equally from those projected in these forward-looking statements, see the risk factors and uncertainties described under the heading "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K. The forward-looking statements contained in this Annual Report on Form 10-K are expressly qualified in their entirety by this cautionary statement. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. Moreover, we operate in an evolving environment. New risk factors and uncertainties may emerge from time to time, and it is not possible for us to predict all risk factors and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

ITEM 1. BUSINESS.

Overview

We are a biopharmaceutical company developing a portfolio of products for the treatment of inherited enzyme deficiencies in the liver using intracellular enzyme replacement therapy, or i-ERT, and expect to generate clinical safety and efficacy data in 2018. We are not aware of any other enzyme replacement therapies for intracellular enzyme deficiencies currently being marketed for inherited enzyme deficiencies in the liver, and believe that the commercial potential for i-ERT is completely untapped and similar to the large and growing $4 billion worldwide market for conventional enzyme replacement therapy, or ERT, which includes drugs such as Cerezyme ® . Our i-ERT approach is enabled by our proprietary Hybrid messenger RNA, or Hybrid mRNA Technology™ platform, which allows synthesis of the missing enzyme inside the cell. Our initial product portfolio targets the three urea cycle disorders ornithine transcarbamylase deficiency, or OTCD, argininosuccinate lyase deficiency, or ASL deficiency, and argininosuccinate synthetase deficiency, or ASS1 deficiency. We have preclinical proofs of concept in two mouse models of the urea cycle disorders showing significant reductions in the level of blood ammonia, which we believe is an approvable endpoint by the Food and Drug Administration, or the FDA, for the demonstration of efficacy in human clinical trials of the urea cycle disorders. To our knowledge, there are no ERT products on the market to treat these diseases, because the urea cycle reaction occurs inside the cell and is inaccessible to the administered enzyme. In contrast, we expect delivery of the missing enzyme using i-ERT with our Hybrid mRNA Technology to be a promising approach to treat these patients. Beyond the urea cycle disorders, we believe there are a significant number of inherited disorders of metabolism in the liver that are candidates for our therapeutic approach and that our Hybrid mRNA Technology can be adapted to develop mRNA therapeutics for the treatment of other inherited liver disorders using our platform.

Our i-ERT approach is accomplished by delivering normal copies of the mRNA that make the missing enzyme inside the liver cell, thereby enabling proper physiological function and correcting the disease. A key challenge with mRNA therapeutics historically has been their satisfactory delivery into the patients' cells. We believe that our Hybrid mRNA Technology addresses these difficulties and enables synthesis of the desired protein in the hepatocyte, which is the chief functional cell type in the liver harboring the metabolic cycles that need to be corrected in metabolic liver diseases. We believe our technology is superior to alternative technologies because, based upon peer-reviewed journal articles and presentations of our competitors and our internal preclinical studies, it results in high-level synthesis of the desired protein in the hepatocyte, has better tolerability and can be repeat-dosed without loss of effectiveness, thus enabling treatment of chronic conditions.

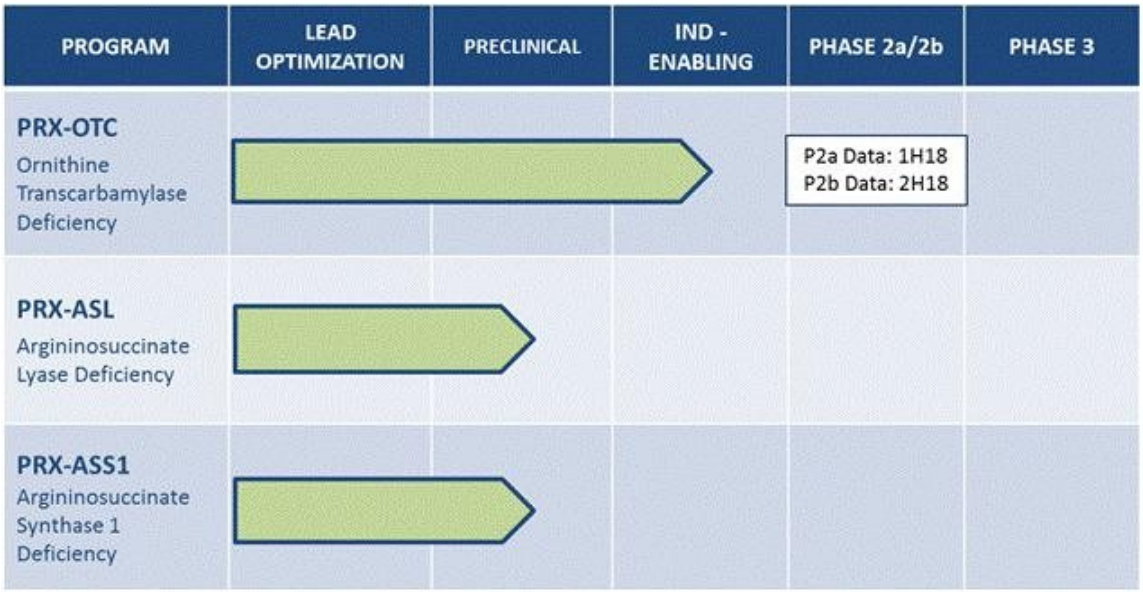
We are focused on inherited, single-gene disorders of metabolism in the liver that result in deficiency of an intracellular enzyme and thus have been unable to be treated with conventional ERT. Some inherited orphan liver diseases, such as the lysosomal storage disorders, can be successfully treated with conventional ERT. However, this approach does not work for many of the inherited orphan liver diseases, including the urea cycle disorders, because the missing enzyme is inside the cell, and the administered enzyme is unable to get inside the target cell where it is needed to be therapeutically active. Our approach is to deliver mRNA encoding the missing enzyme into the cell using our Hybrid mRNA Technology, such that the mRNA makes the missing enzyme inside the cell, restores the intracellular enzyme function and corrects the disease.

As noted above, our initial focus is on urea cycle disorders, which are a group of rare genetic diseases generally characterized by the body's inability to remove ammonia from the blood. The urea cycle consists of several enzymes, including OTC, ASL and ASS1. Since the urea cycle reactions occur inside the cell, conventional ERT does not work as a treatment for these disorders. Urea cycle disorders are caused by a genetic mutation that results in a deficiency of one of the enzymes of the urea cycle that is responsible for removing ammonia from the bloodstream, causing elevated levels of ammonia in the blood. The elevated ammonia then reaches the brain through the circulation, where it causes cumulative and irreversible neurological damage, and can result in coma and death. While currently marketed ammonia scavengers such as Ravicti ® (glycerol phenylbutyrate) and Buphenyl ® (sodium phenylbutyrate) provide palliative care of the symptoms, liver transplant is the only currently available cure for urea cycle disorders. Our goal is to treat the urea cycle disorders by intravenous delivery of mRNA that makes the relevant missing urea cycle enzyme inside the cell, thus reinstating control of blood ammonia. We believe that anticipated improvements in newborn screening and the availability of corrective therapy will lead to improved diagnosis and survival rates among patients with urea cycle disorders.

We have three therapeutic urea cycle disorder programs under development: PRX-OTC to treat OTCD, PRX-ASL to treat ASL deficiency and PRX-ASS1 to treat ASS1 deficiency. Preclinical efficacy has been established for PRX-OTC with two biological measures, including normalization of the level of ammonia in the blood. In June 2016, we selected PRX-OTC as our lead product candidate and demonstrated preclinical proof of concept for the treatment of a second product candidate, PRX-ASL. In 2016, we initiated scale up of the manufacturing of PRX-OTC, and in November 2016, we announced positive safety results from our single escalating dose response study in non-human primates using our Hybrid mRNA Technology. In November 2016, PRX-OTC received orphan drug designation from the FDA. We intend to initiate Investigational New Drug-enabling, or IND-enabling, studies in the first half of 2017 and plan to start manufacturing clinical supplies of the lead urea cycle disorder product candidate consistent with current good manufacturing practices, or cGMP, in the third quarter of 2017. We expect to file an IND application with the FDA in the fourth quarter of 2017 for this candidate and to conduct Phase 2a/2b single- and repeat-dose clinical proof of concept studies in OTCD patients that are expected to generate Phase 2a safety and efficacy data in the first half of 2018 and Phase 2b safety and efficacy data in the second half of 2018, including measurement of reduction in blood ammonia.

We are engaged in discussions with a number of prospective biopharmaceutical companies regarding partnership opportunities focused on our product pipeline, the use of our Hybrid mRNA Technology for the delivery of potential partners' mRNAs and the use of Hybrid mRNA Technology for in vivo gene editing. In vivo gene editing is a type of in vivo genetic engineering in which DNA is inserted, deleted or replaced in the genome of an organism using proteins called nucleases. Gene editing requires the delivery of mRNA and/or DNA into cells, which can be accomplished by several methods, the two most common of which are using engineered viruses as gene delivery vehicles, or viral vectors, and those that use naked DNA/RNA or DNA/RNA complexes, or non-viral methods. Gene editing companies are interested in our Hybrid mRNA Technology for its potential to express nucleases-encoding mRNAs in the hepatocyte, providing a non-viral delivery platform for in vivo gene editing, ultimately correcting the genetic defects in the liver of patients. We believe that our approach offers advantages over viral vectors for in vivo gene editing, which can persist in the patient over the long term, and thus may cause continued modification of the genome after the intended change to the desired gene has been made. If successful, we believe that our technology would enable genes to be added, repaired or deleted in a patient's hepatocytes for therapeutic benefit. To date, we have not entered into any partnerships or collaborations for our current product candidates.

Our pipeline includes our most advanced mRNA therapeutic program for the treatment of OTCD, for which we have shown preclinical proof of concept, and programs for ASL deficiency and ASS1 deficiency which are under development as summarized in the table below:



Our Strategy

Our strategy is to use our proprietary Hybrid mRNA Technology to develop mRNA therapeutics for the treatment of orphan liver diseases. We believe that our focus on urea cycle disorders maximizes the leverage of our know-how and proprietary technology and allows us to build value through our programs by moving them forward into development in a cost-efficient manner with the goal of promptly delivering safe and effective therapies to urea cycle disorder patients in need of effective treatment.

Our business strategy includes the following:

- *Rapidly develop a portfolio of mRNA therapeutics to treat orphan liver diseases that are intractable to ERT, with initial focus on the urea cycle disorders* . In June 2016, we selected PRX-OTC as our lead product candidate and demonstrated preclinical proof of concept for the treatment of a second product candidate, PRX-ASL. In November 2016, we announced positive safety results from our single escalating dose response study in non-human primates using our Hybrid mRNA Technology. In November 2016, PRX-OTC received orphan drug designation from the FDA. We intend to initiate IND-enabling studies in the first half of 2017, file an IND in the fourth quarter of 2017 and expect to generate clinical proof of concept in urea cycle disorder patients in the first half of 2018.

- *Leverage our Hybrid mRNA Technology across a broad range of additional orphan liver diseases* . There are many other orphan liver diseases beyond the urea cycle disorders that we believe would be good candidates for mRNA replacement therapy. Given that the delivery system will be the same across the programs, once the Hybrid mRNA Technology is successful with one mRNA and orphan liver disease, we anticipate that the costs and risks associated with developing new mRNA therapeutics for other orphan liver diseases will be relatively low.

- *Pursue and form strategic collaborations that leverage our Hybrid mRNA Technology* . We are engaged in discussions with potential partners for developing mRNA programs in various disease indications. We intend to pursue partnerships in order to accelerate the development and maximize the market potential of our Hybrid mRNA Technology platform. In particular, we intend to partner with larger biopharmaceutical companies that possess market know-how and marketing capabilities to complete the development and commercialization of mRNA therapeutics. Our Hybrid mRNA Technology also enables us to deliver nuclease-encoding mRNAs to the liver. The combination of our Hybrid mRNA Technology and gene editing technology has the potential to enable in vivo gene editing, to either add or delete gene function in humans, which, if successful, could have a variety of important potential medical applications. For example, deleting gene function could be used for lowering cholesterol, and adding gene function could be used to correct certain types of hemophilia.

Our Competitive Strengths

With our proprietary Hybrid mRNA Technology, intellectual property portfolio and experienced management team, we believe we are well positioned to advance our development candidates and partner our technology platform to expand future development and commercial opportunities. Although our technology is at a preclinical stage of development and will require substantial resources and clinical and regulatory validation of efficacy, we believe that our delivery technology will provide opportunities to create value with therapeutic mRNAs for the treatment of orphan liver diseases in a cost-effective way.

We believe that our competitive strengths include:

- *Specific production of desired proteins in hepatocytes* . Based on the internal preclinical studies we have conducted, the Hybrid mRNA Technology enables protein production specifically in hepatocytes in the liver with minimal impact in other major organs and tissues. This outcome is accomplished by attaching the hepatocyte-specific targeting ligand molecule N-acetyl galactosamine, or GalNAc to the polymer used in our Hybrid mRNA Technology, which results in hepatocyte-specific expression of the desired protein. GalNAc targeting of mRNA expression is a notable aspect of our technology and we are not aware of any competitor that is using GalNAc to target expression of mRNA therapeutics. This specificity limits off-target effects that may occur by producing proteins in tissues outside the liver.

- *Ability to repeat dose* . Our preclinical data shows that the Hybrid mRNA Technology enables repeat dosing at therapeutically efficacious doses without loss of protein production. This ability enables treatment of chronic indications that require multi-dose treatment regimens.

- *Better tolerability relative to other nucleic acid delivery systems* . In our preclinical studies, the Hybrid mRNA Technology has been tested in mice, rats and non-human primates. In all species tested, the delivery formulation was well-tolerated, as demonstrated by minimal or no induction of a variety of immune inflammatory cytokines (inter-cellular signaling chemicals primarily involved in immune-inflammatory mechanisms). Moreover, at doses well above those needed for a therapeutic effect, liver transaminase levels, a measure of liver damage, remained within normal ranges in mice. This ability to dose at high mRNA levels in combination with the ability to multi-dose without loss of expression upon subsequent dosing represents one of the significant strengths of the Hybrid mRNA Technology.

- *Potential for rapid development of follow-on products with unusually low cost and risk* . There are many single-gene inherited metabolic disorders of the liver which may be candidates for our mRNA therapeutic approach. Once proof of concept has been established for one orphan liver disease with the Hybrid mRNA Technology, we believe that the same delivery platform may be used to deliver many different mRNAs. Because our delivery technology platform is largely complete and the sequence of all mRNAs is widely known and in public domain, once we successfully develop an mRNA therapeutic for one of the single-gene inherited metabolic disorders of the liver, we believe that development of an mRNA therapeutic targeting other single-gene inherited metabolic disorders of the liver can be made in a significantly shorter amount of time and at less cost relative to a conventional drug discovery process, which generally takes several years to discover new drugs. In addition, we believe that the precise specificity of mRNA for its target minimizes off-target risks associated with conventional drug development, which we believe will contribute to lower cost and risks. For these reasons, while not mitigating potential future regulatory or clinical risks, and not shortening regulatory or clinical timelines for drug approval, we believe our approach can lead to the generation of new drugs more rapidly and with lower risk compared to conventional drug development.

- *Ability to develop high-barrier to entry products* . Due to our propriety know-how in nucleic acid therapeutics and their delivery, we expect to develop high barrier to entry therapeutics which we believe will result in our products being subject to relatively less competition in the market.

- *Experienced team* . Our management team has an extensive track record and experience in the research, development and delivery of RNA therapeutics. Our management team has over 50 years of combined experience in RNA delivery technologies and RNA therapeutics, and our team is well placed to further develop the Hybrid mRNA Technology for orphan liver disease therapeutics and for gene editing applications.

- *Patent protection for our Hybrid mRNA Technology* . In order to protect our innovations, we have aggressively built upon our extensive and enabling intellectual property estate worldwide. Our portfolio of patents and patent applications includes multiple families and is primarily focused on synthetic polymers and related compositions, the use of polymer and polymer-lipid nanoparticle, or LNP compositions for delivery of mRNA and other therapeutic agents, including the use of polymer-LNP compositions in our core platform technology, and methods for treating protein deficiency diseases such as orphan diseases characterized by single-gene metabolic defects in the liver, including OTCD. As of March 24, 2017, we own or have in-licensed 16 issued U.S. patents, 25 issued foreign patents, and over 15 pending U.S. and foreign patent applications.

While future manufacturing, regulatory and clinical challenges have not yet been addressed by us, our Hybrid mRNA Technology has proven highly effective in preclinical testing. However, to date, none of the above described studies involved human subjects. As such, there can be no assurance that we will achieve the same results upon the commencement of human clinical trials. Should we fail to achieve similar results in human clinical trials, it could result in a material adverse effect on our business and operations. Establishing the efficacy of our technology in human subjects will require substantial funds and could take multiple years. In addition, our successful development is subject to many risks, both known and unknown that may impede our ability to ever bring this technology to market or to generate revenue. See "Risk Factors" beginning on page 34.

The main competitive technologies to provide treatment for our target diseases are adeno-associated virus, or AAV vectors, and mRNA delivery using conventional LNPs. AAV vectors offer the potential of longer-term correction of the liver disease by gene therapy, and Dimension Therapeutics, Inc. announced they had an open IND with the FDA for AAV gene therapies targeting OTCD in December of 2016. These vectors are in clinical development to treat orphan liver diseases such as hemophilia. However, triggering of multiple types of immune response to the virus represents a major challenge facing development of these viral vectors and can make repeat dosing ineffective. If the therapy wanes over time, or if the cells targeted by a first AAV treatment turnover or die, then a repeat administration may be ineffective. mRNAs may also be delivered by conventional LNPs. We believe at least one mRNA/LNP formulation may have been reviewed by the FDA to enter clinical trials for an orphan liver disease indication. While LNPs are effective in delivering mRNA cargo into the liver, and hence, if successfully developed, could become a significant competitive technology for us, LNPs generally contain fusogenic lipids that can activate the innate immune system and result in dose-limiting toxicities.

Achievement of Milestones

During 2016, we achieved a number of milestones which we believe as significant. In June 2016, we demonstrated preclinical proof of concept for the treatment of a second product candidate, PRX-ASL, which further established the breadth of our Hybrid mRNA Technology. This was closely followed by selection of our lead product candidate, PRX-OTC. We tested our Hybrid mRNA Technology's ability to deliver mRNA in a large animal tolerability study with non-human primates. Since there is no large animal model of OTCD, we used human erythropoietin, or hEPO, as a surrogate reporter mRNA, formulated with the same delivery components as PRX-OTC. We believe that the dose responsive increase in hEPO expression, the increase in the hematocrit levels, which indicates higher production of red blood cells promoted by hEPO and the safety and tolerability profile observed in the study have laid the foundation for us to proceed with further preclinical and clinical development of PRX-OTC.

EVENT	Completion
Proof of Concept in Second Disease Model	**2Q 2016 – Achieved**
Declare Lead Development Candidate	**2Q 2016 – Achieved**
Large Animal Tolerability Study	**4Q 2016 – Achieved**

Our Team

We were founded by Robert W. Overell, Ph.D., our president and chief executive officer, and world leaders in polymer-based drug delivery systems Patrick S. Stayton, Ph.D., professor of bioengineering at the University of Washington, and Allan S. Hoffman, Ph.D., professor emeritus of bioengineering at the University of Washington, together with Oliver W. Press, M.D., Ph.D., a member of the Fred Hutchinson Cancer Research Center and a professor of medicine at the University of Washington, and Paul H. Johnson Ph.D., our founding chief scientific officer.

We believe that success in the field of in vivo nucleic acid delivery and therapeutics requires a highly specialized team. We have a highly experienced management team with over 50 years of combined experience in the delivery and development of nucleic acid therapeutics working in state-of-the-art chemistry and biology facilities in Seattle, Washington. In addition to the experience of our management team, leadership in research and development includes Michael Houston, our chief scientific officer who has more than 12 years of experience in oligonucleotide chemistry and delivery systems and was the former vice president of chemistry and formulations at Nastech Pharmaceutical Company Inc., which became MDRNA Inc. and Marina Biotech, Inc., Mary Prieve, Ph.D., vice president of biology, Sean Monahan, Ph.D., vice president of chemistry, each of whom have over 10 years of experience in nucleic acid delivery, and Gordon Brandt, M.D., our chief medical officer, who has served as president and executive vice president of clinical affairs for Nastech Pharmaceutical Company, Inc., which became MDRNA Inc., where he worked on the development of nucleic acid therapeutics from 2004 until 2008. We also use consultants and advisors who provide us with key advice in specific areas. These include James Watson, MBA, who serves as our head of corporate development and most recently served as chief business officer at Alvine Pharmaceuticals, Inc. from 2011 to 2016, and, prior to that, was a managing director and head of private equity at Burrill & Company and chief executive officer of Burrill & Company's merchant banking group; and Stuart Swiedler, M.D., Ph.D., our clinical advisor for orphan drug development, who has been working with us since 2014 and most recently served as senior vice president of clinical affairs at BioMarin Pharmaceutical Inc., an orphan drug company, where for over a 10-year period he contributed to both the non-clinical and clinical aspects of drug development for the regulatory approvals of the orphan drugs Aldurazyme®, Naglazyme® and Kuvan®.

Our Mission and Culture

We are dedicated to the development of mRNA therapeutics that hold promise for treatment of orphan diseases for which few, if any, effective therapeutic options are available. Our guiding principles, against which all employees have been evaluated annually as a key component of our performance management system since our inception, are:

- *Open Communication* . This is especially important in a drug development company, where tremendous value can be built from close collaboration between team members.

- *Teamwork* . Talented multidisciplinary teams, with the right skill set, that collaborate effectively against a common goal can create a practically unstoppable force.

- *Mutual Respect* . We each have different points of view, and nobody is right all of the time. Trust your instincts, but respect those of others too, especially in areas of their expertise.

- *Excellence and Integrity* . We strive for excellence in everything we do, and do it with the highest level of personal and professional integrity.

Company Information

We were incorporated on March 9, 2006 as a Delaware corporation. Our principal executive office is located at 410 W. Harrison Street, Suite 300, Seattle, Washington 98119. Our telephone number is 206-805-6300. Our website address is *www.phaserx.com* . Information contained in, or accessible through, our website does not constitute a part of this Annual Report on Form 10-K.

Our Initial Target Diseases: Urea Cycle Disorders

Our initial target diseases are urea cycle disorders. Urea cycle disorders are a family of inherited rare genetic metabolic disorders, each of which is caused by a mutation that results in a deficiency of one of the enzymes that are necessary for the normal function of the urea cycle to remove ammonia from the bloodstream. When proteins are broken down by the body, ammonia is produced as a waste byproduct. The urea cycle involves a series of biochemical steps which removes ammonia from the blood. Normally, in individuals with a functioning urea cycle, ammonia is converted into a compound called urea and excreted in urine. In patients with urea cycle disorders, the liver's ability to convert ammonia to urea is diminished or absent, and the process of removing ammonia from the bloodstream is disrupted. As a result, excess ammonia accumulates in the blood, a condition known as hyperammonemia. Ammonia is a potent neurotoxin, and when ammonia reaches the brain through the bloodstream, it causes severe medical complications including cumulative and irreversible brain damage, and can cause coma and death.

Urea cycle disorders are diagnosed either through newborn screening or when symptoms occur and are recognized as a urea cycle disorder by further testing. Initial urea cycle disorder symptoms range from catastrophic illness with coma occurring within a few days of birth to milder and non-specific symptoms such as difficulty sleeping, headache, nausea, vomiting, disorientation and seizures, particularly in patients who present later in life.

Urea cycle disorders occur in approximately 1 in 35,000 births in the United States, with OTCD being most common at a rate of approximately 1 in 56,500 live births, followed by ASL deficiency at a rate of approximately 1 in 218,750 live births and ASS1 deficiency at a rate of approximately 1 in 250,000 live births according to the journal article "The Incidence of Urea Cycle Disorders" published in *Molecular Genetics and Metabolism* , 2013, or the Incidence of Urea Cycle Disorders article. Based on demographic data for those patients enrolled in the National Institutes of Health-sponsored urea cycle disorder consortium longitudinal study, "A Longitudinal Study of Urea Cycle Disorders" published in *Molecular Genetics and Metabolism* , 2014, or the Longitudinal Study article, approximately one quarter of patients with urea cycle disorders are diagnosed in the neonatal period (first month of life), seventy percent are diagnosed after the neonatal period, and 5% remain asymptomatic throughout life. According to the Longitudinal Study article, approximately 114 newborns are predicted to be born with a urea cycle disorder in the United States each year, and approximately one quarter of the patients diagnosed in the neonatal period die due to the urea cycle disorder, compared with 11% mortality for patients with late onset disease. In 2015, there were approximately 4 million births in the United States, according to Centers for Disease Control and Prevention (source: *http://www.cdc.gov/nchs/births.htm* , last visited Feb 21, 2017).

Our Development Programs

Our mRNA therapeutics for the urea cycle disorders are intended to provide to patients weekly or once every two week intravenous delivery of mRNA encoding the missing enzyme, thereby allowing the patient to produce the needed enzyme and correcting the disease. Because our approach addresses the underlying cause of the disease by reinstating the normal physiology, it is anticipated that no dietary restriction or special amino acid supplementation will be necessary, and the disease can be managed without hyperammonemic crises or continued neurologic deterioration. For all of our urea cycle disorder programs, the product profile of our candidates is anticipated to include reversal of the enzyme deficiency, which would be expected to correct the disorder by restoring the normal physiology, and normalize plasma ammonia levels, eliminate the need for ammonia scavenger medications and dietary restrictions, and decrease or eliminate hyperammonemic crises and the consequent neurological damage.

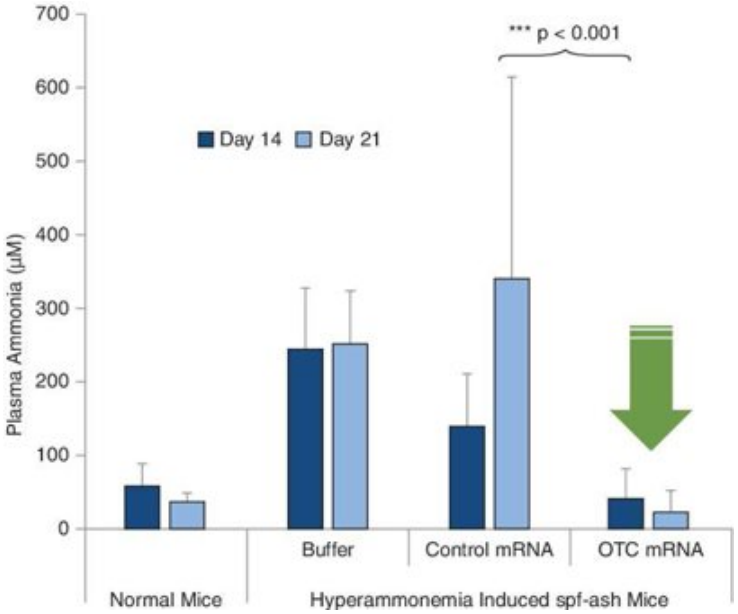
OTCD

Our most advanced program is for OTCD. OTCD is the most common subtype of the urea cycle disorders and affects all ethnic groups and geographic areas. OTC is an enzyme in the urea cycle that removes ammonia in the blood. Patients with severe OTCD rapidly develop hyperammonemia soon after birth and have a disease phenotype which may lead to coma or death in the absence of liver transplant. In some affected individuals, signs and symptoms of OTCD may be less severe, and may not appear until later in life, but most patients show symptoms of OTCD by age 12 which typically manifest as hyperammonemic crises. The gene that codes for OTC is located on the X-chromosome, and hence, the majority of severe patients are male, but females with one abnormal gene can also be affected, usually after the neonatal period, as reported in the journal article "Diagnosis, Symptoms, Frequency and Mortality of 260 Patients with Urea Cycle Disorders from a 21-year, Multicentre Study of Acute Hyperammonaemic Episodes" published in *Acta Paediatrica* , 2008. Patients can present at almost any time of life with a triggering event such as an infection or pregnancy or even a change in diet, resulting in elevations of plasma ammonia concentration. Despite milder presentations in adulthood, patients are at constant risk of ammonia level rising, and hyperammonemia, encephalopathy, cerebral edema, and death can occur.

Preclinical Development

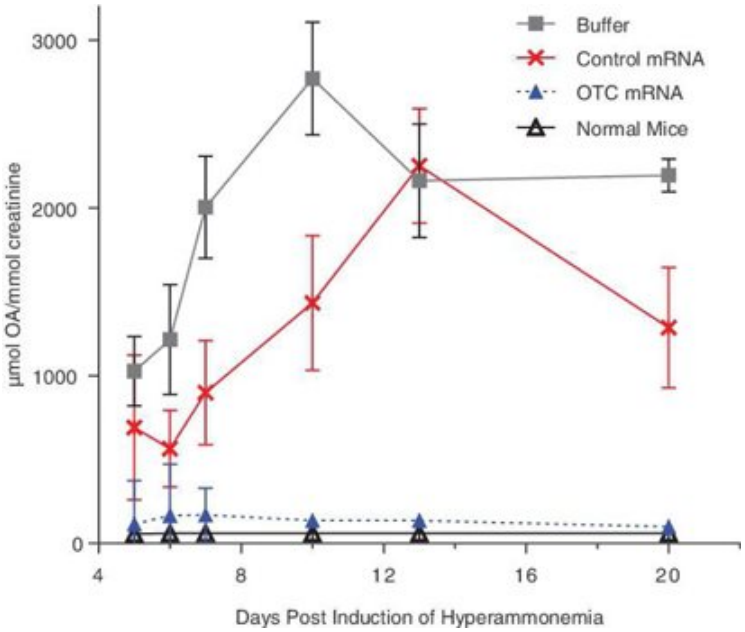
In 2015, we achieved preclinical proof of concept for OTCD in a well-accepted animal model of a human orphan liver disease using *OTC-spf*^{ash} mice. Like human OTCD patients, the *OTC-spf*^{ash} mice have a defective OTC gene, and when OTC expression in these mice is further impaired, the mice recapitulate the human OTCD disease, including elevated blood ammonia rapidly progressing to death, as reported in the journal article "Induction and Prevention of Severe Hyperammonemia in the spf ^{ash} Mouse Model of Ornithine Transcarbamylase Deficiency Using shRNA and rAAV-mediated Gene Delivery" published in *Molecular Therapy* , 2011. Hyperammonemia is induced in these mice by treating the animals with a viral vector containing a short hairpin RNA designed to knock down the remaining mouse OTC mRNA. As the mouse OTC mRNA levels are decreased, OTC enzyme levels also decrease resulting in the mice developing elevated ammonia levels in the blood. Normal mice have ammonia levels of ~50 μM. Delivery of the human OTC mRNA using our Hybrid mRNA Technology resulted in the production of the natural human OTC enzyme and normalization of two key clinical biomarkers, ammonia level in the blood and orotic acid level in the urine when dosed once a week or twice a week. In contrast, the treatment of mice with a human OTC mRNA designed not to be translated (a negative control) resulted in the mice having higher ammonia and orotic acid levels. As shown in the figure below, treatment of mice twice a week with 3 mg/kg doses of a functional human OTC mRNA over a three-week period resulted in a statistically significant reduction in blood ammonia levels and reduced ammonia levels to those observed in the wild type mice. To determine whether data is statistically significant compared to controls we use standard statistical measures, in this case the t-test. The t-test provides a "p-value" representing the probability that random chance could explain the result. In general, a 5% or lower p-value ($p < 0.05$) is considered to be statistically significant. However, it should be noted that statistical significance alone may not be sufficient to establish efficacy by the FDA. Rather, efficacy endpoints are generally agreed upon with the FDA prior to commencement of a study, which may require clinical significance beyond a statistically significant p-value. Notwithstanding that fact, the p-value calculated in this study was $p < 0.001$, as shown in the figure below, meaning that the probability that random chance could explain this result is < 0.1%. Normalization of ammonia levels was also achieved with treatment of mice once a week. The study has shown meaningful reduction in ammonia levels, the endpoint that was evaluated by the FDA in order to grant approval of Ravicti.

Normalization of Ammonia Levels in OTC-spfash Mice Treated with Human OTC mRNA Delivered by Hybrid mRNA Technology



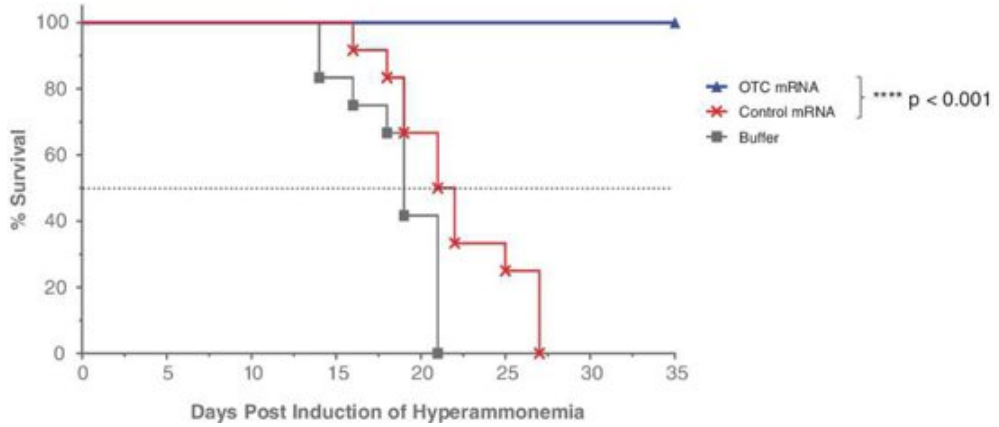
Moreover, levels of the other well-accepted biomarker, urinary orotic acid, were also normalized in this study. As shown in the figure below, treatment of mice twice a week with 3 mg/kg doses of a functional human OTC mRNA over a three-week period demonstrated that the orotic acid levels were maintained at the levels similar to the orotic acid levels in normal mice. Similar results were obtained with treatment of mice once a week. Mice treated with buffer or the negative control mRNA resulted in urinary orotic acid levels that were 10 to 30-fold higher than mice treated once a week or twice a week.

Normalization of Orotic Acid Levels in OTC-spf^{ash} Mice Treated with Human OTC mRNA Delivered by Hybrid mRNA Technology



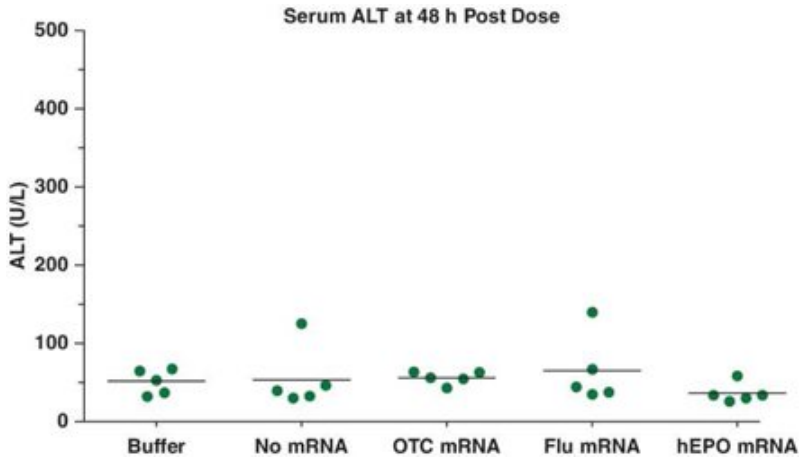
The induction of hyperammonemia in *OTC-spf^{ash}* mice resulted in uncoordinated movements (ataxia), significant body weight loss and, ultimately, death. As shown in the figure below, mice treated with buffer or the negative control mRNA had a median survival of 19 and 21 days, respectively. Mice treated twice a week with 3 mg/kg doses of a functional human OTC mRNA showed complete survival as long as 35 days. Additionally, no signs of ataxia were observed in the treated mice, and all mice in the treated group gained weight. When therapy with the Hybrid mRNA Technology was terminated in these mice, the mice remained disease-free for more than three additional weeks at which time the mice started to succumb to the effects of elevated ammonia levels.

Complete Survival of OTC-spfash Mice Treated with Human OTC mRNA Delivered by Hybrid mRNA Technology in Hyperammonemia Model



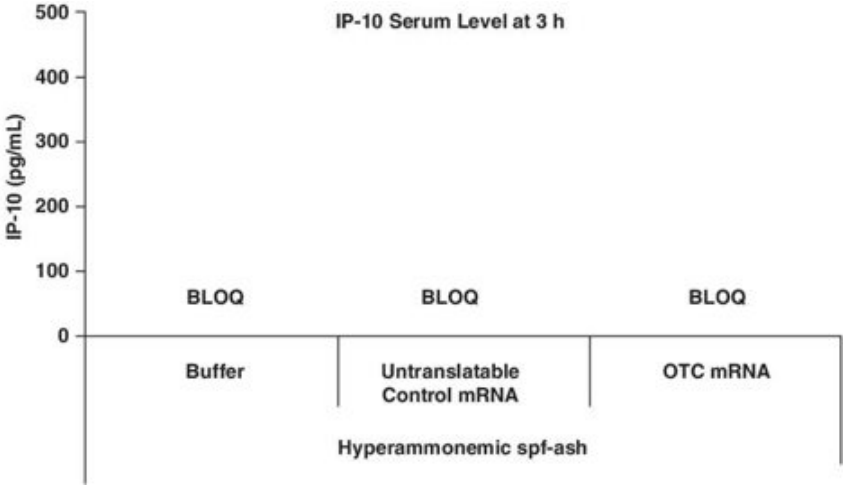
Delivery of the human OTC mRNA using our Hybrid mRNA Technology in the *OTC-spf^{ash}* mice was well tolerated, based on our internal tolerability study with formulation being dosed twice per week for three weeks in *OTC-spf^{ash}* mice, with normal serum chemistries (electrolytes, albumin and creatinine levels) observed 48 hours following dosing, and no elevation of alanine aminotransferase, or ALT, level in the blood, which is a test for liver damage. This is shown in the figure below.

Levels of Liver Enzymes in Mice Dosed with Hybrid mRNA Technology



Moreover, we observed no detection of the cytokine IP-10 in *OTC-spf^{ash}* mice 3 hours following dosing (below limit of quantitation, or BLOQ), indicating no stimulation of the innate immune system.

Levels of the Cytokine IP-10 in OTC-spf^{ash} Mice Treated with Hybrid mRNA Technology



* BLOQ: below limit of quantitation

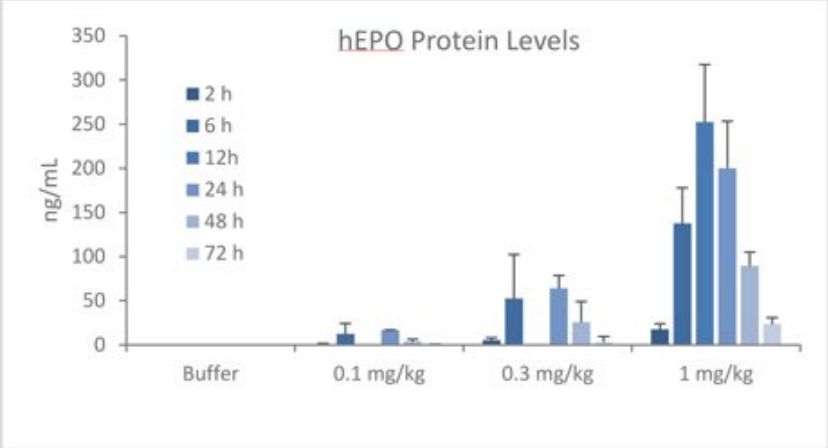
Preclinical Non-GLP Safety Data

In 2017, we plan to conduct formal safety studies to be included in our IND submission to FDA. Such studies must be conducted under good laboratory practices, or GLP. All our other scientific studies are non-GLP studies, although we believe these studies are conducted with high levels of scientific excellence and integrity. In 2016, we performed a number of safety studies using our lead formulation of PRX-OTC in both rats and non-human primates, and, as is customary, these were non-GLP studies. Since there is no large animal model of OTCD, we used hEPO as a surrogate reporter mRNA, formulated with the same delivery components as PRX-OTC. The advantages of using hEPO are that one can easily measure hEPO levels in the blood by a standard ELISA assay, which is an assay used to measure hEPO protein. Additionally, we can determine whether the hEPO that is being produced is biologically active by measuring increase in reticulocytes and hematocrit.

In rats dosed once a week for 5 weeks with 1 mg/kg of hEPO mRNA formulated in our lead formulation, we observed hEPO levels in the blood thousands of fold above steady state levels of the rat protein. During the course of this experiment, there was no diminution in protein concentrations following each mRNA dose, and levels were within 2-fold of each other. Consistent with this high level of hEPO, we observed a significant increase in hematocrit over time. Levels rose from a baseline of approximately 40% to greater than 55% after 5 weeks of treatment. From a safety perspective, we observed no increases in the levels of liver alanine aminotransferase, or ALT, which is generally used to test liver damage, 24 hours after each dose. Moreover, there were no noteworthy changes in serum chemistry and no changes in histopathology in the target tissue liver, or the spleen or kidney tissues.

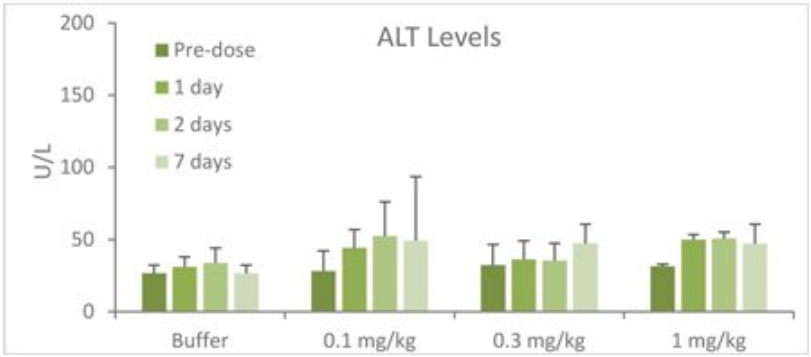
In addition to testing in rats, we have performed testing of the of Hybrid mRNA Technology in non-human primates. In the non-human primate study, hEPO mRNA dosed at 0.1, 0.3 and 1.0 mg/kg delivered with our Hybrid mRNA Technology platform demonstrated dose-dependent increases in levels of hEPO protein thousands of fold above normal physiological levels. Peak levels of hEPO were observed at 12 hours after dosing. In addition, a commensurate increase was also seen in reticulocyte count, which was robust and seen in all dose groups.

Assessment of hEPO Protein Levels in Non-Human Primates Treated with hEPO mRNA Delivered Using Hybrid mRNA Technology

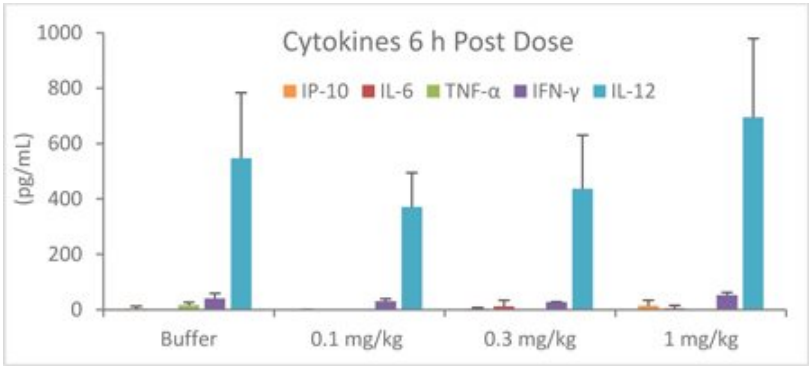


In addition, the formulation was well tolerated in non-human primates with no statistically significant dose-related changes in liver transaminase levels, a measure of liver damage. Moreover, there were no increases in immune inflammatory cytokines observed 6 hours after dosing, including IL-6, TNF- α , IFN- γ , IL-12, or IP-10 .

Assessment of ALT Levels in Non-Human Primates Treated with hEPO mRNA Delivered Using Hybrid mRNA Technology



Assessment of Cytokine Levels in Non-Human Primates Treated with hEPO mRNA Delivered Using Hybrid mRNA Technology



The above results demonstrate the ability of the Hybrid mRNA Technology to deliver an mRNA therapeutic, produce the intended protein and the safety and tolerability of the formulation. Additionally, it demonstrates that our Hybrid mRNA Technology is translatable across multiple species, namely, mouse, rats and non-human primates.

After obtaining this data with hEPO, we performed an additional non-GLP safety study in 2016 in rats with our lead formulation using hOTC as the mRNA cargo. In this study, normal rats were dosed at 1, 3 and 5 mg/kg of hOTC mRNA and the levels of hOTC protein were measured 7 days after dosing by western blot analysis. We observed a linear dose responsive increase in hOTC protein relative to the animals treated with buffer. There were no toxicities associated with elevated levels of OTC in the treated animals. Consistent with our hEPO study, there was no significant change in serum chemistry. More importantly, as we increased the dose of mRNA, we did not observe any changes in liver ALT levels 24 hours after dosing, providing further supportive data that our lead formulation was well tolerated.

With the successful completion of these non-GLP toxicological studies we are now working with our contract manufacturing organizations, or CMOs, to scale up PRX-OTC in preparation for additional non-GLP studies, including dose range finding studies, in which ascending doses of a compound are tested and biodistribution studies are conducted to measure tissue uptake of the compound. We plan to conduct IND-enabling GLP toxicological studies following the foregoing studies.

ASL Deficiency

ASL deficiency is the second subtype of urea cycle disorder we are pursuing as a development program. As in OTCD, ASL deficiency often manifests with rapid-onset hyperammonemia in the newborn period or as a late onset form with episodic hyperammonemia and/or long term complications that include liver dysfunction, neuro-cognitive deficits and hypertension. The accumulation of ammonia, as well as the urea cycle intermediates citrulline and argininosuccinic acid is the biochemical hallmark of ASL deficiency. The incidence of ASL deficiency is estimated at 1 in 218,750 live births, according to the Incidence of Urea Cycle Disorders article.

We have established the ASL hypomorphic mouse model at PhaseRx. This mouse model recapitulates a severe form of the human disease making it a valuable tool for the evaluation of potential lead compounds (Erez et al., Nat Med 17: 1619-1626). In this model, mice have 16% residual ASL enzyme activity resulting in elevated levels of arginosuccinic acid, citrulline and ammonia leading to multi-organ failure and death.

In preliminary studies, we have demonstrated that the ASL hypomorphic mice can express the human protein. Mice treated with 1.4 mg/kg of hASL mRNA with the Hybrid delivery system demonstrated that hASL protein expression was still detected 11 days post-dose. In ASL hypomorphic mice treated with 5 mg/kg mRNA every third and fourth day, statistically significant reduction in plasma ammonia levels were observed relative to buffer treatment animals. Concomitantly, we observed statistically significant reductions in the plasma amino acids arginosuccinic acid and citrulline. These doses were well tolerated and were associated with significant increases in animal body weights in ASL-treated mice. As these were preliminary studies, further formulation and mRNA optimization should result in significantly improved efficacy.

Preclinical Development

In June 2016, preclinical studies in ASL deficiency were conducted using ASL-deficient mice, using the same delivery platform used for our OTCD formulation, which rendered positive proof of concept data for the PRX-ASL. We performed initial studies to examine production of ASL mRNA in normal mice, and following confirmation of the synthesis of the corrected gene, we administered therapeutic ASL mRNA into ASL hypomorphic mice suffering from a genetic mutation, and examined protein production in the liver and reduction of argininosuccinic acid levels in plasma. After two weeks of mRNA treatment, the ASL-deficient mice showed statistically significant reduction in ammonia levels.

ASS1 Deficiency

ASS1 deficiency is the third subtype of urea cycle disorder we are pursuing as a development program. The argininosuccinate synthase 1, or ASS1, enzyme is responsible for combining two amino acids, citrulline made by other enzymes in the urea cycle, and aspartate, to form a molecule called argininosuccinic acid. A series of additional chemical reactions in the urea cycle uses argininosuccinic acid to form urea. If the ASS1 enzyme is absent or defective, then a build-up of citrulline and ammonia in the blood can occur, resulting in hyperammonemia. The incidence of ASS1 deficiency is estimated at 1 in 250,000 live births, according to the Incidence of Urea Cycle Disorders article.

Preclinical Development

We have designed and manufactured the ASS1 mRNA, obtained ASS1-deficient mice and are working with animal disease models for the treatment of ASS1 deficiency internally. We plan to perform initial studies to examine the production of ASS1 mRNA in normal mice, and following confirmation of the synthesis of the corrected gene, we plan to administer therapeutic ASS1 mRNA into ASS1-deficient mice to examine protein production in the liver, reduction of citrulline levels in plasma and presence of argininosuccinic acid levels in plasma. We anticipate using the same delivery platform used for our OTCD formulation.

IND-Enabling Studies and Clinical Development Plans – PRX-OTC

We intend to continue to scale up the manufacturing process for PRX-OTC in the first half of 2017 to initiate IND-enabling studies, including preclinical GLP-compliant toxicology studies in the second half of 2017.

Based on the results of the preclinical studies, we expect to demonstrate safety and clinical efficacy of PRX-OTC in a Phase 2a study in the first half of 2018 and in a Phase 2b study in the second half of 2018 in OTCD patients. The clinical development of PRX-OTC is planned to include a two-stage clinical trial. ThePhase 2a stage will enroll adults and pediatric patients who are currently on ammonia scavenger drugs and protein restricted diet for evaluation of safety; pharmacokinetics, as measured by blood concentration; and pharmacodynamics, as measured by plasma ammonia levels, following administration of our PRX-OTC. The Phase 2b stage is intended to repeat dose adult and pediatric patients.

In 2016 we had a pre-IND meeting with the FDA to gain the FDA's input on manufacturing, toxicology, and clinical programs. In November 2016, the OTCD program received orphan drug designation in the United States. Orphan drug designation is one of the requirements for eligibility for a Rare Pediatric Disease Priority Review Voucher. According to the FDA website, under this program, a sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product.

Market Opportunities

Currently, there is no cure for urea cycle disorders other than liver transplant. Liver transplant is limited by donor availability and patient eligibility, and it is also associated with significant risks and complications, including perioperative morbidity and mortality, liver rejection, and vulnerability to infection due to lifelong immunosuppressant medication. Therefore, liver transplant is an option typically reserved for the most severely affected patients in life-threatening conditions. Moreover, while liver transplantation stops the deleterious effects of the OTCD disease, patients who undergo liver transplantation may have already incurred neurological damage which is not reversible.

Current management of urea cycle disorders includes decreasing ammonia production through the reduction of protein in the diet, supplementation with essential and/or branched chain amino acids, the use of dietary supplements such as arginine and citrulline and ammonia lowering agents, including Ravicti and Buphenyl, FDA-approved ammonia scavenger products currently being marketed by Horizon Pharma plc. Horizon Pharma plc acquired Ravicti and Buphenyl in 2015 through the acquisition of Hyperion Therapeutics Inc. for $958 million.

Ravicti was approved by the FDA in 2013 for chronic management of urea cycle disorders in adult and pediatric patients greater than two years of age. It is a three times daily oral drug that must be used with a protein-restricted diet and amino acid dietary supplements. As reported in the FDA news release, dated February 1, 2013, announcing approval of Ravicti, the major study supporting Ravicti's safety and effectiveness involved 44 adults who had been using Buphenyl. According to this news release, patients were randomly assigned to take Buphenyl or Ravicti for two weeks before being switched to the other product for an additional two weeks. The FDA news release reported that blood testing showed Ravicti was as effective as Buphenyl in controlling ammonia levels. Three additional studies in children and adults provided evidence supporting the long-term safety and effectiveness of Ravicti in patients two years and older. In 2014, Hyperion Therapeutics Inc. reported that the average gross selling price per patient per year for Ravicti was approximately $385,000. The revenue projection for 2017 for Ravicti is $169 million in the United States, based on the sales data from the fourth quarter of 2016 reported by Horizon Pharma plc in its press releases. The revenues for Ravicti are growing at approximately 26% per year based on the sales data from the third quarters of 2015 and 2016 reported by Horizon Pharma plc in its press releases.

Buphenyl was approved by the FDA in 1996 and was the only branded FDA-approved therapy for the chronic management of certain subtypes of urea cycle disorders prior to Ravicti's approval for the same subtypes. Buphenyl is also available for the treatment of urea cycle disorders in select countries throughout Europe, the Middle East, and the Asia-Pacific region. Buphenyl is administered in tablet and powder form and sold in the United States to patients who have not transitioned to Ravicti.

Ammonul (sodium benzoate and phenylacetate), an intravenous therapy marketed by Ucyclyd Pharma, Inc., a wholly owned subsidiary of Valeant Pharmaceuticals International, Inc., was approved by the FDA in the United States in 2005. We believe that Ammonul is the only FDA-approved adjunctive therapy for the treatment of hyperammonemic crises in adult and pediatric patients with the most prevalent urea cycle disorders. Currently, Ammonul is not approved for use outside the United States, but is being prescribed by physicians in parts of Europe.

Current commercial products for treatment of urea cycle disorders such as Ravicti, Buphenyl and Ammonul are ammonia scavengers that provide, in our opinion, palliative care of the symptoms at best and have substantial limitations. When urea cycle disorders are not well controlled, or even in well-controlled patients who experience concurrent illness such as infection, physiological stress such as pregnancy or surgery, or even who simply change their diet, hyperammonemia crises may occur. In a Phase 2 trial of Ravicti, two-thirds of patients with high ammonia levels at the start of the clinical trial still had high ammonia levels at the end of the trial despite taking Ravicti, as reported in the journal article "Phase 2 Comparison of a Novel Ammonia Scavenging Agent with Sodium Phenylbutyrate in Patients with Urea Cycle Disorders: Safety, Pharmacokinetics and Ammonia Control" published in *Molecular Genetics and Metabolism* , 2010. In the Phase 3 trials of Ravicti, sixteen percent of adult patients and 25% of pediatric patients experienced hyperammonemic crises while taking Ravicti during the one year extension trial, according to the journal articles "Ammonia Control and Neurocognitive Outcome among Urea Cycle Disorder Patients Treated with Glycerol Phenylbutyrate" published in *Hepatology* , 2013 and "Glycerol Phenylbutyrate Treatment in Children with Urea Cycle Disorders: Pooled Analysis of Short and Long-term Ammonia Control and Outcomes" as published in *Molecular Genetics and Metabolism* , 2014. In the pivotal Ravicti pediatric studies, 20% of subjects 0-5 years old and 18% of subjects 6-17 years old required a gastric tube for management of feeding while on ammonia scavengers according to the journal articles "Ammonia Control in Children Ages 2 Months Through 5 Years with Urea Cycle Disorders: Comparison of Sodium Phenylbutyrate and Glycerol Phenylbutyrate" published in *The Journal of Pediatrics* in 2013 and "Ammonia Control in Children with Urea Cycle Disorders (UCDs); Phase 2 Comparison of Sodium Phenylbutyrate and Glycerol Phenylbutyrate" published in *Molecular Genetics and Metabolism* in 2011. In addition, Buphenyl has a high pill burden or large quantity of powder and frequent dosing of 3 – 6 times per day and a taste and smell deemed unpleasant by many patients, which makes compliance for many urea cycle disorder patients difficult.

We believe our approach, which is to deliver mRNA encoding the missing enzyme into the cell, thereby making the missing enzyme and reinstating the normal intracellular physiology, offers the potential to correct certain subtypes of urea cycle disorders and avoid the need for scavenger therapy, restrictive diet and dietary supplements. In view of the rapid onset of expression observed with our Hybrid mRNA Technology in our luciferase expression studies in mice, our approach may also lead to more effective treatment of acute hyperammonemic crises in urea cycle disease patients. Additionally, the current ammonia scavengers can only remove a fixed amount of ammonia from the blood: each molecule of Ravicti can remove up to six molecules of ammonia, and each molecule of Buphenyl can remove up to two molecules of ammonia, according to the U.S. package inserts for Ravicti and Buphenyl, respectively. In comparison, there is no fixed limit on the number of ammonia molecules which can be removed following replacement of a missing enzyme.

We are not aware of any other enzyme replacement therapies for intracellular enzyme deficiencies currently being marketed for inherited enzyme deficiencies in the liver, and believe that the commercial potential for i-ERT is completely untapped and similar to the large and growing $4 billion worldwide market for conventional ERT, which includes drugs such as Cerezyme (see sales data for 2015 in the press releases and annual reports filed in 2016 by Sanofi S.A., BioMarin Pharmaceutical Inc., Shire plc and Protalix BioTherapeutics, Inc.). Cerezyme costs approximately $25,000 for a month's course of therapy in 2014, according to a news article published in the Boston Globe (Sept. 2, 2014), and commercially available ERTs list for $290,000 – $1.28 million per patient per year according to goodrx.com (last visited Mar. 11, 2016). Therapeutics for orphan liver diseases treated with ERT with similar incidences to the urea cycle disorders (1/56,500 – 1/250,000) have generated substantial sales, including for Gaucher's disease, with estimated incidence of 1/60,000, according to GeneReviews®, and worldwide sales of $1.2 billion in 2015 according to sales data by Sanofi S.A. and Shire plc; Fabry disease, with estimated incidence of 1/50,000 – 1/117,000, according to GeneReviews, and worldwide sales of $1.1 billion in 2015 according to sales data by Sanofi S.A. and Shire plc; Pompe disease, with estimated incidence of 1/40,000 – 1/100,000, according to GeneReviews, and worldwide sales of $728 million in 2015 according to sales data by Sanofi S.A.; and mucoploysaccharidosis type VI, with estimated incidence of 1/250,000 – 1/600,000 according to Genetics Home Reference and worldwide sales of $303 million in 2015 according to sales data by BioMarin Pharmaceutical Inc. Conventional ERTs are generally dosed intravenously once a week to once every two weeks, according to the article "Enzyme-Replacement Therapies for Lysosomal Storage Diseases" published online by the National Center for Biotechnology Information (*source: http://www.ncbi.nlm.nih.gov/books/NBK117223* , last visited Mar. 11, 2016), and can be given by home infusion or in an outpatient setting, according to the journal article "Intravenous Enzyme Replacement Therapy: Better in Home or Hospital?" published in *British Journal of Nursing* , 2006.

The value that can be created by orphan drug companies early in clinical development is exemplified by Shire plc's acquisition of Dyax Corp. for approximately $5.9 billion, since at the time, Dyax Corp.'s most advanced asset was in a rare disease setting for hereditary angioedema and had efficacy data based on clinical trial results in approximately 40 patients, according to Shire plc's press release (*source: https://www.shire.com/newsroom/2015/november/shire-to-acquire-dyax-corp*). Hereditary angioedema has an incidence of 1/50,000 births, according to the journal article "Hereditary Angioedema: Epidemiology, Management, and Role of Icatibant" published in Biologics, 2013.

Our Hybrid mRNA Technology

mRNA Therapeutics and Competitive Approaches

mRNAs play an essential role in the process of encoding and translating genetic information from DNA to proteins. The genes in DNA encode protein molecules, including enzymes, which are essential building blocks to the functions necessary for life. Expressing a gene means synthesizing proteins encoded by the gene. The information stored within DNA are "read" and expressed in two major steps: transcription and translation. During transcription, the genes in the DNA are transcribed into mRNA, which encodes the protein sequence. mRNA serves as the blueprint for making the desired protein by cellular machinery called ribosomes during translation.

Genetic diseases are the result of a key protein not being correctly coded in the DNA. As a result, the mRNA corresponding to the gene is either defective or missing, resulting in a defective or missing protein. Our therapeutic mRNAs seek to restore the normal mRNA encoding of the normal protein, thereby restoring the missing protein function within target tissues and correcting the disease. In the case of a large number of inherited metabolic diseases of the liver that are caused by single-gene defects, expression, or synthesis, of a therapeutic mRNA providing a functional copy of the missing or defective protein has the potential to correct the genetic disorder.

The main impediment in the development of mRNA therapeutics has been a lack of effective delivery, principally due to the fact that mRNA molecules are (i) fragile and easily degradable by nucleases in the blood, and (ii) large and highly charged molecules that are typically taken up into cellular vesicles called endosomes from which they are unable to cross the endosomal membrane and enter the cytoplasm of the cell. These delivery challenges prevent therapeutic mRNA molecules from reaching the target tissue and being taken up into the cytoplasm of the target cells so that they can be translated into the desired protein of interest. To overcome these impediments, mRNA has typically been formulated into LNPs, which function to protect the mRNA from degradation in the blood and enable uptake of the mRNA inside the cell. While LNPs are effective in delivering mRNA cargo into the liver, and hence, if successfully developed, could become a significant competitive technology for us, LNPs generally contain fusogenic lipids that can activate the innate immune system and result in dose-limiting toxicities, according to the journal articles "Lipid-Based Nanocarriers for RNA Delivery" published in *Current Pharmaceutical Design* , 2015, and "Nanotoxicity: a Key Obstacle to Clinical Translation of siRNA-based Nanomedicine" published in *Nanomedicine* , 2014.

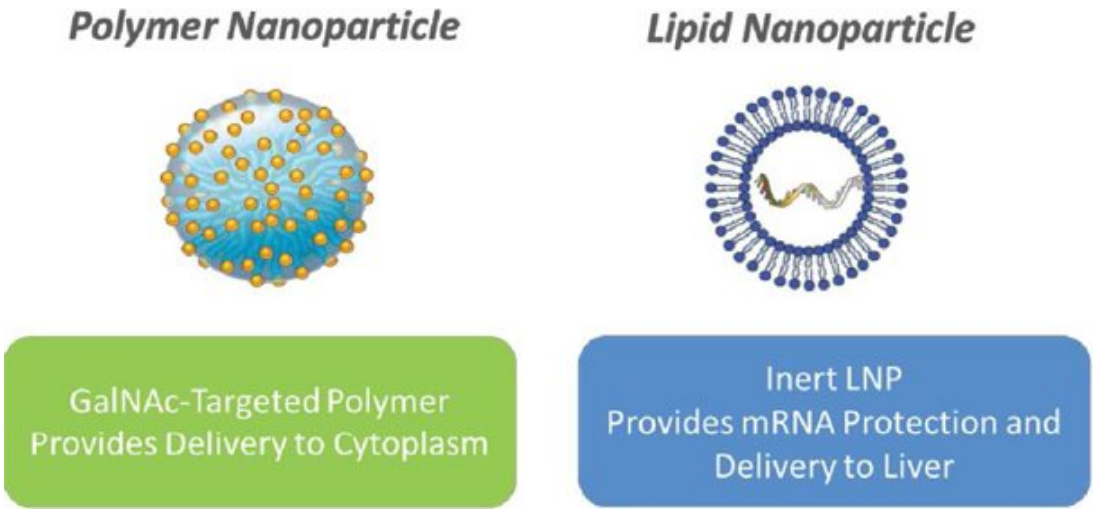
An alternative approach to treating orphan liver diseases is gene therapy using AAV vectors; however, triggering of multiple types of immune response to the virus represents a major challenge facing development of these viral vectors, according to the journal article "Gene Therapy in Liver Diseases: State-of-the-Art and Future Perspectives" published in *Current Gene Therapy* , 2012. The AAV vectors offer the potential of longer-term correction of the liver disease by gene therapy, but they can be susceptible to pre-existing neutralizing antibody-mediated immunity against the virus present in a significant number of patients; they trigger immune responses in the body can prevent repeat dosing, since the initial dose primes the immune system and can neutralize vector given in a subsequent administration; and they can stimulate cell mediated immunity against infected liver hepatocytes, according to the journal articles "Hemophilia Gene Therapy: Caught Between a Cure and an Immune Response" published in *Molecular Therapy* , 2015, and "Immune Responses to AAV Vectors: Overcoming Barriers to Successful Gene Therapy" published in *Blood* , 2013. Additionally AAV vectors may not be effective in treating the new born patients, since AAV-mediated correction of OTCD is durable in adult but not neonatal *OTC-spf* ^{ash} mice, according to a journal article "AAV2/8-mediated Correction of OTC Deficiency Is Robust in Adult but Not Neonatal Spf ^{ash} Mice" published in *Molecular Therapy* , 2009.

Our Hybrid mRNA Technology

Our Hybrid mRNA Technology provides a differentiated polymer-LNP-based formulation approach for the delivery of mRNA into the hepatocytes in the liver. The Hybrid mRNA Technology utilizes our SMARTT Polymer Technology in combination with an inert LNP which functions as a carrier for the mRNA. The LNP, which is comprised of several distinct lipids, encapsulates and protects the mRNA following intravenous injection while it transits the blood and is taken up into the hepatocytes while the polymer delivers mRNAs into the cytoplasm by mediating their escape from endosomes. The synthetic polymers exploit a proprietary mechanism to effect passage of mRNA molecules across the endosomal membrane. Our approach does not require fusogenic lipids typical of competitor LNPs and we believe that is one of the reasons why our delivery system is better tolerated than our competitors' technologies.

Our SMARTT Polymer Technology is comprised of a diblock vinyl polymer comprising two blocks of monomers with distinct delivery functionalities. The polymer is targeted to the asialoglycoprotein receptor on liver hepatocytes by the inclusion of a GalNAc moiety on one end of the polymer. The polymers have a first hydrophilic block comprising 2-3 hydrophilic monomers which impart water solubility to the polymer and a second hydrophobic block comprising 2-3 hydrophobic monomers that are pH-tunable and mediate endosome escape of the mRNA cargo into the cytoplasm. These polymers self-assemble into nanoparticles. The structure of the polymer is shown below.

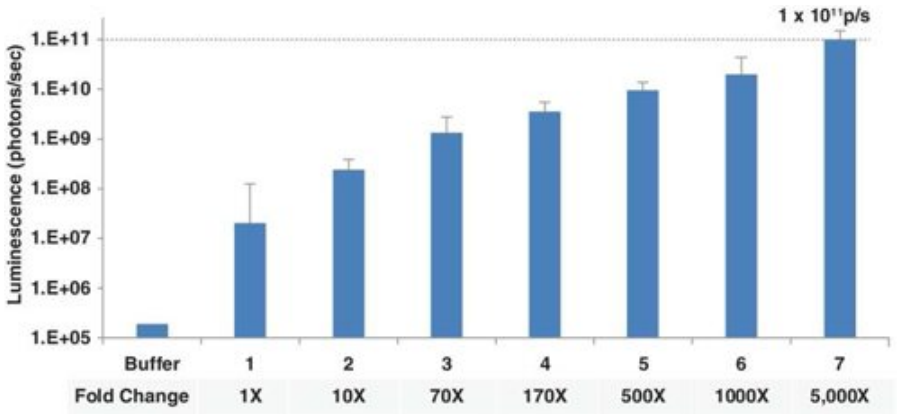
Schematic Representation of the PhaseRx Hybrid mRNA Technology



We have performed two studies in collaboration with external specialist contract research laboratories using one of our polymers as a polymer-siRNA, or small interfering RNA, conjugate. The polymers had the same diblock architecture as shown above, and were similar in composition to the polymers used in the Hybrid mRNA Technology. In the first study, we evaluated the absorption, distribution, metabolism, and excretion of a polymer with a radioactive label in rats which showed rapid uptake into the liver, with greater than 95% of the polymer dose in the liver within two hours after dosing. Very little or no polymer was detected in other tissues or organs. The main route of polymer clearance from the liver was into the bile and then feces with 71% of the dose being cleared into bile within 72 hours after dosing. In the second study, the safety and efficacy of a polymer was evaluated in non-human primates. In a single dose, dose ranging study, primates received doses of a polymer conjugate ranging from 1 to 2.4 mg/kg. The formulation was well tolerated with no significant dose-related changes in serum chemistry, hematology, or coagulation. Moreover, no changes in complement activity or increase in IL-6 cytokine levels, which indicates stimulation of the immune system, were observed, and histopathological evaluation of the liver, kidneys and spleen of treated animals showed no dose-related effects. In addition, our internal studies using dye-labeled siRNA conjugates of our polymers have shown that GalNAc-targeted polymers deliver siRNA effectively to the hepatocytes in vivo, while polymers targeted with mannose were ineffective in mediating siRNA delivery to the hepatocytes.

Our Hybrid mRNA Technology has been shown in our internal preclinical studies to result in synthesis of intended proteins in hepatocytes with a fast onset of action, suggesting highly effective delivery of mRNA molecules, and the synthesis of a number of protein classes including cytosolic proteins, mitochondrial proteins and secreted proteins. By developing a rapid in vivo-based screening program, we have gained valuable information about the structure-activity relationships of formulation components. The figure below illustrates the dramatic changes in activity that have resulted from our formulation screening program showing a 5000-fold improvement in the production of luciferase in the livers of mice treated intravenously with a single 1 mg/kg dose of mRNA encoding luciferase delivered with our Hybrid mRNA Technology, as measured six hours after dosing. The numbers 1 through 7 at the bottom of the figure below represent the successive generations of the Hybrid mRNA Technology that were tested in this assay which showed progressively increased activity. In addition, expression levels within three-fold of maximal luciferase signal were observed within three hours after dosing, which indicates that the synthesis of the desired protein in the liver can be very rapid following administration of the mRNA therapeutic using our Hybrid mRNA Technology. The observed levels of fluorescence for formulation 7 are 1 million-fold above background.

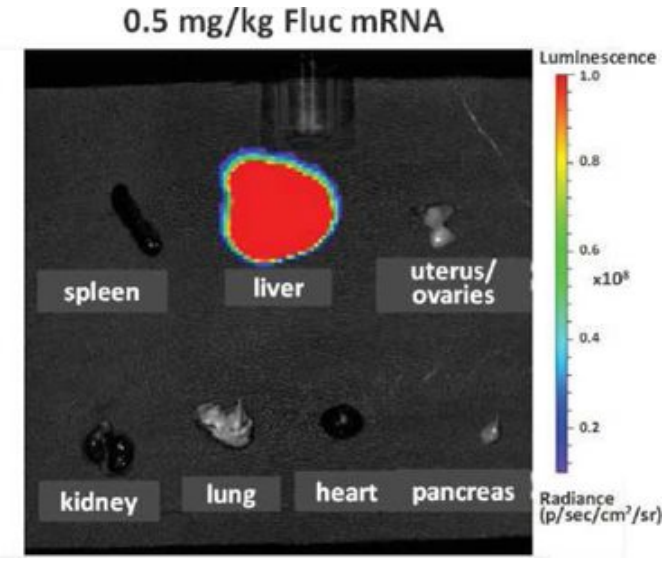
5,000-fold Increase in Activity of Hybrid mRNA Technology Through Formulation Development and Screening as Measured by Luciferase Expression



Moreover, when the Hybrid mRNA technology was used to deliver human erythropoietin mRNA and administered intravenously to mice at a dose of 1 mg/kg, it resulted in supraphysiological levels of the secreted protein erythropoietin 20,000 times above normal levels in untreated mice.

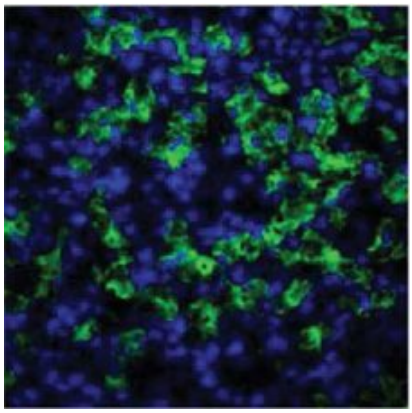
In addition to the ability of the Hybrid mRNA Technology to effect high levels of production of desired proteins, our internal preclinical studies with luciferase mRNA showed that luciferase expression is highly specific to the liver, with little or no expression in immune organs such as the spleen or other tissues. This data is shown in the figure below. Mice were injected intravenously with 0.5 mg/kg of luciferase mRNA delivered using the Hybrid mRNA Technology, and six hours later the various organs were harvested and analyzed for expression of luciferase. As can be seen from the data below, expression of the luciferase mRNA was specifically seen in the liver, with no detectable expression in other organs, including the spleen. This data is in contrast to a recent report with a fusogenic LNP-based mRNA formulation where expression was also observed in the spleen and pancreas, as reported in Optimization of Lipid Nanoparticle Formulations for mRNA Delivery in Vivo with Fractional Factorial and Definitive Screening Designs published in ACS Nanoletters, 2015. We believe that the specificity of mRNA expression to the liver observed with our technology will minimize off-target toxicities that can result from the unintended expression of therapeutic proteins in other tissues.

Imaging of Expression of Luciferase in Individual Organs Dissected from Mice Treated with Luciferase mRNA Delivered using the Hybrid mRNA Technology



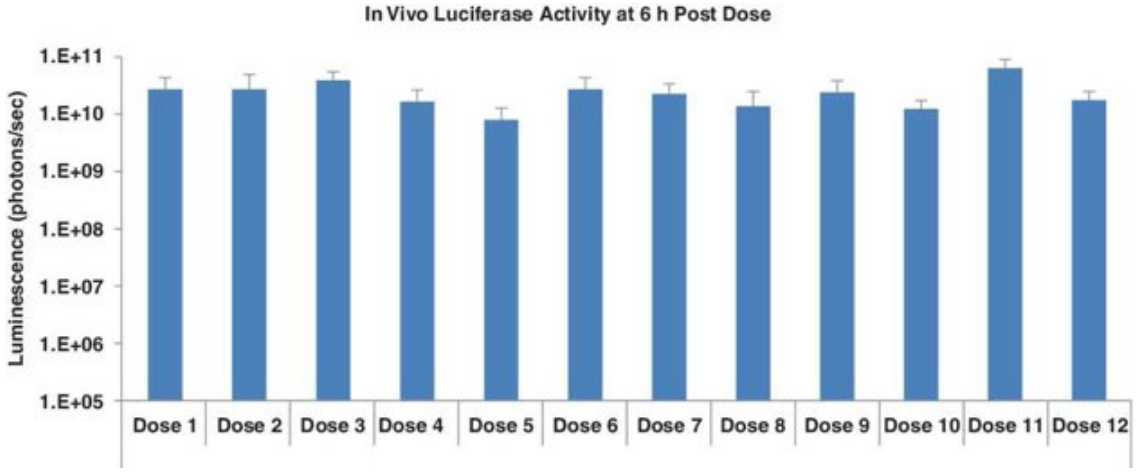
In addition to organ specificity, the expression of the luciferase protein was seen predominantly in the hepatocyte, the desired cell type in the liver, with no apparent expression in Kuppfer cells in the liver lining the walls of the sinusoids. This result is shown in the immunofluorescence figure below in which the luciferase expression occurs as bright green areas that are specifically in the hepatocytes. The blue areas represent nuclei of individual cells. The observed specificity of expression to the hepatocytes, in addition to the organ specificity shown above, is expected to further improve the safety profile of our products.

Immunofluorescent Staining of Luciferase Protein in Liver Section from Mice Treated with Luciferase mRNA Delivered using Hybrid mRNA Technology



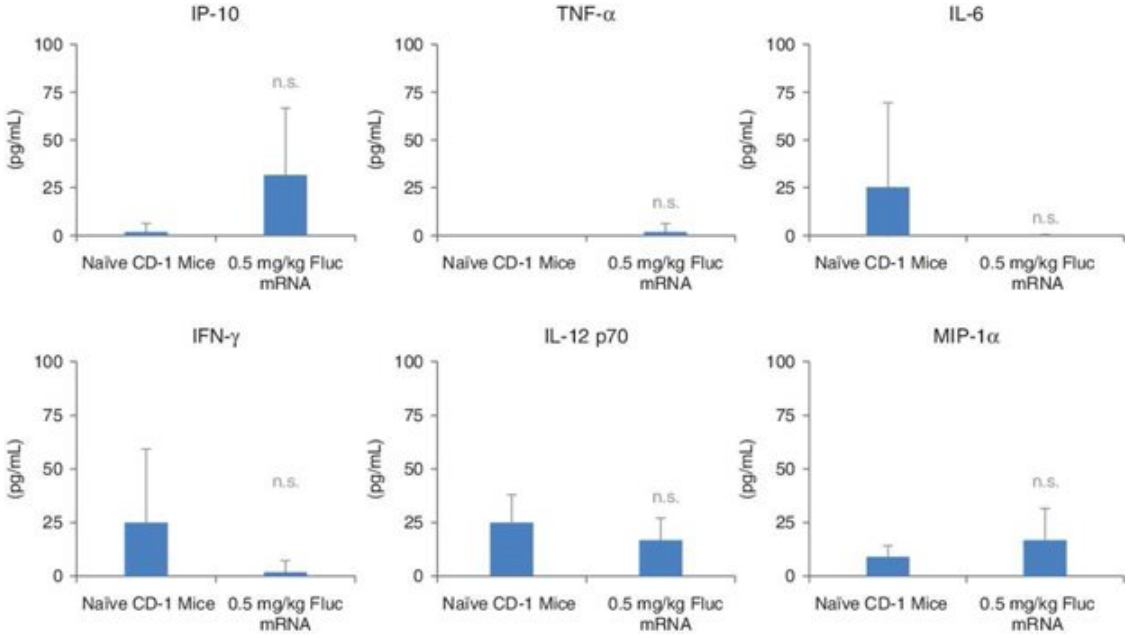
Moreover, in our chronic dosing study, the Hybrid mRNA Technology enabled mRNA to be repeat-dosed every week over a 3-month period without loss of expression at each dose. In the data presented in the figure below mice were treated intravenously once a week for 12 weeks with 0.5 mg/kg of luciferase mRNA formulated with Hybrid mRNA Technology without loss of the luciferase fluorescence signal at each dose given. In these studies, luciferase activity was measured six hours after the weekly dosing. The significance of this result is that our Hybrid mRNA Technology would likely be able to be chronically administered without the loss of potency after each dose that has been observed with other LNP-only formulations, as reported in the journal article "Accelerated Blood Clearance of PEGylated Liposomes following Preceding Liposome Injection: Effects of Lipid Dose and PEG Surface-Density and Chain Length of the First-Dose Liposomes" published in the *Journal of Controlled Release* , 2005.

Luciferase Expression Measured Immediately After Each Dose of a Repeat-Dosing Regimen of the Hybrid mRNA Technology in Mice



Of critical importance to mRNA therapeutics is the ability to avoid unwanted induction of cytokines which can cause dose-limiting toxicities through activation of the innate immune system. This type of an acute response can result in lower levels of protein expression. Mice injected with 0.5 mg/kg of luciferase mRNA delivered using the Hybrid mRNA Technology did not elicit an innate immune response as determined by measuring levels of cytokines, interferon gamma-induced protein 10 (IP-10), tumor necrosis factor alpha (TNF-α), interleuckin-6 (IL-6), interferon gamma (IFN-ϒ), interleukin 12, (IL-12) and macrophage inflammatory protein alpha (MIP-1α), as shown in the figure below. The levels of cytokines observed in all cases were generally similar to untreated mice and differences were not statistically significant. The term "n.s". in each graph, means "not significant" and represents a p-value greater than 0.05. We believe that the levels of cytokine induction observed in the preclinical study support the likelihood of our product candidate having a favorable safety profile, hence offering potential advantages over other mRNA delivery using fusogenic LNPs or AAV-based approaches.

Assessment of Cytokine Levels in Mice Treated with Luciferase mRNA Delivered Using the Hybrid mRNA Technology



We have developed our Hybrid mRNA Technology into a robust system for in vivo mRNA delivery that allows protection of mRNA in the circulation, endosome escape and targeted expression in the hepatocytes. Our mRNA therapeutic candidates using our Hybrid mRNA Technology have proven safe and effective in preclinical models, and have shown proof of concept and efficacy across a number of studies in OTCD mice, including meaningful reduction in ammonia levels in the blood, which is an approvable endpoint by the FDA for the treatment of urea cycle disorders. Our delivery technology is designed to provide a versatile, predictable, reproducible and scalable mRNA delivery system with the ability to manufacture at scale, using a process known as RAFT polymerization which has enabled manufacturing of polymers at the hundreds of kg scale. We believe that our technology enables rapid deployment of mRNA therapeutics to new disease targets, and we intend to leverage our technology platform to develop a pipeline of product candidates for the treatment of many chronic and life-threatening orphan liver diseases. Beyond the urea cycle disorders, these diseases include organic acidemias, a group of diseases with an aggregate incidence of 1 in 1,000 live births according to GeneReviews; glycogen storage diseases, a group of diseases with an aggregate incidence of 1 in 20,000 live births according to Medscape: Glycogen Storage Diseases Types I-VII, 2014; porphyria, a group of diseases with an aggregate incidence of 1 in 75,000 live births according to a journal article "Porphyrias" published in Lancet, 2010; hyperoxalurea, with an incidence of 1 in 175,000 live births according to GeneReviews; phenylketonuria, with an incidence of 1 in 15,000 live births according to a National Institutes of Health Consensus Statement, "Phenylketonuria: Screening and Management" published online in 2000; tyrosinemia type 1 with an incidence of 1 in 100,000 live births according to GeneReviews; and Wilson's Disease, with an incidence of 1 in 30,000 live births according to GeneReviews. We believe the i-ERT market potential is as large as the $4 billion ERT market because (1) the incidences of the diseases treatable by ERT and i-ERT are similar, as noted above, and (2) the numbers of diseases currently treated by ERT (six diseases, according to a brief "Enzyme Replacement Therapies for Lysosomal Storage Diseases" published by the Agency for Healthcare Research and Quality in 2013) are similar to the number of target diseases for i-ERT.

Partnering Opportunities

We believe that our Hybrid mRNA Technology can be of significant interest to potential corporate partners who are interested in developing mRNA therapeutics. There are many companies interested in mRNA therapeutics to treat orphan liver diseases, including Moderna LLC, Alexion Pharmaceuticals, Inc., RaNA Therapeutics and Ultragenyx Pharmaceutical Inc. Also, there are many single-gene inherited metabolic disorders of the liver beyond the urea cycle disorders that we believe may be good candidates for mRNA replacement therapy. Once proof of concept is obtained in one orphan liver disease, we believe our technology can be used to rapidly develop mRNA therapeutics to treat other orphan liver diseases. The mRNA sequences for each of these diseases are readily available in public databases, and we expect those mRNAs can readily be manufactured by contract manufacturers. As a result, we believe that new potential mRNA therapeutics may be efficiently developed by combining different mRNAs with our Hybrid mRNA Technology. Given that the delivery system will be the same across the programs, once the Hybrid mRNA Technology is successful with one mRNA therapeutic to treat an orphan liver disease, we anticipate that the costs and risks associated with developing new mRNA therapeutics for other orphan liver diseases will be relatively low. We are engaged in discussions with potential partners for developing mRNA programs in various disease indications. We intend to pursue partnerships in order to accelerate the development and maximize the market potential of our Hybrid mRNA Technology platform. In particular, we intend to partner with larger biopharmaceutical companies that possess market know-how and marketing capabilities to complete the development and commercialization of mRNA therapeutics.

In addition, the ability of our technology platform to effectively deliver mRNA to the liver hepatocytes provides the potential to apply our technology platform to in vivo gene editing — the modification of the genome of a patient's cells in vivo to either delete genes that are causing disease or to add genes to correct genetic defects, which, if successful, could have a variety of important potential medical applications. For example, deleting gene function could be used to lower levels of drug targets such as PCSK-9 for lowering cholesterol, and adding gene function could be used to correct certain types of hemophilia. We believe that such applicability provides opportunities to form revenue-generating strategic collaborations with partners developing gene editing technologies. We have received indications of interest from gene editing companies to use our technology to introduce gene editing therapeutics into the hepatocytes in order to enable in vivo gene editing. Companies developing mRNA and in vivo gene editing therapeutics have reported to us a common set of challenges that we believe can be addressed by our technology, including in vivo instead of ex vivo delivery, high levels of expression and activity, specificity of expression to the liver, avoidance of off-target effects and ability to use repeat dosing regimens without loss of expression on subsequent dosing. Companies focused on gene editing include bluebird bio, Inc., Cellectis S.A., CRISPR Therapeutics AG, Editas Medicine, Inc., Intellia Therapeutics, Inc., Precision Biosciences, Inc. and Sangamo Biosciences, Inc.

In 2014, we entered into a collaboration and development agreement with Synageva, pursuant to which we and Synageva agreed that we would develop mRNA technologies for the treatment of inherited orphan liver diseases, including development of the Hybrid mRNA Technology. Under this agreement, Synageva had an option to acquire us. This right was not exercised mainly, we believe, because of the acquisition of Synageva by Alexion Pharmaceuticals, Inc. in May 2015, which occurred during Synageva's option period. All rights to the technology and products generated under this collaboration and development agreement have now reverted to us. Subsequent to our collaboration and development agreement with Synageva, we have not entered into any additional partnerships, collaborations or license agreements for our current product candidates.

Competition

The biotechnology industry is characterized by intense and rapidly changing competition to develop new technologies and proprietary products and affected by new technologies, new developments, government regulations, health care legislation, availability of financing and other factors. We compete with numerous other companies that currently operate, or intend to operate, in the industry, including companies that are engaged in RNA-based therapeutic technologies and other manufacturers that may decide to undertake development of such products, as well as other companies that are pursuing non-RNA-based approaches for the treatment of urea cycle disorders. While we believe that our intellectual property portfolio, scientific expertise and our Hybrid mRNA Technology provide us with competitive advantages, we face potential competition from many different sources, including larger and better-funded biotechnology and pharmaceutical companies, who, due to their size, may have significant advantages over us. These larger companies have substantially greater capital resources, larger customer bases, broader product lines, larger sales forces, greater marketing and management resources, larger research and development staffs and larger facilities than ours and have established reputations and relationships with physicians and patients, as well as worldwide distribution channels that are more effective than those we will have. In addition, due to ongoing consolidation in the industry, there are high barriers to entry for small biotechnology companies. For a discussion of some of these advantages and the competitive risks we face, see "Risk Factors — Risk Related to our Industry."

We are aware of several companies that are developing nucleic acid-based therapeutics for orphan liver diseases. There are several companies developing AAV-based approaches to gene therapy including REGENXBIO Inc., Dimension Therapeutics, Inc. and uniQure N.V. Of these, Dimension Therapeutics, Inc. has selected OTCD as one of its development programs as of February 2016. In addition, Moderna LLC is developing injectable modified mRNA therapeutics encoding a variety of proteins. Alexion Pharmaceuticals, Inc. has established an exclusive agreement with Moderna LLC for the discovery and development of mRNA therapeutics to treat rare diseases. In February 2017, Moderna LLC presented preclinical data on methylmalonic acidemia, an orphan liver disease. RaNA Therapeutics acquired the mRNA assets, including a development program for the OTCD, which were divested from Shire plc in January 2017. Arcturus is developing mRNA-based therapeutics for the treatment of OTCD as well as for iron deficiencies, thrombopoietin and cystic fibrosis. Alnylam Pharmaceuticals, Inc. and Dicerna Pharmaceuticals, Inc. are developing a LNP delivery platform for targeted delivery of small interfering RNA, or siRNA, therapeutics to hepatocytes for silencing specific mRNA to prevent disease-causing proteins from being made and are using this approach to develop therapeutics for primary hyperoxalurea and hepatic porphyrias. There are substantial differences regarding what these companies are doing relative to us. Specifically, through our technology we are seeking to deliver and replace a specific missing mRNA in the cell, whereas Alnylam Pharmaceuticals, Inc. and Dicerna Pharmaceuticals, Inc. are decreasing the amount of a specific mRNA. In addition, although Alnylam Pharmaceuticals, Inc. and Dicerna Pharmaceuticals, Inc.'s approach uses a covalent GalNAc conjugate to target the siRNA, we use GalNAc to target the polymer component of the delivery system which enables intracellular delivery of the mRNA.

Promethera Biosciences S.A., a Belgian company, is evaluating stem cell based therapy for treatment of urea cycle disorders in the pediatric population. Promethera Biosciences S.A. has completed a 20 patient Phase 1/2 trial in Europe and is currently enrolling patients in a Phase 2b trial. Other potential therapies for the urea cycle disorders in early stage preclinical or clinical testing include gene therapy and mitochondrial enzyme replacement. For example, Aeglea Biotherapeutics, Inc. has a degrading enzyme treatment in preclinical development for arginase 1 deficiency. Ocera Therapeutics Inc. is developing an ammonia scavenger which they claim has improved properties. Bio Blast Pharma Ltd., an Israeli biopharmaceutical company, is pursuing a mitochondrial protein replacement platform in OTCD, which is currently in preclinical development. Synlogic, Inc. is developing a engineered synthetic biotic designed to change the microbiome in the gut which, according to Synlogic, Inc., could reduce excess ammonia in the blood for the treatment of urea cycle disorders and other forms of hyperammonemia.

Other companies with mRNA delivery technologies that may compete for gene editing partnerships include Arcturus Therapeutics, Inc., Acuitas Therapeutics Inc., Arbutus Biopharma Corporation, CureVac AG, and BioNTech AG.

These companies also compete with us in recruiting personnel and securing licenses to complementary technologies or specific substances that may be critical to the success of our business. They also compete with us for potential funding.

Intellectual Property

We rely on a combination of patents, trade secrets, non-disclosure agreements, and other intellectual property to protect the proprietary technologies that we believe are important to our business. Our success will depend in part on our ability to obtain and maintain patent and other proprietary protection for commercially important inventions and know-how, defend and enforce our patents, maintain our licenses, preserve our trade secrets, and operate without infringing valid and enforceable patents and other proprietary rights of third parties. We also rely on continuing technological innovation to develop, strengthen, and maintain our proprietary position in the field of mRNA therapeutics and delivery.

Our Patent Portfolio

Our portfolio of patents and patent applications includes multiple families that protect various aspects of our business. The patents and patent applications that make up our patent portfolio are primarily focused on synthetic polymers and related compositions, the use of polymer and polymer-LNP compositions for delivery of mRNA and other therapeutic agents, including the use of polymer-LNP compositions in our core platform technology, and methods for treating protein deficiency diseases such as orphan diseases characterized by single-gene metabolic defects in the liver, including OTCD. As of March 24, 2017, we own or have in-licensed 16 issued U.S. patents, 25 issued foreign patents, and over 15 pending U.S. and foreign patent applications:

Case Family	Issued Patents	Pending Applications by Jurisdiction	Owned or In-licensed
Enhanced Transport	US 6,835,393; US 7,374,778; US 8,003,129; US 8,846,106; EP 1044021; AU 758368; CA 2317549		In-licensed
Enhanced Transport	US 7,737,108; US 8,318,816		In-licensed
Temperature and pH-responsive Compositions	US 7,718,193		In-licensed
Diblock Copolymer	US 9,476,063; EP 2281011; AU 2009246327; JP 5911723; KR 10-1661636 CN ZL200980122888.3; CN ZL 201310232498.X; IL 209238; MX 316902; SG 166444; ZA 2010/08729	US, AU, CA, JP, BR, IN	Co-owned; UW's rights in-licensed
Micellic Assemblies	US 9,339,558; EP 2285853; AU 2009246329; CA 2724014; JP 5755563; MX 315375	US, KR	Co-owned; UW's rights in-licensed
Polymeric Carrier	US 9,006,193		Co-owned; UW's rights in-licensed
Heterogeneous Polymeric Micelles	US 9,211,250		Co-owned; UW's rights in-licensed
Bispecific Intracellular Delivery Vehicles	US 8,822,213; 9,220,791	US	Co-owned; UW's rights in-licensed
Multiblock Copolymers	US 9,464,300; EP 2364330; AU 2009313358; CN ZL200980148153.8; JP 5766611; MX 330456; SG 171100; ZA 2011/03289		Co-owned; UW's rights in-licensed
Omega-Functionalized Polymers	US 9,593,169	US	Co-owned; UW's rights in-licensed
Targeting Monomers	US 9,415,113		Co-owned; UW's rights in-licensed
Block Copolymers		US, AU, EP, CA	Owned
Polymer-LNP Delivery		PCT	Owned

A significant portion of our patent portfolio is in-licensed from UW. The UW license, which is exclusive, worldwide, and sublicensable and is described more fully below under "— License Agreements — UW License Agreement," is in the field of drug delivery, human therapeutics, human prophylactics and research reagents. We co-own, with UW, several families within this in-licensed portfolio. The co-owned patent filings include an issued U.S. patent, US 9,339,558, and its granted European counterpart, EP 2285853, covering membrane destabilizing polymer nanoparticle compositions used in our core platform technology. Corresponding patents have also issued in other foreign jurisdictions, including Australia and Canada, and corresponding applications are pending within the United States and Korea. These issued patents are projected to expire in 2029.

The co-owned patent filings also include a second issued U.S. patent, US 9,476,063, and its granted European counterpart, EP 2281011, covering membrane destabilizing polymer compositions used in our core platform technology. Corresponding patents have also issued in other foreign jurisdictions, including Australia, Israel, Japan, and Korea, and corresponding applications are pending within the United States and outside the United States, including Canada and Japan. These issued patents are projected to expire in 2029.

We are the sole owner of an international Patent Cooperation Treaty, or PCT, application with a U.S. provisional application priority claim. The PCT application is directed to our core technologies for mRNA delivery, including membrane destabilizing polymer and LNP drug carrier compositions, compositions and systems comprising a combination of polymer and LNP drug carrier, and methods of using such compositions and systems for delivering therapeutic agents, such as mRNA, into cells, including targeted delivery of mRNA to the liver. This application is further directed to related methods for treating diseases characterized by deficiency of a functional protein by in vivo delivery of mRNA encoding the functional protein, including methods for treating OTCD via liver-specific delivery of OTC-encoding mRNA. Any patent issuing from this application is projected to expire in 2036.

Patent Term

The term of individual patents and patent applications in our portfolio will depend upon the legal term of the patents in the countries in which they are obtained. In most countries, the patent term is 20 years from the date of filing of the patent application or examined priority application, if applicable. For example, if an international PCT application is filed, any patent issuing from the PCT application in a specific country expires 20 years from the filing date of the PCT application. Patents issuing from applications filed in the United States on or after June 8, 1995, will have a term that is twenty years from the filing date of the earliest examined priority application, absent any patent term adjustment for the U.S. Patent and Trademark Office delay.

Under the Hatch-Waxman Act, the term of a patent that covers an FDA-approved drug or biological product may also be eligible for patent term extension, or PTE. PTE permits restoration of a portion of the patent term of a U.S. patent as compensation for the patent term lost during product development and the FDA regulatory review process if approval of the application for the product is the first permitted commercial marketing of a drug or biological product containing that active ingredient. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a new drug application, or NDA, or biologics license application, or BLA, plus the time between the NDA or BLA submission date and the approval of that application. The Hatch-Waxman Act permits the owner of a patent to apply for a PTE for only one patent applicable to an approved drug, and the maximum period of restoration is five years beyond the expiration of the patent. A PTE cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, and a patent can only be extended once, and thus, even if a single patent is applicable to multiple products, it can only be extended based on one product. Similar provisions may be available in Europe and certain other foreign jurisdictions to extend the term of a patent that covers an approved drug. When possible, depending upon the length of clinical trials and other factors involved in the filing of an NDA or BLA, we expect to apply for PTEs for patents covering our product candidates and their methods of use, or to work with our licensors, as owners or co-owners of such patents, to obtain such extensions, if available.

License Agreements

The University of Washington ("UW") License Agreement

In 2006, we obtained from UW an exclusive, worldwide license to polymer technology for drug delivery, human therapeutics, human prophylactics and research reagents used for the in vitro and in vivo delivery and/or uptake of any entity including polymers, particles, nucleic acids, proteins, peptides and/or other molecules into cells, tissues, or organs pursuant to the Exclusive Patent License Agreement, dated as of December 6, 2006, as amended and restated on January 20, 2016, and on February 9, 2016, or the UW License Agreement. Licensed patents include three patent families owned by UW and nine patent families co-owned by us and UW. One of the licensed patent families is co-owned by UW and the University of Massachusetts, and the University of Massachusetts's rights in this patent family are licensed to us under an inter-institutional agreement between UW and the University of Massachusetts.

Under the UW License Agreement, we are obligated to use our commercially reasonable efforts to commercialize, manufacture and maximize sales of the licensed products. The UW License Agreement requires us to pay an annual maintenance fee, low single digit royalty payments based on a percentage of net sales with a minimum annual royalty payment and certain financial and performance milestone payments. The potential aggregate milestone payments are in the low single digit millions of dollars per specific drug target. We and our material sublicensees have the right to sublicense our rights under the UW License Agreement, provided that such sublicensees agree to terms consistent with the UW License Agreement. The UW License Agreement prohibits us from granting a security interest or allowing any person to assert or perfect a security interest in our rights under the UW License Agreement.

The UW License Agreement is effective until either terminated in accordance with the terms of the UW License Agreement or no license patent is valid and subsisting or pending in any country in the territory set forth in the UW License Agreement. UW may terminate the UW License Agreement upon delivery of a written notice of termination if we breach or fail to perform any of our obligations under the UW License Agreement and such breach or failure has not been cured in full within 60 days after the delivery to us of the notice of such breach or failure. UW may also terminate the UW License Agreement upon 10 days' notice to us if we become insolvent. We have the right to terminate our agreement with UW for any reason upon 60 days' notice.

Commonwealth Scientific and Industrial Research Organisation License Agreement

In 2009, we obtained from the Commonwealth Scientific and Industrial Research Organisation, or CSIRO, a non-exclusive, royalty-bearing, worldwide license to RAFT polymerization technology within the field of membrane destabilizing polymers that are used for the delivery of nucleic acids, proteins, peptides and/or other molecules in the diagnosis, prophylaxis or treatment of human disease pursuant to the Non-Exclusive License Agreement, dated as of October 26, 2009, as amended and restated on January 22, 2016, or the CSIRO Agreement.

Under the CSIRO Agreement, we are obligated to use our reasonable commercial endeavors to exploit the licensed patents to maximize the return from that exploitation to us and CSIRO. We are solely responsible for the manufacture, quality control, marketing and promotion of the licensed products we sell under the CSIRO Agreement. The CSIRO Agreement requires an upfront fee, low single digit royalty payments based on a percentage of net sales revenue, and a minimum annual royalty payment. Under the CSIRO Agreement, we have the right to sublicense to manufacture for use/sale by us and to sublicense to make and sell licensed products through multiple layers, provided that such sublicensee agrees to terms consistent with the CSIRO Agreement. We may not assign or encumber any of the rights or obligations under the CSIRO Agreement without CSIRO's written consent, unless the assignment is to the successor of our business or purchaser of our assets.

The CSIRO Agreement is effective until either terminated in accordance with the terms of the CSIRO Agreement or expiration, lapsing or cessation (including by revocation or as a result of a final declaration of invalidity or unenforceability) of the last to expire, lapse or cease of the licensed patents. We have the right to terminate the CSIRO Agreement for any reason upon six months' notice or immediately by notice if CSIRO commits a material breach of its obligations under the CSIRO Agreement which is not remedied within 90 days of notice from us of such breach. CSIRO may immediately terminate the CSIRO Agreement by notice if we commit a material breach of our obligations under the CSIRO Agreement which is not remedied within 90 days of notice from CSIRO of such breach or if we initiate proceedings in a court to contest the validity or enforceability of any licensed patent under the CSIRO Agreement, lodge third party observations to contest the validity or enforceability of any licensed patent or otherwise supply prior art to an examiner or patent office in respect of any licensed patent or actively assists a third party to take any of such actions.

Manufacturing and Suppliers

We do not currently own or operate manufacturing facilities for the production of clinical or commercial quantities of our therapeutic candidates. We have small-scale production capabilities and generally perform early process development for our product candidates to produce quantities of our therapeutic candidates necessary to conduct preclinical studies of our investigational therapeutic candidates. We do not have and we do not currently plan to acquire or develop the facilities or capabilities to manufacture bulk drug substance or filled drug product for use in human clinical studies. We plan to rely on CMOs and third party contractors to generate formulations and produce larger scale amounts of drug substance and the drug product required for our clinical studies. We expect to rely on CMOs and third party contractors to manufacture cGMP drug substance and drug product required for our clinical studies for the foreseeable future. We also plan to contract with CMOs and third party contractors for the labeling, packaging, storage and distribution of investigational drug products. These arrangements allow us to maintain a more flexible infrastructure while focusing our expertise on researching and developing our products.

TriLink BioTechnologies, LLC. supplies us with the mRNA for our PRX-OTC, pursuant to a manufacturing and supply agreement.

To meet our projected needs for commercial manufacturing, third parties with whom we currently work might need to increase their scale of production or we will need to secure alternate suppliers. We believe that there are alternate sources of supply that can satisfy our clinical and commercial requirements, although we cannot be certain that identifying and establishing relationships with such sources, if necessary, would not result in significant delay or material additional costs.

Research and Development

We spent approximately $6.7 million and $4.9 million on research and development activities in each of the fiscal years ended December 31, 2016 and 2015, respectively.

Government Regulation

Pharmaceutical companies are subject to extensive regulation by national, state and local agencies such as the FDA in the United States or the EMA in Europe. The manufacture, distribution, marketing and sale of pharmaceutical products are subject to government regulation in the United States and various foreign countries. Additionally, in the United States, we must follow rules and regulations established by the FDA requiring the presentation of data demonstrating that our products are safe and efficacious and are manufactured in accordance with the cGMP regulations. If we do not comply with applicable requirements, the government may refuse to approve our marketing applications or refuse to allow us to manufacture or market our products, and we may be criminally prosecuted or fined. We and our manufacturers and clinical research organizations may also be subject to regulations under other federal, state and local laws, including, but not limited to, the U.S. Occupational Safety and Health Act, and import, export and customs regulations as well as the laws and regulations of other countries. The United States government has increased its enforcement activity regarding illegal marketing practices domestically and internationally. As a result, pharmaceutical companies must ensure they comply with the Foreign Corrupt Practices Act and federal healthcare fraud and abuse laws, including the False Claims Act.

These regulatory requirements impact our operations and differ from one country to another, so that securing the applicable regulatory approvals of one country does not imply the approval of another country. However, securing the approval of a more stringent body, i.e. the FDA, may facilitate receiving approval by a regulatory authority in a different country where the regulatory requirements are similar or less stringent. The approval procedures involve high costs, are manpower intensive, usually extend over many years and require highly skilled and professional resources.

FDA Approval Process

The steps required to be taken before a new drug may be marketed in the United States generally include:

- completion of preclinical laboratory and animal testing;
- the submission to the FDA of an IND application, which must be evaluated by the FDA before human clinical trials may commence;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the proposed drug for its intended use; and
- submission and approval of a NDA.

Clinical studies are conducted under protocols detailing, among other things, the objectives of the study, what types of patients may enter the study, schedules of tests and procedures, drugs, dosages, and length of study, as well as the parameters to be used in monitoring safety, and the efficacy criteria to be evaluated. A protocol for each clinical study and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

The clinical testing of a drug product candidate generally is conducted in three sequential phases prior to approval, but the phases may overlap or be combined. A fourth, or post approval, phase may include additional clinical studies. The phases are generally as follows:

Phase 1. In Phase 1 clinical studies, the product is tested in a small number of patients with the target condition or disease or in healthy volunteers. These studies are designed to evaluate the safety, dosage tolerance, metabolism and pharmacologic actions of the product candidate in humans, side effects associated with increasing doses, and, in some cases, to gain early evidence on efficacy. The number of participants included in Phase 1 studies generally ranges from 20 to 80.

Phase 2. For Phase 2 studies, in addition to safety, the sponsor evaluates the efficacy of the product candidate on targeted indications to determine the optimal dosage. Phase 2 studies typically are larger than Phase 1 but smaller than Phase 3 studies and may involve several hundred participants.

Phase 3. Phase 3 studies typically involve an expanded patient population at geographically-dispersed test sites. They are performed after preliminary evidence suggesting effectiveness of the product candidate has been obtained and are designed to further evaluate clinical efficacy and safety, to establish the overall benefit-risk relationship of the product candidate and to provide an adequate basis for a potential product approval. Phase 3 studies usually involve several hundred to several thousand participants.

Phase 4. Phase 4 clinical trials are post-marketing studies designed to collect additional safety data as well as potentially expand a product indication. Post-marketing commitments are required of, or agreed to by, a sponsor after the FDA has approved a product for marketing. These studies are used to gain additional information from the treatment of patients in the intended therapeutic indication and to verify a clinical benefit in the case of drugs approved under accelerated approval regulations. If the FDA approves a product while a company has ongoing clinical trials that were not necessary for approval, a company may be able to use the data from these clinical trials to meet all or part of any Phase 4 clinical trial requirement. These clinical trials are often referred to as Phase 4 post-approval or post-marketing commitments. Failure to promptly conduct Phase 4 clinical trials could result in the inability to deliver the product into interstate commerce, misbranding charges, and civil monetary penalties.

For an orphan drug product such as the proposed urea cycle disorder therapies, the clinical development plan is significantly abbreviated due to the limited number of available patients. Orphan drug NDAs are typically based on approximately one hundred or fewer patients, rather than the thousands of patients for a non-orphan drug NDA.

Clinical trials must be conducted in accordance with the FDA's and EMA's good clinical practices, or GCP, requirements. The FDA/EMA may order the temporary or permanent discontinuation of a clinical study at any time or impose other sanctions if it believes that the clinical study is not being conducted in accordance with requirements or that the participants are being exposed to an unacceptable health risk. An institutional review board, or IRB, or Ethics Committee, or EC, generally must approve the clinical trial design and patient informed consent and also may halt a study, either temporarily or permanently, for failure to comply with the IRB/EC's requirements, or may impose other conditions. Additionally, some clinical studies are overseen by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board. This group recommends whether or not a trial may move forward at designated check points based on access to certain data from the study. The clinical study sponsor may also suspend or terminate a clinical trial based on evolving business objectives and/or competitive climate.

As a product candidate moves through the clinical testing phases, manufacturing processes are further defined, refined, controlled and validated. The level of control and validation required by the FDA would generally increase as clinical studies progress. We and the CMOs or third-party manufacturers on which we rely for the manufacture of our product candidates and their respective components are subject to requirements that drugs be manufactured, packaged and labeled in conformity with cGMP. To comply with cGMP requirements, manufacturers must continue to spend time, money and effort to meet requirements relating to personnel, facilities, equipment, production and process, labeling and packaging, quality control, recordkeeping and other requirements.

Assuming completion of all required testing in accordance with all applicable regulatory requirements, detailed information on the product candidate is submitted to the FDA/EMA in the form of an NDA (or MAA for the EMA), requesting approval to market the product for one or more indications, together with payment of a user fee, unless waived. An NDA/MAA includes all relevant data available from pertinent nonclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information on the chemistry, manufacture, control and proposed labeling, among other things. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of the product candidate for its intended use to the satisfaction of the FDA/EMA.

If an NDA submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under the Prescription Drug User Fee Act, or PDUFA, the FDA's goal is to complete its initial review and respond to the applicant within ten months of submission. If the application is determined by FDA to treat a serious condition and would provide a significant improvement in safety or effectiveness, it may qualify for Priority Review, in which case the review goal may be within six months of NDA submission. An orphan drug, such as the proposed urea cycle disorder therapies, would be expected to meet the requirements of Priority Review, and thus be eligible for a six-month review period. However, PDUFA goal dates are not legal mandates and FDA response often occurs several months beyond the original PDUFA goal date. Further, the review process and the target response date under PDUFA may be extended if the FDA requests or the NDA sponsor otherwise provides additional information or clarification regarding information already provided in the NDA. The NDA review process can, accordingly, be very lengthy. During its review of an NDA, the FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it typically follows such recommendations. Data from clinical studies is not always conclusive and the FDA and/or any advisory committee it appoints may interpret data differently than the applicant.

After the FDA evaluates the NDA and inspects manufacturing facilities where the drug product and/or its active pharmaceutical ingredient will be produced, it will either approve commercial marketing of the drug product with prescribing information for specific indications or issue a complete response letter indicating that the application is not ready for approval and stating the conditions that must be met in order to secure approval of the NDA. If the complete response letter requires additional data and the applicant subsequently submits that data, the FDA nevertheless may ultimately decide that the NDA does not satisfy its criteria for approval.

The FDA could also approve the NDA with a Risk Evaluation and Mitigation Strategies plan to mitigate risks, which could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling, development of adequate controls and specifications, or a commitment to conduct post-marketing testing. Such post-marketing testing may include Phase 4 clinical studies and surveillance to further assess and monitor the product's safety and efficacy after approval. Regulatory approval of products for serious or life-threatening indications may require that participants in clinical studies be followed for long periods to determine the overall survival benefit of the drug.

If the FDA/EMA approves one of our therapeutic candidates, we will be required to comply with a number of post-approval regulatory requirements. We would be required to report, among other things, certain adverse reactions and production problems to the FDA/EMA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling for any of our products. Also, quality control and manufacturing procedures must continue to conform to cGMP after approval, which imposes extensive procedural, substantive and record keeping requirements. If we seek to make certain changes to an approved product, including certain manufacturing changes, we will need FDA/EMA review and approval before the change can be implemented. For example, if we change the manufacturer of a product the FDA/EMA may require stability or other data from the new manufacturer, which will take time and is costly to generate, and the delay associated with generating this data may cause interruptions in our ability to meet commercial demand, if any. While physicians may use products for indications that have not been approved by the FDA/EMA, we may not label or promote the product for an indication that has not been approved. Securing FDA/EMA approval for new indications is similar to the process for approval of the original indication and requires, among other things, submitting data from adequate and well-controlled studies that demonstrate the product's safety and efficacy in the new indication. Even if such studies are conducted, the FDA/EMA may not approve any change in a timely fashion, or at all.

We plan to rely, and expect to continue to rely, on third parties for the manufacture of clinical, and future commercial, quantities of our therapeutic candidates. Future FDA/EMA and local inspections may identify compliance issues at these third-party facilities that may disrupt production or distribution or require substantial resources to correct. In addition, discovery of previously unknown problems with a product or the failure to comply with applicable requirements may result in restrictions on a product, manufacturer or holder of an approved NDA/MAA, including withdrawal or recall of the product from the market or other voluntary, FDA/EMA-initiated or judicial action that could delay or prohibit further marketing. Newly discovered or developed safety or efficacy data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. Many of the foregoing could limit the commercial value of an approved product or require us to commit substantial additional resources in connection with the approval of a product. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA/EMA's policies may change, which could delay or prevent regulatory approval of the products under development.

Orphan Drug Designation

The Orphan Drug Act of 1983, or the Orphan Drug Act, encourages manufacturers to seek approval of products intended to treat "rare diseases and conditions" with a prevalence of fewer than 200,000 patients in the United States or for which there is no reasonable expectation of recovering the development costs for the product. For products that receive Orphan Drug designation by the FDA, the Orphan Drug Act provides tax credits for clinical research, FDA assistance with protocol design, eligibility for FDA grants to fund clinical studies, waiver of the FDA application fee, and a period of seven years of marketing exclusivity for the product following FDA marketing approval.

Foreign Regulation

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we must obtain approval by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and the time may be longer or shorter than that required for FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country.

Under European Union regulatory systems, a company may submit an MAA either under a centralized or decentralized procedure. The centralized procedure, which is compulsory for medicines produced by biotechnology, provides for the grant of a single marketing authorization that is valid for all European Union member states.

Reimbursement

In the United States and other countries, sales of any products for which we receive regulatory approval for commercial sale will depend in part on the availability of reimbursement from third-party payors, including government health administrative authorities, managed care providers, private health insurers and other organizations. Each third-party payor may have its own policy regarding what products it will cover, the conditions under which it will cover such products, and how much it will pay for such products. Third-party payors are increasingly examining the medical necessity and cost effectiveness of medical products and services in addition to safety and efficacy and, accordingly, significant uncertainty exists as to the reimbursement status of newly approved therapeutics. Third-party reimbursement adequate to enable us to realize an appropriate return on our investment in research and product development may not be available for our products. The passage of the Medicare Prescription Drug and Modernization Act of 2003, or the MMA, sets forth the requirements for the distribution and pricing of prescription drugs for Medicare beneficiaries, which may affect the marketing of our products. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

In addition, in some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market.

We expect there will continue to be a number of federal and state proposals to implement governmental pricing controls. While we cannot predict whether such legislative or regulatory proposals will be adopted, the adoption of such proposals could have a material adverse effect on our business, financial condition and profitability.

The Patient Protection and Affordable Care Act

In March 2010, President Obama signed into legislation the Patient Protection and Affordable Care Act, or the Affordable Care Act, which resulted in sweeping changes across the health care industry. The Affordable Care Act contained measures designed to promote quality and cost efficiency in health care delivery and to generate budgetary savings in the Medicare and Medicaid programs. Pharmaceuticals represent a significant portion of the cost of providing care, and have therefore been the subject of pricing negotiation, product selection and utilization review. The Affordable Care Act includes significant provisions that encourage state and federal law enforcement agencies to increase activities related to preventing, detecting and prosecuting those who commit fraud, waste and abuse in federal healthcare programs, including Medicare, Medicaid and Tricare. Some of the provisions of the Affordable Care Act have not yet been fully implemented, and certain provisions have been subject to judicial and Congressional challenges. The healthcare regulatory environment in the United States is still in flux, and judicial challenges and legislative initiatives to modify, limit, or repeal the Affordable Care Act continue and may increase in light of the change in administrations following the United States Presidential election. The manner in which the Affordable Care Act continues to evolve could materially affect the extent to which and the amount at which pharmaceuticals are reimbursed by government programs such as Medicare, Medicaid and Tricare. We cannot predict all impacts the Affordable Care Act, or any changes or additional health reform legislation, may have on our products, but they may result in our products being chosen less frequently or the pricing being substantially lowered.

Fraud and abuse laws in the United States

A variety of U.S. federal and state laws apply to the sale, marketing and promotion of drugs that are paid for, directly or indirectly, by U.S. federal or state healthcare programs such as Medicare and Medicaid. The restrictions imposed by these laws are in addition to those imposed by the FDA, the U.S. Federal Trade Commission and corresponding state agencies. Some of these laws significantly restrict or prohibit certain types of sales, marketing and promotional activities by drug manufacturers. Violation of these laws may result in significant criminal, civil and administrative penalties, including imprisonment of individuals, fines and penalties and exclusion or debarment from U.S. federal and state healthcare and other programs. Many private health insurance companies also prohibit payment to entities that have been sanctioned, excluded or debarred by U.S. federal agencies.

Anti-kickback statutes in the United States

The U.S. federal Anti-Kickback Statute prohibits persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual, or the furnishing, arranging for or recommending of a good or service, for which payment may be made in whole or in part under a U.S. federal healthcare program such as the Medicare and Medicaid programs. The definition of "remuneration" has been broadly interpreted to include anything of value, including gifts, discounts, the furnishing of supplies or equipment, payments of cash and waivers of payments. Several courts have interpreted the statute's intent requirement to mean that, if any one purpose of an arrangement involving remuneration is to induce referrals or otherwise generate business involving goods or services reimbursed in whole or in part under U.S. federal healthcare programs, the statute has been violated. Penalties for violations include criminal penalties and civil sanctions such as fines, imprisonment and possible exclusion from Medicare, Medicaid and other U.S. federal healthcare programs. In addition, some kickback allegations have been claimed to violate the U.S. False Claims Act (as discussed below). The reach of the federal Anti-Kickback Statute was broadened by the Affordable Care Act, which, among other things, amends the intent requirement of the federal Anti-Kickback Statute. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. The Affordable Care Act further provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the U.S. False Claims Act or the Civil Monetary Penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

The U.S. federal Anti-Kickback Statute is broad and prohibits many arrangements and practices that are lawful in businesses outside of the healthcare industry. Recognizing that the statute is broad and may technically prohibit many innocuous or beneficial arrangements, the Office of Inspector General of the Department of Health and Human Services, or OIG, has issued a series of regulations, known as the "safe harbors." These safe harbors set forth provisions that, if all their applicable requirements are met, will assure healthcare providers and other parties that they will not be prosecuted under the Anti-Kickback Statute. The failure of a transaction or arrangement to fit precisely within one or more safe harbors does not necessarily mean that it is illegal or that prosecution will be pursued. However, conduct and business arrangements that do not fully satisfy an applicable safe harbor may result in increased scrutiny by government enforcement authorities such as the OIG or the U.S. Department of Justice.

Many states have adopted laws similar to the U.S. federal Anti-Kickback Statute. Some of these state prohibitions are broader than the U.S. federal statute, and apply to the referral of patients and recommendations for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs. Government officials have focused certain enforcement efforts on marketing of healthcare items and services, among other activities, and have brought cases against individuals or entities with sales personnel who allegedly offered unlawful inducements to potential or existing physician customers in an attempt to procure their business.

U.S. False Claims Act

The U.S. False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the U.S. federal government or knowingly making, or causing to be made, a false statement in order to have a false claim paid. The U.S. federal government's interpretation of the scope of the law has in recent years grown increasingly broad. Most states also have statutes or regulations similar to the U.S. False Claims Act, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor. Sanctions under these U.S. federal and state laws may include civil monetary penalties, exclusion of a manufacturer's products from reimbursement under government programs, criminal fines and imprisonment. Several drug manufacturers have been prosecuted under the false claims laws for allegedly providing free drugs to physician customers with the expectation that the physician customers would bill U.S. federal programs for the product. In addition, several recent cases against drug manufacturers have alleged that the manufacturers improperly promoted their products for "off-label" use, outside of the scope of the FDA-approved labeling.

U.S. Health Insurance Portability and Accountability Act of 1996

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created a new U.S. federal healthcare fraud statute that prohibits knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private payors. A violation of this statute is a felony and may result in fines, imprisonment or exclusion from government-sponsored programs. Among other things, HIPAA also imposes new criminal penalties for knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services, along with theft or embezzlement in connection with a healthcare benefits program and willful obstruction of a criminal investigation involving a U.S. federal healthcare offense.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and its implementing regulations, imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates" — independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

If our operations are found to be in violation of any of the federal and state laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including criminal and significant civil monetary penalties, damages, fines, imprisonment, exclusion from participation in government healthcare programs, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business.

Compliance with Environmental Laws

Our compliance with applicable environmental requirements during the years ended December 31, 2016, 2015 and 2014 and subsequently has not had a material effect upon our capital expenditures, earnings or competitive position.

Employees

As of March 24, 2017 we had 21 total employees: 19 full-time employees, 15 of whom were engaged in full-time research and development activities and 4 of whom were engaged in general administration, and 2 part-time employees. None of our employees is represented by any collective bargaining unit. We believe that we maintain good relations with our employees.

ITEM 1A. RISK FACTORS.

The following risk factors, together with all of the other information included or incorporated in this Annual Report on Form 10-K, should be carefully considered. If any of the following risks, either alone or taken together, or other risks not presently known to us or that we currently believe to not be significant, develop into actual events, then our business, financial condition, results of operations or prospects could be materially adversely affected. If that happens, the market price of our common stock could decline, and stockholders may lose all or part of their investment.

Risks Relating to Our Financial Condition and Capital Requirements

We are a development-stage company and have a limited operating history on which to assess our business, have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.

We are a development-stage biotechnology company with a limited operating history. Our business does not generate the cash necessary to finance our operations. We incurred net losses of approximately $20.1 million in 2016 and $7.4 million in 2015. As of December 31, 2016, we had an accumulated deficit of $69.5 million.

We have devoted substantially all of our financial resources to identify, acquire, license and develop our technology and product candidates, including conducting early stage research and preclinical studies, paying interest payments of our term loan and providing general and administrative support for these operations. To date, we have financed our operations primarily through the sale of debt and equity securities. The amount of our future net losses will depend, in part, on the rate of our future expenditures and our ability to obtain funding through equity or debt financings, strategic collaborations or grants. Biopharmaceutical product development, which includes research and development, preclinical studies and human clinical trials, is a time-consuming, expensive and highly speculative process that takes years to complete and involves a substantial degree of risk. Our product candidates are in the early stages of preclinical development. We have established a preclinical proof of concept for two of our product candidates, and it may be several years, if ever, before we have a product candidate approved for commercialization. Even if we obtain regulatory approval to market a product candidate, our future revenue will depend upon the size of any markets in which our product candidates may receive approval, and our ability to achieve sufficient market acceptance, pricing, reimbursement from third-party payors, and adequate market share for our product candidates in those markets.

We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We will require significant additional capital to:

- continue our research and preclinical and clinical development of our product candidates;
- expand the scope of our current preclinical studies for our product candidates;
- advance our programs into more expensive clinical studies;
- initiate additional preclinical, clinical or other studies for our product candidates;
- obtain, change or add additional manufacturers or suppliers;

- seek regulatory and marketing approvals for our product candidates that successfully complete clinical studies;
- establish a sales, marketing, and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- seek to identify, assess, acquire, license, and/or develop other product candidates;
- make milestone or other payments under any license agreements;
- seek to maintain, protect, and expand our intellectual property portfolio;
- seek to attract and retain skilled personnel;
- make interest and principal payments of our term loan;
- create additional infrastructure to support our operations as a public company and our product development and planned future commercialization efforts; and
- address any delays or issues with any of the above, including but not limited to failed studies, complex results, safety issues or other regulatory challenges that require longer follow-up of existing studies, additional major studies or additional supportive studies in order to pursue marketing approval.

Further, the net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance. If we fail to achieve or maintain profitability, it would adversely affect the value of our common stock.

We are dependent on technologies we have licensed and we may need to license in the future, and if we fail to obtain licenses we need, or fail to comply with our payment obligations in the agreements under which we in-license intellectual property and other rights from third parties, we could lose our ability to develop our product candidates.

We currently are dependent on licenses from third parties for certain of our key technologies relating to mRNA delivery, including the licenses from UW, and CSIRO. Under the license agreement with UW, we are required pay all ongoing patent expenses. In addition, we are required to pay UW an annual license maintenance fee, certain milestone payments, and, following regulatory approval from the FDA to market licensed therapeutic products, royalty payments. Under the license agreement with CSIRO, we are required to pay annual royalties and product based royalties. No assurance can be given that we will generate sufficient revenue or raise additional financing to meet our payment obligations in the license agreements with UW or CSIRO or other license agreements we enter into with third parties in the future. Any failure to make the payments required by the license agreements may permit the licensor to terminate the license. If we were to lose or otherwise be unable to maintain these licenses, it would halt our ability to develop our product candidates, which would have an immediate material adverse effect on our business.

We have never generated any revenue from product sales and may never be profitable.

We have experienced significant operating losses since inception. We have no products approved for commercialization and have never generated any revenue from product sales. We are currently developing products based on delivery of mRNAs to correct genetic metabolic defects in the liver. The process of developing such products requires significant research and development efforts, including basic research, preclinical and clinical development, and regulatory approval. These activities, together with our general and administrative expenses, have resulted in operating losses in the past, and there can be no assurance that we can achieve profitability in the future. Our ability to achieve profitability depends on our ability to develop product candidates, conduct preclinical development and clinical trials, obtain necessary regulatory approvals and manufacture, distribute, market and sell our therapeutics. We cannot assure you of the success of any of these activities or predict if or when we will ever become profitable.

We require substantial additional funding to bring our planned products through clinical trials, regulatory approval, manufacturing and marketing and to become profitable. This additional financing may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit, or terminate our product development efforts or other operations.

We are currently advancing our mRNA therapeutic candidates through preclinical development. Developing our product candidates is expensive, and we expect our research and development expenses to increase substantially in connection with our ongoing activities, particularly as we advance our product candidates through clinical studies.

As of December 31, 2016, we had cash, cash equivalents and marketable securities of $15.5 million. Based upon our current expectations, we believe that our currently available cash, cash equivalents and marketable securities will be sufficient to meet our anticipated expenditures for at least the next 12 months. However, we cannot assure you that our plans will not change or that changed circumstances will not result in the depletion of our capital resources more rapidly than we currently anticipate, and we expect that we will require substantial additional capital, whether through the sale of equity or debt securities, entry into strategic partnerships, establishment of other funding facilities, asset sales or other means, in order to continue the research and development and conduct significant preclinical and clinical activities for our lead mRNA product candidates and to support our other ongoing activities.

Our future funding requirements will depend on many factors, including but not limited to:

- the scope, rate of progress, results and cost of our clinical studies, preclinical testing, and other related activities;
- the cost of manufacturing clinical supplies, and establishing commercial supplies of our product candidates and any products that we may develop;
- the number and characteristics of product candidates that we pursue;
- competing technological developments;
- our proprietary patent position, if any, in our products;
- the regulatory approval process for our products;
- the cost and timing of establishing sales, marketing, and distribution capabilities; and
- the terms and timing of any collaborative, licensing, and other arrangements that we may establish, including any required milestone and royalty payments thereunder.

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms may include liquidation or other preferences that adversely affect your rights as a stockholder. The incurrence of indebtedness could result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell, or license intellectual property rights, and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through arrangements with collaborative partners or otherwise at an earlier stage than otherwise would be desirable and we may be required to relinquish rights to some of our technologies or product candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results, and prospects.

If we are unable to obtain funding on a timely basis, we may be required to significantly curtail, delay, or discontinue one or more of our research or development programs or the commercialization of any product candidates or be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition, and results of operations.

Risks Related to our Reliance on Third Parties

We are dependent on technologies we license, and if we lose the right to license such technologies or we fail to license new technologies in the future, our ability to develop new products would be harmed.

We currently are dependent on licenses from third parties for certain of our key technologies relating to mRNA delivery, including the licenses from UW and CSIRO. Our current licenses impose, and any future licenses we enter into are likely to impose, various development, funding, royalty, diligence, sublicensing, insurance and other obligations on us. For example, the Hybrid mRNA Technology we anticipate utilizing in developing our product candidates is based upon a multi-component nanoparticle delivery system that includes our SMARTT Polymer Technology®, which uses novel synthetic polymers we developed pursuant to an exclusive license from UW. UW may terminate the license upon delivery of a written notice of termination if we breach or fail to perform one or more of our duties under the license agreement or if we become insolvent. If our license with respect to any of these technologies is terminated for any reason, the development of the products contemplated by the licenses would be delayed, or suspended altogether, while we seek to license similar technology or develop new non-infringing technology. We may need to obtain rights to additional intellectual property, and the costs of obtaining new licenses may be high, or licenses may be unavailable. If our existing licenses are terminated, the development of the products contemplated by the licenses, including the product candidates for urea cycle disorders we are currently developing, would 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.

We may become dependent on our collaborative arrangements with third parties for a substantial portion of our revenue, and our development and commercialization activities may be delayed or reduced if we fail to initiate, negotiate or maintain successful collaborative arrangements.

We plan to pursue and form partnerships to accelerate the development and maximize the market potential of our mRNA delivery technology. Such potential partners may provide the financial resources, preclinical and clinical development, regulatory compliance, sales, marketing and distribution capabilities required for the success of our business. If we fail to secure or maintain successful collaborative arrangements, our development and commercialization activities may be delayed, reduced or terminated, and our revenues could be materially and adversely impacted.

Over the next several years, we may depend on these types of collaborations for a significant portion of our revenue. The potential future milestone and royalty payments and cost reimbursements from collaboration agreements could provide an important source of financing for our research and development programs, thereby facilitating the application of our technology to the development and commercialization of our products. These collaborative agreements might be terminated either by us or by our partners upon the satisfaction of certain notice requirements. Our partners may not be precluded from independently pursuing competing products and drug delivery approaches or technologies. Even if our partners continue their contributions to our collaborative arrangements, of which there can be no assurance, they may nevertheless determine not to actively pursue the development or commercialization of any resulting products. Our partners may fail to perform their obligations under the collaborative arrangements or may be slow in performing their obligations. In addition, our partners may experience financial difficulties at any time that could prevent them from having available funds to contribute to these collaborations. If our collaborators fail to conduct their commercialization, regulatory compliance, sales and marketing or distribution activities successfully and in a timely manner, or if they terminate or materially modify their agreements with us, the development and commercialization of one or more product candidates could be delayed, curtailed or terminated because we may not have sufficient financial resources or capabilities to continue such development and commercialization on our own.

Although we currently do not have any such partnership agreements, in the future we may receive milestone and/or royalty payments as a result of each of such agreements. If our partner with respect to any agreement terminates the applicable agreement or fails to perform its obligations thereunder, we may not receive any revenues from the technology that we have licensed pursuant to the agreement, including any milestone or royalty payments.

The mRNAs and formulation components for our product candidates are currently acquired from a single or a limited number of suppliers. The loss of these suppliers, or their failure to supply us with the mRNAs and the formulation components, could materially and adversely affect our business.

We currently produce the LNPs and the polymers we need for discovery research programs and preclinical studies of our therapeutic candidates internally. We rely on a few suppliers of our formulation components, and for mRNAs, only a single supplier, TriLink BioTechnologies, LLC. We have signed long-term contracts with some of our suppliers and are currently negotiating long-term contracts with other suppliers. There can be no assurance that sufficient quantities of product candidates could be manufactured if our suppliers are unable or unwilling to supply such materials. It is possible that we may be required to switch suppliers in the foreseeable future. In such case, the process of switching suppliers may be costly and/or time-consuming for us, and that may include the temporary or permanent suspension of a preclinical or clinical study or commercial sales of our candidate products.

The mRNAs we use are highly specialized, and we do not currently have a contractual relationship with suppliers for the mRNAs other than TriLink BioTechnologies, LLC. Although we believe that there are alternate sources of supplies that could satisfy our clinical and commercial requirements with respect to the mRNAs, we cannot guarantee that identifying alternate sources and establishing relationships with such sources would not result in significant delay in the development of our product candidates. Additionally, we may not be able to enter into supply arrangements with alternative suppliers on commercially reasonable terms, or at all. A delay in the development of our product candidates or having to enter into a new agreement with a different third party on less favorable terms than we have with our current suppliers could have a material adverse impact on our business.

We anticipate that we will rely completely on third parties to manufacture certain preclinical and all clinical drug supplies. Our business could be harmed if those third parties fail to provide us with sufficient quantities of drug product, or fail to do so at acceptable quality levels or prices.

We do not currently have, nor do we plan to acquire, the infrastructure or capability internally to manufacture our preclinical and clinical drug supplies for use in the conduct of our clinical studies, and we lack the resources and the capability to manufacture any of our product candidates on a clinical or commercial scale. Our internal manufacturing capabilities are limited to small-scale production of non-cGMP material in quantities necessary to conduct preclinical studies of our product candidates. Our product candidates utilize specialized formulations with polymer and LNP components whose scale-up and manufacturing could be challenging and require specific technical expertise that we may not be able to access on acceptable terms, if at all. We also have very limited experience in such scale-up and manufacturing, requiring us to depend on a limited number of third parties, who might not be able to deliver in a timely manner, or at all. In order to develop products, apply for regulatory approvals and commercialize our products, we will need to develop, contract for, or otherwise arrange for access to the necessary manufacturing capabilities. We anticipate that we will rely on CMOs, and other third party contractors, some of whom may have limited cGMP experience, to manufacture formulations and produce larger scale amounts of drug substance and the drug product required for any clinical trials that we initiate.

The manufacturing process for any products based on our technologies that we or our partners may develop is subject to the FDA and foreign regulatory authority approval process, and we or our partners will need to contract with manufacturers who can meet all applicable FDA and foreign regulatory authority requirements on an ongoing basis. In addition, if we receive the necessary regulatory approval for any product candidate, we also expect to rely on third parties, including our commercial collaborators, to produce materials required for commercial supply. We may experience difficulty in obtaining adequate manufacturing capacity for our needs. If we are unable to obtain or maintain contract manufacturing for these product candidates, or to do so on commercially reasonable terms, we may not be able to successfully develop and commercialize our products.

To the extent that we enter into manufacturing arrangements with third parties, we will depend on these third parties to perform their obligations in a timely manner and consistent with regulatory requirements, including those related to quality control and quality assurance. The failure of a third-party manufacturer to perform its obligations as expected could adversely affect our business in a number of ways, including:

- we may not be able to initiate or continue preclinical and clinical trials of products that are under development;
- we may need to repeat pivotal clinical trials;
- we may be delayed in submitting regulatory applications, or receiving regulatory approvals, for our product candidates;
- we may lose the cooperation of our collaborators;
- our products could be the subject of inspections by regulatory authorities;
- we may be required to cease distribution or recall some or all batches of our products; and
- ultimately, we may not be able to meet commercial demands for our products.

If a third-party manufacturer with whom we contract fails to perform its obligations, we may be forced to manufacture the materials ourselves, for which we may not have the capabilities or resources, or enter into an agreement with a different third-party manufacturer, which we may not be able to do on reasonable terms, if at all. In some cases, the technical skills required to manufacture our product may be unique to the original manufacturer and we may have difficulty transferring such skills to a back-up or alternate manufacturer, or we may be unable to transfer such skills at all. In addition, if we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. We will also be required to demonstrate that the newly manufactured material is similar to the previously manufactured material, or we may need to repeat clinical trials with the newly manufactured material. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget. Furthermore, a manufacturer may possess technology related to the manufacture of our product candidate that such manufacturer owns independently, which would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third party manufacture our products.

We intend to rely on third parties to conduct our preclinical studies and clinical trials and perform other tasks for us. If these third parties do not successfully carry out their contractual duties, meet expected deadlines, or comply with regulatory requirements, we may not be able to obtain regulatory approval for or commercialize our product candidates and our business, financial condition and results of operations could be substantially harmed.

We plan to rely upon third-party CROs, medical institutions, clinical investigators and contract laboratories to monitor and manage data for our licensed ongoing preclinical and clinical programs. We have relied and expect to continue to rely on these parties for execution of our preclinical studies and clinical trials, and we control only certain aspects of their activities. Nevertheless, we maintain responsibility for ensuring that each of our clinical trials and preclinical studies is conducted in accordance with the applicable protocol, legal, regulatory, and scientific standards and our reliance on these third parties does not relieve us of our regulatory responsibilities. We and our CROs and other vendors are required to comply with cGMP, current good clinical practices or cGCP, and current GLP, or cGLP, which are a collection of laws and regulations enforced by the FDA or comparable foreign authorities for all of our product candidates in clinical development. Regulatory authorities enforce these regulations through periodic inspections of manufacturing facilities, preclinical study and clinical trial sponsors, principal investigators, preclinical study and clinical trial sites, and other contractors. If we or any of our CROs or vendors fails to comply with applicable regulations, the data generated in our preclinical studies and clinical trials may be deemed unreliable and the FDA or comparable foreign authorities may require us to perform additional preclinical studies and clinical trials before approving our marketing applications. We cannot assure that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations. In addition, our clinical trials must be conducted with products produced consistent with cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the development and regulatory approval processes.

If any of our relationships with these third-party CROs, medical institutions, clinical investigators or contract laboratories terminate, we may not be able to enter into arrangements with alternative CROs on commercially reasonable terms, or at all. In addition, our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our ongoing preclinical and clinical programs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our protocols, regulatory requirements, or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. CROs may also generate higher costs than anticipated. As a result, our business, financial condition and results of operations and the commercial prospects for our product candidates could be materially and adversely affected, our costs could increase, and our ability to generate revenue could be delayed.

Switching or adding additional CROs, medical institutions, clinical investigators or contract laboratories involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work replacing a previous CRO. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines.

If any of our product candidates are approved for marketing and commercialization and we are unable to develop sales, marketing and distribution capabilities on our own or enter into agreements with third parties to perform these functions on acceptable terms, we will be unable to commercialize successfully any such future products.

We currently have no sales, marketing or distribution capabilities or experience. If any of our product candidates is approved, we will need to develop internal sales, marketing and distribution capabilities to commercialize such products, which would be expensive and time-consuming, or enter into collaborations with third parties to perform these services. If we decide to market our products directly, we will need to commit significant financial and managerial resources to develop a marketing and sales force with technical expertise and supporting distribution, administration and compliance capabilities. If we rely on third parties with such capabilities to market our products or decide to co-promote products with collaborators, we will need to establish and maintain marketing and distribution arrangements with third parties, and there can be no assurance that we will be able to enter into such arrangements on acceptable terms or at all. In entering into third-party marketing or distribution arrangements, any revenue we receive will depend upon the efforts of the third parties and there can be no assurance that such third parties will establish adequate sales and distribution capabilities or be successful in gaining market acceptance of any approved product. If we are not successful in commercializing any product approved in the future, either on our own or through third parties, our business, financial condition, results of operations and prospects could be materially adversely affected.

Risks Related to the Development and Regulatory Approval of Our Product Candidates

The Hybrid mRNA Technology and mRNA-based drug development is unproven and may never lead to marketable products.

Our future success depends on the successful development, by us or together with our future partners, of mRNA-based products and technologies as therapeutic agents. The scientific discoveries that form the basis for our efforts to discover and develop the Hybrid mRNA Technology and mRNA-based therapeutics are relatively new. The scientific evidence to support the feasibility of developing drugs based on these discoveries is both preliminary and limited.

Relatively few mRNA-based therapeutic product candidates have ever been tested in animals or humans, and we are not aware of any mRNA-based therapeutic product having received marketing approval. We currently have only limited preclinical data suggesting that we can deliver mRNA molecules to hepatocytes in the liver using our Hybrid mRNA Technology, as our business plan contemplates, resulting in the intended expression of proteins to treat orphan liver diseases. In addition, mRNA-based compounds delivered using our Hybrid mRNA Technology may not demonstrate in patients the chemical and pharmacological properties ascribed to them in laboratory studies, and they may interact with human biological systems in unforeseen, ineffective or harmful ways. We may make significant expenditures developing mRNA-based therapeutics without success. In addition, our Hybrid mRNA Technology polymer-LNP-based delivery system has never been tested in humans and may not be effective. Our mRNA technology may result in unanticipated side effects that may prevent the further development of our products. As a result, we may never develop a marketable product utilizing our technologies. If we, independently or together with potential future partners, do not develop and commercialize drugs based upon our technologies, our operations will not become profitable, and we may cease operations.

As all of our programs are in preclinical studies or early stage research, we cannot be certain that any of our product candidates will receive regulatory approval or be commercialized. If we are unable to receive regulatory approval or commercialize our product candidates, our business will be adversely affected.

Our key strategy is to discover, develop and commercialize a portfolio of novel proprietary mRNA therapeutics for the treatment of inherited orphan liver diseases through internal efforts and through those of our future strategic partnerships. Our future results of operations depend, to a significant degree, upon our and our collaborators' ability to successfully develop and commercialize our product candidates. To date, no pivotal clinical trials of mRNA therapeutics designed to provide clinically and statistically significant proof of efficacy, or to provide sufficient evidence of safety to justify approval, have been completed. All of our product candidates are in the early stages of development and will require additional preclinical and clinical development and studies to evaluate their toxicology, carcinogenicity and optimize their formulation, management of nonclinical, clinical, and manufacturing activities, regulatory approval, obtaining adequate manufacturing supply, building of a commercial organization, and significant marketing efforts before we generate any revenue from product sales. The development and commercialization process, particularly with respect to innovative products, is both time-consuming and costly and involves a high degree of business risk. Successful product development in the pharmaceutical industry is highly uncertain, and very few research and development projects result in a commercial product. Positive results obtained during early development do not necessarily mean later development will succeed or that regulatory clearances will be obtained. Our development efforts may not lead to commercialization, or even if we ultimately receive regulatory approval for any of these product candidates, we or our potential future partners, if any, may be unable to commercialize them successfully for a variety of reasons, including the following:

- a product candidate may, after additional studies, be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective;
- a product candidate may not receive necessary regulatory approvals in a timely manner, if at all;
- competitors may develop alternatives that render our product candidates (or those of our future partners) obsolete;
- a product candidate may not have a sustainable intellectual property position in major markets;
- a product candidate may not be able to be successfully and profitably produced and marketed; or
- a product candidate may not be accepted by patients, the medical community or third-party payors.

If any of our product candidates fail to demonstrate safety or efficacy at any time or during any phase of development, we would experience potentially significant delays in, or be required to abandon, development of the product candidate.

To date, we have invested substantially all of our efforts and financial resources to identify, acquire, license, and develop our technology and lead compounds, including conducting preclinical studies and providing general and administrative support for these operations. We currently have one product candidate with a preclinical proof of concept and are currently evaluating programs for two other subtypes of urea cycle disorders for a second potential product candidate. None of our product candidates has been approved by the FDA or any foreign regulatory authority, and we do not anticipate that any of our current product candidates will be eligible to receive regulatory approval from the FDA or comparable foreign authorities and begin commercialization for a number of years, if ever. There can be no assurance that any of our product candidates that have entered, or may enter, research or development will ever be successfully commercialized, and delays in any part of the process or the inability to obtain regulatory approval could adversely affect our operating results. If we fail to commercialize one or more of our current product candidates in a timely manner or at all, we may be unable to generate sufficient revenues to attain or maintain profitability, and our financial condition and stock price may decline.

Our data from the OTCD program is limited and may not be indicative of future results.

We have conducted a limited number of experiments in our OTCD program with the hyperammonemia model, and there is significant uncertainty as to whether the early results from our preclinical studies on mice will translate into a successful therapeutic product candidate. Our OTCD program may fail to reach clinical stage for a number of reasons, including the following:

- We have performed a limited number of experiments in the hyperammonemia model.
- We anticipate a minimum level of OTC protein will have to be made to cure OTCD patients, but it is unclear whether the protein levels produced in mice using our OTCD program will be sufficient for the human disease.
- It is unclear whether the doses of mRNA required to normalize ammonia and orotic acid levels in mice will translate into larger animal species and ultimately humans. Dose levels will affect the cost of the ultimate therapeutic and high dosage levels may be cost prohibitive.
- It is unknown if the dosing frequency used in mouse studies will translate into larger animal species and humans. The dosing frequency may be inconsistent with acceptable dosing frequency for a commercial product.
- While the OTC-encoded mRNA treatment appears to be well tolerated in mice, rats and non-human primates, it is unclear whether tolerability studies in animals will fully translate into humans which may be more susceptible to the side effects of the drug.

The development of our product candidates including clinical trials utilizing our technologies will be expensive and time-consuming, and if the development of our product candidates does not produce favorable results or commencement or completion of clinical trials are delayed, we and our collaborators may be unable to commercialize these products.

Our research and development programs with respect to mRNA-based products are at an early stage. To receive regulatory approval for the commercialization of our current product candidates, or any other candidates that we may develop, extensive preclinical studies and adequate and well-controlled clinical trials must be conducted to demonstrate safety and efficacy in humans to the satisfaction of the FDA and comparable foreign authorities. In order to support marketing approval, these agencies typically require successful results in one or more Phase 3 clinical trials, which our current product candidates have not yet reached and may never reach. Preclinical and clinical testing is expensive, can take many years and has an uncertain outcome, and the historical failure rate for product candidates is high. The length of time generally varies substantially according to the type of drug, complexity of clinical trial design, regulatory compliance requirements, intended use of the product candidate and rate of patient enrollment for the clinical trials, and we do not know whether planned clinical trials will begin on time or be completed on schedule, if at all. Delays in the commencement or completion of clinical trials could significantly impact our product development costs. In addition, our clinical trials may also be delayed by the limited number of patients who have the orphan diseases we are pursuing or by slower than expected enrollment.

A failure of one or more preclinical studies or clinical trials can occur at any stage of the development process. We or our future partners may experience numerous unforeseen events during, or as a result of, the preclinical testing and the clinical trial process that could delay or prevent the commencement and completion of clinical trials, and as a result, the receipt of regulatory approval or the commercialization of our product candidates, including:

- preclinical tests or clinical trials may produce negative or inconclusive results, and we or a partner may decide, or a regulator may require us, to conduct additional preclinical testing or clinical trials, or we or a partner may abandon projects that were previously expected to be promising;
- regulators may not authorize us to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- prospective third-party contract research organizations, or CROs, and clinical trial sites may not reach an agreement with us on acceptable terms, or at all;
- enrollment in clinical trials may be slower than anticipated or participants may drop out of clinical trials at a higher rate than anticipated, resulting in significant delays;
- CROs may fail to conduct the clinical trial in accordance with regulatory requirements or clinical protocols or meet their contractual obligations in a timely manner;
- product candidates may have very different chemical and pharmacological properties in humans than in laboratory testing and may interact with human biological systems in unforeseen, ineffective or harmful ways;
- collaborators who may be responsible for the development of our product candidates may not devote sufficient resources to these clinical trials or other preclinical studies of these candidates or conduct them in a timely manner;
- clinical trials may be suspended or terminated if the participants are being exposed to unacceptable health risks;
- regulators, including the FDA, may require that clinical research be held, suspended or terminated for various reasons, including noncompliance with regulatory requirements;
- the cost of clinical trials may be greater than anticipated;
- lack of adequate funding to continue the clinical trial;
- the supply or quality of product candidates or other materials necessary to conduct clinical trials may be insufficient or inadequate; and
- product candidates may not have the desired effects or may include undesirable side effects or the product candidates may have other unexpected characteristics that delay or preclude regulatory approval or limit their commercial use or market acceptance, if approved.

Further, even if the results of preclinical studies or clinical trials are initially positive, it is possible that we will obtain different results in the later stages of drug development or that results seen in clinical trials will not continue with longer term treatment. Drugs in late stages of clinical development may fail to show the desired safety and efficacy traits despite having progressed through initial clinical testing. For example, positive results in early Phase 1 or Phase 2 clinical trials may not be repeated in larger Phase 2 or Phase 3 clinical trials. This product candidate development risk is heightened by any changes in the planned clinical trials compared to the completed clinical trials. As product candidates are developed through preclinical to early to late stage clinical trials towards approval and commercialization, it is customary that various aspects of the development program, such as manufacturing and methods of administration, are altered along the way in an effort to optimize processes and results. While these types of changes are common and are intended to optimize the product candidates for late stage clinical trials, approval and commercialization, such changes carry the risk that they will not achieve these intended objectives. Any of these changes could make the results of our planned clinical trials or other future clinical trials we may initiate less predictable and could cause our product candidates to perform differently, including causing toxicities, which could delay completion of our clinical trials, delay approval of our product candidates, and/or jeopardize our ability to commence product sales and generate revenues.

It is expected that all of the product candidates that may be developed by us or in collaboration with future partners based on our technologies will be prone to the risks of failure inherent in drug development. The clinical trials of any or all of our product candidates could be unsuccessful, which would prevent the commercialization of these drugs. We currently do not have strategic collaborations in place for clinical development of any of our current product candidates. Therefore, in the future, we or any potential future collaborative partner will be responsible for establishing the targeted endpoints and goals for development of our product candidates. These targeted endpoints and goals may be inadequate to demonstrate the safety and efficacy levels required for regulatory approvals. Even if we believe data collected during the development of our product candidates are promising, such data may not be sufficient to support marketing approval by the FDA or comparable foreign authorities. Further, data generated during development can be interpreted in different ways. The FDA or comparable foreign authorities conducts its own independent analysis of some or all of the preclinical and clinical trial data submitted in a regulatory filing and often comes to different and potentially more negative conclusions than the analysis performed by the drug sponsor. Our failure to adequately demonstrate the safety and efficacy of our product candidates would prevent our receipt of regulatory approval, and ultimately the potential commercialization of these product candidates.

We in-license some of the intellectual property related to our product candidates from UW and CSIRO pursuant to the license agreements. Since our experience with our product candidates is limited, we will need to train our existing personnel and hire additional personnel in order to successfully administer and manage our clinical trials and other studies as planned, which may result in delays in completing such planned clinical trials and preclinical studies.

Since we do not currently possess the resources necessary to independently develop and commercialize our product candidates or any other candidates that we may develop, we may seek to enter into collaborative agreements to assist in the development and potential future commercialization of some or all of these assets as a component of our strategic plan. However, our discussions with potential collaborators may not lead to the establishment of collaborations on acceptable terms, if at all, or it may take longer than expected to establish new collaborations, leading to development and potential commercialization delays, which would adversely affect our business, financial condition and results of operations.

If we experience delays in the completion or termination of any clinical trial of our product candidates, the commercial prospects of our product candidates will be harmed, and our ability to commence product sales and generate product revenues from any of our product candidates will be delayed. In addition, any delays in completing our clinical trials will increase our costs and slow down our product candidate development and approval process. Delays in completing our clinical trials could also allow our competitors to obtain marketing approval before we do or shorten the patent protection period during which we may have the exclusive right to commercialize our product candidates. Any of these occurrences may harm our business, financial condition and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

We expect to continue to incur significant research and development expenses, which may make it difficult for us to attain profitability.

We expect to expend substantial funds in research and development, including preclinical studies and clinical trials of our product candidates, and to manufacture and market any product candidates in the event they are approved for commercial sale. We also may need additional funding to develop or acquire complementary companies, technologies and assets, as well as for working capital requirements and other operating and general corporate purposes. Moreover, our planned increases in staffing will dramatically increase our costs in the near and long-term.

Because the successful development of our product candidates 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 sufficient revenue, even if we are able to commercialize any of our product candidates, to become profitable.

Gene editing technology is relatively new, and if we are unable to use our technology in gene editing applications, our revenue opportunities from such partnerships will be limited.

Delivering mRNA encoding gene editing nucleases to the liver involves the relatively new approach of gene editing, and the scientific evidence to support the feasibility of developing drugs based on these discoveries is both preliminary and limited. Gene editing technologies have been subject to only a limited number of animal studies and clinical trials, and we are not aware of any gene editing products that have obtained marketing approval from the FDA. Gene editing in humans may cause deaths, serious adverse events, undesirable side effects, or unexpected characteristics, and if such adverse events were to occur with in vivo gene editing in humans, it could lead to a temporary or permanent cessation of clinical studies and product development in the field of gene editing, which could lead to the termination of any gene editing partnership we enter into with our collaborators. Moreover the regulatory requirements that will govern gene editing product candidates are uncertain and are subject to change. In addition, gene editing products involve new and rapidly evolving technologies that may render our products or processes obsolete or less attractive. We cannot be certain that we will be able to implement technologies on a timely basis or at a cost that is acceptable to us. If we or our potential collaborators are unable to use our delivery technology to develop commercial gene editing products, our revenue opportunities will be limited and our operations may be adversely affected.

We are subject to extensive U.S. and foreign government regulations, including the requirement of approval before products may be marketed. The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time-consuming, and inherently unpredictable. If we are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed.

We and the drug product candidates developed by us or in collaboration with future partners are subject to extensive regulation by governmental authorities in the United States and other countries. Failure to comply with applicable requirements could result in, among other things, any of the following actions:

- warning letters;
- fines and other civil penalties;
- unanticipated expenditures;
- delays in approving or refusal to approve a product candidate;
- product recall or seizure;
- interruption of manufacturing or clinical trials;
- operating restrictions; and
- injunctions and criminal prosecution.

Our product candidates, developed independently or in collaboration with future partners, cannot be marketed in the United States without FDA approval or clearance, and they cannot be marketed in foreign countries without regulatory approval from comparable foreign authority. Neither the FDA nor any foreign regulatory authority has approved any of the product candidates being developed by us based on our technologies. These product candidates are in preclinical development and will have to be approved by the FDA or applicable foreign regulatory authorities before they can be marketed in the United States or abroad. Obtaining regulatory approval requires substantial time, effort, and financial resources, and may be subject to both unexpected and unforeseen delays, including, without limitation, citizen's petitions or other filings with the FDA, and there can be no assurance that any approval will be granted on a timely basis, if at all, or that delays will be resolved favorably or in a timely manner. Specifically, neither our polymer-LNP technology nor, to our knowledge, any mRNA-based therapeutic has been approved as a human therapeutic. We have not obtained regulatory approval for any product candidate, and it is possible that none of our existing product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval. If our product candidates are not approved in a timely fashion, or are not approved at all, our business and financial condition may be adversely affected.

In addition, both before and after regulatory approval, we, our collaborators and our product candidates are subject to numerous requirements by the FDA and foreign regulatory authorities covering, among other things, testing, manufacturing, quality control, labeling, advertising, promotion, distribution and export. These requirements may change and additional government regulations may be promulgated that could affect us, our collaborators or our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. There can be no assurance that neither we nor any of our future partners will be required to incur significant costs to comply with such laws and regulations in the future or that such laws or regulations will not have a material adverse effect upon our business.

Failure to comply with foreign regulatory requirements governing human clinical trials and marketing approval for drugs could prevent the sale of product candidates based on our technologies in foreign markets, which may adversely affect our operating results and financial condition.

We generally plan to seek regulatory approval to commercialize our product candidates in the United States, the European Union, and in additional foreign countries. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement for marketing product candidates based on our technologies outside the United States vary greatly from country to country. We have, and our future partners may have, limited experience in obtaining foreign regulatory approvals. The time required to obtain approvals outside the United States may differ from that required to obtain FDA approval. Neither we nor our future partners may be able to obtain foreign regulatory approvals on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other countries or by the FDA. Failure to comply with these regulatory requirements or obtain required approvals could restrict the development of foreign markets for our product candidates and may have a material adverse effect on our financial condition or results of operations.

Even if regulatory approvals are obtained for our products, such products will be subject to ongoing regulatory review. If we or a partner fail to comply with continuing U.S. and foreign regulations, the approvals to market drugs could be lost and our business would be materially adversely affected.

Following any initial FDA or foreign regulatory approval of any drugs we or a partner may develop, such drugs will continue to be subject to regulatory review, including the review of adverse drug experiences and clinical results that are reported after such drugs are made available to patients. This would include results from any post-marketing studies or vigilance required as a condition of approval. The manufacturer and manufacturing facilities used to make any product candidates will also be subject to periodic review and inspection by regulatory authorities, including the FDA. The discovery of any new or previously unknown problems with the product, manufacturer or facility may result in restrictions on the drug or manufacturer or facility, including withdrawal of the drug from the market. Marketing, advertising and labeling also will be subject to regulatory requirements and continuing regulatory review. The failure to comply with applicable continuing regulatory requirements may result in fines, suspension or withdrawal of regulatory approval, product recalls and seizures, operating restrictions and other adverse consequences.

We have used, and may continue to use, hazardous chemicals and biological materials in our business. Any disputes relating to improper use, handling, storage or disposal of these materials could be time-consuming and costly.

Our research and development operations have involved, and if continued in the future will likely continue to involve, the use of hazardous and biological, potentially infectious, materials. Such use subjects us to the risk of accidental contamination or discharge or any resultant injury from these materials. Federal, state and local laws and regulations govern the use, manufacture, storage, handling and disposal of these materials and specific waste products. We could be subject to damages, fines or penalties in the event of an improper or unauthorized release of, or exposure of individuals to, these hazardous materials, and our liability could be substantial. The costs of complying with these current and future environmental laws and regulations may be significant, thereby impairing our business.

We are also subject to numerous environmental, health and workplace safety laws and regulations, including those governing laboratory procedures, exposure to blood-borne pathogens and the handling of biohazardous materials. 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 these materials. The limits of our workers' compensation insurance are mandated by state law, and our workers' compensation liability is capped at these state-mandated limits. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials. Additional federal, state and local laws and regulations affecting our operations may be adopted in the future. We may incur substantial costs to comply with, and substantial fines or penalties if we violate, any of these laws or regulations.

We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, and health information privacy and security laws. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations may be directly or indirectly through our customers, subject to various federal and state fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act, and physician sunshine laws and regulations. These laws may impact, among other things, our proposed sales, marketing, and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce, or in return for, the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;

- federal civil and criminal false claims laws and civil monetary penalty laws, including the False Claims Act, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent;

- HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;

- HIPAA, as amended by HITECH, and its implementing regulations, which imposes certain requirements relating to the privacy, security, and transmission of individually identifiable health information;

- the federal physician sunshine requirements under the Patient Protection and Affordable Care Act, which requires manufacturers of drugs, devices, biologics, and medical supplies to report annually to the U.S. Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals and ownership and investment interests held by physicians and their immediate family members; and

- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws that may apply to items or services reimbursed by any third-party payor, including commercial insurers, state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. In addition, recent health care reform legislation has strengthened these laws. For example, the Patient Protection and Affordable Care Act, among other things, amends the intent requirement of the federal anti-kickback and criminal healthcare fraud statutes. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it. Moreover, the Patient Protection and Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, exclusion from participation in government health care programs, such as Medicare and Medicaid, imprisonment, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Risks Related to our Intellectual Property

If we are unable to adequately protect our proprietary technology from legal challenges, infringement or alternative technologies, our competitive position may be hurt and our operating results may be negatively impacted.

Our business is based upon the development of mRNA-based therapeutics, and we rely on the issuance of patents, both in the United States and internationally, for protection against competitive technologies. As of March 24, 2017, we own or have in-licensed 16 issued U.S. patents, 25 issued foreign patents, and over 15 pending U.S. and foreign patent applications. Although we believe we exercise the necessary due diligence in the patent filings we make in connection with the patents we own or in-license, our proprietary position is not established until the appropriate regulatory authorities actually issue a patent, which may take several years from initial filing or may never occur.

Moreover, even the established patent positions of pharmaceutical companies are generally uncertain and involve complex legal and factual issues. Although we believe our issued patents are valid, third parties may infringe our patents or may initiate proceedings challenging the validity or enforceability of our patents. The issuance of a patent is not conclusive as to its claim scope, validity or enforceability. Challenges raised in patent infringement litigation we initiate or in proceedings initiated by third parties may result in determinations that our patents have not been infringed or that they are invalid, unenforceable or otherwise subject to limitations. In the event of any such determinations, third parties may be able to use the discoveries or technologies claimed in our patents without paying us licensing fees or royalties, which could significantly diminish the value of these discoveries or technologies. Responding to challenges initiated by third parties, including in response to a suit we initiate regarding infringement or other intellectual property violations, may require significant expenditures and divert the attention of our management and key personnel from other business concerns.

Furthermore, it is possible others will infringe or otherwise circumvent our issued patents and that we will be unable to fund the cost of litigation against them or that we would elect not to pursue litigation. In addition, enforcing our patents against third parties may require significant expenditures regardless of the outcome of such efforts. We also cannot assure you that others have not filed patent applications for technology covered by our pending applications or that we were the first to invent the technology. There may also exist third party patents or patent applications relevant to our potential products that may block or compete with the technologies covered by our patent applications and third parties may independently develop intellectual property similar to our patented intellectual property, which could result in, among other things, interference proceedings in the U.S. Patent and Trademark Office to determine priority of invention.

In addition, we may not be able to protect our established and pending patent positions from competitive technologies, which may provide more effective therapeutic benefit to patients and which may therefore make our products, technology and proprietary position obsolete.

If we are unable to adequately protect our proprietary intellectual property from legal challenges, infringement or alternative technologies, we will not be able to compete effectively in the drug discovery and development business.

We license patent rights from third-party owners or licensees. If such owners or licensees do not properly or successfully obtain, maintain or enforce the patents underlying such licenses, or if they retain or license to others any competing rights, our competitive position and business prospects may be adversely affected.

We do, and will continue to, rely on intellectual property rights licensed from third parties to protect our technology. We are a party to a number of licenses that give us rights to third-party intellectual property that is necessary or useful for our business. See “Business-License Agreements.” We also intend to license additional third-party intellectual property in the future. Our success will depend in part on the ability of our licensors to obtain, maintain and enforce patent protection for our licensed intellectual property, in particular, those patents to which we have secured exclusive rights. Our licensors may not successfully prosecute the patent applications licensed to us. Even if patents issue or are granted, our licensors may fail to maintain these patents, may determine not to pursue litigation against other companies that are infringing these patents, or may pursue litigation less aggressively than we would. Further, we may not obtain exclusive rights, which would allow for third parties to develop competing products. Without protection for, or exclusive right to, the intellectual property we license, other companies might be able to offer substantially identical products for sale, which could adversely affect our competitive business position and harm our business prospects.

If we are unable to protect the confidentiality of our trade secrets or know-how, such proprietary information may be used by others to compete against us.

In addition to filing patents, in an effort to maintain the confidentiality and ownership of our trade secrets, know-how, and other proprietary information, we have typically required parties to whom we disclose confidential information to execute confidentiality or non-disclosure agreements. These parties include our employees, consultants, advisors, and potential or actual collaborators. We also enter into agreements that purport to require the disclosure and assignment to us of the rights to the ideas, development, discoveries, and inventions of our employees, consultants, and advisors while we employ or engage them. However, it is possible that these agreements may be breached, invalidated or rendered unenforceable, and if so, there may not be an adequate corrective remedy available. In addition, others may independently develop substantially equivalent proprietary information and techniques, or otherwise gain access to our trade secrets or know-how. The disclosure to, or independent development by, a competitor of any trade secret, know-how, or other technology not protected by a patent could materially adversely affect any competitive advantage we may have over such a competitor. Furthermore, like many companies in our industry, we may from time to time hire scientific personnel formerly employed by other companies involved in one or more areas similar to the activities we conduct. In some situations, our confidentiality and non-disclosure agreements may conflict with, or be subject to, the rights of third parties with whom our employees, consultants or advisors have prior employment or consulting relationships. Although we have typically required our employees and consultants to maintain the confidentiality of all confidential information of previous employers, we or these individuals may be subject to allegations of trade secret misappropriation or other similar claims as a result of their prior affiliations. If a dispute arises with respect to any proprietary right, enforcement of our rights can be costly and unpredictable and a court may determine that the right belongs to a third party. Our failure to protect our proprietary information and techniques may inhibit or limit our ability to exclude certain competitors from the market and to execute our business strategies.

Because intellectual property rights are of limited duration, expiration of intellectual property rights and licenses will negatively impact our operating results.

Intellectual property rights, such as patents and license agreements based on those patents, generally are of limited duration. Our operating results depend on our patents and intellectual property licenses. Therefore, the expiration or other loss of rights associated with intellectual property and intellectual property licenses can negatively impact our business. For example, due to the extensive time needed to develop, test, and obtain regulatory approval for our therapeutic candidates, any patents that may be issued that protect our therapeutic candidates may expire prior to or early during commercialization. This may reduce or eliminate any market advantages that such patents may give us. Following patent expiration, we may face increased competition through the entry of generic or biosimilar products into the market and a subsequent decline in market share and profits.

Our patent applications may be inadequate in terms of priority, scope or commercial value.

We apply for patents covering our discoveries and technologies as we deem appropriate and as our resources permit. However, we or our partners may fail to apply for patents on important discoveries or technologies in a timely fashion or at all. Also, our pending patent applications, and those that we may file in the future or those we may license from third parties, may not result in the issuance of any patents. These applications may not be sufficient to meet the statutory requirements for patentability, and therefore we may be unable to obtain enforceable patents covering the related discoveries or technologies we may want to commercialize. In addition, because patent applications are maintained in secrecy for approximately 18 months after filing, other parties may have filed patent applications relating to inventions before our applications covering the same or similar inventions. In addition, foreign patent applications are often published initially in local languages, and until an English language translation is available it can be impossible to determine the significance of a third party invention. Any patent applications filed by third parties may prevail over our patent applications or may result in patents that issue alongside patents issued to us, leading to uncertainty over the scope of the patents or the freedom to practice the claimed inventions.

Although we have acquired and in-licensed a number of issued patents, the discoveries or technologies covered by these patents may not have any therapeutic or commercial value. Also, issued patents may not provide commercially meaningful protection against competitors. Other parties may be able to design around our issued patents or independently develop products having effects similar or identical to our patented product candidates. In addition, the scope of our patents is subject to considerable uncertainty and competitors or other parties may obtain similar patents of uncertain scope.

Third-party claims of intellectual property infringement may require us to spend substantial time and money and could prevent us from developing or commercializing our therapeutic candidates.

The development, manufacture, use, offer for sale, sale or importation of our therapeutic candidates may infringe on the claims of third party patents or other intellectual property rights. Also, the nature of claims contained in unpublished patent filings around the world is unknown to us, and it is not possible to know in which countries patent holders may choose for the extension of their filings under the Patent Cooperation Treaty, or other mechanisms. The cost to us of any legal proceeding arising from a third party's assertion of intellectual property rights, even if resolved in our favor, could be substantial. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively because of their substantially greater financial resources. Uncertainties resulting from the initiation and continuation or defense of intellectual property litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace and could result in an injunction prohibiting certain activities. Legal proceedings to resolve third party claims of intellectual property infringement may also absorb significant management time. Consequently, we are unable to guarantee that we will be able to manufacture, use, offer for sale, sell or import our therapeutic candidates in the event of an infringement action or other dispute regarding intellectual property rights.

While we are aware that there are third party patents having claims that may be considered relevant to certain technologies for which we plan to seek regulatory approval, we believe those patents will expire prior to the time we expect to obtain regulatory approval for our first product. The estimated expiration dates for those patents were determined according to information on the face pages of the patents, and certain factors that could influence patent term, such as patent term extension, for example, were not factored into these estimates. Accordingly, the estimated expiration dates of those patents may not be accurate and one or more of those patents may not expire before we obtain regulatory approval for an applicable technology. Owners or licensees of one or more of those patents may bring a patent infringement suit against us. If one or more of those patents are asserted against us, we expect to be able to assert a defense for a safe harbor to patent infringement under 35 U.S.C. 271(e)(1) if certain requirements are met. It is possible that (1) certain of these requirements may not be met, and/or (2) one or more of the third party patents might expire after one or more of our technologies obtain regulatory approval, and consequently we may not successfully assert such a defense to patent infringement. If we are unsuccessful in asserting a defense under 35 U.S.C. 271(e)(1), it is possible we may not prevail in defending against claims of infringement and/or challenging the validity of claims in those patents. We may not successfully develop alternative technologies or enter into agreements by which we obtain rights to applicable patents. These rights, if necessary, may not be available on terms acceptable to us or at all.

In the event of patent infringement claims, or to avoid potential claims, we may choose or be required to seek a license from a third party and would most likely be required to pay license fees or royalties, or both. These licenses may not be available on acceptable terms, or at all. Even if we were able to obtain a license, the rights may be non-exclusive, which could potentially limit our competitive advantage. Ultimately, we could be prevented from commercializing a therapeutic candidate or be forced to cease some aspect of our business operations if, as a result of actual or threatened patent infringement or other claims, we are unable to enter into licenses on acceptable terms. This inability to enter into licenses could harm our business significantly or even prevent us from commercializing one or more therapeutic candidates.

We may be subject to other patent-related litigation or proceedings that could be costly to defend and uncertain in their outcome.

In addition to infringement claims against us, we may in the future become a party to other patent litigation or proceedings before regulatory agencies, including interference, derivation, or post-grant proceedings filed with the U.S. Patent and Trademark Office or opposition proceedings in other foreign patent offices regarding intellectual property rights with respect to our therapeutic candidates, as well as other disputes regarding intellectual property rights with our potential or actual corporate partners, or others with whom we have contractual or other business relationships. Post-issuance proceedings, including oppositions, are not uncommon and we will be required to defend these proceedings as a matter of course. These post-grant procedures may be costly, and there is a risk that we may not prevail.

If we fail to comply with our obligations under any license, collaboration or other agreements, we may be required to pay damages and could lose intellectual property rights that are necessary for developing and protecting our product candidates and delivery technologies or we could lose certain rights to grant sublicenses.

Our current licenses with UW and CSIRO impose, and any future licenses we enter into are likely to impose, various development, commercialization, funding, milestone, royalty, diligence, sublicensing, insurance, patent prosecution and enforcement, and other obligations on us. If we breach any of these obligations, or use the intellectual property licensed to us in an unauthorized manner, we may be required to pay damages and the licensor may have the right to terminate the license, which could result in us being unable to develop, manufacture and sell products that are covered by the licensed technology or enable a competitor to gain access to the licensed technology. Moreover, our licensors may own or control intellectual property that has not been licensed to us and, as a result, we may be subject to claims, regardless of their merit, that we are infringing or otherwise violating the licensor's rights. In addition, while we cannot currently determine the amount of the royalty obligations we would be required to pay on sales of future products, if any, the amounts may be significant. The amount of our future royalty obligations will depend on the technology and intellectual property we use in products that we successfully develop and commercialize, if any. Therefore, even if we successfully develop and commercialize products, we may be unable to achieve or maintain profitability.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on drug candidates throughout the world would be prohibitively expensive. Competitors may use our licensed and owned technologies in jurisdictions where we have not licensed or obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we may obtain or license patent protection, but where patent enforcement is not as strong as that in the United States. These products may compete with our products in jurisdictions where we do not have any issued or licensed patents and any future patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biopharmaceuticals, which could make it difficult for us to stop the infringement of our licensed patents and future patents we may own, or marketing of competing products in violation of our proprietary rights generally. Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our licensed and owned intellectual property both in the United States and abroad. Proceedings to enforce our future patent rights, if any, in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business.

Many countries, including European Union countries, India, Japan and China, have compulsory licensing laws under which a patent owner may be compelled under certain circumstances to grant licenses to third parties. This could limit our potential revenue opportunities. Accordingly, our efforts to enforce intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we own or license.

Risks Related to Our Business Operations

Even if we are successful in developing and commercializing a product candidate, it is possible that the commercial opportunity for mRNA-based therapeutics will be limited.

The product candidates based on our technologies that are being developed are based on new technologies and therapeutic approaches, none of which has been brought to market. Key participants in pharmaceutical marketplaces, such as physicians, third-party payors and consumers, may not accept a product intended to improve therapeutic results based on mRNA mechanisms of action. Accordingly, while we believe there will be a commercial market for mRNA-based therapeutics utilizing our technologies, there can be no assurance that this will be the case, in particular given the novelty of the field. Many factors may affect the market acceptance and commercial success of any potential products, including:

- establishment and demonstration of the effectiveness and safety of the drugs;
- timing of market entry as compared to competitive products and alternative treatments;
- benefits of our drugs relative to their prices and the comparative price of competing products and treatments;
- availability of adequate government and third-party payor reimbursement;

- marketing and distribution support of our products;
- safety, efficacy and ease of administration of our product candidates;
- willingness of patients to accept, and the willingness of medical professionals to prescribe, relatively new therapies; and
- any restrictions on labeled indications.

In addition, we focus our research and product development on treatments for orphan liver diseases. Given the small number of patients who have the diseases that we are targeting, it is critical to our ability to grow and become profitable that we continue to successfully identify patients with these diseases. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including the scientific literature, surveys of clinics, patient foundations, or market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected. The effort to identify patients with diseases we seek to treat is in early stages, and we cannot accurately predict the number of patients for whom treatment might be possible. Additionally, the potentially addressable patient population for each of our product candidates may be limited or may not be amenable to treatment with our product candidates, and new patients may become increasingly difficult to identify or gain access to, which would adversely affect our results of operations and our business.

If we fail to obtain or maintain orphan drug exclusivity for our products, our competitors may sell products to treat the same conditions and our revenue will be reduced. In addition, if a competitor obtains orphan drug designation and is first to market for a product we are developing, it could prevent or delay us from marketing our product.

We currently focus on the development of drugs that are eligible for the FDA and European Union orphan drug designation. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is intended to treat a rare disease or condition, defined as a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, the Committee for Orphan Medicinal Products, or COMP, of the European Medicines Agency, or EMA, grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the European Union community. Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biological product.

In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages, and user-fee waivers. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity. In the European Union, orphan drug designation also entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity is granted following drug or biological product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. If a competitor obtains orphan drug designation and is first to market for a product we are developing, it could prevent or delay us from marketing our product.

Because the extent and scope of patent protection for our products may in some cases be limited, orphan drug designation is especially important for our products for which orphan drug designation may be available. For eligible drugs, we plan to rely on the exclusivity period under the Orphan Drug Act to maintain a competitive position. If we do not obtain orphan drug exclusivity for our drug products and biologic products that do not have broad patent protection, our competitors may then sell the same drug to treat the same condition sooner than if we had obtained orphan drug exclusivity and our revenue will be reduced.

Even though we may obtain orphan drug designation for our products in the United States, we may not be the first to obtain marketing approval for any particular orphan indication due to the uncertainties associated with developing pharmaceutical products. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties can be approved for the same condition. Even with orphan drug exclusivity, if a third party were to prepare or market a product which infringes upon our intellectual property, we may need to initiate litigation, which may be costly, to enforce our rights against such party. Even after an orphan drug is approved, the FDA can subsequently approve the same drug with the same active moiety for the same condition if the FDA concludes that the later drug is safer, more effective, or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

If we are not able to retain our key management or attract and retain qualified scientific, technical and business personnel, our ability to implement our business plan may be adversely affected.

Our success largely depends on the skill, experience and effort of our senior management. The loss of the service of any of these persons, including Robert Overell, Ph.D., our president and chief executive officer, Michael Houston, Ph.D., our chief scientific officer and Gordon Brandt, M.D., our chief medical officer, would likely result in a significant loss in the knowledge and experience that we possess and could significantly delay or prevent successful product development and other business objectives. There is intense competition from numerous pharmaceutical and biotechnology companies, universities, governmental entities and other research institutions, seeking to employ qualified individuals in the technical fields in which we operate, and we may not be able to attract and retain the qualified personnel necessary for the successful development and commercialization of our product candidates.

If our product candidates advance into clinical trials, we may experience difficulties in managing our growth and expanding our operations.

We have limited experience in product development and have not begun clinical trials for any of our product candidates. As our product candidates enter and advance through preclinical studies and any clinical trials, we will need to expand our development, regulatory and manufacturing capabilities or contract with other organizations to provide these capabilities for us. In the future, we expect to have to manage additional relationships with collaborators or partners, suppliers and other organizations. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures. We may not be able to implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls.

We may be required to defend lawsuits or pay damages for product liability claims.

Our business exposes us to significant product liability risks inherent in the development, testing, manufacturing and marketing of therapeutic treatments. We may face substantial product liability exposure in human clinical trials that we may initiate and for products that we sell, or manufacture for others to sell, after regulatory approval. The risk exists even with respect to those drugs that are approved by regulatory agencies for commercial distribution and sale and are manufactured in facilities licensed and regulated by regulatory agencies. Product liability claims could delay or prevent completion of our development programs. If we succeed in marketing products, such claims could result in an FDA investigation of the safety and effectiveness of our products, our manufacturing processes and facilities or our marketing programs and potentially a recall of our products or more serious enforcement action, limitations on the approved indications for which they may be used or suspension or withdrawal of approvals. Regardless of the merits or eventual outcome, liability claims may also result in decreased demand for our products, injury to our reputation, costs to defend the related litigation, a diversion of management's time and our resources, substantial monetary awards to trial participants or patients and a decline in our stock price. We currently do not have product liability insurance. We will need to obtain such insurance as we believe is appropriate for our stage of development and may need to obtain higher levels of such insurance if we were ever to market any of our product candidates. Any insurance we have or may obtain may not provide sufficient coverage against potential liabilities. Furthermore, clinical trial and product liability insurance is becoming increasingly expensive. As a result, we may be unable to obtain sufficient insurance at a reasonable cost to protect us against losses caused by product liability claims that could have a material adverse effect on our business.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, provide accurate information to the FDA, comply with manufacturing standards we may establish, comply with federal and state healthcare fraud and abuse laws and regulations, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee 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 employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

Risks Related to our Industry

The biotechnology and pharmaceutical industries are intensely competitive. If we are unable to compete effectively with existing drugs, new treatment methods and new technologies, we may be unable to commercialize successfully any drugs that we develop.

The biotechnology and pharmaceutical industries are intensely competitive and rapidly changing. Many large pharmaceutical and biotechnology companies, academic institutions, governmental agencies and other public and private research organizations are pursuing the development of novel drugs for the same diseases that we are targeting or expect to target. Many of our competitors have:

- much greater financial, technical and human resources than we have at every stage of the discovery, development, manufacture and commercialization of products;
- more extensive experience in preclinical testing, conducting clinical trials, obtaining regulatory approvals, and in manufacturing, marketing and selling pharmaceutical products;
- product candidates that are based on previously tested or accepted technologies;
- products that have been approved or are in late stages of development; and
- collaborative arrangements in our target markets with leading companies and research institutions.

Products based on our technologies may face competition from drugs that have already been approved and accepted by the medical community for the treatment of the conditions for which we may develop drugs. We also expect to face competition from new drugs that enter the market. We believe a significant number of drugs and delivery technologies are currently under development, and may become commercially available in the future, for the treatment of conditions for which we and our partners may try to develop drugs. These drugs may be more effective, safer, less expensive, or marketed and sold more effectively, than any products we and our partners develop.

If we and our partners successfully develop product candidates based on our technologies, and obtain approval for them, we will face competition based on many different factors, including:

- safety and effectiveness of such products;
- ease with which such products can be administered and the extent to which patients accept relatively new routes of administration;
- timing and scope of regulatory approvals for these products;
- availability and cost of manufacturing, marketing and sales capabilities;
- price;
- reimbursement coverage; and
- patent position.

Our competitors may develop or commercialize products with significant advantages over any products we develop based on any of the factors listed above or on other factors. Our competitors may therefore be more successful in commercializing their products than we are, which could adversely affect our competitive position and business. Competitive products may make any products we develop obsolete or noncompetitive before we can recover the expenses of developing and commercializing our product candidates. Such competitors could also recruit our future employees, which could negatively impact our level of expertise and the ability to execute on our business plan. Furthermore, we also face competition from existing and new treatment methods that reduce or eliminate the need for drugs, such as the use of advanced medical devices. The development of new medical devices or other treatment methods for the diseases we are targeting could make our product candidates noncompetitive, obsolete or uneconomical.

We may be unable to compete successfully against other companies that are working to develop novel drugs and technology platforms using technology similar to ours.

In addition to the competition we face from competing drugs in general, we also face competition from other biotechnology and pharmaceutical companies and medical institutions that are working to develop novel drugs using technology that competes more directly with our own. Among those companies that are or may be working in the field of RNA therapeutics to treat orphan liver disease and/or the urea cycle disorders are: Moderna LLC, Bio Blast Pharma Ltd., Alnylam Pharmaceuticals, Arcturus Therapeutics, Inc., Acuitas Therapeutics, Arbutus Biopharma Corporation, CureVac AG, Dicerna Pharmaceuticals, Inc., Horizon Pharma plc, Ocera Therapeutics, Inc., Cytonet GmbH & Co., Promethera Biosciences S.A., BioNTech AG, Synlogic, Inc. and Aeglea Biotherapeutics, Inc. Any of these, or other, companies may develop their technology more rapidly and more effectively than us.

In addition to competition with respect to our technology and with respect to specific products, we face substantial competition to discover and develop safe and effective means to deliver mRNAs to the hepatocytes. Substantial resources are being expended by third parties, both in academic laboratories and in the corporate sector, in an effort to discover and develop a safe and effective means of delivery into the hepatocytes. If safe and effective means of delivery to the hepatocytes are developed by our competitors, our ability to successfully commercialize a competitive product would be adversely affected.

Many of our competitors, either alone or together with their partners, have substantially greater research and development capabilities and financial, scientific, technical, manufacturing, sales, marketing, distribution, regulatory and other resources and experience than us. They may also have more established relationships with pharmaceutical companies. Even if we and/or our partners are successful in developing products based on our technologies, in order to compete successfully we may need to be first to obtain intellectual property protection for, or to commercialize, such products, or we may need to demonstrate that such products are superior to, or more cost effective than, products developed by our competitors (including therapies that are based on different technologies). If we are not first to protect or market our products, or if we are unable to differentiate our products from those offered by our competitors, any products for which we are able to obtain approval may not be successful.

Universities and public and private research institutions are also potential competitors. While these organizations primarily have educational objectives, they may develop proprietary technologies related to the drug delivery field or secure protection that we may need for development of our technologies and products. We may attempt to license one or more of these proprietary technologies, but these licenses may not be available to us on acceptable terms, if at all.

Any drugs based on our technologies that we develop may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which could have a material adverse effect on our business and financial results.

The success of the products based on our technologies will depend upon the extent to which third-party payors, such as Medicare, Medicaid and other domestic and international government programs, private insurance plans and managed care programs, provide reimbursement for the use of such products. Most third-party payors may deny reimbursement if they determine that a medical product was not used in accordance with cost-effective treatment methods, as determined by the third-party payor, or was used for an unapproved indication.

Third-party payors also may refuse to reimburse for experimental procedures and devices. Furthermore, because our programs are in the early stages of development, we are unable at this time to determine their cost-effectiveness and the level or method of reimbursement. Increasingly, the third-party payors, who reimburse patients, such as government and private insurance plans, are requiring that drug companies provide them with predetermined discounts from list prices, and are challenging the prices charged for medical products. If the price charged for any products based on our technologies that we or our partners develop is inadequate in light of our development and other costs, our profitability could be adversely affected.

We expect that drugs based on our technologies that we or a partner develop may need to be administered under the supervision of a physician. Under currently applicable law, drugs that are not usually self-administered may be eligible for coverage by the Medicare program if they:

- are “incidental” to a physician’s services;
- are “reasonable and necessary” for the diagnosis or treatment of the illness or injury for which they are administered according to accepted standards of medical practice;
- are not excluded as immunizations; and
- have been approved by the FDA.

There may be significant delays in obtaining insurance coverage for newly-approved drugs, and insurance coverage may be more limited than the purpose for which the drug is approved by the FDA. Moreover, eligibility for insurance coverage does not imply that any drug will be reimbursed in all cases or at a rate that covers costs, including research, development, manufacture, sale and distribution. Interim payments for new drugs, if applicable, may also not be sufficient to cover costs and may not be made permanent. Reimbursement may be based on payments for other services and may reflect budgetary constraints or imperfections in Medicare data. Net prices for drugs may be reduced by mandatory discounts or rebates required by government health care programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates. The inability to promptly obtain coverage and profitable reimbursement rates from both government-funded and private payors for new drugs based on our technologies that we or our partners develop could have a material adverse effect on our operating results, our ability to raise capital, and our overall financial condition.

We believe that the efforts of governments and third-party payors to contain or reduce the cost of healthcare and legislative and regulatory proposals to broaden the availability of healthcare will continue to affect the business and financial condition of pharmaceutical and biopharmaceutical companies. A number of legislative and regulatory changes in the healthcare system in the United States and other major healthcare markets have occurred in recent years, and interpretation and application of such changes continue to evolve. These developments have included prescription drug benefit legislation that was enacted and took effect in January 2006, healthcare reform legislation recently enacted by certain states, and implementation of the Patient Protection and Affordable Care Act, or the Affordable Care Act, enacted in 2010 which resulted in significant changes to the health care industry. These developments could, directly or indirectly, affect our ability to sell our products, if approved, at a favorable price.

The Affordable Care Act includes significant provisions that encourage state and federal law enforcement agencies to increase activities related to preventing, detecting and prosecuting those who commit fraud, waste and abuse in federal healthcare programs, including Medicare, Medicaid and Tricare. The Affordable Care Act continues to be implemented through regulation and government activity but is subject to possible, amendment, additional implementing regulations and interpretive guidelines. The manner in which the Affordable Care Act continues to evolve could materially affect the extent to which and the amount at which pharmaceuticals are reimbursed by government programs such as Medicare, Medicaid and Tricare. We cannot predict all impacts the Affordable Care Act may have on our products, but it may result in our products being chosen less frequently or the pricing being substantially lowered. Or, the new legislation could have a positive impact on our future net sales due to increasing the number of persons with healthcare coverage in the United States.

We cannot predict what additional healthcare reform initiatives may be adopted in the future or how federal and state legislative and regulatory developments are likely to evolve, but we expect ongoing initiatives in the United States to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from product candidates based on our technologies that are successfully developed and for which regulatory approval is obtained, and may affect our overall financial condition and ability to develop product candidates.

Risks Related to Ownership of our Common Stock

We expect that our stock price will fluctuate significantly.

The trading price of shares of our common stock may be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this report, these factors include:

- actual or anticipated fluctuations in our results of operations;
- announcement or expectation of additional financing efforts;
- the timing and results of preclinical studies for our urea cycle disorder programs and any product candidates that we may develop;
- commencement or termination of collaborations for our product development and research programs;
- failure or discontinuation of any of our product development and research programs;
- variance in our financial performance from the expectations of market analysts;
- announcements by us or our competitors of results of preclinical studies, clinical trials, or regulatory approvals of product candidates, significant business developments, changes in distributor relationships, acquisitions or expansion plans;
- adverse regulatory decisions;

- changes in the prices of our raw materials or the products we sell;
- data concerning the safety and efficacy profile of our products;
- sales of our common stock by us, our insiders, or other stockholders;
- expiration of market stand-off or lock-up agreements;
- our involvement in litigation;
- our sale of common stock or other securities in the future;
- market conditions in our industry;
- changes in key personnel;
- the trading volume of our common stock;
- changes in the structure of healthcare payment systems;
- changes in the estimation of the future size and growth rate of our markets;
- the recruitment or departure of key personnel;
- developments or disputes concerning patent applications, issued patents, or other proprietary rights;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry, and market conditions; and
- the other factors described in the "Risk Factors" section of this Annual Report on Form 10-K.

In recent years, the stock markets in general have experienced extreme price and volume fluctuations, especially in the biotechnology sector. Broad market and industry factors may materially harm the market price of shares of our common stock, regardless of our operating performance. In the past, following periods of volatility in the market price of a company's securities, securities class action litigation has often been instituted against that company. If we were involved in any similar litigation, we could incur substantial costs and our management's attention and resources could be diverted.

The market price of our common stock could be negatively affected by future sales of our common stock in the public market by our existing stockholders and lenders.

Sales by us or our stockholders of a substantial number of shares of our common stock in the public market, or the perception that these sales might occur, could cause the market price of our common stock to decline or could impair our ability to raise capital through a future sale of our equity securities.

As of December 31, 2016, we had 11,690,329 shares of common stock outstanding. The resale of 4,745,174 shares, or 40.6% of our outstanding shares as of December 31, 2016 is currently prohibited or otherwise restricted as a result of securities law provisions, market standoff agreements entered into by our stockholders with us or lock-up agreements entered into by our stockholders with the underwriters of our IPO; however, subject to applicable securities law restrictions, these shares will be able to be sold in the public market beginning as follows:

- 4,290,981 shares of our outstanding shares of common stock beneficially owned by certain stockholders who are subject to lock-up agreements, each of which, subject to limited exceptions, restricts transfer of the stockholder's shares of common stock for a period of 12 months after the closing of our IPO without the prior written consent of Titan Multi-Strategy Fund I, LTD., one of the lenders from the bridge loan financing we received in December 2015; provided that, after 180 days following the IPO, the foregoing restrictions will automatically terminate if for 20 consecutive trading days on each such trading day (x) the closing price of our common stock is at least 150% of the IPO price for our common stock and (y) the trading volume of our common stock is not less than 100,000 shares; provided further that, Titan Multi-Strategy Fund I, LTD. may unilaterally waive any term of the lock-up agreement ("Category 1");

- 454,193 shares of our outstanding shares of common stock beneficially owned by certain stockholders and option holders who are subject to lock-up agreements, each of which, subject to limited exceptions, restricts transfer of the stockholder's shares of common stock for a period of 12 months after the closing of our IPO without our prior written consent, which restriction will terminate in accordance with the same terms as Category 1; provided further that, we may unilaterally waive any term of the lock-up agreement ("Category 2");

As noted above, we or Titan Multi-Strategy Fund I, LTD., as applicable, may, in our or their sole discretion, and at any time without notice, release all or any portion of the shares subject to the corresponding lock-up agreements. After the expiration of the lock-up period, these shares can be resold into the public markets in accordance with the requirements of Rule 144, subject to certain volume limitations. In addition, we have also registered the offer and sale of all of the outstanding options of our 2006 Plan as of May 17, 2016 and all of the shares of common stock issuable under the PhaseRx, Inc. 2016 Long-Term Incentive Plan, and such shares are freely transferable, except for any shares held by "affiliates," as such term is defined in Rule 144 under the Securities Act of 1933, as amended. The market price of our common stock may drop significantly when the restrictions on resale by our existing stockholders lapse and these stockholders are able to sell our common stock into the market.

Upon the expiration of the lock-up restrictions described above, the number of shares of our common stock that are potentially available for sale in the open market will increase materially, which could make it harder for the value of our common stock to appreciate unless there is a corresponding increase in demand for our common stock. This increase in available shares could cause the value of your investment in our common stock to decrease.

In addition, a sale by us of additional shares of common stock or similar securities in order to raise capital might have a similar negative impact on the share price of our common stock. A decline in the price of shares of our common stock might impede our ability to raise capital through the issuance of additional shares of common stock or other equity securities, and may cause you to lose part or all of your investment in our common stock.

The concentration of the capital stock ownership with our insiders may limit the ability of the stockholders to influence corporate matters.

As of December 31, 2016, our executive officers, directors, 5% or greater stockholders, and their respective affiliated entities in the aggregate beneficially owned approximately 56.5% of our outstanding common stock. As a result, these stockholders, acting together, have control over matters that require approval by our stockholders, including the election of directors and approval of significant corporate transactions. Corporate actions might be taken even if other stockholders oppose them. This concentration of ownership might also have the effect of delaying or preventing a corporate transaction that other stockholders may view as beneficial.

We have broad discretion in the use of a portion of the net proceeds from our IPO and our investment of these proceeds may not yield a favorable return. We may invest the proceeds of the offering in ways with which investors disagree.

Our management has broad discretion in the application of the net proceeds from our May 2016 IPO in ways our stockholders may not agree with or that do not yield a favorable return, if at all. If we do not invest or apply the proceeds in ways that improve our operating results, we may fail to achieve expected financial results, which could cause a material adverse effect on our business, financial condition and results of operation.

If securities or industry analysts do not publish research or reports about our business, or publish negative reports about our business, our share price and trading volume could decline.

The trading market for our common stock will, to some extent, depend 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. If one or more of the analysts who cover us downgrade our shares or change their opinion of our shares, our share price would likely decline. If one or more of these analysts cease coverage of us 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.

We do not intend to pay dividends for the foreseeable future, which could reduce the attractiveness of our stock to some investors.

We currently intend to retain any future earnings to finance the operation and expansion of our business, and we do not expect to declare or pay any dividends in the foreseeable future. As a result, you may only receive a return on your investment in our common stock if the market price of our common stock increases. In addition, our loan and security agreement with Hercules Capital, Inc. ("Hercules"), dated June 7, 2016, prohibits us from declaring or paying cash dividends or making cash distributions on any class of our capital stock. See "Dividend Policy." Any return to stockholders will therefore be limited to the increase, if any, of our share price.

An active public trading market for our common stock may not be sustained.

Prior to our IPO in May 2016, there was no public market for our common stock. Although our common stock is listed on The NASDAQ Capital Market, the market for our shares has demonstrated varying levels of trading activity. Furthermore, an active trading market may not be sustained in the future. The lack of an active market may impair your ability to sell your shares at the time you wish to sell them or at a price that you consider reasonable. The lack of an active market may also reduce the fair value of your shares. An inactive market may also impair our ability to raise capital to continue to fund operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

Provisions in our certificate of incorporation and bylaws and Delaware law may discourage, delay or prevent a change of control of our company and, therefore, may depress the trading price of our stock.

Our certificate of incorporation and bylaws contain certain provisions that may discourage, delay or prevent a change of control that our stockholders may consider favorable. These provisions:

- authorize the issuance of "blank check" preferred stock that our board of directors could issue to increase the number of outstanding shares to discourage a takeover attempt;
- prohibit stockholder action to elect or remove directors by majority written consent;
- provide that the board of directors is expressly authorized to make, alter or repeal our bylaws;
- prohibit our stockholders from calling a special meeting of stockholders; and
- establish advance notice requirements for nominations for elections to our board of directors or for proposing matters that can be acted upon by stockholders at stockholder meetings.

***Our certificate of incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employee* s.**

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our certificate of incorporation or our bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. The choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees. Alternatively, if a court were to find the choice of forum provision contained in our certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business and financial condition.

Financial reporting obligations of being a public company in the United States are expensive and time-consuming, and our management will be required to devote substantial time to compliance matters.

As a public company whose common stock is listed on The NASDAQ Capital Market, we incur significant additional accounting, legal and other expenses that we did not incur as a private company, including costs associated with our reporting requirements under the Securities Exchange Act of 1934, as amended, or other rules and regulations, implemented by the Securities and Exchange Commission and The NASDAQ Stock Market LLC. Following our IPO, we are working with our legal and accounting advisors to identify those areas in which changes should be made to our financial and management control systems to manage our growth and our obligations as a public company. These areas include corporate governance, corporate control, disclosure controls and procedures in financial reporting and accounting systems. We have made, and will continue to make, changes in these and other areas. However, the expenses that will be required in order to operate as a public company are, and could continue to be, material, particularly if we cease to be an "emerging growth company." Compliance with the various reporting and other requirements applicable to public companies will also require considerable time and attention of management. In addition, the changes we have made and make may not be sufficient to allow us to satisfy our obligations as a public company on a timely basis.

As an "emerging growth company," as defined in the Jumpstart Our Business Startups Act, or the JOBS Act, we may take advantage of certain temporary exemptions from various reporting requirements, including, but not limited to, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes Oxley Act of 2002 (and the rules and regulations of the Securities and Exchange Commission thereunder). When these exemptions cease to apply, we expect to incur additional expenses and devote increased management effort toward ensuring compliance with them. We cannot predict or estimate the amount of additional costs we may incur as a result of becoming a public company or the timing of such costs. In addition, once we no longer qualify as an "emerging growth company" under the JOBS Act and lose the ability to rely on the exemptions related thereto, depending on our status as per Rule 12b-2 of the Securities Exchange Act of 1934, as amended, our independent registered public accounting firm may also need to attest to the effectiveness of our internal control over financial reporting under Section 404. We will be performing the system and process evaluation and testing (and any necessary remediation) required to comply with the management certification and eventual auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act when we are no longer an emerging growth company. This process will require the investment of substantial time and resources, including by our senior management. As a result, this process may divert internal resources and take a significant amount of time and effort to complete.

Changes in the laws and regulations affecting public companies will result in increased costs to us as we respond to their requirements. These laws and regulations could make it more difficult or more costly for us to obtain certain types of insurance, including director and officer liability insurance, and we may be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. We cannot predict or estimate the amount or timing of additional costs we may incur in order to comply with such requirements.

If we are not able to implement the requirements of Section 404 of the Sarbanes-Oxley Act of 2002 in a timely manner or with adequate compliance, we may be subject to sanctions by regulatory authorities.

Section 404 of the Sarbanes-Oxley Act of 2002 and the related rules adopted by the Securities and Exchange Commission and the Public Company Accounting Oversight Board require that we evaluate and determine the effectiveness of our internal controls over financial reporting and, starting with our annual report for fiscal year 2017, provide a management report on the effectiveness of our internal control over financial reporting. If we have a material weakness in our internal control over financial reporting, we may not detect errors on a timely basis and our consolidated financial statements may be materially misstated. We will be evaluating our internal controls systems to allow management to report on, and eventually allow our independent auditors to attest to, our internal controls. We will be performing the system and process evaluation and testing (and any necessary remediation) required to comply with the management certification and eventual auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act. The aforementioned auditor attestation requirements will not apply to us until we are not an "emerging growth company" or 2021, whichever comes first.

We cannot be certain as to the timing of completion of our evaluation, testing and remediation actions or the impact of the same on our operations. If we are not able to implement the requirements of Section 404 in a timely manner or with adequate compliance, we may be subject to sanctions or investigation by regulatory authorities, such as the SEC or The NASDAQ Stock Market LLC. Any such action could adversely affect our financial results or investors' confidence in us and could cause our stock price to fall. Moreover, if we are not able to comply with the requirements of Section 404 in a timely manner, or if we or our independent registered public accounting firm identifies deficiencies in our internal controls that are deemed to be material weaknesses, we could be subject to sanctions or investigations by NASDAQ, the Securities Exchange Commission or other regulatory authorities, which would entail expenditure of additional financial and management resources and could materially adversely affect our stock price. Inferior internal controls could also cause us to fail to meet our reporting obligations or cause investors to lose confidence in our reported financial information, which could have a negative effect on our stock price.

We may be subject to securities litigation, which is expensive and could divert management attention.

In the past, companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. We may be the target of this type of litigation in the future. Litigation of this type could result in substantial costs and diversion of management's attention and resources, which could seriously hurt our business. Any adverse determination in litigation could also subject us to significant liabilities.

In the event that we fail to satisfy any of the listing requirements of The NASDAQ Capital Market, our common stock may be delisted, which could affect our market price and liquidity.

Our common stock is listed on The NASDAQ Capital Market. For continued listing on The NASDAQ Capital Market, we will be required to comply with the continued listing requirements, including the minimum market capitalization standard, the corporate governance requirements and the minimum closing bid price requirement, among other requirements. In the event that we fail to satisfy any of the listing requirements of The NASDAQ Capital Market, our common stock may be delisted. If our securities are delisted from trading on The NASDAQ Stock Market, and we are not able to list our securities on another exchange or to have them quoted on The NASDAQ Stock Market, our securities could be quoted on the OTC Bulletin Board or on the "pink sheets." As a result, we could face significant adverse consequences including:

- a limited availability of market quotations for our securities;
- a determination that our common stock is a "penny stock," which would require brokers trading in our common stock to adhere to more stringent rules and possibly result in a reduced level of trading activity in the secondary trading market for our securities;
- a limited amount of news and analyst coverage; and
- a decreased ability to issue additional securities (including pursuant to short-form registration statements on Form S-3 or obtain additional financing in the future).

We are an "emerging growth company" and may elect to comply with reduced public company reporting requirements, which could make our common stock less attractive to investors.

We are an "emerging growth company," as defined in the JOBS Act. For as long as we continue to be an "emerging growth company", we may take advantage of exemptions from various reporting requirements that are applicable to other public reporting companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports. We could be an "emerging growth company" up until the December 31 st following the fifth anniversary after our first equity offering, although circumstances could cause us to lose that status earlier if our annual revenues exceed $1.0 billion, if we issue more than $1.0 billion in non-convertible debt in any three-year period or if the market value of our common stock held by non-affiliates exceeds $700.0 million as of any June 30 th , in which case we would no longer be an "emerging growth company" as of the following December 31 st . We cannot predict if investors will find our securities less attractive because we may rely on these exemptions. If some investors find our securities less attractive as a result, there may be a less active trading market for our securities and the price of our securities may be more volatile.

Even after we no longer qualify as an "emerging growth company", we may still qualify as a "smaller reporting company," which would allow us to take advantage of many of the same exemptions from disclosure requirements including exemption from compliance with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

Risks Related to our Indebtedness

Our obligations under our outstanding term loan are secured by all of our assets other than intellectual property, so if we default on those obligations, the lender could foreclose on our assets. As a result of these security interests, such assets would only be available to satisfy claims of our general creditors or to holders of our equity securities if we were to become insolvent at a time when the value of such assets exceeded the amount of our indebtedness and other obligations.

Hercules, the lender under our term loan has a security interest in all of our assets other than our intellectual property. As a result, if we default under our obligations to the lender, the lender could foreclose on its security interests and liquidate some or all of these assets, which would harm our business, financial condition and results of operations. The principal amount of the term loan as of December 31,2016, was $6,000,000.

In the event of a default in connection with our bankruptcy, insolvency, liquidation, or reorganization, the lender would have a prior right to substantially all of our assets to the exclusion of our general creditors. In that event, our assets would first be used to repay in full all indebtedness and other obligations secured by the lender, resulting in all or a portion of our assets being unavailable to satisfy the claims of any unsecured indebtedness. Only after satisfying the claims of any unsecured creditors would any amount be available for our equity holders. These events of default include, among other things, our failure to pay any amounts due under the loan and security agreement or any of the other loan documents, a breach of covenants under the loan and security agreement, our insolvency, a material adverse effect occurring, the occurrence of certain defaults under certain other indebtedness or certain final judgments against us.

The pledge of these assets and other restrictions may limit our flexibility in raising capital for other purposes. Because substantially all of our assets are pledged under the term loan, our ability to incur additional secured indebtedness or to sell or dispose of assets to raise capital may be impaired, which could have an adverse effect on our financial flexibility.

Our outstanding term loan obligations may adversely affect our cash flow and our ability to operate our business.

Pursuant to the terms of our loan and security agreement, the lender made a term loan to us in aggregate amount of $6.0 million. We are required to make monthly payments of interest in the amount of approximately $48,000 until June 2017 and monthly payments of interest and principal in the amount of approximately $225,000 per month from July 2017 until the loan matures. The principal amount of the term loan as of December 31, 2016, was $6.0 million. The term loan under the loan and security agreement, as amended, matures on December 2, 2019.

The terms of our term loan could have negative consequences to us, such as:

- we may be unable to obtain additional financing to fund working capital, operating losses, capital expenditures or acquisitions on terms acceptable to us, or at all;
- the amount of our interest expense may increase because our term loan has a variable rate of interest at any time dependent on the prime rate.

- we may be more vulnerable to economic downturns and adverse developments in our industry or the economy in general.

Our ability to meet our expenses and debt obligations will depend on our future performance, which will be affected by financial, business, economic, regulatory and other factors. We will be unable to control many of these factors, such as economic conditions. We cannot be certain that we will continue to have sufficient capital to allow us to pay the principal and interest on our debt and meet any other obligations. If we do not have enough money to service our debt, we may be required, but unable to refinance all or part of our existing debt, sell assets, borrow money or raise equity on terms acceptable to us, if at all, and the lender could foreclose on its security interests and liquidate some or all of our assets.

Our loan and security agreement contains covenants that could limit our financing options and liquidity position, which would limit our ability to grow our business.

Covenants in our loan and security agreement impose operating and financial restrictions on us. These restrictions prohibit or limit our ability to, among other things:

- pay cash dividends to our stockholders;
- redeem or repurchase our common stock or other equity;
- incur additional indebtedness;
- permit liens on assets;
- make certain investments (including through the acquisition of stock, shares, partnership or limited liability company interests, any loan, advance or capital contribution); and
- sell, lease, license, lend or otherwise convey an interest in a material portion of our assets.

These restrictions may limit our ability to obtain additional financing, withstand downturns in our business or take advantage of business opportunities. Moreover, additional debt financing we may seek, if permitted, may contain terms that include more restrictive covenants, may require repayment on an accelerated schedule or may impose other obligations that limit our ability to grow our business, acquire needed assets, or take other actions we might otherwise consider appropriate or desirable.

ITEM 1B. UNRESOLVED STAFF COMMENTS.

Not applicable.

ITEM 2. PROPERTIES.

We currently lease office and laboratory space and storage space in Seattle, Washington, which consists of approximately 11,676 square feet and 2,896 square feet, respectively. The term of the leases for our office and laboratory facility commenced on May 1, 2010, and extends through November 30, 2021. Rent expense for the year ended December 31, 2016, was approximately $833,000. We estimate that the aggregate minimum payments under our two leases will be $615,000 in 2017.

We may require additional space and facilities as our business expands.

ITEM 3. LEGAL PROCEEDINGS.

From time to time, we may be involved in litigation relating to claims arising out of our operations in the normal course of business. We are not currently a party to any legal proceedings, the adverse outcome of which, in our management's opinion, individually or in the aggregate, would have a material adverse effect on the results of our operations or financial position. There are no material proceedings in which any of our directors, officers or affiliates or any registered or beneficial stockholder of more than 5% of our common stock is an adverse party or has a material interest adverse to our interest.

ITEM 4. MINE SAFETY DISCLOSURES.

Not applicable.

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES.

Market Information

Our common stock began trading on the NASDAQ Capital Market on May 18, 2016 under the symbol "PZRX." Prior to that date, there was no public trading market for our common stock. The following table sets forth for the periods indicated the high and low sales price per share of our common stock as reported on The NASDAQ Capital Market for the period indicated:

	High	Low
Year Ended December 31, 2016		
Fourth Quarter	$ 3.30	$ 0.96
Third Quarter	$ 4.40	$ 2.20
Second Quarter (from May 18, 2016)	$ 5.77	$ 3.61

Holders of Common Stock

As of March 20, 2017, there were approximately 39 stockholders of record of our common stock.

Dividend Policy

We have not paid dividends to our stockholders since inception and do not plan to pay cash dividends in the foreseeable future. Any future declaration of dividends will depend on our earnings, capital requirements, financial condition, prospects and any other factors that our board of directors deems relevant, as well as compliance with the requirements of state law. In general, as a Delaware corporation, we may pay dividends out of surplus capital or, if there is no surplus capital, out of net profits for the fiscal year in which a dividend is declared and/or the preceding fiscal year. In addition our loan and security agreement with Hercules, dated June 7, 2016, prohibits us from declaring or paying cash dividends or making cash distributions on any class of our capital stock. We currently intend to retain earnings, if any, for reinvestment in our business.

Unregistered Sales of Securities

None.

Issuer Purchases of Equity Securities

We did not repurchase any of our equity securities during the fourth quarter of the fiscal year ended December 31, 2016.

Use of Proceeds from the Sale of Registered Securities

On May 17, 2016, the Registration Statement on Form S-1 (File No. 333-210811) for our IPO of common stock was declared effective by the Securities and Exchange Commission, pursuant to which we sold an aggregate 3,700,000 shares of common stock at a public offering price of $5.00 per share for an aggregate offering price of $18.5 million. Laidlaw & Company (UK) Ltd. and Roth Capital Partners, LLC acted as joint book-running managers, and Laidlaw & Company (UK) Ltd. acted as the representative of the underwriters. We received net proceeds from the IPO of approximately $16.5 million, after deducting approximately $2.0 million of underwriting discounts, commissions and offering expenses. None of these expenses consisted of payments made by us to directors, officers or persons owning 10% or more of our common stock or to their associates, or to our affiliates.

As of December 31, 2016, approximately $6.8 million of the $16.5 million of net proceeds from our IPO had been used, of which approximately $440,000 was used to pay off the original issue discount promissory note, $184,000 was used to achieve preclinical proof of concept for the treatment of a second urea cycle disorder and approximately $426,000 was used to select a urea cycle disorder product candidate for further development, $1.2 million was used in preclinical activities, $2.3 million was used to scale up the manufacturing of PRX-OTC and $2.3 million was used in general and administrative expenses. None of these payments consisted of payments made by us to directors, officers or persons owning 10% or more of our common stock or to their associates, or to our affiliates, other than payments made in the ordinary course of business to officers for salaries and to non-employee directors as compensation for board or board committee services and as fees for consulting services.

We expect to use the proceeds from our IPO in connection with our ongoing activities as described in our final prospectus dated May 17, 2016, filed with the Securities and Exchange Commission pursuant to Rule 424(b)(4) under the Securities Act on May 18, 2016, as we:

- scale up the manufacturing of the lead urea cycle disorder product candidate;
- complete GMP-manufacturing and GLP-compliant toxicology studies; and
- file an IND application with the FDA for this product candidate.

We have broad discretion in the use of the net proceeds from our IPO. We may find it necessary or advisable to use the net proceeds from this offering for other purposes than those described in our final prospectus.

The Registration Statement on Form S-1 included a prospectus to be used in connection with the potential resale by certain selling stockholders of up to an aggregate of 1,021,525 shares of our common stock issuable upon mandatory conversion of certain of our outstanding loans upon completion of the IPO. We did not receive any proceeds from the sale by selling stockholders of shares of common stock registered on the Registration Statement on Form S-1.

ITEM 6. SELECTED FINANCIAL DATA.

Not applicable.

PART II

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS OF OPERATIONS.

The following discussion and analysis summarizes the significant factors affecting our operating results, financial condition, liquidity and cash flows as of and for the periods presented below. The following discussion and analysis should be read in conjunction with our audited consolidated financial statements and related notes included elsewhere in this Annual Report on Form 10-K. Unless the context provides otherwise, all references in this Annual Report on Form 10-K to "PhaseRx," "we," "us," "our," the "Company," or similar terms, refer to PhaseRx, Inc. and its directly and indirectly owned subsidiaries on a consolidated basis.

Overview

We are a biopharmaceutical company developing a portfolio of products for the treatment of inherited enzyme deficiencies in the liver using intracellular enzyme replacement therapy, or i-ERT, and expect to generate clinical safety and efficacy data in 2018. We are not aware of any other enzyme replacement therapies for intracellular enzyme deficiencies currently being marketed for inherited enzyme deficiencies in the liver, and believe that the commercial potential for i-ERT is completely untapped and similar to the large and growing $4 billion worldwide market for conventional ERT, which includes drugs such as Cerezyme. Our i-ERT approach is enabled by our proprietary Hybrid mRNA Technology platform, which allows synthesis of the missing enzyme inside the cell. Our initial product portfolio targets the three urea cycle disorders ornithine transcarbamylase deficiency, or OTCD, argininosuccinate lyase deficiency, or ASL deficiency, and argininosuccinate synthetase deficiency, or ASS1 deficiency. We have preclinical proofs of concept in two mouse models of the urea cycle disorders showing significant reductions in the level of blood ammonia, which we believe is an approvable endpoint by the FDA for the demonstration of efficacy in human clinical trials of the urea cycle disorders. To our knowledge, there are no ERT products on the market to treat these diseases, because the urea cycle reaction occurs inside the cell and is inaccessible to the administered enzyme. In contrast, we expect delivery of the missing enzyme using i-ERT with our Hybrid mRNA Technology to be a promising approach to treat these patients. Beyond the urea cycle disorders, we believe there are a significant number of inherited disorders of metabolism in the liver that are candidates for our therapeutic approach and that our Hybrid mRNA Technology can be adapted to develop mRNA therapeutics for the treatment of other inherited liver disorders using our platform.

Our i-ERT approach is accomplished by delivering normal copies of the mRNA that make the missing enzyme inside the liver cell, thereby enabling proper physiological function and correcting the disease. A key challenge with mRNA therapeutics historically has been their satisfactory delivery into the patients' cells. We believe that our Hybrid mRNA Technology addresses these difficulties and enables synthesis of the desired protein in the hepatocyte, which is the chief functional cell type in the liver harboring the metabolic cycles that need to be corrected in metabolic liver diseases. We believe our technology is superior to alternative technologies because, based upon peer-reviewed journal articles and presentations of our competitors and our internal preclinical studies, it results in high-level synthesis of the desired protein in the hepatocyte, has better tolerability and can be repeat-dosed without loss of effectiveness, thus enabling treatment of chronic conditions.

We are focused on inherited, single-gene disorders of metabolism in the liver that result in deficiency of an intracellular enzyme and thus have been unable to be treated with conventional ERT. Some inherited orphan liver diseases, such as the lysosomal storage disorders, can be successfully treated with conventional ERT. However, this approach does not work for many of the inherited orphan liver diseases, including the urea cycle disorders, because the missing enzyme is inside the cell, and the administered enzyme is unable to get inside the target cell where it is needed to be therapeutically active. Our approach is to deliver mRNA encoding the missing enzyme into the cell using our Hybrid mRNA Technology, such that the mRNA makes the missing enzyme inside the cell, restores the intracellular enzyme function and corrects the disease.

As noted above, our initial focus is on urea cycle disorders, which are a group of rare genetic diseases generally characterized by the body's inability to remove ammonia from the blood. The urea cycle consists of several enzymes, including OTC, ASL and ASS1. Since the urea cycle reactions occur inside the cell, conventional ERT does not work as a treatment for these disorders. Urea cycle disorders are caused by a genetic mutation that results in a deficiency of one of the enzymes of the urea cycle that is responsible for removing ammonia from the bloodstream, causing elevated levels of ammonia in the blood. The elevated ammonia then reaches the brain through the circulation, where it causes cumulative and irreversible neurological damage, and can result in coma and death. While currently marketed ammonia scavengers such as Ravicti (glycerol phenylbutyrate) and Buphenyl (sodium phenylbutyrate) provide palliative care of the symptoms, liver transplant is the only currently available cure for urea cycle disorders. Our goal is to treat the urea cycle disorders by intravenous delivery of mRNA that makes the relevant missing urea cycle enzyme inside the cell, thus reinstating control of blood ammonia. We believe that anticipated improvements in newborn screening and the availability of corrective therapy will lead to improved diagnosis and survival rates among patients with urea cycle disorders.

We have three therapeutic urea cycle disorder programs under development: PRX-OTC to treat OTCD, PRX-ASL to treat ASL deficiency and PRX-ASS1 to treat ASS1 deficiency. Preclinical efficacy has been established for PRX-OTC with two biological measures, including normalization of the level of ammonia in the blood. In June 2016, we selected PRX-OTC as our lead product candidate and demonstrated preclinical proof of concept for the treatment of a second product candidate, PRX-ASL. In 2016, we initiated scale up of the manufacturing of PRX-OTC, and in November 2016, we announced positive safety results from our single escalating dose response study in non-human primates using our Hybrid mRNA Technology. In November 2016, PRX-OTC received orphan drug designation from the FDA. We intend to initiate IND-enabling studies in the first half of 2017 and plan to start manufacturing clinical supplies of the lead urea cycle disorder product candidate consistent with current good manufacturing practices, or cGMP, in the third quarter of 2017. We expect to file an IND application with the FDA in the fourth quarter of 2017 for this candidate and to conduct Phase 2a/2b single- and repeat-dose clinical proof of concept studies in OTCD patients that are expected to generate Phase 2a safety and efficacy data in the first half of 2018 and Phase 2b safety and efficacy data in the second half of 2018, including measurement of reduction in blood ammonia.

Financial Overview

Our operations have been funded, to date, primarily through the sale of our common stock in the IPO, debt financing, a series of private placements of convertible preferred stock and issuance of convertible notes and warrants. From our inception through December 31, 2016, we have raised an aggregate of approximately $69.6 million to fund our operations, of which approximately $16.5 million, net of $2.0 million in costs, was from our IPO in May 2016, $25.7 million was from the issuance of preferred stock and approximately $20.2 million was from the issuance of convertible notes and warrants and $5.7 million, net of $307,000 in costs, from a secured term loan from Hercules. In addition, we received a $1.5 million upfront fee from Synageva BioPharma Corp., or Synageva, in 2014 pursuant to a collaboration and development agreement with Synageva.

Operating Losses

Since our inception, we have incurred significant operating losses. Our net losses were $20.1 million and $7.4 million for the year ended December 31, 2016 and 2015, respectively. As of December 31, 2016, we had an accumulated deficit of $69.5 million. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and from year to year. We anticipate that our expenses will increase significantly as we plan to conduct our preclinical studies, scale up the manufacturing process, advance our research programs into clinical trials, continue to discover, validate and develop additional product candidates, expand and protect our intellectual property portfolio, and hire additional development and scientific personnel. In addition, we expect to incur additional costs associated with operating as a public company.

Revenue

We currently do not have any products approved for sale in any jurisdiction and have not generated any revenue from product sales.

Research and Development Expenses

Our research and development expenses consist primarily of costs incurred for our research activities, including our drug discovery efforts, and the development of our product candidates, which include the following:

- employee-related expenses, including salaries, benefits, travel and stock-based compensation;

- external research and development expenses incurred under arrangements with third parties, such as consulting fees, research testing and preclinical studies of our product candidates;
- laboratory supplies, and acquiring, developing and manufacturing preclinical study materials;
- license fees; and
- costs of facilities, depreciation and other expenses.

Research and development costs are expensed as incurred. In certain circumstances, we will make non-refundable advance payments to purchase goods and services for future use pursuant to contractual arrangements. In those instances, we defer and recognize an expense in the period that we receive or consume the goods or services.

At any point in time, we typically have various early stage research and drug discovery projects ongoing. Our internal resources, employees and infrastructure are not directly tied to any one research or drug discovery project and are typically deployed across multiple projects. As such, we do not maintain information regarding the costs incurred for these early stage research and drug discovery programs on a project-specific basis.

The nature and efforts required to complete a prospective research and development project are typically indeterminable at very early stages when research is primarily conceptual and may have multiple applications. Once a focus towards developing a specific product candidate has been developed, we obtain more visibility into the efforts that may be required to reach conclusion of the development phase. However, there are inherent risks and uncertainties in developing novel biologics in a rapidly-changing industry environment. To obtain approval of a product candidate from the FDA, we must, among other requirements, submit data supporting safety and efficacy as well as detailed information on the manufacture and composition of the product candidate. In most cases, this entails extensive laboratory tests and preclinical and clinical trials. The collection of this data, as well as the preparation of applications for review by the FDA, is costly in time and effort, and may require significant capital investment.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and related benefits, including stock-based compensation, related to our executive, finance and support functions and not otherwise included in research and development expenses. Other general and administrative expenses include allocated facility related costs not otherwise included in research and development expenses, professional fees for auditing, tax, investor relations, legal services and travel expenses. We expect that general and administrative expenses will increase in the future as we expand our operating activities and incur additional costs associated with being a publicly-traded company. These increases will include legal fees, accounting fees, directors' and officers' liability insurance premiums and fees associated with investor relations.

Interest Expense

Interest expense consists primarily of cash and non-cash interest expense related to our convertible notes and term loans.

On June 7, 2016, we entered into a loan and security agreement by and among us, the several banks and other financial institutions or entities from time to time parties to the loan and security agreement and Hercules, in its capacity as administrative agent for itself and the lenders, pursuant to which the lenders agreed to make a term loan available to us for working capital and general business purposes, in a principal amount of up to $8 million, or the Hercules Loan. On June 7, 2016, the lenders funded $6 million of the term loan, and we received $5.7 million, net of issuance costs. The draw period for an additional $2 million as set forth in the loan and security agreement expired on December 15, 2016.

The Hercules Loan bears interest at a floating annual rate equal to the greater of (i) 9.25% and (ii) the sum of (a) 9.25%, plus (b) the prime rate as reported by The Wall Street Journal minus 3.50%, resulting in a rate of 9.50% as of December 31, 2016. We are required to make interest payments in cash on the first business day of each month, beginning on July 1, 2016. The Term Loan will begin amortizing on July 3, 2017, in equal monthly installments of principal and interest, with such payments beginning on July 3, 2017, and continuing on the first business day of each month thereafter until the Term Loan is repaid. The final maturity date of the Term Loan is December 2, 2019. Upon repayment of the term loan, we also require to pay an end of term charge to the Lenders equal to 5.85% of the aggregate original principal amount of all Term Loan advances extended by the Lenders to us.

On May 2, 2016, we issued an original issue discount promissory note in the aggregate amount of $440,000 payable to a lender in exchange for a $400,000 loan. The note was repaid after the closing of the IPO.

On December 21, 2015, we entered into a loan and security agreement with 17 investors, pursuant to which these investors made term loans to us in the aggregate principal amount of $4.0 million. Interest accrued on the term loans at the rate of 5% per annum. The entire outstanding principal balance of $4.0 million of the term loans together with all accrued and unpaid interest of $86,000 were converted into 1,021,525 shares of our common stock upon the closing of our IPO, at a conversion price equal to 80% of the IPO offering price. The value of the beneficial conversion feature of $1.0 million was recorded as a discount with an offsetting credit to additional paid-in capital. The discount was fully amortized to interest expense on the conversion date.

Prior to 2016 we issued to investors, including beneficial owners of more than 5% of our capital stock, convertible promissory notes, in the aggregate principal amount of $16.2 million and seven-year warrants to purchase shares of the same class and series of capital stock into which the notes convert. The notes carried interest at a rate of 8% per annum. On December 11, 2015, the noteholders agreed that for purposes of calculating the number of conversion shares, the notes ceased accruing interest as of December 31, 2015. The accrued interest payable on convertible notes payable totaled $3.2 million as of December 31, 2015. Immediately prior to the consummation of the IPO, the convertible notes and unpaid accrued interest thereon were converted into 2,788,880 shares of our common stock, and the seven-year warrants to purchase 2,452,242 shares of preferred stock with an exercise price of $0.01 were exercised on a cashless basis to purchase 303,096 shares of our common stock. Warrants to purchase 1,049,999 shares of preferred stock with an exercise price of $1.00 expired upon the IPO.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our audited consolidated financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles, or U.S. GAAP. The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to accrued expenses and stock-based compensation. We base our estimates on historical experience, known trends and events, and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

Revenue Recognition

Non-refundable, up-front payments received in connection with collaborative research and development agreements are deferred and recognized on a straight-line basis, unless evidence suggests that the revenue is earned or obligations are fulfilled in a different pattern, over the contractual term of the arrangement or the expected period during which those specified services will be performed, whichever is longer.

Research and Development Costs

Research and development costs are expensed as incurred. Research and development costs include salaries and personnel related costs, consulting fees, fees paid for contract research services, the costs of laboratory supplies, equipment and facilities, license fees and other external costs. Non-refundable advance payments for goods or services to be received in the future for use in research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

Fair Value of Financial Instruments

We establish the fair value of our assets and liabilities using the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. We established a fair value hierarchy based on the inputs used to measure fair value. The three levels of the fair value hierarchy are as follows:

Level 1: Quoted prices in active markets for identical assets or liabilities.

Level 2: Inputs, other than the quoted prices in active markets, that are observable either directly or indirectly.

Level 3: Unobservable inputs in which little or no market data exists, therefore determined using estimates and assumptions developed by us, which reflect those that a market participant would use.

We may apply the fair value option to any eligible financial assets or liabilities, which permits an instrument by instrument irrevocable election to account for selected financial assets and liabilities at fair value. To date, we have not applied this election.

Derivative Financial Instruments

We evaluate our financial instruments such as convertible preferred stock and convertible notes to determine if such instruments are derivatives or contain features that qualify as embedded derivatives. For derivative financial instruments that are accounted for as liabilities, the derivative instrument is initially recorded at its fair value and is then revalued at each reporting date, with changes in the fair value reported in the statements of operations. The classification of derivative instruments, including whether such instruments should be recorded as liabilities or as equity, is evaluated at the end of each reporting period. Derivative instrument liabilities are classified in the balance sheet as current or non-current based on whether or not net-cash settlement of the derivative instrument could be required within 12 months of the balance sheet date. At each reporting date, we review our convertible securities to determine their classification is appropriate.

Deferred Financing Costs

We defer costs related to the issuance of debt which are included on the accompanying balance sheets as a deduction from the debt liability. Deferred financing costs are amortized over the term of the related loan and are included as a component of interest expense on the accompanying statements of operations.

Warrant Liabilities

Warrants to purchase our redeemable convertible preferred stock are classified as liabilities and are recorded at their estimated fair value. We use the Black-Scholes option pricing model to evaluate the fair value of the warrants. The use of the Black-Scholes option pricing model requires management to make assumptions with respect to volatility, expected option term and fair value of our common stock. In each reporting period, any change in fair value of the warrants is recorded as expense in the case of an increase in fair value and income in the case of a decrease in fair value.

Redeemable Convertible Preferred Stock

We initially record redeemable convertible preferred stock that may be redeemed at the option of the holder or based upon the occurrence of events not under our control outside of stockholders' deficit at the value of the proceeds received, net of issuance costs. The difference between the original carrying value and the redemption value is accreted at each reporting period on a straight line basis so that the carrying value equals the redemption value on the redemption date. In the absence of retained earnings, these accretion charges are recorded against additional paid-in capital, if any, and then to accumulated deficit.

Stock-Based Compensation

We expense the cost of employee services received in exchange for an award of equity instruments based on the grant date fair value of such instruments. We use the Black-Scholes option pricing model to calculate the fair value of any equity instruments on the grant date. We recognize stock-based compensation, net of estimated forfeitures, on the graded-vesting method as expense over the requisite service period. The use of the Black-Scholes option pricing model requires management to make assumptions with respect to volatility, expected option term and fair value of our common stock. Measurement of stock-based compensation for options granted to non-employees is subject to periodic adjustment as the underlying equity instruments vest. We have granted options with performance conditions to certain executive officers, directors and consultants. At each reporting date, we evaluate whether the achievement of the performance conditions is probable. Compensation expense is recorded over the appropriate service period based upon our assessment of the achievement of each performance condition or the occurrence of the event which will trigger the options to vest.

We recorded stock-based compensation expense in the Statements of Operations as follows (in thousands):

	Years Ended December 31,	
	2016	2015
Research and development	$ 294	$ 17
General and administrative	633	4
	$ 927	$ 21

All stock options are granted at a price no less than the fair value per share of our common stock. Prior to the IPO, the fair value of our common stock underlying options granted was determined by the board of directors who relied, in part, upon independent third party valuation analyses and input from our management on each grant date. We used valuation techniques and methods that rely on recommendations by the American Institute of Certified Public Accountants, or AICPA, in its Accounting and Valuation Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation* , 2013, and conformed to generally accepted valuation practices. A number of objective and subjective factors were considered including:

- our capital structure and the price at which we issued our preferred stock and the rights, preferences and privileges of the preferred stock as compared to those of our common stock;
- our results of operations, financial position and our future business plans;
- the material risks related to our business, the state of the development of our target markets and the pace of adoption of our chosen technology platforms;
- achievement of enterprise milestones, including research results and our entry into or termination of collaboration and license agreements;
- the market performance of publicly traded companies in the life sciences and biotechnology sectors;
- external market conditions affecting the life sciences and biotechnology industry sectors; and
- the likelihood of achieving a liquidity event for the holders of our common stock, preferred stock and stock options, such as an initial public offering given prevailing market conditions.

Valuation of Stock Option Grants in 2015

Our board of directors granted a total of 21,588 stock options with weighted average exercise prices of $0.1066 per share in the year ended December 31, 2015.

On the grant dates during 2015, in addition to the objective and subjective factors discussed above, our board of directors also relied in part upon valuations prepared by independent valuation specialists which utilized the Option Pricing Method, or OPM, to determine the value of our common stock. The OPM treats the rights of the holders of preferred and common stock as equivalent to call options on the enterprise's value, with exercises prices based on the liquidation preferences at the time of a liquidity event. The common stock is modeled as a call option that gives its owner the right, but not the obligation, to buy the underlying equity value at a predetermined or exercise price. In the model, the exercise price is based on a comparison with the equity value rather than, as in the case of a "regular" call option, a comparison with a per-share stock price. Thus, common stock is considered to be a call option with a claim on the equity at an exercise price equal to the remaining value immediately after the preferred stock is liquidated. The OPM has commonly used the Black-Scholes model to price the call option. One of the critical inputs into the OPM is the total equity value for the enterprise, which was estimated using the discounted cash flow method under the income approach.

Valuation of Stock Option Grants in 2016 prior to our IPO

Our board of directors granted stock options to purchase a total of 245,580 shares in the period between January 1, 2016 to May 17, 2016 with a weighted average exercise price of $1.82 per share.

Other than the factors listed above, our board of directors also relied in part upon valuations prepared by the same independent valuation specialists which utilized Probability-Weighted Expected Return Method, or PWERM, to determine the value of our common stock. The PWERM analyzes the present value of the returns afforded to common stockholders under several future stockholder exit or liquidity event scenarios including:

- an initial public offering with a high valuation on or before December 31, 2016;
- an initial public offering with a low valuation on or before June 30, 2016;
- a strategic merger or sale of our company on or before July 31, 2016; and
- continued operations assuming the company will continue to obtain financing through issuing of preferred stock or convertible notes.

The valuations of the two initial public offering scenarios were estimated by our management based on discussions with investment bankers. Employing a simple market approach, these initial public offering valuations were compared to similar metrics for recent initial public offerings of biotechnology companies in order to gain comfort that the estimated initial public offering values were not unreasonable. The valuation in the merger or sale scenario was based on the estimates developed for the initial public offering scenarios and assumes that potential acquirers emerge during the initial public offering process with offers at the upper end of the range contemplated in the initial public offering scenarios. The valuation in the continued operations scenario was estimated using the cost approach based on aggregate invested capital. The PWERM used probability weightings of 55% for the initial public offering (high) scenario, 20% for the initial public offering (low) scenario, 5% for a strategic merger or sale of our company, and 20% for continued operations. The probability weighting assigned to the respective exit scenarios were based on management's expected near-term and long-term funding requirements and an assessment of the current financing and biotechnology industry environment at the time of the valuation. The valuation also applied a discount for lack of marketability of 40% to reflect the fact that there was no market mechanism to sell our shares, and as such, the stockholders need to wait for a liquidity event such as an initial public offering or a sale of the company to enable the sale of the common stock.

Income Taxes

We account for income taxes under the liability method. Under this method, deferred tax assets and liabilities are determined based on differences between financial reporting and tax reporting bases of assets and liabilities and are measured using enacted tax rates and laws that are expected to be in effect when the differences are expected to reverse. Realization of deferred tax assets is dependent upon future earnings, the timing and amount of which are uncertain.

We utilize a two-step approach to recognize and measure uncertain tax positions. The first step is to evaluate the tax position for recognition by determining if the weight of available evidence indicates that it is more likely than not that the position will be sustained upon tax authority examination, including resolution of related appeals or litigation processes, if any. The second step is to measure the tax benefit as the largest amount that is more than 50% likely of being realized upon ultimate settlement.

JOBS Act

Section 107 of the Jumpstart Our Business Startups Act, or JOBS Act, provides that an "emerging growth company" can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act for complying with new or revised accounting standards. Thus, an "emerging growth company" can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this extended transition period and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other companies.

Recent Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board, or FASB, issued Accounting Standard Update, or ASU, No. 2014-09, *Revenue from Contracts with Customers (Topic 606)* , which supersedes the revenue recognition requirements in ASC 605, *Revenue Recognition* . This ASU is based on the principle that revenue is recognized to depict the transfer of goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. The ASU also requires additional disclosure about the nature, amount, timing and uncertainty of revenue and cash flows arising from customer contracts, including significant judgments and changes in judgments and assets recognized from costs incurred to obtain or fulfill a contract. The ASU is effective for public entities for annual periods beginning after December 15, 2017. In June 2015, the FASB deferred for one year the effective date of the new revenue guidance, with an option that would permit companies to adopt the standard as early as the original effective date. Early adoption prior to the original effective date is not permitted. We are evaluating the impact this guidance may have on our revenue recognition, but do not expect that the adoption will have a material impact on our consolidated financial statements.

In February 2016, the FASB issued ASU 2016-02, *Leases (Topic 842).* The ASU is intended to provide more transparent and economically neutral information about the assets and liabilities that arise from leases than previous guidance. The ASU is effective for public entities for annual periods beginning on or after December 15, 2018. Early adoption is permitted, and adoption must be applied on a modified retrospective basis. We are evaluating the impact of this guidance on our consolidated financial statements.

In March 2016, the FASB issued ASU 2016-09, *Improvements to Employee Share-Based Payment Accounting,* which amends ASC 718, *Compensation — Stock Compensation* . The ASU includes provisions intended to simplify various provisions related to how share-based payments are accounted for and presented in the financial statements. The ASU is effective for public entities for annual periods beginning on or after December 15, 2016 and interim periods within that reporting period. Early adoption is permitted in any interim or annual period. We are evaluating the impact of this guidance but do not expect that the adoption will have a material impact on our consolidated financial statements.

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments: Credit Losses,* that changes the impairment model for most financial instruments, including trade receivables from an incurred loss method to a new forward-looking approach, based on expected losses. The estimate of expected credit losses will require entities to incorporate considerations of historical information, current information and reasonable and supportable forecasts. This ASU is effective for us in the first quarter of 2020 and must be adopted using a modified retrospective transition approach. We are evaluating the impact of this guidance but do not expect that the adoption will have a material impact on our consolidated financial statements.

In August 2016, the FASB issued ASU 2016-15, *Statement of Cash Flows: Classification of Certain Cash Receipts and Cash Payments,* that clarifies how certain cash receipts and cash payments are presented and classified in the statement of cash flows. The ASU is effective for us in the first quarter of 2018 with early adoption permitted and must be applied retrospectively to all periods presented. We are evaluating the impact of this guidance but do not expect that the adoption will have a material impact on our consolidated financial statements.

Results of Operations

Comparison of the Years Ended December 31, 2016 and 2015

The following table sets forth information concerning our operating results for the years ended December 31, 2016 and 2015:

	For the Year Ended December 31,		Dollar	%
	2016	2015	Change	Change
	(in thousands)			
Statement of operations data:				
Revenue	$ -	$ 375	$ (375)	-100.0%
Operating expenses:				
Research and development	6,662	4,883	1,779	36.4%
General and administrative	4,153	1,299	2,854	219.7%
Noncash financial advising fees	7,515	-	7,515	-%
Total operating expenses	18,330	6,182	12,148	196.5%
Loss from operations	(18,330)	(5,807)	(12,523)	215.7%
Interest income	61	—	61	-%
Interest expense	(2,058)	(1,649)	(409)	24.8%
Other income (loss), net	190	79	111	140.5%
Total other income (expense)	(1,807)	(1,570)	(237)	15.1%
Net loss	$ (20,137)	$ (7,377)	$ (12,760)	173.0%

Revenue

Revenue decreased to zero for the year ended December 31, 2016 from $375,000 for the year ended December 31, 2015. To date, we have not generated revenue from the sale of any products. The $375,000 recorded as revenue in the year ended December 31, 2015 was related to our development agreement with Synageva which expired in 2015.

Research and Development Expenses

Our research and development expenses were $6.7 million and $4.9 million in the years ended December 31, 2016 and 2015, respectively. Excluding a decrease in depreciation expense of $167,000 in 2016, research and development expenses increased by $1.9 million, or 42%, for the year ended December 31, 2016, compared to research and development expenses for the year ended December 31, 2015. The increase was primarily due to an increase in our research activities to execute the development plan for our lead drug candidate, PRX-OTC. For the year ended December 31, 2016, costs for preclinical studies and scaling up manufacturing increased by $708,000, our payroll costs increased by $608,000, noncash stock-based compensation increased by $277,000, costs for laboratory supplies increased by $184,000 and costs for our research facility increased by $169,000. The decrease in depreciation expenses was predominantly due to our leasehold improvements and some of our laboratory equipment having been fully depreciated in 2015.

General and Administrative Expenses

General and administrative expenses were $4.2 million for the year ended December 31, 2016, which was an increase of approximately $2.9 million or 220%, compared to general and administrative expenses of $1.3 million for the year ended December 31, 2015. The increase was primarily due to additional costs of $1.5 million associated with our IPO and meeting requirements for being a publicly-traded company, including legal, consulting, travel expenses, insurance and investor relation fees. Additionally, compensation costs increased by $1.4 million due to a $800,000 increase in headcount and compensation and $629,000 increase from increased noncash stock-based compensation expense.

Noncash Financial Advising Fees

In the year ended December 31, 2016, we recorded $7.5 million of noncash financial advising fees related to our IPO.

In December 2015, we engaged Palladium Capital Advisors, LLC, or Palladium, to serve as a non-exclusive agent in connection with a bridge loan financing and as a non-exclusive advisor in connection with our IPO and for the provision of general capital markets advice. Prior to the consummation of the bridge loan financing, we determined, following discussions with Palladium, to request certain of our stockholders to transfer an aggregate of 1,393,880 shares of our common stock to Titan Multi-Strategy Fund I, LTD, or Titan, and certain of its third-party designees at a nominal purchase price in order to induce Titan to serve as the initial committed investor in the bridge financing and also in expectation of receiving other support from Titan, Palladium and their respective contacts in connection with our proposed initial public offering, including introductions to certain prospective underwriters. The sales of shares were completed immediately prior to the IPO. We recorded the fair value of this stock amounting to $7.0 million, based on the IPO price of $5.00 per share, as a non cash financial advising fee to reflect the economic benefits that we received from the contributions by our principal stockholders.

We also issued Palladium, as consideration for serving as a non-exclusive advisor, 112,000 shares of our common stock in June 2016. We valued the stock based on the IPO price of $5.00 per share as we determined that the fair market value of the stock was more readily determinable than the fair value of the services received. The $560,000 fair value of the stock was recorded as a noncash financial advising fee in June 2016.

Interest Expense

Interest expense increased by approximately $409,000, or 25%, to $2.1 million for the year ended December 31, 2016, from $1.6 million for the year ended December 31, 2015. The increase in our interest expense was primarily due to the amortization of the value of the beneficial conversion feature of the convertible loan of $1.1 million from the December 2015 bridge loan financing upon the closing of our IPO in May 2016, partially offset by the decrease in our interest expenses as a result of the lower outstanding debt balance and its related amortization of debt discount following the conversion of the outstanding convertible notes upon the IPO.

Liquidity and Capital Resources

From inception to December 31, 2016, we have incurred an accumulated deficit of $69.5 million. We have financed our operations since inception primarily with the net proceeds of approximately $16.5 million from the sale of our common stock in our IPO in May 2016, the net proceeds of $5.7 million from Hercules, $25.7 million from the sales of shares of our convertible preferred stock and $20.2 million from the issuance of convertible notes and warrants. At December 31, 2016, we had $15.5 million of cash, cash equivalents and marketable securities. We anticipate that we will continue to incur losses, and that such losses will increase over the next several years due to development costs associated with our urea cycle disorder programs. We expect that our research and development and general and administrative expenses will continue to increase and, as a result, we will need additional capital to fund our operations, which we may raise through a combination of equity offerings, debt financings, other third-party funding and other collaborations and strategic alliances.

Initial Public Offering

On May 23, 2016, we closed our IPO and sold 3,700,000 shares of common stock at a price of $5.00 per share to the public. The aggregate net proceeds received by us from the offering, net of underwriting discounts and commissions and offering expenses, were $16.5 million.

Hercules Loan – June 2016 Loan and Security Agreement

On June 7, 2016, we entered into a loan and security agreement by and among us, the several banks and other financial institutions or entities from time to time parties to the loan and security agreement and Hercules, in its capacity as administrative agent for itself and the lenders, pursuant to which the lenders agreed to make a term loan available to us for working capital and general business purposes, in a principal amount of up to $8 million. On June 7, 2016, the lenders funded $6 million of the term loan, and we received $5.7 million, net of related expenses. An additional $2 million may be requested by us during the period commencing upon us entering into an arms-length strategic corporate development transaction that is validating in the agent's and lenders' sole discretion, or the Milestone Event, and ending upon the earlier to occur of (a) December 15, 2016, (b) the date which is 45 days after the consummation of the Milestone Event and (c) the occurrence of an event of default under the loan and security agreement. The draw period for the additional $2 million expired on December 15, 2016. The Hercules Loan is secured by substantially all of our assets other than our intellectual property.

The Hercules Loan bears interest at a floating annual rate equal to the greater of (i) 9.25% and (ii) the sum of (a) 9.25%, plus (b) the prime rate as reported by The Wall Street Journal minus 3.50%, resulting in a rate of 9.50% as of December 31, 2016. Beginning on July 1, 2016, we are required to make interest payments in cash on the first business day of each month. The Hercules Loan will begin amortizing on July 3, 2017, in equal monthly installments of principal and interest, with such payments beginning on July 3, 2017, and continuing on the first business day of each month thereafter until the Hercules Loan is repaid. The final maturity date of the Hercules Loan is December 2, 2019. Upon repayment of the Hercules Loan, we are required to pay an end of term charge to the lenders equal to 5.85% of the aggregate original principal amount of all Hercules Loan advances extended by the lenders to us.

At our option, we may prepay all or any portion of the outstanding principal balance and all accrued and unpaid interest with respect to the principal balance being prepaid of the Hercules Loan, subject to a prepayment fee of 3.00% of the amount prepaid if the prepayment occurs on or prior to June 7, 2017, 2.00% of the amount prepaid if the prepayment occurs after June 7, 2017 but on or prior to June 7, 2018, or 1.00% of the amount prepaid if the prepayment occurs after June 7, 2018.

Convertible Loan- Bridge Loan Financing - December 2015 Loan and Security Agreement

On December 11, 2015, we issued a promissory note to Titan in exchange for $500,000. On December 21, 2015, we entered into a loan and security agreement with 17 investors, which was subsequently amended on April 6, 2016, pursuant to which Titan converted its note and certain investors made new term loans to us in the aggregate principal amount of $4.0 million. The term loans closed on December 21, 2015, and we received from the escrow agent net proceeds of approximately $3.2 million, after deducting certain fees and expenses. Interest accrued on the term loans at the rate of 5% per annum. The entire outstanding principal amount of the term loans together with all accrued and unpaid interest thereon converted into shares of our common stock upon the closing of our IPO.

Convertible Notes

Prior to 2016 we issued to investors, including beneficial owners of more than 5% of our capital stock, convertible promissory notes, in the aggregate principal amount of $16.2 million and seven-year warrants to purchase shares of the same class and series of capital stock into which the notes convert. The notes carried interest at a rate of 8% per annum. On December 11, 2015, the noteholders agreed that for purposes of calculating the number of conversion shares, the notes ceased accruing interest as of December 31, 2015. The accrued interest payable on convertible notes payable totaled $3.2 million as of December 31, 2015. Immediately prior to the consummation of the IPO, the convertible notes and unpaid accrued interest thereon were converted into 2,788,880 shares of our common stock, and the seven-year warrants to purchase 2,452,242 shares of preferred stock with an exercise price of $0.01 were exercised on a cashless basis to purchase 303,096 shares of our common stock. Warrants to purchase 1,049,999 shares of preferred stock with an exercise price of $1.00 expired upon the IPO.

Promissory Note

On May 2, 2016, we issued an original issue discount promissory note in the aggregate amount of $440,000 payable to a lender in exchange for a $400,000 loan. The note was repaid after the closing of the IPO.

We believe that our existing cash, cash equivalents and marketable securities as of December 31, 2016 will be sufficient to meet our anticipated cash requirements for at least 12 months from the date the consolidated financial statements are issued. In addition, we intend to pursue a combination of sales of additional equity securities and strategic partnerships to further finance our operations. However, our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement that involves risks and uncertainties, and actual results could vary materially. We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect.

Our primary uses of cash are to fund operating expenses, research and development expenditures and to pay interest and principle payments of our loan. Cash used to fund operating expenses is impacted by the timing of when we pay these expenses, as reflected in the change in our outstanding accounts payable and accrued expenses.

Our future capital requirements are difficult to forecast and will depend on many factors, including:

- the initiation, progress, timing and completion of preclinical studies of our lead product and potential product candidates;
- the number and characteristics of product candidates that we pursue;
- the progress, costs and results of our clinical trials;
- the terms and timing of any other strategic alliance, licensing and other arrangements that we may establish;
- the outcome, timing and cost of regulatory approvals;
- delays that may be caused by changing regulatory requirements;
- the costs and timing of hiring new employees to support our continued growth;
- the costs required for operating a public company; and
- the extent to which we acquire or invest in businesses, products or technologies.

The following table shows a summary of our cash flows for the years ended December 31, 2015 and 2016 (in thousands):

	Year Ended December 31,	
	2016	2015
Net Cash provided by (used in)		
Operating activities	$ (9,811)	$ (5,980)
Investing activities	(5,664)	(114)
Financing activities	22,168	7,353
	$ 6,693	$ 1,259

Operating Activities

Net cash used in operating activities increased to $9.8 million for the year ended December 31, 2016, from $6.0 million for the year ended December 31, 2015. The increase in net cash used in the year ended December 31, 2016 of $3.8 million was primarily due to increased payroll costs of approximately $1.4 million from increased headcount and salaries and $1.5 million in costs associated with our IPO and costs of being a publicly-traded company including legal, consulting, travel expenses and insurance. Research and development costs also increased by $892,000 due to an increase in research activities as we continued to develop our portfolio of products for the treatment of inherited enzyme deficiencies in the liver and to execute the development plan of our lead drug candidate PRX-OTC.

Investing Activities

Net cash used in investing activities increased from $114,000 for the year ended December 31, 2015 to $5.7 million for the year ended December 31, 2016. The increase in net cash used in the year ended December 31, 2016 was primarily due to investing $13.0 million of our excess cash in investment grade marketable securities, partially offset by $7.5 million from the maturity of the marketable securities.

Financing Activities

Net cash provided by financing activities increased from $7.4 million for the year ended December 31, 2015 to $22.2 million for the year ended December 31, 2016. The increase in net cash provided by financing activities in the year ended December 31, 2016 was primarily due to the net proceeds of $16.5 million from our IPO and the net proceeds of $5.7 million from the Hercules Loan received in June 2016. Net cash provided by financing activities in the year ended December 31, 2015 was $7.4 million, which was the net proceeds from the issuance of convertible notes and warrants.

Off-Balance Sheet Arrangements

We have not engaged in any off-balance sheet financing arrangements through special purpose entities.

Emerging Growth Company Status

Section 107 of the JOBS Act provides that an "emerging growth company" can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act for complying with new or revised accounting standards. In other words, an "emerging growth company" can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to "opt out" of such extended transition period, and as a result, we will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-emerging growth companies. Section 107 of the JOBS Act provides that our decision to opt out of the extended transition period for complying with new or revised accounting standards is irrevocable.

We have elected to avail ourselves of the following provisions of the JOBS Act:

- not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act;
- reduced disclosure obligations regarding executive compensation in our periodic reports, proxy statements and registration statements; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK.

Not applicable.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA.

Our Consolidated Financial Statements and the relevant notes to those statements are attached to this Annual Report on Form 10-K beginning on page F-1.

PhaseRx, Inc.

Index to Consolidated Financial Statements

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Shareholders
PhaseRx, Inc.
Seattle, Washington

We have audited the accompanying consolidated balance sheets of PhaseRx, Inc. ("the Company") as of December 31, 2016 and 2015, and the related consolidated statements of operations, comprehensive loss, stockholders' equity (deficit), and cash flows for the years then ended. These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement. The Company has determined that it is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. Our audit included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the consolidated financial position of PhaseRx, Inc. as of December 31, 2016 and 2015, and the consolidated results of its operations and its cash flows for the years then ended, in conformity with accounting principles generally accepted in the United States.

/S/ PETERSON SULLIVAN LLP

Seattle, Washington
March 27, 2017

PhaseRx, Inc.

Consolidated Balance Sheets
(In thousands, except share and per share amounts)

	December 31,	
	2016	**2015**
Assets		
Current assets		
Cash and cash equivalents	$ 9,983	$ 3,290
Marketable securities	5,496	-
Prepaids and other current assets	698	388
Total current assets	16,177	3,678
Property and equipment, net	271	236
Total assets	$ 16,448	$ 3,914
Liabilities, Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)		
Current liabilities		
Accounts payable	$ 515	$ 396
Accrued liabilities	884	445
Accrued interest	49	3,199
Current portion of term loan payable	576	-
Convertible notes, net of debt discount	-	19,841
Deferred rent	-	47
Total current liabilities	2,024	23,928
Term loan payable, net of debt discount and current portion	5,127	-
Preferred stock warrant liability	-	3,163
Total liabilities	7,151	27,091
Commitments and contingencies (Note 11)		
Redeemable convertible preferred stock		
Series A, $0.0001 par value, no shares and 45,100,000 shares authorized at December 31, 2016 and 2015, respectively; no shares and 20,216,583 shares issued and outstanding at December 31, 2016 and 2015, respectively; aggregate liquidation preference of $20,217 at December 31, 2015	-	20,212
Series A-1, $0.0001 par value, no shares and 10,500,000 shares authorized at December 31, 2016 and 2015, respectively; no shares and 5,500,000 shares issued and outstanding at December 31, 2016 and 2015, respectively; aggregate liquidation preference of $5,500 at December 31, 2015	-	5,500
Stockholders' equity (deficit)		
Preferred stock, $0.0001 par value, 5,000,000 and no shares authorized at December 31, 2016 and 2015, respectively; no shares outstanding at December 31, 2016 and 2015	-	-
Common stock, $0.0001 par value; 50,000,000 and 65,600,000 shares authorized at December 31, 2016 and 2015, respectively; 11,690,329 and 532,885 shares issued and outstanding at December 31, 2016 and 2015, respectively	1	1
Additional paid-in capital	78,773	453
Accumulated other comprehensive income	3	-
Accumulated deficit	(69,480)	(49,343)
Total stockholders' equity (deficit)	9,297	(48,889)
Total liabilities, redeemable convertible preferred stock and stockholders' equity (deficit)	$ 16,448	$ 3,914

See Notes to Consolidated Financial Statements

PhaseRx, Inc.

Consolidated Statements of Operations
(In thousands, except per share amounts)

	Year Ended December 31,	
	2016	**2015**
Revenue	$ -	$ 375
Operating expenses		
Research and development	6,662	4,883
General and administrative	4,153	1,299
Noncash financial advising fees	7,515	-
Total operating expenses	18,330	6,182
Loss from operations	(18,330)	(5,807)
Interest income	61	-
Interest expense	(2,058)	(1,649)
Other income, net	190	79
Total other income (expense)	(1,807)	(1,570)
Net loss attributable to common stockholders	$ (20,137)	$ (7,377)
Net loss per share attributable to common stockholders, basic and diluted	$ (2.68)	$ (14.22)
Shares used in computation of basic and diluted net loss per share attributable to common stockholders	7,524	519

See Notes to Consolidated Financial Statements

PhaseRx, Inc.

Consolidated Statements of Comprehensive Loss
(In thousands)

	Year ended December 31,	
	2016	**2015**
Net loss	$ (20,137)	$ (7,377)
Other comprehensive income:		
Unrealized gain on marketable securities	3	-
Comprehensive loss	$ (20,134)	$ (7,377)

See Notes to Consolidated Financial Statements

PhaseRx, Inc.

Consolidated Statements of Stockholders' Equity (Deficit)
(in thousands, except share amounts)

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Income	Accumulated Deficit	Stockholders' Equity (Deficit)
	Shares	Amount				
Balance, January 1, 2015	437,261	$ 1	$ 429	$ -	$ (41,966)	$ (41,536)
Exercise of options	1,780	-				
Exercise of common stock warrants	93,844	-	10	-	-	10
Stock-based compensation	-	-	21	-	-	21
Accretion of Series A Preferred Stock	-	-	(7)	-	-	(7)
Net loss	-	-	-	-	(7,377)	(7,377)
Balance, December 31, 2015	532,885	1	453	-	(49,343)	(48,889)
Debt discount for beneficial conversion feature on bridge loan	-	-	1,021	-	-	1,021
Issuance of stock in initial public offering, net of $2,025 in offering costs	3,700,000	-	16,475	-	-	16,475
Issuance of common stock to financial advisor, noncash	112,000	-	560	-	-	560
Conversion of preferred stock	3,229,975	-	25,716	-	-	25,716
Conversion of notes payable and related accrued interest	2,788,880	-	19,404	-	-	19,404
Conversion of bridge loan and related accrued interest	1,021,525	-	4,086	-	-	4,086
Cashless exercise of warrants	303,096	-	2,440	-	-	2,440
Exercise of options	1,968	-	-	-	-	-
Noncash financial advising fees	-	-	6,955	-	-	6,955
Warrant liability reclassified to equity upon expiration	-	-	535	-	-	535
Debt discount for warrant issued with term loan payable	-	-	205	-	-	205
Stock-based compensation	-	-	927	-	-	927
Accretion of Series A Preferred Stock	-	-	(4)	-	-	(4)
Unrealized gain on marketable securities	-	-	-	3	-	3
Net loss	-	-	-	-	(20,137)	(20,137)
Balance, December 31, 2016	11,690,329	$ 1	$ 78,773	$ 3	$ (69,480)	$ 9,297

See Notes to Consolidated Financial Statements

PhaseRx, Inc.

Consolidated Statements of Cash Flows
(In thousands)

	Year Ended December 31,	
	2016	**2015**
Operating activities		
Net loss	$ (20,137)	$ (7,377)
Adjustments to reconcile net loss to net cash used in operating activities		
Noncash financial advising fees	7,515	-
Amortization of debt discount	1,610	505
Depreciation and amortization	136	331
Stock-based compensation	927	21
Noncash interest expense	127	1,144
Deferred contract revenue	-	(375)
Preferred stock warrant liability	(190)	(79)
Changes in operating assets and liabilities		
Prepaids and other current assets	(310)	(213)
Accounts payable	119	199
Accrued liabilities	439	10
Deferred rent	(47)	(146)
Net cash used in operating activities	(9,811)	(5,980)
Investing activities		
Purchases of marketable securities	(12,993)	-
Maturities of marketable securities	7,500	-
Purchases of property and equipment	(171)	(114)
Net cash used in investing activities	(5,664)	(114)
Financing activities		
Proceeds from issuance of common stock, net of issuance costs	16,475	-
Proceeds from issuance of term loan, net of issuance costs	5,693	-
Proceeds from issuance of convertible note, net of issuance costs	-	7,343
Proceeds from exercise of common stock warrants	-	10
Proceeds from issuance of original issue discount promissory note	400	-
Payment of original issue discount promissory note	(400)	-
Net cash provided by financing activities	22,168	7,353
Net increase in cash and cash equivalents	6,693	1,259
Cash and cash equivalents		
Beginning of period	3,290	2,031
End of period	$ 9,983	$ 3,290
Supplemental information		
Accretion of Series A Preferred Stock	$ 4	$ 7
Conversion of preferred stock into common stock	25,716	-
Conversion of notes payable into common stock	19,404	-
Conversion of bridge loan into common stock	4,086	-
Cashless exercise of warrants	2,440	-
Debt discount for beneficial conversion feature on bridge loan	1,021	-
Warrant liability reclassified to equity upon expiration	535	-
Cash paid during the period for interest	323	-
Debt discount for warrant issued in connection with term loan payable	205	-

See Notes to Consolidated Financial Statements

1. Business and Organization

PhaseRx, Inc. (referred to as "PhaseRx", the "Company," "we," "us," or "our") was incorporated in the State of Delaware on March 9, 2006 and is located in Seattle, Washington. We are a biopharmaceutical company developing a portfolio of products for the treatment of inherited enzyme deficiencies in the liver using intracellular enzyme replacement therapy, or i-ERT. Our i-ERT approach is enabled by our proprietary Hybrid messenger RNA, or mRNA, Technology platform, which allows synthesis of the missing enzyme inside the cell. Our initial product portfolio targets the three urea cycle disorders ornithine transcarbamylase deficiency, or OTCD, argininosuccinate lyase deficiency, or ASL deficiency, and argininosuccinate synthetase deficiency, or ASS1 deficiency.

During 2016, we achieved a number of milestones which we believe as significant. In June 2016, we demonstrated preclinical proof of concept for the treatment of a second product candidate, PRX-ASL, which further established the breadth of our Hybrid mRNA Technology. This was closely followed by selection of our lead product candidate, PRX-OTC. We also tested our Hybrid mRNA Technology's ability to deliver mRNA in a large animal tolerability study with non-human primates. In November 2016, the OTCD program received orphan drug designation in the United States.

We expect to obtain human clinical safety and efficacy data in OTCD patients for our first clinical program in 2018.

Initial Public Offering

In May 2016, we completed our initial public offering ("IPO") and sold 3,700,000 shares of common stock at a price of $5.00 per share to the public. The shares began trading on The NASDAQ Capital Market on May 18, 2016. The aggregate net proceeds received by us from the IPO, net of underwriting discounts and commissions and offering expenses, was $16.5 million. Immediately prior to the pricing of the IPO, all then outstanding shares of our convertible preferred stock, convertible notes and loans were converted into 7,040,380 shares of common stock and warrants were exercised by cashless exercise to purchase 303,096 shares of common stock. The related carrying value of shares of preferred stock, notes and warrants in the aggregate amount of $51.6 million was reclassified as common stock and additional paid-in capital. Additionally, we amended and restated our certificate of incorporation, effective May 17, 2016 to, among other things, change the authorized number of shares of common stock to 50,000,000 and the authorized number of shares of preferred stock to 5,000,000.

Liquidity

Our activities since inception have consisted principally of performing research and development activities and raising capital. Our activities are subject to significant risks and uncertainties, including possible failure of preclinical testing and failing to secure additional funding before we achieve sustainable revenue and profit from operations. As of December 31, 2016, we had an accumulated deficit of $69.5 million. Prior to the IPO, our recurring operating losses raised substantial doubt about our ability to continue as a going concern. In 2016, we have strengthened our financial position after we successfully completed the IPO and secured a term loan with Hercules Capital, Inc. ("Hercules") (see detailed disclosure in note 6). Our ability to fund our development plan in the future, including completion of the IND-enabling studies, scaling up of manufacturing and advancing our product candidate through clinical studies, will depend on the amount and timing of cash receipts from equity fund raisings and strategic collaboration. We believe our cash, cash equivalents and marketable securities balance of $15.5 million at December 31, 2016 is sufficient to fund our operations for at least 12 months from the date the consolidated financial statements are issued.

2. Summary of Significant Accounting Policies

Conversion Price Amendment

On May 17, 2016, immediately prior to our IPO we amended our third amended and restated certificate of incorporation to reduce the conversion price of our preferred stock to $0.747165 per share.

Reverse Stock Split

On May 17, 2016, following the effectiveness of the conversion price amendment, we effected a reverse stock split at a ratio of 1-for-10.656096 of our issued and outstanding shares of common stock. The shares of common stock subject to then issued and outstanding stock options were adjusted accordingly to reflect the reverse stock split.

All information presented in these financial statements and related notes reflect the 1-for-10.656096 reverse stock split of our outstanding shares of common stock, stock options and warrants and the amendment to the conversion price of our preferred stock.

Principles of Consolidation

The consolidated financial statements include the accounts of PhaseRx and its wholly owned subsidiary which was formed in December 2016. All material intercompany transactions and balances have been eliminated in consolidation.

Reclassification

Certain balances from prior period have been reclassified in order to conform to the current period presentation.

Use of Estimates

The preparation of consolidated financial statements in conformity with GAAP requires our management to make estimates and assumptions that affect the reported amount of assets, liabilities, revenue and expenses, and related disclosure of contingent assets and liabilities. Actual results could differ from those estimates.

In preparing these consolidated financial statements, management has made its best estimates and judgments of certain amounts included in the consolidated financial statements, giving due consideration to materiality. On an ongoing basis, we evaluate our estimates, including those related to revenue recognition, fair value measurements, financing activities, accruals and other contingencies.

Cash Equivalents and Marketable Securities

We invest our excess cash in investment grade short- to intermediate-term fixed income securities. Such investments are included in cash and cash equivalents or marketable securities, on the balance sheets, classified as available-for-sale and reported at fair value with unrealized gains and losses included in accumulated other comprehensive income (loss). Realized gains and losses on the sale of these securities are recognized in net income or loss. We consider all highly liquid investments with original maturities at purchase of 90 days or less to be cash equivalents, an investment with a maturity greater than twelve months from the balance sheet date as long-term marketable securities and a maturity less than twelve months as short-term at the balance sheet date. Our cash equivalents and marketable securities consist principally of commercial paper and money market securities.

Interest earned on securities is included in interest income. Gains are recognized when realized in our statements of operations. Losses are recognized when realized or when we have determined that an other-than-temporary decline in fair value has occurred. The cost of securities sold is based on the specific identification method.

We periodically evaluate whether declines in fair values of our investments below their cost are other-than-temporary. This evaluation consists of several qualitative and quantitative factors regarding the severity and duration of the unrealized loss as well as our ability and intent to hold the investment until a forecasted recovery occurs. Factors considered include quoted market prices, recent financial results and operating trends, credit quality of debt instrument issuers, other publicly available information that may affect the value of our investments, duration and severity of the decline in value, and our strategy and intentions for holding the investment. Additionally, we assess whether it is more likely than not we will be required to sell any investment before recovery of its amortized cost basis.

Property and Equipment

Property and equipment are stated at cost, net of accumulated depreciation and amortization. The cost of property and equipment is depreciated or amortized using the straight-line method over the following estimated useful lives:

Computer equipment and software	2 – 3 years
Office equipment and furniture	5 – 7 years
Laboratory Equipment	5 years

Leasehold improvements are amortized using the straight-line method over the shorter of the estimated useful life of the asset or the lease term.

Fair Value of Financial Instruments

We establish the fair value of our assets and liabilities using the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. We established a fair value hierarchy based on the inputs used to measure fair value. The three levels of the fair value hierarchy are as follows:

Level 1: Quoted prices in active markets for identical assets or liabilities.

Level 2: Inputs, other than the quoted prices in active markets that are observable either directly or indirectly.

Level 3: Unobservable inputs in which little or no market data exists, therefore determined using estimates and assumptions developed by us, which reflect those that a market participant would use.

We measure and report at fair value our cash equivalents and marketable securities. The carrying value of accounts payable and accrued liabilities approximate their respective fair values due to their relative short maturities. The carrying value of our 8% convertible notes payable and Hercules term loan approximate fair values because their interest rates are reflective of the rate we could obtain on debt with similar terms and conditions. The carrying value of the 5% convertible term loans was approximately $3.7 million as of December 31, 2015. See Note 6 — Term Loan, Convertible Notes Payable and Other Debt for further discussion. We estimated the fair value of the preferred stock warrant liability using Level 3 inputs.

We may apply the fair value option to any eligible financial assets or liabilities, which permits an instrument by instrument irrevocable election to account for selected financial assets and liabilities at fair value. To date, we have not applied this election.

Derivative Financial Instruments

We evaluate our financial instruments such as convertible preferred stock and convertible notes to determine if such instruments are derivatives or contain features that qualify as embedded derivatives. For derivative financial instruments that are accounted for as liabilities, the derivative instrument is initially recorded at its fair value and is then revalued at each reporting date, with changes in the fair value reported in the statements of operations. The classification of derivative instruments, including whether such instruments should be recorded as liabilities or as equity, is evaluated at the end of each reporting period. Derivative instrument liabilities are classified in the balance sheet as current or non-current based on whether or not net-cash settlement of the derivative instrument could be required within 12 months of the balance sheet date. At each reporting date, we review our convertible securities to determine their classification is appropriate.

Deferred Financing Costs

We defer costs related to the issuance of debt and include them on the accompanying balance sheets as a deduction from the debt liability. Deferred financing costs are amortized over the term of the related loan and are included as a component of interest expense on the accompanying statements of operations.

Warrant Liabilities

Warrants to purchase our redeemable convertible preferred stock are classified as liabilities and are recorded at their estimated fair value. We use the Black-Scholes option pricing model to evaluate the fair value of the warrants. In each reporting period, any change in the fair value of the warrants are recorded as expense in the case of an increase in fair value and income in the case of a decrease in fair value.

Redeemable Convertible Preferred Stock

We initially record redeemable convertible preferred stock that may be redeemed at the option of the holder or based upon the occurrence of events not under our control outside of stockholders' deficit at the value of the proceeds received, net of issuance costs. The difference between the original carrying value and the redemption value is accreted at each reporting period on a straight line basis so that the carrying value equals the redemption value on the redemption date. In the absence of retained earnings, these accretion charges are recorded against additional paid-in capital, if any, and then to accumulated deficit.

Revenue Recognition

Non-refundable, up-front payments received in connection with collaborative research and development agreements are deferred and recognized on a straight-line basis, unless evidence suggests that the revenue is earned or obligations are fulfilled in a different pattern, over the contractual term of the arrangement or the expected period during which those specified services will be performed, whichever is longer.

Research and Development Costs

Research and development costs are expensed as incurred. Research and development costs include salaries and personnel related costs, consulting fees, fees paid for contract research services, the costs of laboratory supplies, equipment and facilities, license fees and other external costs. Non-refundable advance payments for goods or services to be received in the future for use in research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

Stock-Based Compensation

We expense the cost of employee services received in exchange for an award of equity instruments based on the grant date fair value of such instruments. We use the Black-Scholes option pricing model to calculate the fair value of any equity instruments on the grant date. We recognize stock-based compensation, net of estimated forfeitures, on the graded-vesting method as expense over the requisite service period. The use of the Black-Scholes option pricing model requires management to make assumptions with respect to volatility, expected option term and fair value of our common stock. Measurement of stock-based compensation for options granted to nonemployees is subject to periodic adjustment as the underlying equity instruments vest.

We have granted stock options with performance conditions to certain executive officers, directors and nonemployee consultants. At each reporting date, we evaluate whether the achievement of the performance conditions is probable. Compensation expense is recorded over the appropriate service period based upon our assessment of achievement of each performance condition or the occurrence of the event which will trigger the options to vest.

Net Loss Per Share Attributable to Common Stockholders

The computation of basic and diluted net loss per share attributable to common stockholders is calculated by dividing the net loss by the weighted average number of common stock outstanding during the period and excludes all outstanding stock options, warrants, preferred stock, as well as shares issuable upon conversion of all outstanding convertible notes and term loans from the calculation of diluted net loss per common share, as all such securities are anti-dilutive to the computation for all the periods presented. For the years ended December 31, 2016 and 2015, the computation of diluted net loss per share excluded 1,828,606 and 6,564,910 shares, respectively.

The following table presents the calculation of basic and diluted net loss per share (in thousands):

	Year ended December 31,	
	2016	2015
Net loss attributable to common stockholders	$ (20,137)	$ (7,377)
Weighted average shares used in computation of basic and diluted net loss per share attributable to common stockholders	7,524	519
Basic and diluted net loss per share attributable to common stockholders	$ (2.68)	$ (14.22)

Income Taxes

We account for income taxes under the liability method. Under this method, deferred tax assets and liabilities are determined based on differences between financial reporting and tax reporting bases of assets and liabilities and are measured using enacted tax rates and laws that are expected to be in effect when the differences are expected to reverse. Realization of deferred tax assets is dependent upon future earnings, the timing and amount of which are uncertain.

We utilize a two-step approach to recognize and measure uncertain tax positions. The first step is to evaluate the tax position for recognition by determining if the weight of available evidence indicates that it is more likely than not that the position will be sustained upon tax authority examination, including resolution of related appeals or litigation processes, if any. The second step is to measure the tax benefit as the largest amount that is more than 50% likely of being realized upon ultimate settlement.

Concentration of Risk

We are exposed to credit risk from our deposits of cash and cash equivalents in excess of amounts insured by the Federal Deposit Insurance Corporation. We have not experienced any losses on our deposits of cash and cash equivalents since inception. Our cash and cash equivalents balances of $9.8 million and $3.0 million as of December 31, 2016 and 2015, respectively, were uninsured.

Segment Reporting

Operating segments are defined as components of an enterprise engaging in business activities from which it may earn revenues and incur expenses, for which discrete financial information is available and whose operating results are regularly reviewed by the chief operating decision maker in deciding how to allocate resources and in assessing performance. We view our operations and manage our business in one operating segment and all of our operations are in the United States.

Recent Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board, or FASB, issued Accounting Standard Update, or ASU, No. 2014-09, *Revenue from Contracts with Customers (Topic 606)* , which supersedes the revenue recognition requirements in ASC 605, *Revenue Recognition* . This ASU is based on the principle that revenue is recognized to depict the transfer of goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. The ASU also requires additional disclosure about the nature, amount, timing and uncertainty of revenue and cash flows arising from customer contracts, including significant judgments and changes in judgments and assets recognized from costs incurred to obtain or fulfill a contract. The ASU is effective for public entities for annual periods beginning after December 15, 2017. In June 2015, the FASB deferred for one year the effective date of the new revenue guidance, with an option that would permit companies to adopt the standard as early as the original effective date. Early adoption prior to the original effective date is not permitted. We are evaluating the impact this guidance may have on our revenue recognition and new required disclosures, but do not expect that the adoption will have a material impact on our consolidated financial statements.

In February 2016, the FASB issued ASU 2016-02, *Leases (Topic 842).* The ASU is intended to provide more transparent and economically neutral information about the assets and liabilities that arise from leases than previous guidance. The ASU is effective for public entities for annual periods beginning on or after December 15, 2018. Early adoption is permitted, and adoption must be applied on a modified retrospective basis. We are evaluating the impact of this guidance on our consolidated financial statements.

In March 2016, the FASB issued ASU 2016-09, *Improvements to Employee Share-Based Payment Accounting* which amends ASC 718, *Compensation — Stock Compensation* . The ASU includes provisions intended to simplify various provisions related to how share-based payments are accounted for and presented in the financial statements. The ASU is effective for public entities for annual periods beginning on or after December 15, 2016 and interim periods within that reporting period. Early adoption is permitted in any interim or annual period. We are evaluating the impact of this guidance but do not expect that the adoption will have a material impact on our consolidated financial statements.

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments: Credit Losses* that changes the impairment model for most financial instruments, including trade receivables from an incurred loss method to a new forward-looking approach, based on expected losses. The estimate of expected credit losses will require entities to incorporate considerations of historical information, current information and reasonable and supportable forecasts. This ASU is effective for us in the first quarter of 2020 and must be adopted using a modified retrospective transition approach. We are evaluating the impact of this guidance but do not expect that the adoption will have a material impact on our consolidated financial statements.

In August 2016, the FASB issued ASU 2016-15, *Statement of Cash Flows: Classification of Certain Cash Receipts and Cash Payments,* that clarifies how certain cash receipts and cash payments are presented and classified in the statement of cash flows. The ASU is effective for us in the first quarter of 2018 with early adoption permitted and must be applied retrospectively to all periods presented. We are evaluating the impact of this guidance but do not expect that the adoption will have a material impact on our consolidated financial statements.

3. Cash Equivalents and Marketable Securities

We did not have any available-for-sale security holdings in 2015. Securities available-for-sale at cost and fair market value by contractual maturity as of December 31, 2016 were as follows:

	Cost or Amortized Cost	Fair Value
	(In thousands)	
Due in one year or less	$ 5,493	$ 5,496
Due after one year through two years	-	-
	$ 5,493	$ 5,496

We did not incur any realized gains and losses on sales of available-for-sale securities for the year ended December 31, 2016. None of the securities have been in a continuous unrealized loss position for more than 12 months as of December 31, 2016.

Marketable securities available-for-sale consisted of the following as of December 31, 2016:

	Cost or Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
	(In thousands)			
Commercial paper	$ 5,493	$ 3	$ -	$ 5,496
	$ 5,493	$ 3	$ -	$ 5,496

Fair values were determined for each individual security in the investment portfolio. We utilize third-party pricing services for all security valuations. We review the pricing methodology, including the collection of market information, used by the third-party pricing services. On a periodic basis, we also review and validate the pricing information received from the third-party providers.

4. Property and Equipment

Property and equipment consisted of the following (in thousands):

	December 31,	
	2016	**2015**
Computer and office equipment	$ 249	$ 244
Laboratory equipment	2,273	2,107
Leasehold improvements	881	881
	3,403	3,232
Less: Accumulated depreciation and amortization	(3,132)	(2,996)
	$ 271	$ 236

Depreciation and amortization expenses were $136,000 and $331,000 in the years ended December 31, 2016 and 2015, respectively.

5. Accrued Liabilities

Accrued liabilities consisted of the following (in thousands):

	December 31,	
	2016	2015
Compensation and benefits	$ 681	$ 209
Other accrued liabilities	203	236
	$ 884	$ 445

6. Term Loan, Convertible Notes Payable and Other Debt

Hercules Term Loan and Warrants

On June 7, 2016, we entered into a Loan and Security Agreement (the "Loan Agreement") by and among us, the several banks and other financial institutions or entities from time to time parties to the Loan Agreement (the "Lenders") and Hercules Capital, Inc. ("Hercules"), in its capacity as administrative agent for itself and the Lenders, pursuant to which the Lenders agreed to make a term loan available to us for working capital and general business purposes, in a principal amount of up to $8 million (the "Term Loan"). On June 7, 2016, the Lenders funded $6 million of the Term Loan. An additional $2 million of the Term Loan could have been requested by us during the period commencing upon us entering into an arms-length strategic corporate development transaction that is validating in the agent's and Lenders' sole discretion (the "Milestone Event") and ending upon the earlier to occur of (a) December 15, 2016, (b) the date which is 45 days after the consummation of the Milestone Event and (c) the occurrence of an event of default under the Loan Agreement. The draw period of the additional $2 million of the Term Loan expired on December 15, 2016. The Term Loan is secured by substantially all of our assets other than our intellectual property.

The Term Loan bears interest at a floating annual rate equal to the greater of (i) 9.25% and (ii) the sum of (a) 9.25%, plus (b) the prime rate as reported by The Wall Street Journal minus 3.50%, resulting in a rate of 9.50% as of December 31, 2016. We are required to make interest payments in cash on the first business day of each month, beginning on July 1, 2016. The Term Loan will begin amortizing on July 3, 2017, in equal monthly installments of principal and interest, with such payments beginning on July 3, 2017, and continuing on the first business day of each month thereafter until the Term Loan is repaid. The final maturity date of the Term Loan is December 2, 2019. Upon repayment of the term loan, we are required to pay an end of term charge to the Lenders equal to 5.85% of the aggregate original principal amount of all Term Loan advances extended by the Lenders to us.

At our option, we may prepay all or any portion of the outstanding principal balance and all accrued and unpaid interest with respect to the principal balance being prepaid of the Term Loan, subject to a prepayment fee of 3% of the amount prepaid if the prepayment occurs on or prior to June 7, 2017, 2% of the amount prepaid if the prepayment occurs after June 7, 2017 but on or prior to June 7, 2018, or 1% of the amount prepaid if the prepayment occurs after June 7, 2018.

As of December 31, 2016, Term Loan principal payments due each year are as follows (in thousands):

2017	$ 1,084
2018	2,334
2019	2,582
Total principal payments	6,000
Less unamortized debt discount	(297)
Balance, December 31, 2016	$ 5,703

In connection with the Loan Agreement, we also issued to Hercules Technology III, L.P., as the sole Lender on June 7, 2016, a warrant to purchase up to 63,000 shares of common stock at an exercise price of $5.00 per share. The warrant may be exercised either for cash or on a cashless "net exercise" basis. The warrant is immediately exercisable and expires on June 7, 2021.

The warrant issued to Hercules Technology III L.P. met the requirements to be accounted for as equity. The fair value of $212,000 of the warrant was determined using the Black-Scholes option model with the following assumptions: no dividend yield; expected life of 5 years; risk-free interest rate of 1.23%; and volatility rate of 81.6%. The proceeds from the Term Loan were allocated between the debt and warrant based on their relative fair values. The relative fair value of the warrant amounted to $205,000 and was recorded as an increase in the additional paid-in capital and debt discount.

The total debt discount, inclusive of the end of term charge and other fees, amounted to $659,000 and is being amortized to interest expense over the term of the Term Loan.

Promissory Note

On May 2, 2016, we issued an original issue discount promissory note in the aggregate amount of $440,000 payable to a lender in exchange for a $400,000 loan. The note was repaid after the closing of the IPO.

Convertible Notes Payable

Convertible notes payable consisted of the following (in thousands):

	December 31,	
	2016	**2015**
8% convertible notes payable on or after February 1,2013	$ -	$ 3,600
8% convertible notes payable on or after July 2, 2013	-	1,600
8% convertible notes payable on or after June 10, 2013	-	3,000
8% convertible notes payable on or after December 28, 2013	-	1,400
8% convertible notes payable on or after March 19, 2014	-	1,400
8% convertible notes payable on or after June 4, 2014	-	1,540
8% convertible notes payable on or after October 29, 2015	-	825
8% convertible notes payable on or after December 17, 2015	-	1,650
8% convertible notes payable on or after March 31, 2016	-	1,200
5% convertible notes payable on December 21, 2016	-	4,000
Aggregate principal of convertible notes payable	-	20,215
Debt discount and deferred debt issuance costs	-	(374)
Convertible notes payable, net	$ -	$ 19,841

8% Convertible Notes Payable

In April, June, August and October 2015, we issued and sold to investors, including some beneficial owners of more than 5% of our capital stock, convertible promissory notes, in the aggregate principal amount of $3.7 million. In the years prior to 2015, we issued and sold to investors, including some beneficial owners of more than 5% of our capital stock, convertible promissory notes, in the aggregate principal amount of $12.5 million. The notes carried interest at a rate of 8% per annum. We also issued seven-year warrants to purchase shares of the same class and series of capital stock into which the notes convert. On December 11, 2015, the note holders agreed that for purposes of calculating the number of conversion shares, the notes would cease accruing interest as of December 31, 2015. The accrued interest payable on the 8% convertible notes totaled $3.2 million as of December 31, 2015. Immediately prior to the consummation of the IPO, all of the convertible notes and unpaid accrued interest thereon were converted into 2,788,880 shares of common stock, and the seven-year warrants to purchase 2,452,242 shares of preferred stock with an exercise price of $0.01 were exercised on a cashless basis resulting in the issuance of 303,096 shares of common stock.

The fair value of the warrants were recorded as debt discount and warrant liabilities upon issuance of the convertible notes on the balance sheets because the warrants were exercisable into redeemable Series A Preferred Stock. The debt discount was amortized to interest expense over the term of the notes. The fair value of the warrant liabilities were re-measured at each reporting period using the Black-Scholes option pricing model. Any increase in fair value was recorded as expense and any decrease in the fair value was recorded as income in the statement of operations. The warrant liabilities were zero and $3.2 million as of December 31, 2016 and 2015, respectively.

5% Convertible Term Loans

On December 21, 2015, we entered into a loan and security agreement with 17 investors, pursuant to which these investors made term loans to us in the aggregate principal amount of $4.0 million. Interest accrued on the term loans at the rate of 5% per annum. The maturity date of the term loans was December 21, 2016, unless earlier converted into equity or otherwise repaid. The entire outstanding principal amount of the term loans together with all accrued and unpaid interest of $86,000 were converted into 1,021,525 shares of our common stock upon the closing of the IPO, at a conversion price equal to 80% of the IPO offering price. The value of the beneficial conversion feature of $1.0 million was recorded as a debt discount with an offsetting credit to additional paid in capital. The discount was fully amortized to interest expense on the conversion date. .

We incurred debt issuance costs of $332,000 related to these convertible notes and term loans in 2015 which were amortized to interest expense over the term of the notes and term loans.

7. Fair Value Measurements

The following table sets forth the fair value of our assets and liabilities measured at fair value at December 31, 2016 and 2015:

	December 31, 2016			
Description	Balance	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
	(In thousands)			
Financial Assets:				
Money market	$ 7,731	$ 7,731	$ -	$ -
Commercial paper	7,544	-	7,544	-
Total financial assets	$ 15,275	$ 7,731	$ 7,544	$ -
Add Cash:	204			
Total cash, cash equivalents and marketable securities	$ 15,479			
Financial Liabilities:				
Preferred stock warrant liability	$ -	$ -	$ -	$ -
Total financial liabilities	$ -	$ -	$ -	$ -

Description	December 31, 2015 Balance	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
		(In thousands)		
Financial Assets:				
Money market	$ -	$ -	$ -	$ -
Commercial paper				
Total financial assets	$ -	$ -	$ -	$ -
Add Cash:	$ 3,290			
Total cash, cash equivalents and marketable securities	$ 3,290			
Financial Liabilities:				
Preferred stock warrant liability	$ 3,163	$ -	$ -	$ 3,163
Total financial liabilities	$ 3,163	$ -	$ -	$ 3,163

The seven-year warrants exercisable into Series A Preferred Stock were issued in connection with the issuance of the 8% convertible notes. We determined the fair value of the warrants using the Black-Scholes option pricing model with the following assumptions (level 3 inputs): no dividend yield; expected life ranging from 3.1 to 7.0 years; risk-free interest rates ranging from 1.3% to 2.1%; and volatility rates ranging from 84.0% to 97.7%. The value of the underlying Series A Preferred Stock was assumed to be equal to Series A Preferred Stock liquidation preference value of $1.00 per share.

The changes in the balances of the Level 3 Series A Preferred Stock warrant liability measured at fair value for the years ended December 31, 2016 and 2015 were as follows (in thousands):

	Preferred Stock Warrant Liability
Balance, January 1, 2015	$ 2,695
Additional preferred stock warrants issued	547
Change in fair value	(79)
Balance, December 31, 2015	3,163
Warrants exercised	(2,438)
Warrants expired	(535)
Change in fair value	(190)
Balance, December 31, 2016	$ -

8. Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)

Redeemable Convertible Preferred Stock

We had 20,216,583 shares of Series A Preferred Stock, held of record by 15 stockholders and 5,500,000 shares of Series A-1 Preferred Stock, held of record by one stockholder, outstanding as of December 31, 2015. All of the Series A and Series A-1 Preferred Stock were converted into an aggregate of 3,229,975 shares of common stock immediately prior to the pricing of the IPO.

Pursuant to our fourth amended and restated certificate of incorporation, we are authorized to issue 5,000,000 shares of preferred stock. Our fourth amended and restated certificate of incorporation authorized our board of directors, without any further stockholder action or approval, to issue these shares in one or more classes or series, to establish from time to time the number of shares to be included in each class or series and to fix the rights, preferences and privileges of the shares of each wholly unissued class or series and any of its qualifications, limitations or restrictions. There was no preferred stock issued or outstanding as of December 31, 2016.

Warrants

In February 2015, we received an aggregate of $10,000 total proceeds when certain warrant holders exercised their warrants to purchase 93,844 shares of common stock at an exercise price of $0.11 per share.

As discussed above, immediately prior to the consummation of our IPO, seven-year warrants to purchase 2,452,242 shares of preferred stock with an exercise price of $0.01 were exercised on a cashless basis resulting in the issuance of 303,096 shares of common stock.

As of December 31, 2016, we have an outstanding warrant to purchase 63,000 shares of our common stock at $5.00 per shares issued to Hercules Technology III, L.P. in connection with the Term Loan We also had an outstanding warrant issued to a former lender to purchase 14,133 shares of common stock at an exercise price of $7.96 per share that expires on December 1, 2020.

Common Stock

In connection with a bridge loan financing and our IPO, in December 2015 and in February 2016, some of our investors, who collectively beneficially owned the majority of our common stock, entered into stock purchase agreements with Titan Multi-Strategy Fund I, LTD ("Titan") and certain of its third-party designees pursuant to which, concurrently with the closing of the IPO, sold an aggregate of 1,393,880 shares of our common stock to Titan and certain of its third-party designees at a nominal purchase price.

We recorded the fair value of this stock amounting to $7.0 million, based on the IPO price of $5.00 per share, as a noncash financial advising fee in our statement of operations to reflect the economic benefits that we received from our principal stockholders.

We have also issued to Palladium Capital Advisors, LLC, as consideration for serving as a non-exclusive advisor in connection with our IPO and financing activities, 112,000 shares of our common stock in 2016. We valued the stock based on the IPO price of $5.00 per share. The $560,000 fair value of the stock was recorded as a noncash financial advising fee during the year ended December 31, 2016.

We have reserved for future issuance the following number of shares of common stock as of December 31, 2016 and 2015, respectively:

	December 31,	
	2016	2015
Stock options outstanding	1,751,473	443,779
Stock options available for grant	465,265	30,319
Exercise of common stock warrants	77,133	—
Exercise of Series A Preferred Stock warrants	-	454,014
Convertible notes payable	-	2,437,142
Issuance of Series A Preferred Stock	-	2,539,182
Issuance of Series A-1 preferred stock	-	690,793
	2,293,871	6,595,229

Stock Option Plans

2006 Stock Plan

The PhaseRx, Inc. 2006 Stock Plan, as amended and restated on June 13, 2014, as subsequently amended, which we refer to as the 2006 Stock Plan, was adopted by our board of directors in March 2006 and approved by our stockholders in April 2006. Our 2006 Stock Plan provides for the grant of incentive stock options, within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended, to our employees, and for the grant of non-statutory stock options and stock purchase rights to our employees, directors and consultants. Immediately prior to the IPO, the 2006 Stock Plan ceased to be available for future issuances of awards, and we will not grant any additional awards under the 2006 Stock Plan. However, our 2006 Stock Plan will continue to govern the terms and conditions of outstanding awards granted thereunder.

2016 Long-Term Incentive Plan

On February 8, 2016, our board of directors approved the 2016 Long-Term Incentive Plan, which we refer to as the 2016 Plan. The 2016 Plan provides for the granting of incentive stock options, within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended, to our employees and for the granting of nonqualified stock options, restricted stock, stock appreciation rights, restricted stock units, performance awards, dividend equivalent rights, and other awards to our employees, directors and consultants.

The 2016 Plan became effective immediately prior to the IPO. We have initially reserved a total of 1,532,299 shares of our common stock for awards under the 2016 Plan, provided that, such aggregate number of shares reserved for awards will automatically increase on January 1, of each year, in an amount equal to 5% of the total number of shares of common stock outstanding on December 31, of the preceding calendar year. On January 1, 2017, the number of shares reserved for issuance under the 2016 Plan was automatically increased by 584,516 shares, to an aggregate of 2,116,815 shares. Unless terminated earlier by the board of directors, the 2016 Plan will expire on the tenth anniversary of its effective date, or May 17, 2026.

As of December 31, 2016, shares available for future issuances under the 2016 Stock plan are as follows:

	Shares Available for Future Issuances
Balance, January 1, 2016	-
Shares authorized based on 2016 Long-Term Incentive Plan	1,532,299
Granted	(1,095,237)
Forfeited or expired	28,203
Balance, December 31, 2016	465,265

Stock-Based Compensation

We granted incentive stock options to employees and members of the board of directors for their services on the board of directors and nonqualified stock options to nonemployee consultants for their consulting services. Options, in general, either vest in 48 equal installments on each monthly anniversary or 25% on the first year anniversary and 1/48 th equal installments on each monthly anniversary of the date of grant, such that options are fully vested on the four-year anniversary of the date of grant. For stock options granted to employees, members of the board of directors, and nonemployee consultants, we estimate the grant date fair value of each option award using the Black-Scholes option pricing model. We recognize stock-based compensation, net of estimated forfeitures, on the graded-vesting method as expense over the requisite service period. Measurement of stock-based compensation for options granted to nonemployees is subject to periodic adjustment as the underlying equity instruments vest. We have granted options with performance conditions to certain executive officers, directors and nonemployee consultant. At each reporting date, we evaluate whether the achievement of the performance conditions is probable. Compensation expense is recorded over the appropriate service period based upon our assessment of achievement of each performance condition or the occurrence of the event which will trigger the options to vest.

We recorded employee stock-based compensation expense of $927,000 and $21,000 for the years ended December 31, 2016 and 2015, respectively. At December 31, 2016, the total unrecognized compensation cost of $1.6 million will be recognized over the weighted-average remaining service period of approximately 2.0 years. We have not recognized any expenses related to the performance condition options granted to a nonemployee consultant as the achievement of the performance condition was not deemed probable at December 31, 2016.

Stock-based compensation expense has been included in the Statement of Operations as follows (in thousands):

	Year Ended December 31,	
	2016	2015
Research and development	$ 294	$ 17
General and administrative	633	4
	$ 927	$ 21

A summary of our employee and nonemployee stock option activity and related information follows:

	Year ended December 31,			
	2016		2015	
	Options	Weighted- Average Exercise Price	Options	Weighted- Average Exercise Price
Outstanding – beginning of period	443,779	$ 0.9537	440,776	$ 0.9795
Options granted	1,340,817	3.1136	21,588	0.1066
Options exercised	(1,968)	0.0407	(1,780)	0.1066
Options forfeited	(31,155)	4.5989	(16,805)	0.6318
Outstanding – end of period	1,751,473	$ 2.5434	443,779	$ 0.9537
Exercisable – end of period	466,403	$ 1.8853	257,383	$ 1.3934
Weighted-average fair value of options granted during the period		$ 2.2677		$ 0.092

The following table summarizes information about our options outstanding at December 31, 2016:

Exercise Prices	Number of Options	Weighted-Average Exercise Price	Number of Options Exercisable	Weighted-Average Remaining Contractual Life (years)
$ 0.0020 - $1.0656	280,019	$ 0.1723	178,803	6.97
$ 1.4500	384,900	1.4500	500	9.94
$ 1.8115 - $2.3443	396,442	2.0206	182,467	7.19
$ 2.6640 - $3.1600	216,181	3.1417	46,439	9.36
$ 4.2900	50,000	4.2900	5,208	9.50
$ 5.0800	423,931	5.0800	52,986	9.42
	1,751,473	$ 2.5434	466,403	8.64

The aggregate intrinsic value of stock options outstanding at December 31, 2016 was $424,000 and for options exercisable was $240,000. The intrinsic value of outstanding and exercisable stock options was calculated as the quoted market price of the stock at the balance sheet date less the exercise price of the option. The total intrinsic value of options exercised during the year ended December 31, 2016 was $3,000.

The fair value of the stock options was estimated at the date of grant using the Black Scholes option-pricing model with the following weighted average assumptions:

	Year Ended December 31,	
	2016	2015
Weighted average estimated fair value per share	$ 2.2677	$ 0.092
Weighted average assumptions:		
Dividend yields	—	—
Expected term (years)	5.9	6.9
Risk free interest rate	1.5%	1.6%
Volatility	80.3%	89.6%

The risk-free interest rates used in the Black-Scholes option pricing model are based on the implied yield currently available in United States Treasury securities at maturity with an equivalent term. We have limited stock option exercise information. Accordingly, the expected term of stock options granted was calculated using the simplified method, which represents the average of the contractual term of the stock option and the weighted-average vesting period of the stock option. We have not declared or paid any dividends and do not currently expect to do so in the foreseeable future. The value of our underlying common stock is determined by the board of directors relied in part upon the report of third party valuation specialists and input from our management prior to the IPO. Expected volatility is based on an average volatility of stock prices for a group of similar publicly traded companies. The fair value of each stock option award is estimated on the date of grant using the Black-Scholes option pricing model.

9. Income Taxes

As of December 31, 2016, we had a gross operating loss carryforward for federal income tax purposes of approximately $39.5 million, portions of which will begin to expire in 2028. Utilization of some of the federal operating loss and credit carryforwards are subject to annual limitations due to the “change in ownership” provisions of the Internal Revenue Code of 1986 and similar state provisions. The annual limitations may result in the expiration of net operating losses and credits before utilization. We have federal credits of approximately $1.3 million which will begin to expire in 2028. These tax credits are subject to the same limitations discussed above. Deferred income taxes reflect the net tax effects of loss and credit carryforwards and temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. Significant components of our deferred tax assets for federal taxes are as follows:

	December 31,	
	2016	2015
	(in thousands)	
Deferred tax assets:		
Net operating loss carryforward	$ 13,815	$ 10,816
Capitalized research and development expenses	4,666	3,969
Research and other credits	1,275	1,021
Other	572	284
	20,328	16,090
Less: Valuation allowance	(20,328)	(16,090)
Total deferred tax assets	$ —	$ —

The income tax provision (benefit) related to continuing operations differs from the amounts computed by applying the statutory income tax rate of 35% to pretax loss as follows:

	Year Ended December 31,	
	2016	2015
	(in thousands)	
U.S. Federal provision (benefit)		
Loss before provision for income taxes	$ (20,137)	$ (7,377)
At statutory rate of 35%	$ (7,047)	$ (2,582)
Change in valuation allowance	4,238	2,222
IPO costs	2,434	-
Tax credits	(254)	(188)
Stock based compensation	178	7
Nondeductible expenses	451	541
Total	$ —	$ —

10. Significant Agreement

On April 4, 2014, we entered into an exclusive development and option agreement, or development agreement, with Synageva BioPharma Corp., or Synageva, pursuant to which we agreed to conduct certain development activities in connection with the development of our mRNA and polymer products. Under the development agreement, Synageva had an option to acquire us through a merger of a wholly-owned subsidiary of Synageva with and into us. In partial consideration of our obligations under the development agreement, Synageva paid us a non-refundable upfront fee in the aggregate amount of $1.5 million. In addition, on April 9, 2014 and October 23, 2014, in two separate closings, we issued to an affiliate of Synageva an aggregate of 5,500,000 shares of our Series A-1 preferred stock for aggregate cash proceeds of $5.5 million as described more fully above under Note 8. Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit). The development agreement with Synageva has expired in accordance with its terms. We recognized $375,000 during the year ended December 31, 2015 under the agreement.

11. Commitments and Contingencies

In February 2010, we entered into two lease agreements for approximately 14,200 square feet of office, research and development facilities, which became effective in May 2010. The landlord of the facilities is an investor in the Company. Each lease was for a 65 month term, with a five-year renewal option. Both of the lease agreements included reduced rental payments in the initial years of the 65 month term. We calculated the total rent due over the lease term and recorded equal monthly rent expense over the term. Differences between the recorded rent expense and actual rent paid each month resulted in an increase or decrease to deferred rent. We also received incentives from the landlord totaling $605,000 to fund certain tenant improvements. These improvements were capitalized as leasehold improvements, with a corresponding credit recorded to deferred rent. The deferred rent balance was reduced in equal monthly installments over the lease term as a reduction to rent expense.

In September 2016, we extended the term of the lease agreements through November 30, 2021 and revised the square footage to 14,600. In addition to minimum rent, the leases also require payment of real estate taxes, insurance, common area maintenance charge and other costs. These costs are not included in the table below. We recognize rent expense under such arrangements on a straight-line basis over the effective term of the leases. The following table summarizes our future minimum lease commitments for the years ending December 31 (in thousands):

2017	$	615
2018		633
2019		652
2020		672
2021		633
Total minimum lease payments	$	3,205

Rent expense totaled $833,000 and $689,000 for the years ended December 31, 2016 and 2015, respectively.

12. Employee Benefit Plan

We have a 401(k) plan for employees who meet eligibility requirements. Eligible employees may contribute from 1% up to the maximum permitted by Internal Revenue Service limitations in 1% increments. Our contributions to the plans are discretionary as determined by the Board of Directors. There were no employer contributions in 2016 and 2015.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE.

None.

ITEM 9A. CONTROLS AND PROCEDURES.

Evaluation of Disclosure Controls and Procedures

Our principal executive officer and principal financial officer, after evaluating the effectiveness of our disclosure controls and procedures (as defined in Securities Exchange Act of 1934, as amended Rules 13a-15(e) and 15d-15(e)) as of the end of the period covered by this Form 10-K, have concluded that, based on such evaluation, our disclosure controls and procedures were effective to ensure that information required to be disclosed by us in the reports that we file or submit under the Exchange Act of 1934 is recorded, processed, summarized and reported, within the time periods specified in the Securities and Exchange Commission's rules and forms, and is accumulated and communicated to our management, including our principal executive and principal financial officers, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure.

In designing and evaluating our disclosure controls and procedures, our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives, and our management necessarily is required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Management's Annual Report on Internal Control Over Financial Reporting.

This Annual Report does not include a report of management's assessment regarding internal control over financial reporting due to a transition period established by rules of the Securities and Exchange Commission for newly public companies.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting, identified in connection with the evaluation of such internal control that occurred during our last fiscal quarter ended December 31, 2016 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION.

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE.

The information required in response to this Item 10 will be set forth in our [definitive] proxy statement on Schedule 14A for the 2017 annual meeting of stockholders, which shall be filed with the Securities and Exchange Commission no later than 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K (the "Proxy Statement"), and is incorporated herein by reference.

We have adopted a Corporate Code of Conduct and Ethics and Whistleblower Policy (the "Corporate Code") that applies to all of our directors and employees, including the principal executive officer and the principal financial officer. The full text of our Corporate Code is published on the Investor section of our website at www.phaserx.com. We intend to disclose any future amendments to certain provisions of the Corporate Code, or any waivers of such provisions granted to executive officers and directors, on this website promptly following the date of any such amendment or waiver.

ITEM 11. EXECUTIVE COMPENSATION.

The information required in response to this Item 11 will be set forth in our Proxy Statement and is incorporated herein by reference.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS.

The information required in response to this Item 12 will be set forth in our Proxy Statement and is incorporated herein by reference.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE.

The information required in response to this Item 13 will be set forth in our Proxy Statement and is incorporated herein by reference.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES.

The information required in response to this Item 14 will be set forth in our Proxy Statement and is incorporated herein by reference.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES.

The following are filed as part of this Annual Report:

1. Financial Statements

The financial statements filed as part of this Annual Report are included in "Item 8. Financial Statements and Supplementary Data."

2. Financial Statement Schedules

All schedules have been omitted since the required information is not present, or not present in amounts sufficient to require submission of the schedule, or because the information required is included in the Consolidated Financial Statements or the Notes thereto.

3. Exhibits

The following exhibits are required by Item 601 of Regulation S-K.

Please see the "Exhibit Index," which is incorporated herein by reference, following the signature page for a list of our exhibits.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Dated: March 27, 2017

PHASERX, INC.

By: /s/ Robert W. Overell
Robert W. Overell
President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Robert W. Overell Robert W. Overell, Ph.D.	Chief Executive Officer, President and Director (Principal Executive Officer and Principal Financial Officer)	March 27, 2017
/s/ Shing-Yin Tsui Shing-Yin (Helen) Tsui	Senior Vice President, Finance and Secretary (Principal Accounting Officer)	March 27, 2017
/s/ Steven Gillis Steven Gillis, Ph.D.	Chairman of the Board	March 27, 2017
/s/ Peggy V. Phillips Peggy V. Phillips	Director	March 27, 2017
/s/ Brian G. Atwood Brian G. Atwood	Director	March 27, 2017
/s/ John A. Schmidt John A. Schmidt, Jr., M.D.	Director	March 27, 2017
/s/ Paul H. Johnson Paul H. Johnson, Ph.D.	Director	March 27, 2017
/s/ Michelle Griffin Michelle Griffin	Director	March 27, 2017

EXHIBIT INDEX

Exhibit No.	Description of Exhibit
3.1	Fourth amended and Restated Certificate of Incorporation, as amended, as presently in effect (incorporated by reference to Exhibit 3.1 to Current Report on Form 8-K filed with the Securities and Exchange Commission on May 23, 2016)
3.2	Amended and Restated Bylaws, as presently in effect (incorporated by reference to Exhibit 3.2 to Current Report on Form 8-K filed with the Securities and Exchange Commission on May 23, 2016)
4.1	Form of Common Stock Certificate (incorporated by reference to Exhibit 4.1 to Registration Statement on Form S-1/A filed with the Securities and Exchange Commission on May 2, 2016)
4.2	PhaseRx, Inc. Second Amended and Restated Investors' Rights Agreement, dated November 17, 2014, by and among PhaseRx, Inc. by and among PhaseRx, Inc., Series A Investors listed on Exhibit A thereto, Series A-1 Investor listed on Exhibit A-1 thereto and the Founders listed on Exhibit B thereto (incorporated by reference to Exhibit 4.2 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
4.3	Registration Rights Agreement, dated February 29, 2016, among PhaseRx, Inc. and each of the several lenders signatory thereto (incorporated by reference to Exhibit 4.2 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.1†	Second Amended and Restated Exclusive Patent License Agreement, dated February 9, 2016, by and between PhaseRx, Inc. and the University of Washington (incorporated by reference to Exhibit 10.1 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.2†	Amended and Restated RAFT Non-Exclusive License Agreement, dated as of on January 22, 2016, by and between Commonwealth Scientific and Industrial Research Organisation and PhaseRx, Inc. (incorporated by reference to Exhibit 10.2 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.3	Lease Agreement, dated February 9, 2010, between ARE-SEATTLE NO. 10, LLC and PhaseRx, Inc., for 410 Elliott, Seattle, Washington (incorporated by reference to Exhibit 10.3 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.4	First Amendment to Lease Agreement, dated October 1, 2014, by and between ARE-SEATTLE NO. 10, LLC and PhaseRx, Inc., for 410 Elliott, Seattle, Washington (incorporated by reference to Exhibit 10.4 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.5	Second Amendment to Lease, dated May 21, 2015, by and between ARE-SEATTLE NO. 10, LLC and PhaseRx, Inc., for 410 Elliott, Seattle, Washington (incorporated by reference to Exhibit 10.5 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.6	Third Amendment to Lease, dated September 8, 2015, by and between ARE-SEATTLE NO. 10, LLC and PhaseRx, Inc., for 410 Elliott, Seattle, Washington (incorporated by reference to Exhibit 10.6 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.7	Lease Agreement, dated February 9, 2010, between ARE-SEATTLE NO. 10, LLC and PhaseRx, Inc., for 410 W. Harrison, Seattle, Washington (incorporated by reference to Exhibit 10.7 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.8	First Amendment to Lease, dated July 1, 2010, by and between ARE-SEATTLE NO. 10, LLC and PhaseRx, Inc., for 410 W. Harrison, Seattle, Washington (incorporated by reference to Exhibit 10.8 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.9	Second Amendment to Lease, dated April 4, 2011, by and between ARE-SEATTLE NO. 10, LLC and PhaseRx, Inc., for 410 W. Harrison, Seattle, Washington (incorporated by reference to Exhibit 10.9 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.10	Third Amendment to Lease, dated October 1, 2014, by and between ARE-SEATTLE NO. 10, LLC and PhaseRx, Inc., for 410 W. Harrison, Seattle, Washington (incorporated by reference to Exhibit 10.10 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)

10.11	Fourth Amendment to Lease, dated May 21, 2015, by and between ARE-SEATTLE NO. 10, LLC and PhaseRx, Inc., for 410 W. Harrison, Seattle, Washington (incorporated by reference to Exhibit 10.11 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.12	Fifth Amendment to Lease, dated September 8, 2015, by and between ARE-SEATTLE NO. 10, LLC and PhaseRx, Inc., for 410 W. Harrison, Seattle, Washington (incorporated by reference to Exhibit 10.12 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.13∞	Form of Indemnification Agreement (incorporated by reference to Exhibit 10.13 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.14∞	PhaseRx, Inc. 2006 Stock Plan, as amended and restated on June 13, 2014 (incorporated by reference to Exhibit 10.14 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.15∞	First Amendment to the PhaseRx, Inc. 2006 Stock Plan, dated as of February 8, 2016 (incorporated by reference to Exhibit 10.15 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.16∞	Form of Stock Option Agreement under the PhaseRx, Inc. 2006 Stock Plan (incorporated by reference to Exhibit 10.16 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.17∞	PhaseRx, Inc. 2016 Long-Term Incentive Plan (incorporated by reference to Exhibit 10.1 to Current Report on Form 8-K filed with the Securities and Exchange Commission on May 23, 2016)
10.18∞	Form of Nonqualified Stock Option Agreement under the PhaseRx, Inc. 2016 Long-Term Incentive Plan (incorporated by reference to Exhibit 10.18 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.19∞	Form of Incentive Stock Option Agreement under the PhaseRx, Inc. 2016 Long-Term Incentive Plan (incorporated by reference to Exhibit 10.19 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.20∞	Employment Offer Letter Agreement, dated August 17, 2009, between PhaseRx, Inc. and Robert W. Overell, Ph.D. (incorporated by reference to Exhibit 10.20 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.21∞	Employment Offer Letter Agreement, dated December 17, 2013, between PhaseRx, Inc. and Michael Houston, Ph.D. (incorporated by reference to Exhibit 10.21 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.22∞	Amendment to Employment Offer Letter Agreement, dated August 15, 2014, between PhaseRx, Inc. and Michael Houston, Ph.D. (incorporated by reference to Exhibit 10.22 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.23∞	Employment Offer Letter Agreement, dated December 21, 2015, between PhaseRx, Inc. and Helen Tsui (incorporated by reference to Exhibit 10.23 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.24∞	Consulting Agreement, dated July 2, 2013, between PhaseRx, Inc. and Paul H. Johnson, Ph.D. (incorporated by reference to Exhibit 10.24 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.25∞	Amendment to Amended and Restated Consulting Agreement, dated January 2, 2014, between PhaseRx, Inc. and Paul H. Johnson, Ph.D. (incorporated by reference to Exhibit 10.25 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.26∞	Amendment No. 2 to Consulting Agreement, dated February 10, 2016, between PhaseRx, Inc. and Paul H. Johnson, Ph.D. (incorporated by reference to Exhibit 10.26 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.27∞	Consulting Agreement, dated November 1, 2010, between PhaseRx, Inc. and John A. Schmidt, Jr., M.D. LLC (incorporated by reference to Exhibit 10.27 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)

10.28∞	Amendment to Amended and Restated Consulting Agreement, dated June 1, 2011, between PhaseRx, Inc. and John A. Schmidt, Jr., M.D. LLC (incorporated by reference to Exhibit 10.28 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.29∞	Amendment No. 2 to Amended and Restated Consulting Agreement, dated April 1, 2012, between PhaseRx, Inc. and John A. Schmidt, Jr., M.D. LLC (incorporated by reference to Exhibit 10.29 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.30∞	Amendment No. 3 to Consulting Agreement, dated February 10, 2016, between PhaseRx, Inc. and John A. Schmidt, Jr., M.D. LLC (incorporated by reference to Exhibit 10.30 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.31	Loan and Security Agreement, dated December 21, 2015, by and among PhaseRx, Inc., the financial institutions and individuals listed on Annex A thereto, and Titan Multi-Strategy Fund I, LTD. (incorporated by reference to Exhibit 10.31 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.32	Subordination Agreement, dated December 21, 2015, by and among the parties identified on Schedule A thereto, as subordinated lenders, PhaseRx, Inc., and Titan Multi-Strategy Fund I, LTD., in its capacity as a senior lender and in its capacity as representative for itself and the other senior lenders (incorporated by reference to Exhibit 10.32 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.33∞	Amendment to Amended and Restated Offer Letter Agreement, dated as of March 13, 2016, between PhaseRx, Inc. and Robert W. Overell, Ph.D. (incorporated by reference to Exhibit 10.33 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.34	Fourth Amendment to Lease, dated February 23, 2016, by and between ARE-SEATTLE NO. 10, LLC and PhaseRx, Inc., for 410 Elliott, Seattle, Washington (incorporated by reference to Exhibit 10.34 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.35	Sixth Amendment to Lease, dated February 23, 2016, by and between ARE-SEATTLE NO. 10, LLC and PhaseRx, Inc., for 410 W. Harrison, Seattle, Washington (incorporated by reference to Exhibit 10.35 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.36	Amendment to Loan and Security Agreement, dated as of April 6, 2016, by and among PhaseRx, Inc. and the lenders who are signatories thereto (incorporated by reference to Exhibit 10.36 to Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 18, 2016)
10.37	Amended and Restated Subordination Agreement, dated as of May 2, 2016, by and among the parties identified on Schedule A thereto, as subordinated lenders, PhaseRx, Inc., and Titan Multi-Strategy Fund I, LTD., in its capacity as a senior lender and in its capacity as representative for itself and the parties identified on Schedule B thereto, as initial senior lenders, and the parties identified on Schedule C thereto, as additional senior lenders (incorporated by reference to Exhibit 10.37 to Registration Statement on Form S-1/A filed with the Securities and Exchange Commission on May 2, 2016)
10.34	Loan and Security Agreement, dated June 7, 2016, by and among PhaseRx, Inc. and each of its qualified subsidiaries, the several banks and other financial institutions or entities from time to time parties thereto, and Hercules Capital, Inc. in its capacity as administrative agent for itself and the lenders (incorporated by reference to Exhibit 10.1 to Current Report on Form 8-K filed with the Securities and Exchange Commission on June 9, 2016)
10.35	Warrant Agreement, dated June 7, 2016 (incorporated by reference to Exhibit 10.2 to Current Report on Form 8-K filed with the Securities and Exchange Commission on June 9, 2016)
10.36∞	Form of Amendment to Incentive Stock Option Agreement under the PhaseRx, Inc. 2016 Long-Term Incentive Plan, for grants made prior to June 30, 2016 (incorporated by reference to Exhibit 10.4 to Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 2, 2016)
10.37∞	Form of Amendment to Director Nonqualified Stock Option Agreement under the PhaseRx, Inc. 2016 Long-Term Incentive Plan, for grants made prior to June 30, 2016 (incorporated by reference to Exhibit 10.5 to Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 2, 2016)
10.38∞	Form of Amendment to Employee Nonqualified Stock Option Agreement under the PhaseRx, Inc. 2016 Long-Term Incentive Plan, for grants made prior to June 30, 2016 (incorporated by reference to Exhibit 10.6 to Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 2, 2016)

10.39∞	Form of Incentive Stock Option Agreement under the PhaseRx, Inc. 2016 Long-Term Incentive Plan, effective as of June 30, 2016 (incorporated by reference to Exhibit 10.7 to Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 2, 2016)
10.40∞	Form of Employee Nonqualified Stock Option Agreement under the PhaseRx, Inc. 2016 Long-Term Incentive Plan effective as of June 30, 2016 (incorporated by reference to Exhibit 10.8 to Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 2, 2016)
10.41∞	Form of Director Nonqualified Stock Option Agreement under the PhaseRx, Inc. 2016 Long-Term Incentive Plan effective as of June 30, 2016 (incorporated by reference to Exhibit 10.9 to Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 2, 2016)
10.42∞	Amendment No. 3 to Consulting Agreement dated June 30, 2016, between PhaseRx, Inc. and Paul H. Johnson, Ph. D. (incorporated by reference to Exhibit 10.10 to Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 2, 2016)
10.43	Seventh amendment to Lease, dated September 27, 2016, by and between ARE-SEATTLE No. 10, LLC and PhaseRx, Inc., for 410 W. Harrison, Seattle, Washington (incorporated by reference to Exhibit 10.1 to Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 7, 2016)
10.44	Fifth amendment to Lease, dated September 27, 2016, by and between ARE-SEATTLE No. 10 LLC and PhaseRx, Inc., for 410 Elliott, Seattle, Washington (incorporated by reference to Exhibit 10.2 to Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 7, 2016)
21.1*	Subsidiaries of the Company
23.1*	Consent of Peterson Sullivan LLP, an Independent Registered Public Accounting Firm
31.1*	Certification of the Principal Executive Officer and Principal Financial Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2*	Certification of the Principal Accounting Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1*	Certification of Principal Executive Officer and Principal Financial Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
32.2*	Certification of Principal Accounting Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101*	The following materials from the Registrant's Annual Report on Form 10-K for the year ended December 31, 2016, formatted in XBRL (eXtensible Business Reporting Language): (i) Consolidated Balance Sheets, (ii) Consolidated Statements of Operations, (iii) Consolidated Statement of Changes in Stockholders' Equity, (iv) Consolidated Statements of Cash Flows, and (v) Notes to Consolidated Financial Statements.

∞ Denotes management compensation plan or contract.
* Filed herewith.

† Confidential treatment was granted for certain provisions omitted from this Exhibit pursuant to Rule 406 promulgated under the Securities Act of 1933, as amended. The omitted information has been filed separately with the Securities and Exchange Commission.

Exhibit 21.1

PhaseRx, Inc.
List of Subsidiaries

The following is a list of each subsidiary of PhaseRx, Inc., a Delaware corporation, as of March 27, 2016, and the country in which each such subsidiary is organized.

Name of Subsidiary*	**Jurisdiction of Incorporation**
PhaseRx Ireland Limited	Ireland

* No subsidiary does business under any name other than as listed above.

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference into Registration Statement No. 333-213103 on Form S-8 of our report dated March 27, 2017, relating to the 2016 consolidated financial statements of PhaseRx, Inc. ("the Company"), appearing in this Annual Report on Form 10-K of the Company for the year ended December 31, 2016.

/S/ PETERSON SULLIVAN LLP

Seattle, Washington
March 27, 2017

Exhibit 31.1

CERTIFICATIONS UNDER SECTION 302

I, Robert W. Overell, certify that:

1. I have reviewed this Annual Report on Form 10-K of PhaseRx, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   c) disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) all significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 27, 2017

/s/ Robert Overell
Robert W. Overell
Chief Executive Officer
(Principal Executive Officer and Principal Financial Officer)

Exhibit 31.2

CERTIFICATIONS UNDER SECTION 302

I, Shing-Yin (Helen) Tsui, certify that:

1. I have reviewed this Annual Report on Form 10-K of PhaseRx, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   c) disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) all significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 27, 2017

/s/ Shing-Yin Tsui
Shing-Yin (Helen) Tsui
Senior Vice President, Finance and Secretary
(Principal Accounting Officer)

Exhibit 32.1

CERTIFICATIONS UNDER SECTION 906

Pursuant to section 906 of the Sarbanes-Oxley Act of 2002 (subsections (a) and (b) of section 1350, chapter 63 of title 18, United States Code), the undersigned officer of PhaseRx, Inc., a Delaware corporation (the "Company"), does hereby certify, to such officer's knowledge, that:

The Annual Report for the year ended December 31, 2016 (the "Form 10-K") of the Company fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and the information contained in the Form 10-K fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 27, 2017

/s/ Robert Overell

Robert W. Overell
Chief Executive Officer
(Principal Executive Officer and Principal Financial Officer)

Exhibit 32.2

CERTIFICATIONS UNDER SECTION 906

Pursuant to section 906 of the Sarbanes-Oxley Act of 2002 (subsections (a) and (b) of section 1350, chapter 63 of title 18, United States Code), the undersigned officer of PhaseRx, Inc., a Delaware corporation (the "Company"), does hereby certify, to such officer's knowledge, that:

The Annual Report for the year ended December 31, 2016 (the "Form 10-K") of the Company fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and the information contained in the Form 10-K fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 27, 2017

/s/ Shing-Yin Tsui

Shing-Yin (Helen) Tsui
Senior Vice President, Finance and Secretary
(Principal Accounting Officer)