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, 2018

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: 001-38268

ALLENA PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**45-2729920**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification Number)**
One Newton Executive Park, Suite 202 Newton, MA	**02462**
(Address of principal executive offices)	**(Zip Code)**

(617) 467-4577
(Registrant's telephone number, including area code)

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

Title of each class	**Name of exchange on which registered**
Common Stock, $0.001 Par Value	The Nasdaq Global Select 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 every Interactive Data File to be submitted 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 such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the 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, a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☐	Accelerated filer	☒
Non-accelerated filer	☐	Smaller reporting company	☐
Emerging growth company	☒		

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

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 June 29, 2018, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of Common Stock held by non-affiliates of the registrant computed by reference to the price of the registrant's Common Stock (based on the last reported sale price on the Nasdaq Global Select Market as of such date) was $150,081,377.

As of March 1, 2019 there were 20,815,014 shares of the registrant's Common Stock, $0.001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A within 120 days of the end of the fiscal year ended December 31, 2018. Portions of such definitive proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K.

Allena Pharmaceuticals, Inc.
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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements. These statements include all matters that are not related to present facts or current conditions or that are not historical facts, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans, objectives of management and expected market growth. The words "anticipate," "believe," "could," "continue," "should," "predict," "estimate," "expect," "intend," "may," "plan," "potentially," "will," "may," "would," or the negative of these terms or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements.

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 financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions described in the section titled "Risk Factors" and elsewhere in this Annual Report on Form 10-K, regarding, among other things:

- the design and conduct of our planned Phase 3 clinical program of ALLN-177 in enteric hyperoxaluria;
- the number, designs, results and timing of our clinical trials and preclinical studies and the timing of the availability of data from these trials and activities;
- our ability to enroll a sufficient number of patients and the ability of subjects in our clinical trials to adhere to the protocol, including capsule and dietary regimen and urinary collection requirements;
- the therapeutic benefits, effectiveness and safety of ALLN-177, ALLN-346 and our future product candidates;
- our ability to receive regulatory approval for our product candidates in the United States, Europe and other geographies;
- our ability to obtain, on satisfactory terms or at all, the financing required to support operations, development, clinical trials, and commercialization of products;
- our reliance on third parties for the planning, conduct and monitoring of clinical trials and for the manufacture of clinical drug supplies and drug product;
- potential changes in regulatory requirements, and delays or negative outcomes from the regulatory approval process;
- our estimates of the size and characteristics of the markets that may be addressed by ALLN-177 and ALLN-346;
- the market acceptance of ALLN-177, ALLN-346 or any future product candidates that are approved for marketing in the United States or other countries;
- our ability to successfully commercialize ALLN-177 with a targeted sales force;
- the safety and efficacy of therapeutics marketed by our competitors that are targeted to indications which our product candidates have been developed to treat;
- our ability to utilize our proprietary technological approach to develop and commercialize ALLN-346 and future product candidates;
- potential collaborators to license and commercialize ALLN-177, if approved, or any products for which we receive regulatory approval in the future outside of the United States;
- our heavy dependence on licensed intellectual property, including our ability to source and maintain licenses from third-party owners;

- our ability to protect our intellectual property and operate our business without infringing upon the intellectual property rights of others;
- our ability to attract, retain and motivate key personnel;
- our ability to generate revenue and become profitable;
- our estimates regarding our capital requirements and our need for additional financing.

These risks are not exhaustive. Other sections of this Annual Report on Form 10-K may include additional factors that could adversely impact our business and financial performance. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements.

We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the "Risk Factors" section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make. No forward-looking statement is a guarantee of future performance.

You should read this Annual Report on Form 10-K and the documents that we reference herein and have filed as exhibits hereto as a part completely and with the understanding that our actual future results may be materially different from what we expect. The forward-looking statements in this Annual Report on Form 10-K represent our views as of the date of this Annual Report on Form 10-K. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we have no current intention of doing so except to the extent required by applicable law. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this Annual Report on Form 10-K.

PART I

Unless the context otherwise requires, we use the terms "Allena," "the Company," "we," "us," "our" and similar designations in this Annual Report on Form 10-K to refer to Allena Pharmaceuticals, Inc. and its wholly owned subsidiaries.

ITEM 1. BUSINESS

Overview

We are a late-stage, clinical biopharmaceutical company dedicated to developing and commercializing first-in-class, oral enzyme therapeutics to treat patients with rare and severe metabolic and kidney disorders. We are focused on metabolic disorders that result in excess accumulation of certain metabolites that can cause kidney stones, damage the kidney, and potentially lead to chronic kidney disease, or CKD, and end-stage renal disease, or ESRD. Our lead product candidate, reloxaliase (formerly known as ALLN-177), is a first-in-class, oral enzyme therapeutic that we are developing for the treatment of hyperoxaluria, a metabolic disorder characterized by markedly elevated urinary oxalate levels and commonly associated with kidney stones, CKD and other serious kidney diseases. There are currently no approved therapies for the treatment of hyperoxaluria.

Reloxaliase, a crystalline formulation of the enzyme oxalate decarboxylase, has been designed to specifically degrade oxalate within the GI tract, limiting systemic absorption of oxalate into the bloodstream. Oxalate is endogenously produced as an end product of normal cellular metabolism and is also absorbed through the GI tract from a typical diet. Humans lack the innate capacity to digest oxalate and primarily depend on renal excretion to eliminate it from the body. Although oxalate has no identified biological function, it is known to damage the kidney when present in excess amounts, a condition called hyperoxaluria. Hyperoxaluria is characterized by significantly elevated oxalate levels in the urine, or urinary oxalate excretion, due to either overproduction of oxalate by the liver from a genetic defect, called primary hyperoxaluria, or from over absorption of oxalate from the diet, called secondary hyperoxaluria. Secondary hyperoxaluria is further characterized either as enteric, resulting from a chronic and unremediable underlying GI disorder associated with malabsorption, such as bariatric surgery complications or Crohn's disease, which predisposes patients to excess oxalate absorption, or idiopathic, meaning the underlying cause is unknown. Enteric hyperoxaluria is the more severe type of secondary hyperoxaluria.

We have conducted a robust clinical development program of reloxaliase, including three Phase 2 clinical trials, which demonstrated reductions of urinary oxalate excretion in patients with secondary hyperoxaluria, particularly in patients with enteric hyperoxaluria. Reloxaliase has also been well tolerated in clinical trials to date. Based on these data, the high unmet medical need, the enzyme's specific mechanism of action, and the significant market opportunity, we are initially developing reloxaliase for adult patients with enteric hyperoxaluria.

In March 2018, we initiated URIROX-1 (formerly Study 301), the first of our two Phase 3 clinical trials in support of our planned Biologics License Application, or BLA, for reloxaliase in patients with enteric hyperoxaluria. URIROX-1 is the largest randomized, controlled trial of a novel therapeutic ever initiated in patients with enteric hyperoxaluria. We expect to announce topline data from this trial in the second half of 2019. In the fourth quarter of 2018 we initiated URIROX-2 (formerly Study 302), our second pivotal Phase 3 trial of reloxaliase in patients with enteric hyperoxaluria. The primary efficacy endpoint for URIROX-2 is the percent change from baseline in 24-hour urinary oxalate, or UOx, excretion during Weeks 1-4, comparing reduction in the average UOx excretion across Weeks 1-4 with reloxaliase to placebo, the same primary efficacy endpoint as URIROX-1.

The FDA has advised us that it agrees with our strategy to pursue a BLA submission for reloxaliase using the accelerated approval regulatory pathway. Accordingly, we intend to use data from the URIROX-2 trial to first support a filing for accelerated approval for reloxaliase and thereafter to verify its clinical benefit associated with reduction in kidney stone disease progression, which is the primary long-term endpoint of the study. URIROX-2 also incorporates adaptive design elements that allow for increases in sample size and duration of treatment based on accrued kidney stone disease progression rates and the conditional probability of achieving ultimate statistical success in the long-term follow-up phase of the trial. We currently expect to submit a BLA to the FDA after 400 patients have been randomized and followed in URIROX-2 for six months. For the long-term follow-up phase of the trial, subjects would continue in the study for a minimum treatment period of two years to confirm clinical benefit post-approval.

The FDA has also granted separate orphan drug designations for reloxaliase for the treatment of primary hyperoxaluria and for the treatment of pediatric hyperoxaluria. In addition, the European Commission has granted orphan designation for reloxaliase for the treatment of primary hyperoxaluria. In light of these designations, we initiated an open-label Phase 2 clinical trial (Study 206) in March 2018 in adolescents and adults with primary hyperoxaluria or enteric hyperoxaluria, who also have elevated levels of oxalate in the blood, or hyperoxalemia, which can lead to systemic oxalosis, a potentially fatal disorder

associated with deposition of oxalate in tissues. We expect to announce initial data from Study 206 in the second quarter of 2019 and topline data in the second half of 2019.

The first clinical manifestation of hyperoxaluria is often a kidney stone; however, the disorder can be variable in its presentation. Patients with severe hyperoxaluria may have recurrent kidney stones or experience infrequent or no kidney stones, yet still develop CKD and end-stage renal disease, which can be fatal. Systemic oxalosis, which typically occurs in patients with primary or severe secondary hyperoxaluria and declining kidney function, refers to the presence of excess oxalate throughout the body, including the blood, bones, joints, eyes and heart.

We estimate there are approximately 200,000 to 250,000 patients in the United States with enteric hyperoxaluria and kidney stones. We plan to target this market initially. There are no FDA approved therapies for enteric hyperoxaluria. We believe that a therapeutic agent that reduces urine oxalate levels in this population could be commercialized into a potential multi-billion dollar U.S. market without any approved therapies at present. Primary hyperoxaluria, an ultra-rare genetic disease, is estimated to affect approximately 1 in 58,000, or approximately 5,000 patients, in the United States. Among patients with primary hyperoxaluria, about 50 percent will have kidney failure by age 15, and about 80 percent will have kidney failure by age 30. There are no FDA approved therapies for primary hyperoxaluria, and the most severe patients may be treated with a liver and/or kidney transplant. Patients with enteric hyperoxaluria can have levels of urinary oxalate excretion as high as patients with primary hyperoxaluria and a comparable renal burden.

Systemic oxalosis is an ultra-rare, potentially fatal condition that results from the progression of primary or enteric hyperoxaluria. Excess oxalate that cannot be eliminated by the kidneys begins to accumulate in the tissue throughout the body, including the blood, bones, joints, eyes, heart and kidneys. The deposition of oxalate crystals can increase the risk of kidney inflammation, fibrosis, and progressive kidney failure. This damage to the kidney further reduces the kidney's ability to eliminate oxalate, causing a vicious cycle that can accelerate the loss of renal function. Patients who develop ESRD secondary to hyperoxaluria require frequent hemodialysis—approximately 6 or 7 times per week—with or without supplemental peritoneal dialysis while awaiting kidney transplantation to prevent or limit systemic oxalosis.

We believe our proprietary know-how in enzyme technology allows for the design, development, formulation, and scalable manufacturing of non-absorbed and stable enzymes delivered orally and in sufficient doses for activity in the GI tract. This approach enables us to develop enzyme therapies that degrade metabolites within the GI tract, which reduces potentially toxic metabolite levels in the blood and urine, and in turn, diminishes the disease burden on the kidney over time. The general therapeutic approach of deploying a non-absorbed drug into the GI tract to reduce metabolic disease burden in patients with kidney disease has been proven successful in several therapeutic categories. Utilizing our proprietary technological approach, we conceived and developed our first two product candidates, reloxaliase and ALLN-346, which are novel, oral enzyme therapeutics for the treatment of hyperoxaluria and hyperuricemia. Our proprietary and scalable manufacturing capabilities have enabled us to produce large quantities of reloxaliase sufficiently to support our clinical and commercial strategy, with costs anticipated to be comparable to small molecule therapeutics.

We have designed our second product candidate, ALLN-346, an orally administered, novel, urate degrading enzyme, for patients with hyperuricemia and gout in the setting of advanced CKD. Hyperuricemia, or elevated levels of uric acid in the blood, results from overproduction or insufficient excretion of urate, or often a combination of the two. Humans lack urate oxidase, an enzyme that degrades uric acid in a wide range of other organisms, including animals, plants, bacteria and fungi. Hyperuricemia is the major predisposing condition for gout, a disease that most commonly manifests with acute flares of arthritis, and can also lead to chronic arthritis and joint damage and palpable deposits of urate crystals in the skin. Hyperuricemia can also lead to increased uric acid excretion in the urine and subsequently to kidney stone formation and kidney damage, also known as urate nephropathy. In addition, hyperuricemia has been linked to hypertension, CKD, glucose intolerance, dyslipidemia, insulin resistance and obesity.

We engineered ALLN-346 to degrade urate in the GI tract and, in turn, reduce the urate burden on the kidney and lower the risk of urate-related complications. ALLN-346 is targeted to lower serum uric acid in patients with CKD, who have decreased renal function and diminished capacity for urinary excretion of uric acid. Patients with renal impairment who have hyperuricemia and gout are often not optimally managed due to limitations of available therapies, including decreased tolerability, dose restrictions, drug-drug interactions, contraindications and increased risk for long-term morbidity and mortality. An estimated 375,000 patients in the United States have refractory gout and CKD.

Our Product Candidate Pipeline

Using our proprietary technological approach, we have developed a pipeline of first-in-class, oral, non-absorbed enzyme therapeutic candidates to treat patients with rare and severe metabolic disorders that affect the kidney. Our lead product

candidate, reloxaliase, is an oral enzyme therapeutic that we are developing for the treatment of hyperoxaluria, for which there are currently no approved therapies. Our second product candidate, ALLN-346, is being developed for patients with hyperuricemia and moderate to severe CKD. Hyperuricemia, or elevated levels of uric acid in the blood, is commonly associated with gout as well as kidney stones and kidney disorders.

Strategy

Our goal is to become the leader in developing and commercializing first-in-class, oral, non-absorbed enzyme therapeutics to treat patients with rare and severe metabolic and kidney disorders. To achieve this goal, we are executing on the following strategy:

- ***Obtain regulatory approval in the United States for our lead product candidate, reloxaliase, for enteric hyperoxaluria in adults using the accelerated approval regulatory pathway***- We have conducted a robust Phase 2 clinical development program of reloxaliase in patients with secondary hyperoxaluria, which demonstrated significant reductions of urinary oxalate excretion in patients with enteric hyperoxaluria. Based on these data and the high unmet need, we are initially developing reloxaliase for enteric hyperoxaluria. Moreover, we believe the mechanism of action of reloxaliase, which degrades oxalate in the GI tract, is particularly well-targeted to treat enteric hyperoxaluria where excess oxalate absorption is driven by an underlying GI disorder. In March of 2018, we initiated URIROX-1, our first Phase 3 clinical trial in support of our planned BLA for reloxaliase in patients with enteric hyperoxaluria, with topline data anticipated in the second half of 2019. In the fourth quarter of 2018 we initiated URIROX-2 (formerly Study 302), our second pivotal Phase 3 trial of reloxaliase in patients with enteric hyperoxaluria. The FDA has advised us that it agrees with our strategy to pursue a BLA submission for reloxaliase using the accelerated approval regulatory pathway. We expect to submit a BLA to the FDA after 400 patients have been randomized and followed for six months. For the long-term follow-up phase of the trial, subjects would continue in the study for a minimum treatment period of two years to confirm clinical benefit post-approval.

- ***Commercialize reloxaliase***-We have worldwide commercialization and development rights to reloxaliase. We intend to independently pursue regulatory approval of reloxaliase in patients with enteric hyperoxaluria in the United States and, if approved, to commercialize the product by building a focused commercial organization in the United States specifically to target nephrologists and urologists who treat patients with hyperoxaluria, particularly at kidney stone clinics.

- ***Advance development of reloxaliase for other severe forms of hyperoxaluria***- Systemic oxalosis is an ultra-rare potentially life threatening condition that results from the progression of primary or enteric hyperoxaluria. Our preclinical studies in models of primary hyperoxaluria and severe secondary hyperoxaluria have demonstrated that reloxaliase significantly reduced oxalate levels in the urine and plasma. The FDA has granted separate orphan drug designations for reloxaliase for the treatment of primary hyperoxaluria and for the treatment of pediatric hyperoxaluria (primary and secondary). In light of these designations, we initiated an open-label Phase 2 clinical

trial (Study 206) in March 2018 in adolescents and adults with primary hyperoxaluria or enteric hyperoxaluria, who also have elevated levels of oxalate in the blood, or hyperoxalemia, which can lead to systemic oxalosis, a potentially fatal disorder associated deposition of oxalate in tissues. We expect to announce initial data from Study 206 in the second quarter of 2019 and topline data from Study 206 in the second half of 2019. In addition, we plan to seek breakthrough designation where appropriate.

- ***Obtain regulatory approval in Europe for our lead product candidate, reloxaliase***- The prevalence of severe hyperoxaluria in Europe is comparable to that in the United States. Based on a market research project we commissioned, enteric hyperoxaluria is estimated to affect roughly 300,000 people in the EU5 (France, Germany, Italy, Spain and the United Kingdom). Also analogous to the US, primary hyperoxaluria is estimated to affect approximately 5,000 people in the European Union according to the European Commission's Platform on Rare Diseases Registration. As a result, we plan to pursue regulatory approval for patients with severe hyperoxaluria in Europe in conjunction with our pursuit of approval in the United States. We received Scientific Advice on the design of our proposed Phase 3 program from the regulatory agencies of three countries in the European Union. In these meetings, we discussed the results of our Phase 2 clinical program in secondary hyperoxaluria, our proposed pivotal Phase 3 program in enteric hyperoxaluria, and potential regulatory pathways for approval in Europe. Following these non-binding regulatory interactions, we believe that our Phase 3 program, if successful, could be eligible for a Marketing Authorization Application, or MAA via the conditional approval pathway, which is similar to the FDA's accelerated approval pathway. We have initiated European sites for URIROX-1 and Study 206 and also plan to do so for URIROX-2.

- ***Advance development of ALLN-346-***ALLN-346 is an orally administered, novel urate degrading enzyme that has been optimized for stability in the GI tract. This proprietary enzyme was designed by our scientists to degrade urate in the GI tract and in turn, reduce the urate burden on the kidney and lower the risk of urate-related complications. ALLN-346 is targeted to lower serum uric acid in patients with CKD, who have decreased renal function and diminished capacity for urinary excretion of uric acid. In June 2018, we announced completion of a preclinical proof-of-concept study and presented the data at the American College of Rheumatology meeting on October 22, 2018. The poster presentation included data demonstrating urate reduction in a urate oxidase knock-out mouse model, an animal model of severe hyperuricemia with kidney damage due to urate crystal deposition. After one week of treatment, mice treated with ALLN-346 achieved a robust reduction in urate burden on the kidney, as evidenced by normalization in urine uric acid and a significant reduction in plasma urate. We believe this study supports our selection of ALLN-346 as our lead product candidate for the treatment of hyperuricemia in patients with gout and associated CKD. Based on the results of this study, we are scaling our manufacturing processes to support customary toxicology and additional preclinical studies. Subject to the successful completion of these activities, we expect to file an IND for ALLN-346 with the FDA in the second half of 2019 and to initiate our first clinical trial evaluating the efficacy and safety of ALLN-346 in patients with hyperuricemia and gout, including patients with CKD in the first half of 2020.

- ***Explore collaboration opportunities for our product candidates in markets outside of the United States*.** We intend to explore collaborations to commercialize our product candidates, including reloxaliase, outside of the United States. However, depending on our evaluation of these market opportunities and the strategic merits of these collaboration opportunities, we may decide to retain commercial rights in key markets.

- ***Use our proprietary technological approach to develop additional orally-administered enzyme therapies that degrade metabolites in the GI tract.*** We are employing a proprietary technological approach that allows for the design, development, formulation, and scalable manufacturing of oral, non-absorbed, stable enzymes that degrade a specific metabolite within the GI tract. We believe our expertise in orally administered gut-restricted enzyme therapeutics has the potential to serve as a product engine that can be utilized to address other rare and severe metabolic disorders with high unmet medical needs. We plan to continue to expand our platform to create, develop, and bring to market additional first-in-class product candidates.

Competitive Strengths

We believe the following competitive strengths will help us achieve our strategy:

- Therapeutic focus on rare and severe metabolic disorders that affect the kidney and have high unmet medical needs due to the absence of approved or effective therapies;

- Lead product candidate, reloxaliase, with clear mechanism of action and consistent evidence of activity and tolerability across preclinical studies and multiple Phase 1 and 2 trials to support our pivotal Phase 3 program;
- Second product candidate, ALLN-346, which demonstrated a robust reduction in both plasma and urine uric acid levels in an animal proof-of-concept study, and which we are advancing towards an expected IND filing in 2019 and initiation of our first clinical study in the first half of 2020;
- Proprietary technological approach that allows us to design, formulate and deliver non-absorbed and stable enzymes orally and in sufficient doses for activity in the GI tract. This approach enables us to develop enzyme therapies that utilize the GI tract to degrade metabolites, such as oxalate and urate, reducing plasma and urine levels, and in turn, reducing their disease burden on the kidney over time;
- Management team with substantial experience in developing and commercializing pharmaceutical products for metabolic and kidney disorders;
- Strong relationships with key opinion leaders and patient advocacy groups that provide access to the industry's leading experts on hyperoxaluria and other metabolic and kidney disorders; and
- Support from leading healthcare-focused investors and board members with experience in building and operating life science companies.

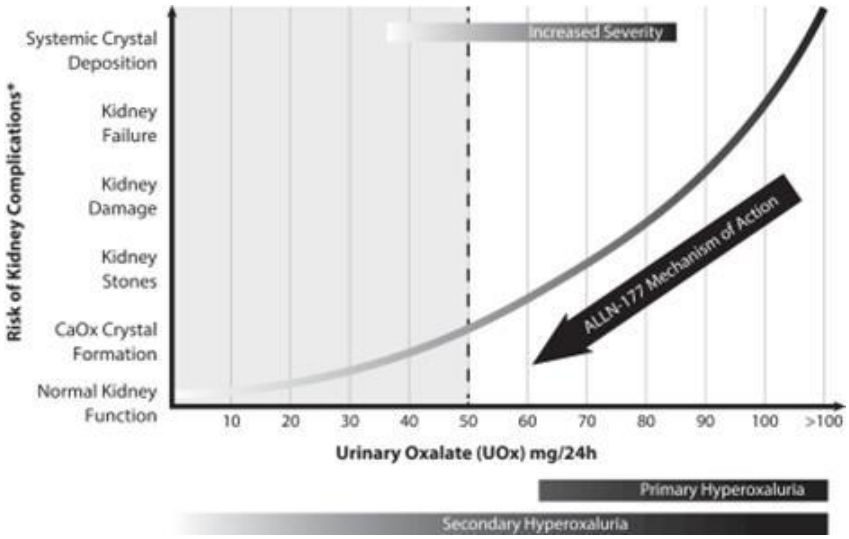
Reloxaliase

Overview of Oxalate and Hyperoxaluria

Oxalate is endogenously produced as an end product of normal cellular metabolism and is also absorbed from a typical diet. Oxalate is present in many foods, especially healthy foods like plants, including green leafy vegetables, fruits and nuts, because plants utilize oxalate to store calcium. Oxalate does not have a known productive role in normal human physiology. Humans lack the innate capacity to digest oxalate, and oxalate is largely excreted unchanged by the kidney in the urine. In addition, bacteria in the GI tract, especially *Oxalobacter formigenes*, play a variable role in degrading oxalate in some patients. Progressively elevated levels of oxalate in the urine increase the risk for kidney stones and other serious kidney diseases.

Hyperoxaluria is a serious metabolic disorder characterized by markedly elevated levels of urinary oxalate excretion, due to either overproduction of oxalate by the liver from a genetic defect, called primary hyperoxaluria, or from over absorption of oxalate from the diet, called secondary hyperoxaluria. Secondary hyperoxaluria often leads to recurrent and frequent kidney stones, placing this patient population at higher risk for CKD, and end-stage renal disease, or ESRD. Secondary hyperoxaluria is further characterized either as enteric, resulting from a chronic and unremediable underlying GI disorder associated with malabsorption, or idiopathic, meaning the underlying cause is unknown. Enteric hyperoxaluria is the more severe type of secondary hyperoxaluria since the underlying GI disorder predisposes patients to chronic excess oxalate absorption. Given this hyperabsorption, patients with enteric hyperoxaluria can have levels of urinary oxalate excretion comparable to patients with primary hyperoxaluria.

The diagnosis and subsequent management of hyperoxaluria are typically based on measurements of oxalate levels in samples of urine voided and collected over a full 24 hour period, referred to as 24 hour urinary oxalate excretion. Hyperoxaluria is generally defined as levels of urinary oxalate excretion greater than 40 mg/24 hour at ages beyond infancy. While there is no firmly established level of urinary oxalate excretion that results in kidney stone formation, the scientific literature suggests that sustained urinary oxalate excretion above 30-40 mg/24 hour increases the risk of stone formation and that higher baseline urinary oxalate excretion is predictive of future stone events. Independent academic studies have shown that an increase in urinary oxalate excretion of approximately 10 mg/24 hour can increase the risk of significant adverse kidney complications. We consider severe hyperoxaluria as having levels of oxalate in the urine greater than 50 mg/24 hour. For example, the average urinary oxalate excretion level at baseline for the subjects with enteric hyperoxaluria in our most recently completed Phase 2 clinical trial was 103 mg/24 hour. Analysis of data from our clinical trials and multiple independent studies, including, but not limited to, peer-reviewed academic studies published in *Nephron* in 1980, *The New England Journal of Medicine* in 1994 and 2002, *Kidney International* in 2006 and 2008, the *Urology Journal* in 2011, the *Clinical Journal of the American Society of Nephrology* in 2016 and, most recently, *the Journal of the American Society of Nephrology Abstract Supplement* in 2017, suggest that a therapeutic strategy that reduces urinary oxalate excretion per 24 hours by approximately 20% could result in a 25-50% reduction in the incidence of kidney stone recurrence (in the short term) and may increase renal survival (in the long term).



* The complications noted in the figure represent a general progression of kidney harm and disease associated with increasing urinary oxalate excretion levels. Not all patients experience this progression and there is considerable variability among individuals between urinary oxalate excretion levels and kidney function and disease.

Secondary Hyperoxaluria

Secondary hyperoxaluria, or increased urinary oxalate excretion resulting from excess absorption of oxalate from the GI tract, falls into two categories:

- **Enteric**, the more severe form of secondary hyperoxaluria, which results from an underlying chronic and unremediable GI disorder; and
- **Idiopathic**, which has no known cause. Some patients with idiopathic hyperoxaluria can have severe disease characterized by hyperabsorption of oxalate with manifestations similar to enteric patients.

Enteric hyperoxaluria is most commonly seen as a complication of malabsorptive bariatric surgical procedures, such as Roux-en-Y gastric bypass, and can also be related to inflammatory bowel disease, such as Crohn's disease, or other conditions associated with GI malabsorption, including cystic fibrosis, pancreatic insufficiency, celiac disease or short bowel syndrome following surgical resection of the bowel. Enteric hyperoxaluria is the more severe type of secondary hyperoxaluria since the underlying GI disorder predisposes patients to chronic excess oxalate absorption. Given this hyperabsorption, patients with enteric hyperoxaluria can have markedly high levels of urinary oxalate excretion that can result in recurrent kidney stones, progressive calcium oxalate (CaOx) deposits in the kidney, or nephrocalcinosis, systemic oxalosis, CKD and ESRD. We

estimate there are approximately 200,000 to 250,000 patients in the United States with enteric hyperoxaluria and kidney stones. We plan to target this market initially. There are no FDA approved therapies for enteric hyperoxaluria. We believe that a therapeutic agent that reduces urine oxalate levels in this population could be commercialized into a potential multi-billion dollar U.S. market without any approved therapies at present.

Idiopathic hyperoxaluria has no known underlying cause and patients with the disorder exhibit varying levels of oxalate absorption from their diet. A number of physiological parameters influence the absorption of dietary oxalate, including intestinal pH and transit time, type of diet, and the amount of other compounds and elements, such as calcium and magnesium, present in the GI tract. Consequently, a subgroup of patients with idiopathic hyperoxaluria hyperabsorbs oxalate from their diets at levels similar to those patients with enteric hyperoxaluria.

Primary Hyperoxaluria

Primary hyperoxaluria, a type of severe hyperoxaluria, is a rare genetic disorder that can result in kidney stone disease, kidney damage, and kidney failure, which may lead to death. Primary hyperoxaluria has three main types, PH1, PH2, and PH3, with each categorization representing the particular genetic enzyme deficiency that drives the overproduction of oxalate, mainly in the liver, and massive excretion of oxalate in the urine. The most severe and common type of primary hyperoxaluria is PH1. These patients typically develop recurrent kidney stones with progressive nephrocalcinosis and end stage renal disease by 20-30 years of age. Among patients with primary hyperoxaluria, about 50 percent will have kidney failure by age 15, and about 80 percent will have kidney failure by age 30. Primary hyperoxaluria is estimated to affect approximately 1 in 58,000, or approximately 5,000 patients in the United States, and approximately 0.1 in 10,000 people, or approximately 5,000 patients in the Europe. There are no FDA approved therapies for primary hyperoxaluria, and the most severe patients may be treated with a liver and/or kidney transplant. Patients with enteric hyperoxaluria can have levels of urinary oxalate excretion as high as patients with primary hyperoxaluria and a comparable renal burden.

Hyperoxaluria-Patient Journey and Progression of Disease

The first clinical manifestation of hyperoxaluria is often a kidney stone; however, the disorder can be variable in its presentation. Patients with severe hyperoxaluria may have recurrent kidney stones or experience infrequent or no kidney stones, yet still develop CKD and ESRD, which can be fatal. The risk for kidney stones increases with progressively elevated levels of urinary oxalate excretion. Up to 80% of kidney stones contain oxalate; therefore hyperoxaluria is a primary driver of kidney stones and reducing urinary oxalate is a scientifically targeted approach to prevent kidney stone episodes. Patients experiencing a kidney stone typically go to the emergency room for treatment due to the intense physical pain, as the kidney stone may take hours to days to pass or require interventional surgical procedures to remove it if it is too large to pass on its own. Kidney stones affect approximately 1 in 11 people in the United States at some point in their lives and the likelihood of recurrence has been estimated to be as high as 50% within 5 years of the initial event. Based on a project completed in 2016 by Health Advances, a strategic consulting firm for the healthcare industry that we engaged to conduct market research, approximately 5 million patients have been affected by recurrent calcium oxalate kidney stones in the United States.

Given the debilitating and recurrent nature of kidney stones, patients suffering from recurrent kidney stones bear significant social and financial burdens and are therefore highly motivated to prevent further relapse. Patients with enteric hyperoxaluria tend to have more frequent and more complicated kidney stone episodes and other kidney disorders as a result of their underlying GI disorders and predisposition to chronic excess oxalate absorption. For example, an additional project completed by Health Advances for us in 2017, which included analysis of peer-reviewed academic studies in two patient populations with GI malabsorption (Roux-en-Y gastric bypass and short bowel syndrome), suggested that these patients had a significantly higher kidney stone risk and rate of kidney stone recurrence than the general population of patients with kidney stones. They also had a significantly higher rate of intervention to remove kidney stones. This significant burden of disease in patients with enteric hyperoxaluria is consistent with the clinical presentation of patients participating in our Phase 2 clinical program. In October 2018 we presented data at the American Society of Nephrology conference which included composite data, details on kidney stone burden, and case studies from 33 patients with enteric hyperoxaluria who enrolled across our three Phase 2 studies of reloxaliase. Data from these 33 patients showed that a majority of the patients experienced persistently high 24-hour urinary oxalate (UOx) excretion, despite following standard-of-care guidance for diet and hydration. On average, these subjects experienced six stones prior to enrollment. Among 20 patients for whom kidney stone burden was assessed by a computerized tomography, or CT, scan, 16 had at least one kidney stone detected at enrollment (80%), with an average of three stones present. Additionally, 20% of patients presenting with a kidney stone had very large stones, which could require urological intervention. In addition to kidney stone burden, nearly 30% of subjects had moderate CKD (stage 3). Based upon a separate analysis of claims data obtained from Truvan Health Analytics, part of the IBM Watson Health business, we estimate that enteric hyperoxaluria patients with new onset kidney stones, including those who have developed new onset CKD, on average incur approximately $66,000 annually in direct medical costs within a 4-year period after a malabsorptive surgical procedure or underlying GI disease diagnosis associated with risk of enteric hyperoxaluria.

Further, people with kidney stones have a two times greater risk of CKD and ESRD and a higher risk of stroke and heart attack than the general population. Managing CKD and ESRD is complex as many metabolic factors, such as phosphorus, potassium and parathyroid hormone, are out of balance, often requiring treatment with multiple therapeutic agents. Patients who develop ESRD secondary to hyperoxaluria require frequent hemodialysis-approximately 6 or 7 times per week-with or without supplemental peritoneal dialysis while awaiting kidney transplantation to prevent or limit systemic oxalosis. Systemic oxalosis, which typically occurs in patients with primary or severe secondary hyperoxaluria and declining kidney function, refers to the presence of excess oxalate throughout the body, including the blood, bones, joints, eyes and heart. Elevated levels of oxalate in the blood is referred to as hyperoxalemia. For example, a publication in Kidney International in 2018 provided a systematic review on secondary oxalate nephropathy case reports (108 patients total), the majority attributable to enteric hyperoxaluria. In this study, oxalate crystal deposition was universally found in the kidneys, suggesting a causal role for the oxalate crystals. With a mean follow-up of 12.9 months, renal replacement therapy (dialysis) was required in >50% of patients with most patients remaining dialysis-dependent and an overall mortality rate was 33%.

Patients with enteric hyperoxaluria are at risk for developing CKD, and those who receive a kidney transplant for ESRD due to oxalate-related kidney damage remain at risk for recurrent oxalate-related kidney damage. Primary and enteric hyperoxaluria patients with high urinary oxalate concentrations can develop nephrocalcinosis, which can lead to kidney failure.

Hyperoxaluria Current Treatment and Unmet Need

There is no approved pharmacologic therapy for the reduction of urinary oxalate excretion in patients with hyperoxaluria, either primary or secondary. Existing treatment options for hyperoxaluria generally are non-specific and include high fluid intake to increase urine output to more than two to three liters per day, a diet low in salt and oxalate, oral citrate and/or calcium and/or magnesium supplementation and, exclusively for the subset of responsive patients with the most severe form of primary hyperoxaluria (PH1), orthophosphate and Vitamin B6 supplementation. Despite these strategies, many patients continue to experience hyperoxaluria with recurrent kidney stones and continued risk for long-term kidney damage. Consequently, we believe patients afflicted with severe hyperoxaluria could greatly benefit from a therapy that reliably lowers oxalate levels in the body and therefore reduces the burden on the kidney to filter and then excrete the metabolite in the urine.

There are no FDA-approved therapies for enteric hyperoxaluria and no approved pharmacologic therapies specifically directed at reducing oxalate absorption driven by an underlying GI disorder. Current management of enteric hyperoxaluria relies on strategies to reduce dietary oxalate intake, increase calcium intake and drink large volumes of fluid. Increased oral fluid intake results in increased urine volume, with the goal of decreasing the saturation of oxalate in the urine and therefore reducing the risk of kidney stone formation and/or more severe kidney diseases. However, because patients with enteric hyperoxaluria have an underlying GI condition predisposing them to chronically hyperabsorb oxalate, this population often finds it particularly difficult to consistently ingest the quantities of fluid required to maintain adequate urine volume. In addition, recommendations for a low oxalate diet are somewhat in conflict with general recommendations for a healthy diet of largely plant-based foods. Many plants are high in oxalate, making it difficult to adhere to a low oxalate diet, given the relatively large number of healthy foods with moderate or high oxalate content. The limited medicinal options to treat calcium oxalate kidney stones, including thiazide diuretics and potassium citrate, have suboptimal efficacy, are not targeted to oxalate, and can be difficult to tolerate in patients with GI diseases.

We believe that reloxaliase can address unmet medical needs for patients with severe hyperoxaluria, who experience recurrent kidney stones, CKD, end-stage renal disease and other serious kidney diseases. Reloxaliase, if approved, would be the first therapeutic option that directly degrades oxalate in the GI tract using a mechanism of action specifically targeted to reducing excess absorption of oxalate.

Our Solution: Reloxaliase

Our lead product candidate, reloxaliase, is a first-in-class, non-absorbed, orally-administered enzyme for the treatment of hyperoxaluria. Reloxaliase, a crystalline formulation of the enzyme oxalate decarboxylase, has been designed to specifically degrade oxalate into formate and carbon dioxide within the GI tract, thus limiting systemic absorption of oxalate into the bloodstream. The decrease in systemic absorption reduces the burden on the kidney to filter and then excrete oxalate in the urine and, in turn, reduces the risk of kidney stones and other serious kidney diseases.

We are initially developing reloxaliase for adult patients with enteric hyperoxaluria. As summarized in the table below, we have evaluated reloxaliase in 113 subjects with secondary hyperoxaluria in three Phase 2 clinical trials, of whom 33 subjects had enteric hyperoxaluria, and a Phase 1 clinical trial with 33 healthy volunteers with diet-induced hyperoxaluria. Based on these data, particularly the significant reductions in urinary oxalate excretion observed in patients with enteric hyperoxaluria in our Phase 2 clinical program, we initiated URIROX-1, the first of two Phase 3 clinical trials in March 2018, with topline data anticipated in the second half of 2019. In the fourth quarter of 2018 we initiated URIROX-2 (formerly Study

302), our second pivotal Phase 3 trial of reloxaliase in patients with enteric hyperoxaluria. The FDA has advised us that it agrees with our strategy to pursue a BLA submission for reloxaliase using the accelerated approval regulatory pathway. We expect to submit a BLA to the FDA after 400 patients have been randomized and followed for six months. For the long-term follow-up phase of the trial, subjects would continue in the study for a minimum treatment period of two years to confirm clinical benefit post-approval.

In addition, the FDA has granted separate orphan drug designations for reloxaliase for the treatment of primary hyperoxaluria and for the treatment of pediatric hyperoxaluria. The European Commission has also granted orphan designation for reloxaliase for the treatment of primary hyperoxaluria. In light of these designations, we initiated an open-label Phase 2 clinical trial (Study 206) in March 2018 in adolescents and adults with primary hyperoxaluria or enteric hyperoxaluria, who also have elevated levels of oxalate in the blood, or hyperoxalemia, which can lead to systemic oxalosis, a potentially fatal disorder associated deposition of oxalate in tissues. We expect to announce initial data from Study 206 in the second quarter of 2019 and topline data from Study 206 in the second half of 2019.

Clinical Development Program

Overview

Since 2012, we have conducted a robust clinical development program of reloxaliase in healthy volunteers and patients with secondary hyperoxaluria. As a result, we have developed key insights into hyperoxaluria, clinical trials in patients with hyperoxaluria and the activity and tolerability of reloxaliase in this patient population. In our Phase 1 clinical trial in healthy volunteers, we demonstrated proof of concept that the GI tract could be used for reducing the renal oxalate burden, as measured by 24 hour urinary oxalate excretion. Our Phase 2 clinical program was designed to identify the optimal patient population, registrational endpoint and trial design for our planned pivotal Phase 3 program. In the aggregate, our clinical development program to date has demonstrated that:

- reloxaliase can substantially reduce urinary oxalate excretion in patients with enteric hyperoxaluria;
- reloxaliase has been well-tolerated, with no drug-related serious or severe adverse events; and
- the effect of reloxaliase was specific to oxalate, with minimal to no changes in non-oxalate urine parameters.

The table below summarizes our clinical trial experience with reloxaliase to date.

Trial	Trial dates	Design	N (Subjects)	Trial Population	Trial Objectives
713	August 2015 to January 2017	Phase 2, multi-center, randomized, double-blind, placebo-controlled	67	Secondary hyperoxaluria patients	Evaluate safety and efficacy of ALLN-177 to reduce urinary oxalate excretion over 28 days
396	June 2014 to December 2014	Phase 2, multi-center, open-label, single arm	16	Kidney stone formers with secondary hyperoxaluria	Evaluate safety and efficacy of ALLN-177 to reduce urinary oxalate excretion over 4 days
649	July 2015 to July 2016	Phase 2, multi-center, randomized, double-blind, placebo-controlled, crossover	30	Kidney stone formers with secondary hyperoxaluria	Evaluate safety and efficacy of 3 different doses of ALLN-177 to reduce urinary oxalate excretion over 7 days
183	May 2013 to November 2013	Phase 1, single-center, double-blind, randomized, placebo-controlled crossover	33	Healthy volunteers on a controlled high oxalate diet	Evaluate safety and efficacy of ALLN-177 over 7 days

Summary of Completed Phase 2 Clinical Trials

Study 713-Phase 2 Clinical Trial in Patients with Secondary Hyperoxaluria

We completed a multi-center, randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of reloxaliase in patients with secondary hyperoxaluria. The enrollment criteria consisted of patients with either idiopathic or enteric hyperoxaluria with at least 50 mg/24 hour in urinary oxalate, or UOx, excretion at screening, most of whom had a history of kidney stones. We designed the trial to measure the ability of reloxaliase to reduce UOx levels in this patient population, with additional planned analysis in subgroups of secondary hyperoxaluria. The primary endpoint was reduction in UOx excretion from baseline to Week 4. We specified key secondary endpoints including a measure of time-weighted average, or TWA, 24 hour UOx excretion over the four weeks of the trial and percent change in UOx excretion from baseline to Week 4. TWA 24 hour UOx excretion is the average of all 24 hour UOx excretion values obtained while on study

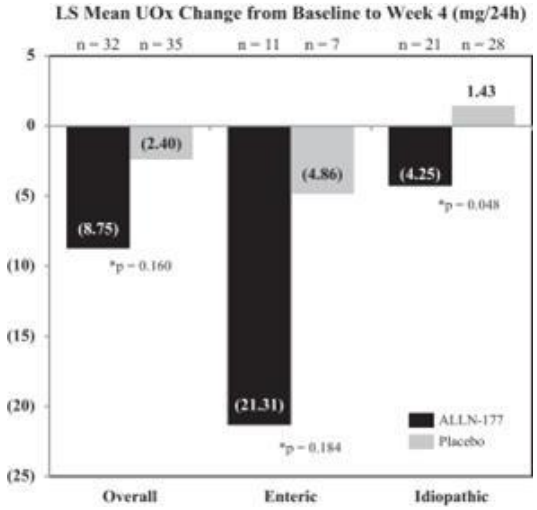
drug (reloxaliase or placebo), with each value weighted for the number of days since the last urine collection. We believe this measurement better captures the durability of metabolic control. We also performed various post-hoc analyses on the data.

In the trial, 71 subjects were randomized to receive either a 7,500 unit oral dose of reloxaliase or placebo three times per day with meals, for 28 days. A total of 67 subjects received treatment (32 reloxaliase and 35 placebo), and comprised the modified intent-to-treat and safety populations. Subjects with enteric hyperoxaluria accounted for 34% of the reloxaliase group (11 subjects) and 20% of the placebo group (7 subjects). Subjects with idiopathic hyperoxaluria accounted for 66% of the reloxaliase group (21 subjects) and 80% of the placebo group (28 subjects). On average, subjects with enteric hyperoxaluria had markedly higher UOx excretion levels at baseline (103 mg/24 hour) than the subjects with idiopathic hyperoxaluria (57 mg/24 hour), and despite consuming roughly half the amount of dietary oxalate as idiopathic subjects, their baseline UOx excretion levels were approximately twice as high.

Key efficacy results from this Phase 2 clinical trial included:

- In the overall population, reduction in 24 hour UOx excretion from baseline to Week 4 (the primary endpoint of the trial) was greater in subjects treated with reloxaliase (LS mean[1] = -8.75 mg/24 hour) compared to subjects who received placebo (LS mean = -2.40 mg/24 hour); however, the difference between treatment groups (LS mean = -6.35 mg/24 hour) did not reach statistical significance (p[2] = 0.160).

- In the subgroup with enteric hyperoxaluria, reduction in 24 hour UOx excretion from baseline to Week 4 was substantially greater in subjects treated with reloxaliase (LS mean = -21.31 mg/24 hour) compared to subjects who received placebo (LS mean = -4.86 mg/24 hour), and the treatment difference was LS mean = -16.45 mg/24 hour (p = 0.184). The magnitude of the treatment effect was substantially greater than what was observed in the overall population.

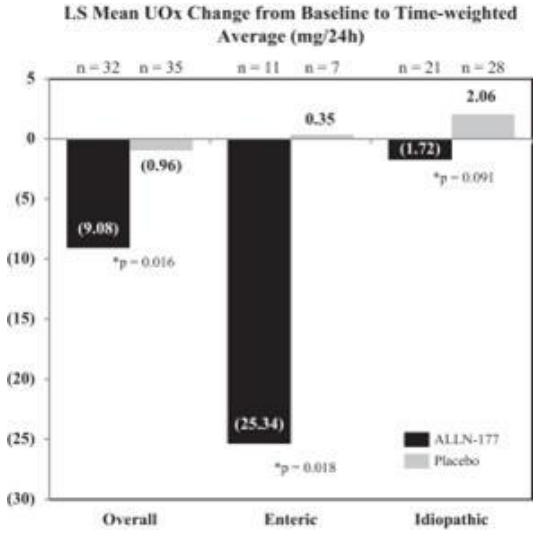


- In the overall population, reduction in 24 hour UOx excretion from baseline to TWA across Weeks 1-4 (a key pre-specified secondary endpoint of the trial) was substantially greater in subjects treated with reloxaliase (LS mean = -9.08 mg/24 hour) compared to subjects who received placebo (LS mean = -0.96 mg/24 hour), and the difference between treatment groups was LS mean = -8.13 mg/24 hour (p = 0.016).

- In the subgroup with enteric hyperoxaluria, reduction in 24 hour UOx excretion from baseline to TWA across Weeks 1-4 was substantially greater in subjects treated with reloxaliase (LS mean = -25.34 mg/24 hour) compared to subjects who received placebo (LS mean = +0.35 mg/24 hour), and the treatment difference was LS mean = -25.69 mg/24 hour (p==0.018). As with the primary efficacy endpoint, the magnitude of the treatment effect was substantially greater than what was observed in the overall population.

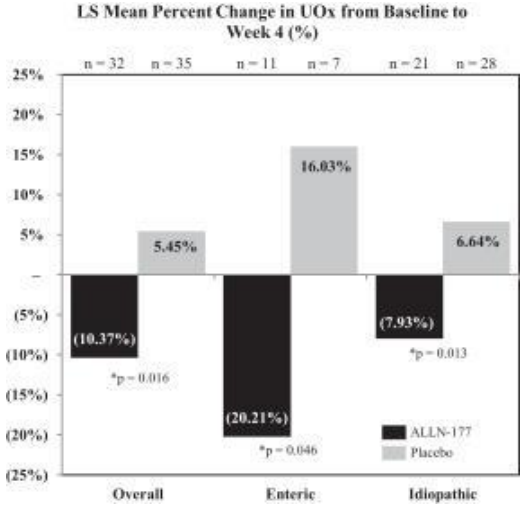
1 LS mean, or least squares mean, is an average calculated based on a linear model that is adjusted for other terms, such as covariates, and is less sensitive to missing data.

2 A p-value is a conventional statistical method for measuring the statistical significance of clinical results. A p-value of 0.05 or less is generally considered to represent statistical significance, meaning that there is a less than 1-in-20 likelihood that the observed results occurred by chance.



- In the overall population, percent reduction in 24 hour UOx excretion from baseline to Week 4 (a pre-specified secondary endpoint of the trial) was greater in subjects treated with reloxaliase (LS mean = -10.37%) compared to subjects who received placebo (LS mean = +5.45%), and the treatment difference was LS mean = -15.81% (p = 0.016).

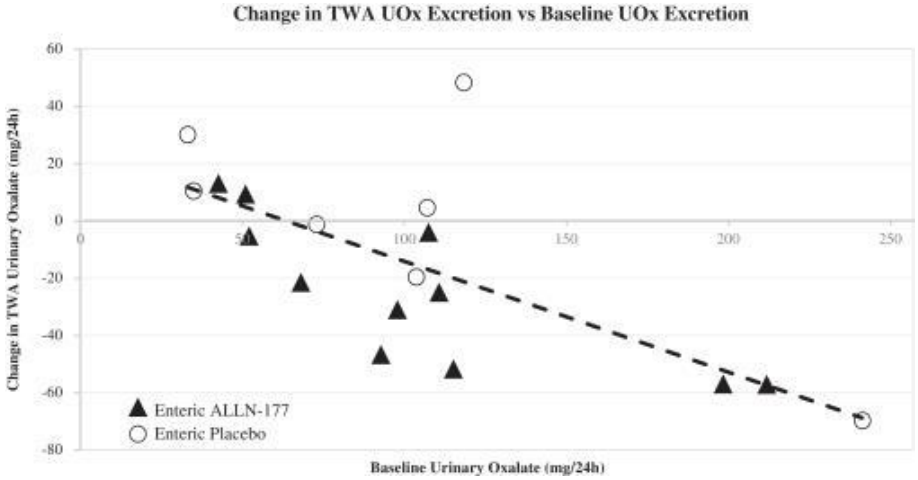
- In the subgroup with enteric hyperoxaluria, percent reduction in 24 hour UOx excretion from baseline to Week 4 was substantially greater in subjects treated with reloxaliase (LS mean = -20.21%) compared to subjects who received placebo (LS mean = +16.03%), and the treatment difference was LS mean = -36.25% (p = 0.046). The magnitude of the treatment effect was substantially greater than what was observed in the overall population.



- In the overall population, the proportion of subjects with a ≥ 20% reduction in 24 hour UOx excretion from baseline to TWA across Weeks 1 to 4 (a post-hoc analysis) was greater in subjects treated with reloxaliase (40.6%) compared to subjects who received placebo (8.6%), with an odds ratio[3], or OR, of 9.59 (p = 0.006).

3 Odds ratio is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given treatment with reloxaliase compared to the odds of the outcome occurring in placebo subjects.

- In the subgroup with enteric hyperoxaluria, as illustrated by the figure below, the proportion of subjects with a ≥ 20% reduction in 24 hour UOx excretion from baseline to TWA across Weeks 1 to 4 was substantially greater in subjects treated with reloxaliase (63.6%) compared to subjects who received placebo (14.3%), with an OR of 9.35 (p = 0.092).



Additional key findings:

- The trial demonstrated reloxaliase to be well tolerated and all 32 subjects treated with reloxaliase completed the trial. Treatment emergent adverse events, or TEAEs, were reported at a lower incidence in subjects receiving reloxaliase (16 subjects or 50.0%) compared to subjects receiving placebo (22 subjects or 62.9%). The incidence of TEAEs that were considered related to the study drug was also lower in subjects treated with reloxaliase (9.4%) compared with subjects who received placebo (22.9%). Among subjects with enteric hyperoxaluria, TEAEs were also reported at a lower frequency in the reloxaliase group (6 of 11 subjects, or 54.5%) compared with the placebo group (5 of 7 subjects, or 71.4%). Similar to the overall population, GI-related TEAEs (the most common type of adverse event) were reported at a lower frequency in the reloxaliase group (3 of 11 subjects, or 27.3%) compared with the placebo group (3 of 7 subjects, or 42.9%). While two subjects in the placebo group experienced TEAEs (nausea and dermatitis) that led to withdrawal from the trial, there were no TEAEs that led to withdrawal from the trial among the subjects treated with reloxaliase. There were no deaths, severe or serious adverse events, or SAEs, reported during the trial. There were no clinically important changes in laboratory values, vital signs or physical examinations.

- We observed intra-individual variability in UOx excretion that may have arisen from changes in diet, metabolic activity, hydration status or other factors. Consequently, we believe TWA UOx excretion per 24 hours over the study period is a clinically meaningful endpoint because it reflects the physiological effect of metabolic control of UOx excretion over time and dampens the effect of intra-individual variability in 24 hour UOx excretion. There have been several approved metabolic disease therapies that utilized a TWA measure as the endpoint for their pivotal clinical program.

- The effects of reloxaliase were observed to be highly specific to oxalate, as there were minimal to no changes in other non-oxalate urine parameters, such as calcium, citrate, sodium and urinary volume, between baseline and Week 4 in subjects on reloxaliase.

- We observed from diet recall data that subjects with enteric hyperoxaluria consumed on average more than three meals per day and more than two snacks per day. On average, they consumed 28% of their total daily oxalate intake from snacks, with snacks accounting for 40-50% of daily oxalate intake in some subjects. In the trial, subjects received either a 7,500 unit oral dose of reloxaliase (22,500 units/day) or placebo three times per day with meals. As a result of their eating patterns, subjects in the subgroup with enteric hyperoxaluria therefore consumed

a significant portion of their daily oxalate intake without treatment. Patients with enteric hyperoxaluria often have individualized dietary patterns, particularly patients following bariatric surgery, who are typically advised to eat frequent, smaller meals. These data informed our decision to tailor the dosing regimen in our pivotal Phase 3 clinical program for patients with enteric hyperoxaluria in order to maximize the therapeutic effect of reloxaliase. We will dose subjects in URIROX-1 with 7,500 units of reloxaliase with each meal and/or snack, up to five times per day (up to 37,500 units/day). This dosing regimen is consistent with the eating patterns of patients with enteric hyperoxaluria and is designed to provide reloxaliase at most meals and snacks in order to maximize the degradation of oxalate ingested.

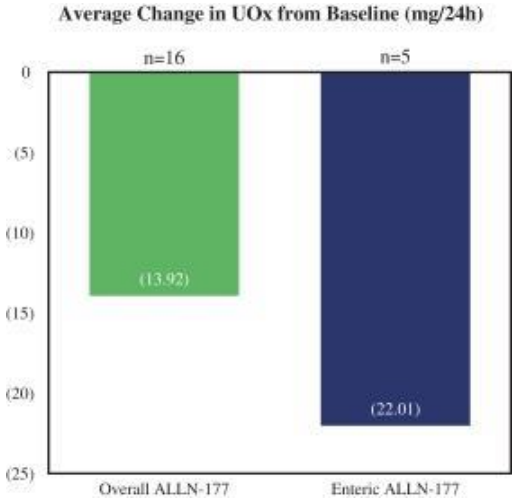
This trial was the largest randomized controlled trial ever conducted in hyperoxaluria and key elements served as the blueprint for our pivotal Phase 3 program. Although the trial did not achieve the primary efficacy endpoint, we observed substantial reductions in UOx excretion in several key pre-specified secondary endpoints, particularly in patients with enteric hyperoxaluria. Moreover, due to observed variability in UOx excretion, we believe that an analytical approach based upon TWA most appropriately indicates the therapeutic effect of reloxaliase in patients with enteric hyperoxaluria. As a result, we chose as the primary endpoint of URIROX-1 the percent change from baseline in 24 hour UOx excretion averaged during Weeks 1-4 of the four-week treatment period. In addition, we observed reloxaliase to be well tolerated and highly specific to oxalate.

Study 396-Phase 2 Clinical Trial in Patients with Secondary Hyperoxaluria

We conducted a proof of concept clinical trial in patients with secondary hyperoxaluria. This trial was a multi-center, open-label, single arm trial to evaluate the safety and efficacy of reloxaliase treatment in 16 patients with secondary hyperoxaluria and kidney stones, many of whom were receiving treatment in kidney stone clinics to manage kidney stone disease (e.g. low oxalate diet and high oral fluid intake, thiazide diuretics and potassium citrate). In the trial, all subjects were treated with a 7,500 unit oral dose of reloxaliase three times per day with meals for four days.

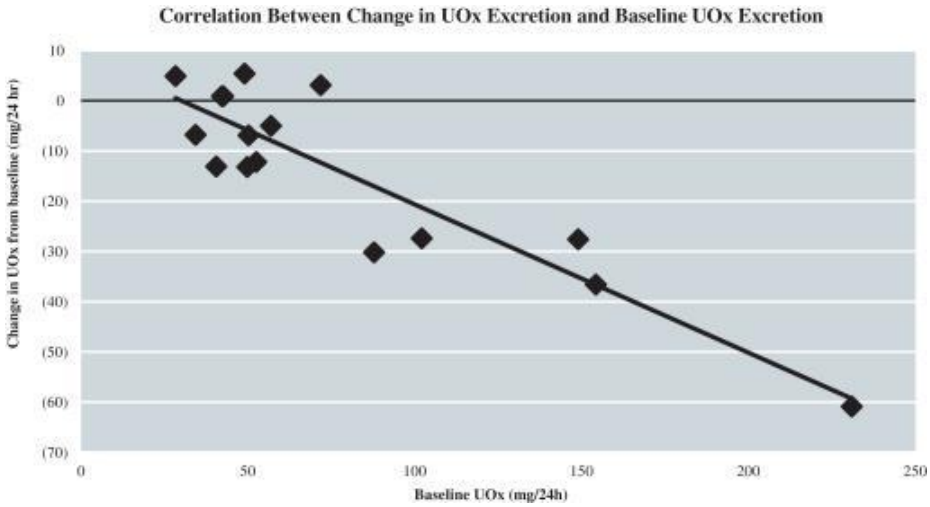
Key results from this Phase 2 clinical trial included:

- Subjects had an average reduction in UOx excretion of -13.92 mg/24 hour ($p = 0.0084$). The five subjects with enteric hyperoxaluria experienced a substantially greater average reduction in UOx excretion of -22.01 mg/24 hour as illustrated by the chart below.



- Overall, 11 of 16 subjects, or 69%, had some reduction in UOx excretion levels, in whom the mean reduction was 23%.

- The reduction in 24 hour UOx excretion was correlated with baseline UOx, demonstrating that subjects with higher UOx excretion levels at baseline showed greater reduction in UOx levels after taking reloxaliase, as shown in the figure below.



- The trial demonstrated reloxaliase to be well tolerated. No deaths, SAEs, or other significant adverse events occurred in this trial. No subject was withdrawn from the study due to an adverse event. There were no clinically significant hematology or serum biochemistry abnormal values reported during the trial.

Study 649-Phase 2 Clinical Trial in Patients with Secondary Hyperoxaluria

We conducted a randomized, double-blind, placebo-controlled, crossover trial with an adaptive design to evaluate the efficacy and safety of three different doses of reloxaliase compared with placebo, administered for seven days, in subjects with kidney stones and secondary hyperoxaluria. Subjects were randomized to treatment sequences in a crossover fashion. A crossover trial is a longitudinal study in which subjects receive a sequence of different treatment arms during the course of the trial. Each treatment sequence consisted of two seven-day treatment periods separated by a seven-day washout period. Throughout the trial, each subject participated in two of the four treatment arms, which included a 1,500 unit oral dose of reloxaliase, a 3,000 unit oral dose of reloxaliase, a 7,500 unit oral dose of reloxaliase or placebo, with meals three times a day. A total of 32 subjects were randomized; two subjects were not treated, resulting in a total of 30 subjects included in the analyses.

Randomization in the reloxaliase low and mid-dose groups was halted after the first Adaptive Design Review Committee review of data on the first 12 subjects, resulting in only a small number of subjects in those two groups. The trial stopped enrolling in July 2016 following the second planned interim analysis once 24 subjects' data were available, due to the inability to differentiate among the treatment arms.

A post-hoc evaluation of the data was conducted to attempt to determine factors which may have influenced the inability of reloxaliase to demonstrate a statistically significant difference from placebo. While no clear factor was identified to account for the lack of differentiation between reloxaliase and placebo, we believe the lack of effect may have been due to variability in dietary oxalate ingestion, measurement of UOx excretion and the complexities inherent in the short-cycle, crossover study design.

All three doses of reloxaliase were well tolerated in this study. No deaths, SAEs, or other significant AEs occurred. One subject who received the 1,500 unit oral dose of reloxaliase per meal three times per day experienced an SAE after the seven-day washout period during the first dosing day of reloxaliase at the 7,500 unit oral dose that led to withdrawal from the trial. The event was considered not related to study drug by the investigator. No other subjects withdrew due to a TEAE during the trial.

Pivotal Phase 3 URIROX Program and Regulatory Pathway

Our pivotal Phase 3 program for reloxaliase consists of two global, randomized, double-blind, placebo-controlled clinical trials evaluating efficacy and safety of reloxaliase in adult patients with enteric hyperoxaluria and UOx ≥ 50 mg/24 hours, called URIROX-1 (formerly Study 301) and URIROX-2 (formerly Study 302). We expect that both trials will be conducted in the United States, Canada and Europe, and, in the case of URIROX-2, potentially other geographies.

We initiated URIROX-1 in March 2018. A total of 124 subjects are planned for randomization equally into two arms for a four-week treatment period. Subjects will self-administer either 284 mg (equivalent to 7,500 units) of reloxaliase or placebo with each meal or snack, up to five times per day, consistent with the eating patterns of patients with enteric hyperoxaluria. URIROX-1 has the same primary and key secondary efficacy endpoints as URIROX-2. The primary endpoint for the study is the percent change from baseline in 24-hour urinary oxalate, or UOx, excretion during Weeks 1-4, comparing reduction in the average UOx excretion across Weeks 1-4 with reloxaliase to placebo. Secondary endpoints include proportion of subjects with a ≥20% reduction from baseline in 24-hour UOx excretion averaged during Weeks 1-4. URIROX-1 is the largest randomized, controlled trial of a novel therapeutic ever initiated in patients with enteric hyperoxaluria. We expect to announce topline data from the URIROX-1 trial in the second half of 2019.

We initiated URIROX-2 in the fourth quarter of 2018. URIROX-2 is a multicenter, global, randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of reloxaliase in patients with enteric hyperoxaluria, over a minimum treatment period of two years. The trial is designed to enroll 400 patients with 24-hour UOx excretion greater than or equal to 50 mg and a history of kidney stones, and will include patients with normal kidney function as well as chronic kidney disease (defined as an estimated glomerular filtration rate (eGFR) greater than or equal to 30). Patients will be randomized 1:1 to reloxaliase vs. placebo and will take 284 mg (equivalent to 7,500 units) of reloxaliase or placebo with each meal or snack up to five times per day, consistent with the eating patterns of patients with enteric hyperoxaluria.

The primary efficacy endpoint for URIROX-2 is the percent change from baseline in 24-hour UOx excretion during Weeks 1-4, comparing mean reduction in the average UOx excretion across Weeks 1-4 with reloxaliase to placebo. Secondary endpoints include the proportion of subjects with a ≥20% reduction from baseline in 24-hour UOx excretion measured during Weeks 1-4 and percent change from baseline in 24-hour UOx excretion during Weeks 16 to 24. The primary long-term efficacy endpoint to confirm clinical benefit is the proportion of subjects with kidney stone disease progression, defined as a composite of either symptomatic kidney stone(s) or finding of new or enlarged kidney stone(s) using imaging, over a minimum treatment period of two years. Secondary long-term efficacy endpoints to confirm clinical benefit include change in eGFR from baseline and emergency room visits, hospitalizations or procedures for the management of kidney stones.

The FDA has advised us that they agree with our overall strategy to obtain accelerated approval for reloxaliase. The data generated from the URIROX-1 and URIROX-2 trials could thus potentially form the basis of an accelerated approval of reloxaliase using reduction in UOx as a surrogate endpoint, with the final results from the URIROX-2 trial used to confirm clinical benefit post-approval. We expect that our data package for accelerated approval would include a conditional power estimate based on the effect of reloxaliase on reducing kidney stone disease progression as assessed with interim data from the URIROX-2 trial, the effects of reloxaliase on reduction of UOx in the URIROX-1 and URIROX-2 trials, and further support for the model relating UOx levels to kidney stone disease progression, including but not limited to available data obtained in the URIROX-2 trial. We expect to submit a BLA to the FDA after 400 patients have been randomized and followed for six months. For the long-term follow-up phase of the trial, subjects would continue in the study for a minimum treatment period of two years to confirm clinical benefit post-approval.

The FDA has also advised us that part of its assessment of the adequacy of the URIROX-2 trial to support accelerated approval will be both the size of the effect seen on UOx in this trial and on our ability to support the model of the relationship between UOx levels and stone formation rates, which model can be informed by data generated in the URIROX-2 trial as well as other data sources. This approach is consistent with the FDA's published guidance on the accelerated approval pathway, which provides that clinical data from a single clinical trial can be used to both support accelerated approval and verify the clinical benefit. This guidance stipulates that the protocol and statistical analysis plan should clearly account for an analysis of the surrogate endpoint data to provide support for accelerated approval, with continuation of the randomized trial(s) to obtain data on the clinical endpoint that will be the basis for verifying the clinical benefit. In light of this guidance, URIROX-2 incorporates adaptive design elements that, through sample size re-estimations, will, if necessary, allow for increases in sample size and duration of treatment, based on accrued kidney stone disease progression rates and the conditional probability of achieving ultimate success in the long-term follow-up phase of the trial as reviewed by the FDA. Based on the outcome of our planned sample size re-estimations we may be required to increase the number of patients treated and/or extend the follow-up period before we are able to submit a BLA for reloxaliase using the accelerated approval pathway.

For a discussion about the risks related to our pivotal Phase 3 clinical program, please see "Risk Factors—Risks Related to Drug Development, Regulatory Approval and Commercialization," including, but not limited to, the specific risk factor titled "Although we have reached alignment with the FDA on the design of URIROX-2, our second pivotal Phase 3 trial of reloxaliase in patients with enteric hyperoxaluria, and our strategy to pursue a BLA submission for reloxaliase using the accelerated approval regulatory pathway, the clinical data we generate from our Phase 3 clinical program and/or the data we derive from third party datasets may not be sufficient to satisfy the FDA that we are eligible to use the accelerated approval regulatory pathway…"

In addition, we have conducted Scientific Advice meetings with regulatory authorities in three countries within the European Union, and discussed the results of our Phase 2 clinical program, our proposed pivotal Phase 3 program as described above and potential pathways for regulatory approval of reloxaliase in Europe. Subject to future anticipated interactions with the European Medical Agency (EMA), we believe that our proposed Phase 3 program, if successful, could support the filing of a future MAA application in the European Union via the conditional approval pathway, which is similar to the FDA's accelerated approval pathway.

Finally, the Kidney Health Initiative, or the KHI, a public-private partnership established in 2012 by the American Society of Nephrology in collaboration with stakeholders in the renal community, including the FDA, recently launched a project on oxalate disorders with the Oxalosis and Hyperoxaluria Foundation. The project, called "Identification of Appropriate Endpoints for Clinical Trials in Hyperoxaluria", is led by John C. Lieske, M.D., FASN, of the Mayo Clinic. The Oxalosis and Hyperoxaluria Foundation is an organization dedicated to the awareness, understanding and treatment of hyperoxaluria and oxalosis for healthcare professionals, patients and their families. An anticipated output of the KHI project is a document that summarizes consensus recommendations regarding appropriate biochemical endpoints for clinical trials in hyperoxaluria.

Summary of Completed Phase 1 Clinical Trial-Study 183

We completed a single-center, double-blind, randomized, placebo-controlled crossover Phase 1 clinical trial to evaluate the safety and provide initial proof of concept of activity of reloxaliase in healthy volunteers. We fed 33 healthy adult subjects an oxalate-rich diet in order to induce transient dietary hyperoxaluria. Each subject then received either a 7,500 unit oral dose of reloxaliase or placebo three times per day with meals for seven days while continuing on the oxalate-rich diet. The high-oxalate diet increased baseline UOx excretion per 24 hours from a mean of 27.2 mg/24 hour to a mean 80.8 mg/24 hour. reloxaliase demonstrated significantly reduced UOx excretion with a mean reduction of -11.54 mg/24 hour compared to placebo ($p = 0.0002$). The mean reduction in the 18 of 30 subjects, or 60%, defined as responders (i.e. those who had > 5 mg/24 hour reduction in UOx excretion) was -20 mg/24 hour. No deaths, SAEs, or other significant AEs occurred during this trial, and no differences in the pattern of TEAEs were observed while on reloxaliase or placebo.

Summary of Preclinical Studies

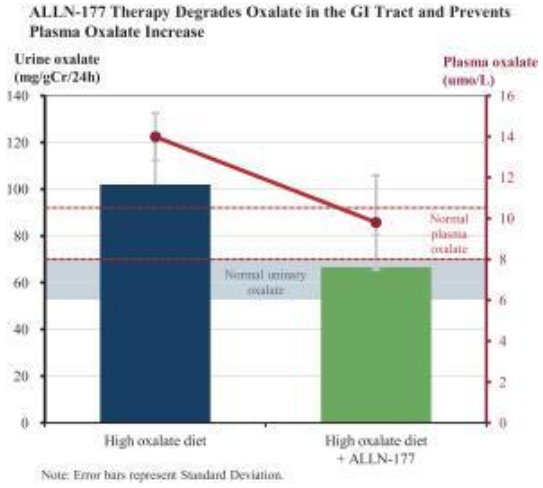
We have completed a series of preclinical studies to assess the pharmacology and toxicology of reloxaliase. Based on the results from these studies, which demonstrated, among other things, that reloxaliase remains in the GI tract and is not detected for systemic absorptions, we believe the preclinical program for reloxaliase is substantially complete.

Pharmacology Studies

We have conducted an extensive pharmacology program consisting of a total of nine rodent and pig studies of reloxaliase. Our pharmacology studies provided confirmation of our hypothesis that orally administered oxalate decarboxylase, the active enzyme in reloxaliase, can reduce or normalize UOx levels by degrading both endogenously produced and dietary oxalate in rodent and pig models of hyperoxaluria and kidney damage. The pharmacology program for reloxaliase includes five studies in rodent models of primary and enteric hyperoxaluria (e.g. Roux-en-Y gastric bypass, or RYGB bariatric surgery) and four in pig dietary models of severe and enteric hyperoxaluria, designed to mimic these disorders in humans. Results of these preclinical studies demonstrated that reloxaliase was well tolerated and reduced or normalized UOx excretion in a dose-dependent manner in all forms of hyperoxaluria.

The initial pharmacology studies were completed in rodent models of primary hyperoxaluria (e.g. genetic model) and enteric hyperoxaluria (e.g. genetic and surgical models). In the primary hyperoxaluria mouse model, oxalate decarboxylase, the active enzyme in reloxaliase, was shown to be capable of acting on endogenously produced oxalate and to reduce urinary oxalate levels in a dose-dependent manner, preventing nephrocalcinosis, maintaining creatinine clearance (an important measure of kidney function) and increasing survival. In the RYGB rat model, oxalate decarboxylase reduced urine oxalate in a dose dependent manner and normalized UOx excretion.

Based on the results from testing oxalate decarboxylase in the rodent models, we and our scientific collaborators developed a pig model of hyperoxaluria to further assess the therapeutic and tolerability effects of different doses and formulations of reloxaliase, all in an effort to inform and de-risk our clinical development program in patients with hyperoxaluria. These studies were conducted in pig models of hyperoxaluria since, at the functional level, humans and pigs share many similarities with regard to kidneys, the urinary tract and the GI tract. The pig studies demonstrated that reloxaliase, administered orally with meals, reduced UOx excretion by degrading oxalate in the GI tract. Treatment was well tolerated, and resulted in mean reduction in UOx of between 12-30% relative to the control group. We observed the reduction in UOx excretion to be correlated with the severity of hyperoxaluria and treatment dose. More specifically, in a pig model where severe hyperoxaluria and hyperoxalemia were induced with an infusion of potassium oxalate salt, reloxaliase reduced hyperoxalemia and prevented further impairment of kidney function. Finally, in a pig model where chronic dietary hyperoxaluria was induced by a human-like high oxalate diet, resulting in an above-normal increase in plasma oxalate levels, we observed that therapy with reloxaliase normalized both plasma and urinary oxalate levels as illustrated in the figure below.



Taken together, these studies support the potential efficacy and mechanistic rationale of reloxaliase as a novel and thus far well-tolerated treatment for reducing hyperoxaluria, hyperoxalemia, and progressive nephrocalcinosis and CKD in patients with either primary or secondary hyperoxaluria. They provide *in vivo* mechanistic confirmation that supports our proposed pivotal Phase 3 clinical program in adults with enteric hyperoxaluria and our Phase 2 clinical trial in adolescents and adults with primary hyperoxaluria or enteric hyperoxaluria who also have hyperoxalemia, both of which can lead to systemic oxalosis. In addition, these preclinical studies were submitted as scientific evidence to demonstrate the proof of concept for reloxaliase as a treatment for primary hyperoxaluria, which led to the orphan drug designations for reloxaliase for the treatment of primary hyperoxaluria by the FDA and the European Commission.

Toxicology Studies

To support our clinical development program of reloxaliase, we conducted a total of six toxicity studies in rats and dogs. These studies demonstrated that reloxaliase was well tolerated in animals. We conducted our first two studies which demonstrated that oral administration of reloxaliase for 14 days was well tolerated in animals at doses up to 200 mg/kg/day (which corresponds to 2,000 units/kg/day). We also performed an additional 2-week repeated dose toxicology study of reloxaliase in rats at doses up to 4,860 units/kg/day, approximately 13 times the dose used in our Phase 1 clinical trial of reloxaliase, for a 60 kg subject.

To support clinical trials of longer duration, we conducted two 28-day repeat-dose toxicology studies in rats and dogs. These studies demonstrated that twice-daily oral administration of reloxaliase was well tolerated for 28 consecutive days at 520 mg/kg/day. The NOAEL, or no-observed-adverse-effect-level, or highest concentration of drug which caused no detectable adverse effect, was 7,000 units/kg/day in both species. This concentration was approximately 18 times the highest dose used in Study 713, our 28-day Phase 2 clinical trial, for a 60 kg subject.

We have also completed a six month chronic toxicology study of reloxaliase in rats. It demonstrated that twice-daily oral administration of reloxaliase was well tolerated for 26 consecutive weeks at 520 mg/kg/day (6,618 units/kg/day) with the NOAEL approximately 11 times greater for a 60 kg subject than we expect to use in our pivotal Phase 3 clinical program. In each study, the NOAEL was the highest dose evaluated in that particular study.

Based on the results from these studies, which demonstrated, among other things, that reloxaliase is not systemically absorbed, and feedback from the FDA, we believe the preclinical program for reloxaliase is substantially complete, and no carcinogenicity, genotoxicity, or reproductive toxicity studies are planned.

In connection with our preparations for our pivotal Phase 3 clinical program, we considered the best mechanism to study the potential for drug-drug interactions in patients treated with reloxaliase and also the potential effects of formate generation resulting from reloxaliase's degradation of oxalate. Based on feedback from the FDA, we [conducted] an *in vitro* assessment to evaluate the potential for systemic drug interactions. Based on extensive scientific evidence, we believe that the level of formate generation derived from reloxaliase and oxalate is below limits generally regarded as safe. We plan to test this in humans in Study 206, as these patients have an established heavy systemic burden on oxalate and would be expected to generate formate based on reloxaliase's mechanism of action. The nature of additional studies, if any, will be determined by the results of these initial investigations.

Summary of Phase 2 Clinical Program for Reloxaliase in Primary and Severe Hyperoxaluria

Our preclinical pharmacology studies in models of primary hyperoxaluria have demonstrated that reloxaliase significantly reduced oxalate levels in the urine and plasma. The FDA has granted separate orphan drug designations for reloxaliase for the treatment of primary hyperoxaluria and for the treatment of pediatric hyperoxaluria. In addition, the European Commission has granted orphan designation for reloxaliase for the treatment of primary hyperoxaluria. In light of these designations, we initiated an open-label Phase 2 clinical trial (Study 206) in March 2018 in adolescents and adults with primary hyperoxaluria or enteric hyperoxaluria, who also have elevated levels of oxalate in the blood, or hyperoxalemia, which can lead to systemic oxalosis, a potentially fatal disorder associated with deposition of oxalate in tissues. We expect to announce initial data from Study 206 in the second quarter of 2019 and topline data in the second half of 2019.

Systemic oxalosis refers to the presence of excess oxalate throughout the body, including the bones, joints, eyes and heart, which occurs when the kidney fails to excrete oxalate from the body, leading to elevated oxalate levels in the blood and deposition in the tissues. Our Phase 2 clinical trial utilizes an open-label basket trial design with a 12-week treatment period and will enroll subsets of patients suffering from complications of severe hyperoxaluria, including adults and adolescents with primary hyperoxaluria or enteric hyperoxaluria who also have hyperoxalemia. More specifically, we plan to enroll subjects $\geq$12 years of age with primary or enteric hyperoxaluria, approximately 50% each, screened for baseline UOx excretion greater than 40 mg/24 hr and plasma oxalate levels greater than 5 µmol/L. Since these patients typically have varying degrees of renal impairment, such as CKD, dialysis subjects will be allowed, but limited to approximately 25% of total enrollment as extensive tissue oxalate deposition may obscure a potential signal of lowering plasma oxalate levels. The endpoints for this study include change from baseline in plasma oxalate and 24-hour UOx excretion. A peer-reviewed study published in the *New England Journal of Medicine* in 1994 demonstrated that treatment with orthophosphate and Vitamin B6 in a subset of patients with primary hyperoxaluria reduced UOx excretion by approximately 10% annually over 10 years, which showed preservation of renal function in these patients. In light of this data, we believe that the ability of reloxaliase to degrade oxalate in the GI tract to prevent systemic oxalate absorption and therefore decrease the renal oxalate burden is well suited for testing in these patient populations. If reloxaliase can reduce urine and plasma oxalate levels in these patients, it may be able to diminish the amount of systemic oxalate available for calcium oxalate crystal formation and deposition in the kidney and other organs or tissues.

Other Potential Indications for Reloxaliase-Idiopathic Hyperoxaluria

We believe the mechanism of action of reloxaliase, which is designed to degrade oxalate in the GI tract, is particularly well-targeted to treat enteric hyperoxaluria where excess oxalate absorption is driven by an underlying GI disorder. While hyperabsorption of oxalate is typically a characteristic of enteric hyperoxaluria, we believe there is a subgroup of patients with idiopathic hyperoxaluria that hyperabsorbs oxalate from their diets at levels similar to those patients with enteric hyperoxaluria. We confirmed these pathophysiological traits in both enteric and idiopathic patients in a prospective controlled clinical trial designed to identify patients who hyperabsorb oxalate (Study 204) in 22 patients with secondary hyperoxaluria, with no study drug administration. Although subjects with enteric hyperoxaluria had greater average oxalate absorption than the subjects with idiopathic hyperoxaluria, approximately 40% of the subjects with idiopathic hyperoxaluria approached absorption levels observed in subjects with enteric disorders. Consequently, although we are initially targeting reloxaliase for patients with enteric hyperoxaluria, we believe the product candidate holds promise in treating the subset of patients with idiopathic hyperoxaluria who hyperabsorb oxalate.

ALLN-346

Overview of Hyperuricemia & Gout

Hyperuricemia, or elevated levels of uric acid in the blood, results from overproduction or insufficient excretion of urate, or often a combination of the two. Humans lack urate oxidase, an enzyme that degrades uric acid in a wide range of other

organisms, including animals, plants, bacteria and fungi. Hyperuricemia can be a predisposing condition for gout and kidney stones, and is also intricately linked with various metabolic disorders, including hypertension, CKD, glucose intolerance, dyslipidemia, insulin resistance and obesity. Hyperuricemia may also be an independent risk factor for cardiovascular disease.

Gout is a kind of arthritis caused by excess uric acid in the blood. When uric acid levels in the blood are too high, hard crystals may form in the joints, causing attacks of sudden burning pain, stiffness, and swelling. These attacks can happen over and over unless gout is treated. Over time, they can harm joints, tendons, and other tissues.

Current Therapeutic Options and Their Limitations

We engaged a healthcare strategy consulting firm who estimated the gout market for urate lowering therapies to be approximately $1 billion in the U.S. and concluded that it was incompletely served by existing therapies. Several of the current drugs approved for gout raise concerns over lack of efficacy or increased toxicity in patients with reduced kidney function. There are approximately 850,000 hyperuricemia patients with moderate to severe CKD on urate lowering therapy of which approximately 375,000 have uncontrolled gout. Hyperuricemic and gout patients with renal impairment are more challenging to manage due to limitations of existing therapies. These limitations include poor tolerability, reduced efficacy, dose restriction and contraindications. Co-morbidities (e.g. cardiovascular disease) are common in this patient population and may also limit urate lowering therapeutic options. Accordingly, there is a significant unmet need for a safe and effective therapy that can be used in patients with renal impairment.

Our Solution

We have designed our second product candidate, ALLN-346, an orally administered, novel, urate degrading enzyme, for patients with hyperuricemia and gout in the setting of CKD. Hyperuricemia, or elevated levels of uric acid in the blood, results from overproduction or insufficient excretion of urate, or often a combination of the two. Humans lack urate oxidase, an enzyme that degrades uric acid in a wide range of other organisms, including animals, plants, bacteria and fungi. Hyperuricemia is associated with gout, a kind of arthritis caused by excess uric acid in the blood that leads to the formation of hard crystals in the joints. Hyperuricemia can also lead to increased uric acid excretion in the urine and subsequently to kidney stone formation and kidney damage, also known as urate nephropathy. In addition, hyperuricemia has been linked to hypertension, CKD, glucose intolerance, dyslipidemia, insulin resistance and obesity.

We engineered ALLN-346 to degrade urate in the GI tract and, in turn, reduce the urate burden on the kidney and lower the risk of urate-related complications. ALLN-346 is targeted to lower serum uric acid in patients with CKD, who have decreased renal function and diminished capacity for urinary excretion of uric acid. Patients with renal impairment who have hyperuricemia and gout are often not optimally managed due to limitations of available therapies, including decreased tolerability, dose restrictions, drug-drug interactions and contraindications. An estimated 375,000 patients in the United States have refractory gout and CKD. We presented data from an animal proof-of-concept study at the American College of Rheumatology meeting in October 2018. The poster presentation from this meeting includes data demonstrating urate reduction in a urate oxidase knock-out mouse model, an animal model of severe hyperuricemia with kidney damage due to urate crystal deposition. After one week of treatment, mice treated with ALLN-346 achieved a substantial reduction in urate burden on the kidney, as evidence by normalization in urine uric acid, and a significant reduction in plasma urate.

Our Proprietary Technological Approach

Expertise in Enzyme Technology

We believe our proprietary know-how in enzyme technology allows for the design, development, formulation, and scalable manufacturing of non-absorbed and stable enzymes delivered orally and in sufficient doses for activity in the GI tract. This approach enables us to develop enzyme therapies that degrade metabolites within the GI tract, which reduces potentially toxic metabolite levels in the blood and urine, and in turn, diminishes the disease burden on the kidney over time. The general therapeutic approach of deploying a non-absorbed drug into the GI tract to reduce metabolic disease burden in patients with kidney disease has been proven successful in several therapeutic categories. Utilizing our proprietary technological approach, we conceived and are developing our first two product candidates, reloxaliase and ALLN-346, which are novel, oral enzyme therapeutics for the treatment of hyperoxaluria and hyperuricemia. Our proprietary and scalable manufacturing capabilities have enabled us to produce large quantities of reloxaliase sufficiently to support our clinical and commercial strategy, with costs anticipated to be comparable to small molecule therapeutics.

One of the technologies that we use in our lead product candidate, reloxaliase, is protein crystallization, which stabilizes a highly active form of the oxalate degrading enzyme, oxalate decarboxylase, ensuring effective transit through the GI tract, as well as stabilization at room temperature for convenient storage. Crystallized enzymes are more stable, pure and concentrated than enzymes in solution. For example, one enzyme crystal may contain several billion molecules of the underlying enzyme.

These characteristics improve storage and delivery, permitting delivery of the enzyme molecules with fewer capsules. Once an enzyme is in the crystallized state, we can formulate it for oral delivery. Within the GI tract, the crystalized enzyme is stable and protected from proteolytic degradation, yet sufficiently porous for metabolites to pass through and be degraded by the enzyme. The general therapeutic approach of deploying a non-absorbed drug into the GI tract to reduce metabolic disease burden in patients with kidney disease has been proven successful in several therapeutic categories. For example, Renagel and Renvela, marketed by Sanofi, remove excess levels of phosphate in the body in patients with CKD by delivering drug to the GI tract, where it binds to phosphate and removes it from the body through the bowel.

Our knowledge base from reloxaliase provides us with a useful template for our other research and preclinical programs that rely on the same fundamental science and therapeutic strategy. We anticipate that our second product candidate, ALLN-346, a first-in-class uricase enzyme, will utilize several proprietary technologies to ensure its stabilization in the GI tract as well as other attractive manufacturing, clinical and commercial attributes similar to reloxaliase.

Manufacturing

Reloxaliase is an oral, solid dosage form of crystalline recombinant oxalate decarboxylase enzyme that is produced using a combination of traditional and novel manufacturing processes. The methods of production for reloxaliase have been carefully selected for cost-effectiveness and ease of scaling. We believe our manufacturing technology enables us to produce large quantities of our oral enzyme product candidates, sufficiently to support our clinical and commercial strategy, with costs anticipated to be comparable to small molecule therapeutics. Working in collaboration with top-tier development and manufacturing companies, we have completed several successive scale-ups to the manufacturing process in support of increasing clinical trial demand and in planning for commercialization.

Manufacturing biologic drugs is generally a complex and cost intensive process because they are manufactured in living systems or cells and tend to be large complex molecules. Since the living systems used to produce biologics can be sensitive to minor changes in manufacturing techniques, small process differences can significantly affect the nature of the finished biologic and, most importantly, the way it functions in the body.

Production of reloxaliase occurs utilizing scientifically developed know-how, delivering high productivity from host bacterial cells. The entire biomass is harvested and processed through primary recovery and downstream purification unit operations, resulting in the recovery of large quantities of oxalate decarboxylase. The purified and concentrated product is crystallized, dried into a protein powder and formulated for production as an oral capsule. The oral capsule presentation has attractive properties of pharmaceutical activity and stability suitable for further development and ultimate commercial use. Over the course of our development of reloxaliase, we have been able to increase enzyme yield and activity through improvements to our manufacturing processes, thereby reducing the pill burden of our therapeutic candidate. As a result, the dosing regimen for our pivotal Phase 3 program will be two capsules per dosing compared to five capsules per dosing in our Phase 2 clinical program.

Drug product production starts with dried oxalate decarboxylase crystals, then uses tailored pharmaceutical techniques to blend, densify and encapsulate the product candidate, which is an oral, solid-dose formulation of the crystallized enzyme. We have secured development and supply agreements with premiere global drug product contract manufacturing organizations suited to meet the needs of commercialization for reloxaliase. Finally, we forecast cost of goods sold for reloxaliase to be comparable to traditional oral small molecules over the course of its commercialization life cycle.

Commercialization Strategy

We hold worldwide commercialization and development rights to all of our first-in-class, oral, non-absorbed enzyme therapeutic product candidates. The FDA has granted separate orphan drug designations for our lead product candidate, reloxaliase, for the treatment of primary hyperoxaluria and for the treatment pediatric hyperoxaluria (primary and secondary hyperoxaluria). In addition, the European Commission has granted orphan designation for reloxaliase for the treatment of primary hyperoxaluria.

Reloxaliase, if approved, has the potential to be the first therapeutic option for patients with severe hyperoxaluria. We intend to independently pursue regulatory approval of reloxaliase in patients with enteric hyperoxaluria in the United States and, if approved, to commercialize the product by building a focused commercial organization in the United States specifically to target nephrologists and urologists who treat patients with hyperoxaluria, particularly at kidney stone clinics. In addition, we plan to build a marketing organization that will conceive and implement marketing strategies for any product that we directly commercialize. The responsibilities of the marketing organization would include developing commercialization initiatives for each approved product and establishing and maintaining relationships with researchers, practitioners and key opinion leaders for rare and severe metabolic and kidney disorders.

Outside of the United States, we intend to explore collaborations to commercialize our product candidates, including reloxaliase. Depending on our evaluation of these market opportunities and the strategic merits of these collaboration opportunities, we may decide to retain commercial rights in key markets.

Competition

Our industry is highly competitive and subject to rapid and significant technological change as researchers learn more about diseases and develop new technologies and treatments. Our potential competitors include primarily large pharmaceutical, biotechnology companies and specialty pharmaceutical companies. Key competitive factors affecting the commercial success of reloxaliase, ALLN-346 and any other product candidates we may develop are likely to be efficacy, safety and tolerability profile, reliability, convenience of administration, price and reimbursement.

There is no approved pharmacologic therapy for the reduction of urinary oxalate excretion in patients with hyperoxaluria, either primary or secondary. Existing treatment options for hyperoxaluria generally are non-specific and include high fluid intake to increase urine output to more than two to three liters per day, a diet low in salt and oxalate, oral citrate and/or calcium and/or magnesium supplementation and orthophosphate and Vitamin B6, exclusively for the specific subset of responsive patients with the most severe form of primary hyperoxaluria (PH1).

We are aware of other companies pursuing oxalate reduction in both primary and secondary hyperoxaluria. For example, Alnylam is conducting an ongoing pivotal Phase 3 study under the Accelerated Approval pathway for the treatment of patients with primary hyperoxaluria Type 1. Dicerna is conducting ongoing clinical development for the treatment of primary hyperoxaluria Types 1-3. Oxthera AB (Sweden) and Captozyme (U.S.) are developing orally delivered products to degrade oxalate in the stomach and GI tract. Oxthera is conducting Phase 3 clinical trials for Oxabact, *Oxalobacter formigenes*, indicated for the treatment of primary hyperoxaluria.

Intellectual Property

We strive to protect the proprietary technologies that we believe are important to our business, including seeking and maintaining patents intended to cover the composition of matter of our product candidates, their methods of use and processes for their manufacture, and any other aspects of inventions that are commercially important to the development of our business. We also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. `

We plan to continue to expand our intellectual property estate by filing patent applications directed to compositions, methods of treatment, dosage forms, and dosage regimens that we identify during the course of our business. Our success will depend on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, defend and enforce our patents, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and proprietary rights of third parties. We also rely on know-how, continuing technological innovation and in-licensing opportunities to develop and maintain our proprietary position.

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and patent scope can be reinterpreted by the courts after issuance. Moreover, many jurisdictions permit third parties to challenge issued patents in administrative proceedings, which may result in further narrowing or even cancellation of patent claims. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any or our issued patents will provide sufficient protection from competitors. Any of our patents may be challenged, circumvented, or invalidated by third parties.

Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months or potentially even longer, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of the priority of inventions covered by pending patent applications. Moreover, we may have to participate in interference proceedings or derivation proceedings declared by the U.S. Patent and Trademark Office, or the USPTO, to determine priority of invention.

Patents

As of March 1, 2019, we own or have rights in 5 issued U.S. patents, 18 issued foreign patents, 6 pending U.S. patent applications, and 6 pending foreign patent applications.

With regard to reloxaliase, we have exclusively licensed from Althea Technologies, Inc. (now known as Ajinomoto Althea, Inc.), or Althea, one issued U.S. patent with method of use claims directed to the reduction of oxalate in a mammal by orally administering a composition containing uncrosslinked oxalate decarboxylase crystals, which is scheduled to expire in 2027, without taking a potential patent term extension into account. This U.S. patent belongs to a family of patents that includes a granted Canadian patent and a granted European patent, which has been validated in a number of countries including Denmark, France, Germany, Ireland, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, and the UK; and a patent application pending in China. This patent family also includes a U.S. patent with method of use claims directed to a method of reducing oxalate with oxalate decarboxylase crystals in an extracorporeal device, which is scheduled to expire in 2027, without taking a potential patent term extension into account.

In addition, we own two U.S. patents One with composition of matter claims directed to a pharmaceutical composition comprising biologically active uncrosslinked oxalate decarboxylase crystals, which is scheduled to expire in 2027, without taking a patent term extension into account; and another with composition of matter claims directed to a capsule containing crystals of spray-dried oxalate decarboxylase and method of use claims directed to a method of reducing oxalate in a mammal suffering from a disorder, *e.g.*, primary hyperoxaluria and enteric hyperoxaluria, using such a capsule, which is scheduled to expire in 2034, without taking a potential patent term extension into account.

Another family of patent applications that we own are pending in the U.S., Canada, Europe, Israel and Japan with composition of matter claims directed to a composition comprising a peritoneal dialysis solution and uncrosslinked crystals of oxalate decarboxylase for use in reducing oxalate during a dialysis-based treatment, which, if granted, would be scheduled to expire in 2034, without taking a patent term extension into account.

With regard to ALLN-346, we own a U.S. provisional patent application with composition of matter claims directed to novel recombinant uricase enzymes and method of use claims directed to treating certain diseases associated with elevated levels of uric acid with such enzymes. A U.S. patent claiming the benefit of the provisional application, if issued, would be expected to expire in 2038, without taking a patent term extension into account.

In the United States, the term of a patent covering an FDA-approved drug may be eligible for a patent term extension under the Hatch-Waxman Act as compensation for the loss of patent term during the FDA regulatory review process. The period of extension may be up to five years beyond the expiration of the patent, but cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval. Only one patent among those eligible for an extension may be extended. Similar provisions are available in Europe and in certain other jurisdictions to extend the term of a patent that covers an approved drug. For example, it is possible that an issued U.S. patent covering reloxaliase or its use may be entitled to a patent term extension. If reloxaliase receives FDA approval, we intend to apply for a patent term extension, if available, to extend the term of a patent that covers the approved product. We also intend to seek patent term extensions in any jurisdictions where they are available, however, there is no guarantee that the applicable authorities, including the FDA, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions.

In addition to patent protection, we also rely on trade secret protection for our proprietary information that is not amenable to, or that we do not consider appropriate for, patent protection, including, for example, certain aspects of our manufacturing procedures. However, trade secrets can be difficult to protect. Although we take steps to protect our proprietary information, including restricting access to our premises and our confidential information, as well as entering into agreements with our employees, consultants, advisors and potential collaborators, third parties may independently develop the same or similar proprietary information or may otherwise gain access to our proprietary information. As a result, we may be unable to meaningfully protect our trade secrets and proprietary information.

Althea License Agreement

In March 2012, we entered into a license agreement with Althea, as amended in March 2016, pursuant to which Althea granted us an exclusive, worldwide, royalty-bearing, sublicensable license under specified intellectual property rights relating to, among other things, oxalate decarboxylase and ALTU-237, now called reloxaliase, to develop, use, make, have made, market, offer to sell, sell, have sold, distribute, import or otherwise exploit licensed products. Althea expressly retains all rights under the licensed patents that are not granted to us under the agreement, which we refer to as Althea's retained rights. We have the right to sublicense our licensed rights, provided that each sublicense agreement must be in writing and consistent with the terms of the license agreement. We are obligated to use commercially reasonable efforts to develop and commercialize the licensed products for the treatment of hyperoxaluria.

Under the license agreement, we reimbursed Althea for patent-related fees and costs totaling $0.1 million in the aggregate and have issued to Althea a total of 88,186 shares of our common stock. Althea is entitled to receive regulatory

milestone payments totaling up to $31.0 million in the aggregate. We are also obligated to make additional payments to Althea of up to an aggregate of $25.0 million based upon the occurrence of certain sales milestones. Althea is entitled to receive mid-single-digit percentage royalties on net sales of licensed products, made by us, our affiliates, or our sublicensees, subject to certain reductions for any royalty payments required to be made by us to acquire patent rights, however, such royalty payments cannot be reduced below an aggregate minimum floor. The milestone payments are not creditable against royalties. The royalty term will expire on a licensed product-by-licensed product and country-by-country basis upon the later of the expiration of the last-to-expire valid patent claim that covers the composition, manufacture, or use of such licensed product in such country, or the tenth anniversary of the date of the first commercial sale of such licensed product in such country.

We have the first right, but not the obligation, to prosecute, defend, maintain and enforce certain product-specific patent rights licensed under the agreement, and Althea has the exclusive right to prosecute, defend, maintain and enforce all other licensed patent rights. If we are controlling any lawsuits regarding the licensed patents, we cannot enter into a settlement without the prior written consent of Althea. Any sums recovered in such lawsuits will be shared between us and Althea. Unless terminated earlier, the term of the license agreement will expire on date of the last-to-expire royalty term. We have the right to terminate the agreement for convenience upon 60 days prior written notice to Althea. Either party may terminate the agreement after a 60-day notice period in the event of an uncured material breach by the other party. If we terminate the agreement for convenience or if Althea terminates the agreement for cause, we grant Althea a right of first negotiation, exercisable for the 30-day period after such termination, to obtain an exclusive license to certain patent rights and data controlled by us that are related to the licensed products and to have all investigational new drug applications, or INDs (other than the IND for reloxaliase), transferred to Althea.

In addition, pursuant to a letter agreement we entered into with Althea in June 2017, and subject to a fully paid-up exclusive worldwide license that we grant to Althea with respect to Althea's retained rights, Althea assigned certain U.S. patent rights to us. We agreed to continue to comply with our obligations under the license agreement, including our obligation to make milestone and royalty payments to Althea. Upon any termination or expiration of the license agreement, we are obligated to assign such patent rights back to Althea.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products, including biological products. In addition, some jurisdictions regulate the pricing of pharmaceutical products. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Licensure and Regulation of Biologics in the United States

In the United States, our candidate products are regulated as biological products, or biologics, under the Public Health Service Act, or PHSA, and the Federal Food, Drug, and Cosmetic Act, or FDCA, and their implementing regulations. The failure to comply with the applicable U.S. requirements at any time during the product development process, including nonclinical testing, clinical testing, the approval process or post-approval process, may subject an applicant to delays in the conduct of a study, regulatory review and approval, and/or administrative or judicial sanctions. These sanctions may include, but are not limited to, the U.S. Food and Drug Administration's, or FDA's, refusal to allow an applicant to proceed with clinical testing, refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, warning or untitled letters, adverse publicity, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, and civil or criminal investigations and penalties brought by the FDA or the Department of Justice, or DOJ, or other governmental entities.

An applicant seeking approval to market and distribute a new biologic in the United States generally must satisfactorily complete each of the following steps:

- nonclinical laboratory tests, animal studies and formulation studies all performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- submission to the FDA of an IND for human clinical testing, which must become effective before human clinical trials may begin;

- approval by an institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials to establish the safety, potency, and purity of the product candidate for each proposed indication, in accordance with Good Clinical Practices, or GCP;
- preparation and submission to the FDA of a Biologic License Application, or BLA, for a biologic product requesting marketing for one or more proposed indications, including submission of detailed information on the manufacture and composition of the product in clinical development and proposed labeling;
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities, including those of third parties, at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements and to assure that the facilities, methods, and controls are adequate to preserve the product's identity, strength, quality, and purity;
- satisfactory completion of any FDA audits of the nonclinical and clinical study sites to assure compliance with GLPs and GCPs, respectively, and the integrity of clinical data in support of the BLA;
- payment of user fees and securing FDA approval of the BLA and licensure of the new biologic product; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and any post-approval studies required by the FDA.

Nonclinical Studies and Investigational New Drug Application

Before testing any biologic product candidate in humans, the product candidate must undergo nonclinical testing. Nonclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as animal studies to evaluate the potential for efficacy and toxicity. The conduct of the nonclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements. The results of the nonclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND. The IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions about the product or conduct of the proposed clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns before the clinical trial can begin.

As a result, submission of the IND may result in the FDA not allowing the trial to commence or allowing the trial to commence on the terms originally specified by the sponsor in the IND. If the FDA raises concerns or questions either during this initial 30-day period, or at any time during the IND process, it may choose to impose a partial or complete clinical hold. A complete clinical hold issued by the FDA would delay either a proposed clinical study or cause suspension of an ongoing study, until all outstanding concerns have been adequately addressed and the FDA has notified the company that investigation may proceed. This could cause significant delays or difficulties in completing planned clinical trials in a timely manner. A partial clinical hold places restrictions on a clinical trial, such as limiting the doses administered or the duration of the trial. The FDA may impose clinical holds on a biologic product candidate at any time before or during clinical trials due to safety concerns or non-compliance. If the FDA imposes a clinical hold, trials may not recommence without FDA authorization and then only under terms authorized by the FDA.

Human Clinical Trials in Support of a BLA

Clinical trials involve the administration of the investigational product candidate to healthy volunteers or patients with the disease to be treated under the supervision of a qualified principal investigator in accordance with GCP requirements. Clinical trials are conducted under study protocols detailing, among other things, the objectives of the study, inclusion and exclusion criteria, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a foreign clinical trial is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of the BLA so long as the clinical trial is well-designed and well-conducted in

accordance with GCP, including review and approval by an independent ethics committee, and the FDA is able to validate the study data through an onsite inspection, if necessary.

Further, each clinical trial must be reviewed and approved by an institutional review board, or IRB, either centrally or individually at each institution at which the clinical trial will be conducted. The IRB will consider, among other things, clinical trial design, patient informed consent, ethical factors, and the safety of human subjects. An IRB must operate in compliance with FDA regulations. The FDA, IRB, or the clinical trial sponsor may suspend or discontinue a clinical trial at any time for various reasons, including a finding that the clinical trial is not being conducted in accordance with FDA requirements or the subjects or patients are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive GCP rules and the requirements for informed consent. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group may recommend continuation of the study as planned, changes in study conduct, or cessation of the study at designated check points based on access to certain data from the study. Information about certain clinical studies must be submitted within specific timeframes to the National Institutes of Health for public dissemination at www.clinicaltrials.gov.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined. Additional studies may be required after approval.

- *Phase 1* clinical trials are initially conducted in a limited population to test the product candidate for safety, including adverse effects, dose tolerance, absorption, metabolism, distribution, excretion, and pharmacodynamics in healthy humans or, on occasion, in patients, such as cancer patients.

- *Phase 2* clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly Phase 3 clinical trials.

- *Phase 3* clinical trials proceed if the Phase 2 clinical trials demonstrate that a dose range of the product candidate is potentially effective and has an acceptable safety profile. Phase 3 clinical trials are undertaken within an expanded patient population to further evaluate dosage, provide substantial evidence of clinical efficacy, and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial sites. A well-controlled, statistically robust Phase 3 trial may be designed to deliver the data that regulatory authorities will use to decide whether or not to approve, and, if approved, how to appropriately label a biologic; such Phase 3 studies are referred to as “pivotal.”

In some cases, the FDA may approve a BLA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate’s safety and effectiveness after approval. Such post-approval trials are typically referred to as Phase 4 clinical trials. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication and to document a clinical benefit in the case of biologics 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 or to request a change in the product labeling. Failure to exhibit due diligence with regard to conducting Phase 4 clinical trials could result in withdrawal of approval for products.

Compliance with cGMP Requirements

Before approving a BLA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in full compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. The PHSA emphasizes the importance of manufacturing control for products like biologics whose attributes cannot be precisely defined.

Manufacturers and others involved in the manufacture and distribution of products must also register their establishments with the FDA and certain state agencies. Both domestic and foreign manufacturing establishments must register and provide additional information to the FDA upon their initial participation in the manufacturing process. Any product manufactured by or imported from a facility that has not registered, whether foreign or domestic, is deemed misbranded under the FDCA. Establishments may be subject to periodic unannounced inspections by government authorities to ensure compliance with cGMPs and other laws. Manufacturers may have to provide, on request, electronic or physical records regarding their establishments. Delaying, denying, limiting, or refusing inspection by the FDA may lead to a product being deemed to be adulterated.

Review and Approval of a BLA

The results of product candidate development, nonclinical testing, and clinical trials, including negative or ambiguous results as well as positive findings, are submitted to the FDA as part of a BLA requesting license to market the product. The BLA must contain extensive manufacturing information and detailed information on the composition of the product and proposed labeling as well as payment of a user fee.

The FDA has 60 days after submission of the application to conduct an initial review to determine whether it is sufficient to accept for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. Once the submission has been accepted for filing, the FDA begins an in-depth review of the application. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act, or the PDUFA, the FDA has ten months in which to complete its initial review of a standard application and respond to the applicant, and six months for a priority review of the application. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs. The review process may often be significantly extended by FDA requests for additional information or clarification. The review process and the PDUFA goal date may be extended by three months if the FDA requests or if the applicant otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Under the PHSA, the FDA may approve a BLA if it determines that the product is safe, pure, and potent and the facility where the product will be manufactured meets standards designed to ensure that it continues to be safe, pure, and potent.

On the basis of the FDA's evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities and any FDA audits of nonclinical and clinical study sites to assure compliance with GLPs and GCPs, respectively, the FDA may issue an approval letter, denial letter, or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. If the application is not approved, the FDA may issue a complete response letter, which will contain the conditions that must be met in order to secure final approval of the application, and when possible will outline recommended actions the sponsor might take to obtain approval of the application. Sponsors that receive a complete response letter may submit to the FDA information that represents a complete response to the issues identified by the FDA. Such resubmissions are classified under PDUFA as either Class 1 or Class 2. The classification of a resubmission is based on the information submitted by an applicant in response to an action letter. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has two months to review a Class 1 resubmission and six months to review a Class 2 resubmission. The FDA will not approve an application until issues identified in the complete response letter have been addressed. If an applicant does not resubmit the BLA in response to a complete response letter, the applicant may withdraw the original application or request an opportunity for a hearing. The FDA issues a denial letter if it determines that the establishment or product does not meet the agency's requirements.

The FDA may also refer the application to an advisory committee for review, evaluation, and recommendation as to whether the application should be approved. In particular, the FDA may refer applications for novel biologic products or biologic products that present difficult questions of safety or efficacy to an advisory committee. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates, and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

If the FDA approves a new product, it may limit the approved indications for use of the product. It may also require that contraindications, warnings or precautions be included in the product labeling. In addition, the FDA may call for post-approval studies, including Phase 4 clinical trials, to further assess the product's safety after approval. The agency may also require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, to help ensure that the benefits of the product outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patent registries. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Fast Track, Breakthrough Therapy and Priority Review Designations

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are referred to as fast track designation, breakthrough therapy designation, and priority review designation.

Specifically, the FDA may designate a product for fast track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For fast track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a fast track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a fast track application does not begin until the last section of the application is submitted. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, a product may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case- by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a product, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a product.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or

decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the product from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

The 21st Century Cures Act

The 21st Century Cures Act, which was signed into law in December 2016, requires the FDA to establish a process for the qualification of drug development tools that may be used to support or obtain licensure of a biological product or support of the investigational use of a biological product. A drug development tool includes a biomarker, a clinical outcome assessment, and any other method, material, or measure that the FDA determines aids drug development and regulatory review. A biomarker is a characteristic, such as a physiologic, pathologic, or anatomic characteristic or measurement, that is objectively measured and evaluated as an indicator of normal biological processes, pathologic processes, or biological responses to a therapeutic intervention and includes a surrogate endpoint. A clinical outcome assessment is a measurement of a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions and includes a patient-reported outcome.

The 21st Century Cures Act also requires that, for approval of any BLAs submitted after June 12, 2017, the FDA shall make public a brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of the application. Patient experience data includes data that are collected by any persons, including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers and drug manufacturers, and are intended to provide information about patients' experiences with a disease or condition, including the impact of such disease or condition, or a related therapy, on patients' lives and patient preferences with respect to treatment of such disease or condition.

Post-Approval Regulation

If regulatory approval for marketing of a product or new indication for an existing product is obtained, the sponsor will be required to comply with all regular post-approval regulatory requirements as well as any post-approval requirements that the FDA has imposed as part of the approval process. The sponsor will be required to report certain adverse reactions and production problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling requirements. Manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon manufacturers. Accordingly, the sponsor and its third-party manufacturers must continue to expend time, money, and effort in the areas of production and quality control to maintain compliance with cGMP regulations and other regulatory requirements.

A biologic product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official lot release, the manufacturer must submit samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot, to the FDA. The FDA may in addition perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety, purity, potency, and effectiveness of pharmaceutical products.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;

- fines, untitled letters or warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Pharmaceutical products may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

Orphan Drug Designation

Orphan drug designation in the United States is designed to encourage sponsors to develop products intended for rare diseases or conditions. In the United States, a rare disease or condition is statutorily defined as a condition that affects fewer than 200,000 individuals in the United States or that affects more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available the biologic for the disease or condition will be recovered from sales of the product in the United States. The FDA has granted Orphan Drug Designation to reloxaliase for the treatment of primary hyperoxaluria and pediatric hyperoxaluria. This includes both children with secondary hyperoxaluria, attributable to excess GI absorption of oxalate, as well as the rare condition primary hyperoxaluria, a genetic defect of one of several liver enzymes.

Orphan drug designation qualifies a company for tax credits and market exclusivity for seven years following the date of the product's marketing approval if granted by the FDA. An application for designation as an orphan product can be made any time prior to the filing of an application for approval to market the product. A product becomes an orphan when it receives orphan drug designation from the Office of Orphan Products Development, or OOPD, at the FDA based on acceptable confidential requests made under the regulatory provisions. The product must then go through the review and approval process like any other product.

A sponsor may request orphan drug designation of a previously unapproved product or new orphan indication for an already marketed product. In addition, a sponsor of a product that is otherwise the same product as an already approved orphan drug may seek and obtain orphan drug designation for the subsequent product for the same rare disease or condition if it can present a plausible hypothesis that its product may be clinically superior to the first drug. More than one sponsor may receive orphan drug designation for the same product for the same rare disease or condition, but each sponsor seeking orphan drug designation must file a complete request for designation.

The period of exclusivity begins on the date that the marketing application is approved by the FDA and applies only to the indication for which the product has been designated. The FDA may approve a second application for the same product for a different use or a second application for a clinically superior version of the product for the same use. The FDA cannot, however, approve the same product made by another manufacturer for the same indication during the market exclusivity period unless it has the consent of the sponsor or the sponsor is unable to provide sufficient quantities.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, as amended, a BLA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data

requirements. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six month exclusivity may be granted if a BLA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application.

Biosimilars and Exclusivity

The Affordable Care Act, which was signed into law in March 2010, included a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCIA. The BPCIA established a regulatory scheme authorizing the FDA to approve biosimilars and interchangeable biosimilars. To date, seventeen biosimilar products have been approved by the FDA for use in the United States. No interchangeable biosimilars, however, have been approved. The FDA has issued several guidance documents outlining an approach to review and approval of biosimilars.

Under the BPCIA, a manufacturer may submit an application for licensure of a biologic product that is "biosimilar to" or "interchangeable with" a previously approved biological product or "reference product." In order for the FDA to approve a biosimilar product, it must find that there are no clinically meaningful differences between the reference product and proposed biosimilar product in terms of safety, purity, and potency. For the FDA to approve a biosimilar product as interchangeable with a reference product, the agency must find that the biosimilar product can be expected to produce the same clinical results as the reference product, and (for products administered multiple times) that the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date of approval of the reference product. The FDA may not approve a biosimilar product until 12 years from the date on which the reference product was approved. Even if a product is considered to be a reference product eligible for exclusivity, another company could market a competing version of that product if the FDA approves a full BLA for such product containing the sponsor's own nonclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity, and potency of their product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products. At this juncture, it is unclear whether products deemed "interchangeable" by the FDA will, in fact, be readily substituted by pharmacies, which are governed by state pharmacy law.

Patent Term Restoration and Extension

A patent claiming a new biologic product may be eligible for a limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments, which permits a patent restoration of up to five years for patent term lost during product development and FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date of an IND and the submission date of a marketing application, plus the time between the submission date of a marketing application and the ultimate approval date, provided the sponsor acted with diligence. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Regulation and Procedures Governing Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a company also must comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically,

the process governing approval of medicinal products in the European Union, or EU, generally follows the same lines as in the United States. It entails satisfactory completion of nonclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by these authorities before the product can be marketed and sold in the EU.

Clinical Trial Approval

Pursuant to the currently applicable Clinical Trials Directive 2001/20/EC and the Directive 2005/28/EC on GCP, a system for the approval of clinical trials in the EU has been implemented through national legislation of the member states. Under this system, an applicant must obtain approval from the competent national authority of an EU member state in which the clinical trial is to be conducted, or in multiple member states if the clinical trial is to be conducted in a number of member states. Furthermore, the applicant may only start a clinical trial at a specific study site after the independent ethics committee has issued a favorable opinion. The clinical trial application, or CTA, must be accompanied by an investigational medicinal product dossier with supporting information prescribed by Directive 2001/20/EC and Directive 2005/28/EC and corresponding national laws of the member states and further detailed in applicable guidance documents.

In April 2014, the EU adopted a new Clinical Trials Regulation (EU) No 536/2014, which is set to replace the current Clinical Trials Directive 2001/20/EC. It is expected that the new Clinical Trials Regulation (EU) No 536/2014 will apply in 2019 with a three-year transition period. It will overhaul the current system of approvals for clinical trials in the EU. Specifically, the new regulation, which will be directly applicable in all member states, aims at simplifying and streamlining the approval of clinical trials in the EU. For instance, the new Clinical Trials Regulation provides for a streamlined application procedure via a single entry point and strictly defined deadlines for the assessment of clinical trial applications.

Marketing Authorization

To obtain a marketing authorization for a product under the EU regulatory system, an applicant must submit an MAA, either under a centralized procedure administered by the European Medicines Authority, or EMA, or one of the procedures administered by competent authorities in EU Member States (decentralized procedure, national procedure, or mutual recognition procedure). A marketing authorization may be granted only to an applicant established in the EU. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the EU, an applicant must demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, class waiver, or a deferral for one or more of the measures included in the PIP.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all EU member states. Pursuant to Regulation (EC) No. 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the EMA is responsible for conducting an initial assessment of a product. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation may be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and, in particular, from the viewpoint of therapeutic innovation. If the CHMP accepts such a request, the time limit of 210 days will be reduced to 150 days, but it is possible that the CHMP may revert to the standard time limit for the centralized procedure if it determines that it is no longer appropriate to conduct an accelerated assessment.

Regulatory Data Protection in the European Union

In the European Union, new chemical entities approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Regulation (EC) No 726/2004, as amended, and Directive 2001/83/EC, as amended. Data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application for a period of eight years. During the additional two-year period of market exclusivity, a generic marketing authorization application can be submitted, and the innovator's data may be referenced, but no generic medicinal product can be marketed

until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, nonclinical tests and clinical trials.

Periods of Authorization and Renewals

A marketing authorization is valid for five years, in principle, and it may be renewed after five years on the basis of a reevaluation of the risk benefit balance by the EMA or by the competent authority of the authorizing member state. To that end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization is valid for an unlimited period, unless the European Commission or the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal period. Any authorization that is not followed by the placement of the drug on the EU market (in the case of the centralized procedure) or on the market of the authorizing member state within three years after authorization ceases to be valid.

Regulatory Requirements after Marketing Authorization

Following approval, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of the medicinal product. These include compliance with the EU's stringent pharmacovigilance or safety reporting rules, pursuant to which post-authorization studies and additional monitoring obligations can be imposed. In addition, the manufacturing of authorized products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the EMA's GMP requirements and comparable requirements of other regulatory bodies in the EU, which mandate the methods, facilities, and controls used in manufacturing, processing and packing of drugs to assure their safety and identity. Finally, the marketing and promotion of authorized products, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the European Union under Directive 2001/83EC, as amended.

Orphan Drug Designation and Exclusivity

Regulation (EC) No 141/2000 and Regulation (EC) No. 847/2000 provide that a product can be designated as an orphan drug by the European Commission if its sponsor can establish: that the product is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the drug in the EU would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention, or treatment of the condition in question that has been authorized in the EU or, if such method exists, the drug will be of significant benefit to those affected by that condition.

An orphan drug designation provides a number of benefits, including fee reductions, regulatory assistance, and the possibility to apply for a centralized EU marketing authorization. Marketing authorization for an orphan drug leads to a ten-year period of market exclusivity. During this market exclusivity period, neither the EMA nor the European Commission or the member states can accept an application or grant a marketing authorization for a "similar medicinal product." A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. The market exclusivity period for the authorized therapeutic indication may, however, be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan drug designation because, for example, the product is sufficiently profitable not to justify market exclusivity.

Coverage, Pricing, and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we may seek regulatory approval by the FDA or other government authorities. In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use any product candidates we may develop unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of such

product candidates. Even if any product candidates we may develop are approved, sales of such product candidates will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers, and managed care organizations, provide coverage, and establish adequate reimbursement levels for, such product candidates. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover any product candidates we may develop could reduce physician utilization of such product candidates once approved and have a material adverse effect on our sales, results of operations and financial condition. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor. Third-party reimbursement and coverage may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of pharmaceuticals have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement, and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Further, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the Trump administration have each indicated that it will continue to pursue new legislative and/or administrative measures to control drug costs. Individual state legislatures have become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing. Some of these measures include price or patient reimbursement constraints, discounts, restrictions on certain product access, marketing cost disclosure and transparency measures, and, in some cases, measures designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Outside the United States, ensuring adequate coverage and payment for any product candidates we may develop will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of any product candidates we may develop to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost effectiveness of a particular product candidate to currently available therapies (so called health technology assessments, or HTAs) in order to obtain reimbursement or pricing approval. For example, the European Union provides options for its member states to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. E.U. member states may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other member states allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the European Union have increased the amount of discounts required on pharmaceuticals and these efforts

could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the European Union. The downward pressure on health care costs in general, particularly prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic, and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various European Union member states, and parallel trade (arbitrage between low-priced and high-priced member states), can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products, if approved in those countries.

Healthcare Law and Regulation

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of pharmaceutical products that are granted marketing approval. Arrangements with providers, consultants, third-party payors, and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, reporting of payments to physicians and teaching physicians and patient privacy laws and regulations and other healthcare laws and regulations that may constrain our business and/or financial arrangements. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving, or providing remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;

- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things: knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent; making a false statement or record material to a false or fraudulent claim or obligation to pay or transmit money or property to the federal government; or knowingly concealing or knowingly and improperly avoiding or decreasing an obligation to pay money to the federal government. In addition, the government may assert that a claim including items and services resulting from a violation of the federal Anti-Kickback Statute constitutes a false of fraudulent claim for purposes of the False Claims Act;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- the anti-inducement law which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person know or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security, and transmission of individually identifiable health information;

- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, collectively the ACA, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the U.S. Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring pharmaceutical manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Healthcare Reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States.

By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the United States Congress enacted the ACA, which, among other things, includes changes to the coverage and payment for products under government health care programs. Among the provisions of the ACA of importance to our potential product candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic products, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;

- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans;

- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for products that are inhaled, infused, instilled, implanted or injected;

- expanded the types of entities eligible for the 340B drug discount program;

- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale-discount off the negotiated price of applicable products to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient products to be covered under Medicare Part D;

- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and

- established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription product spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation from 2011 to 2019.

Some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, that while not a law, is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the ACA. In May 2017, the House of Representatives passed legislation to repeal and replace parts of the ACA. To date, while Congress has not passed comprehensive repeal legislation, it has enacted laws that modify certain provisions of the ACA such as removing or delaying penalties, starting January 1, 2019, for not complying with the ACA's individual mandate to carry health insurance, delaying the implementation of certain ACA-mandated fees, and increasing the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D. On December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. The Trump administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. It is unclear how this decision and any subsequent appeals and other efforts to repeal and replace the ACA will impact the ACA and our business. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results. We continue to evaluate the effect that the Affordable Care Act and its possible repeal and replacement could have on our business.

In addition, since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2027 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers, and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Additionally, recent healthcare reform legislation has strengthened federal and state healthcare fraud and abuse laws. For example, the ACA amends the intent requirement of the federal Anti-Kickback Statute and criminal healthcare fraud statutes to clarify that liability under these statutes does not require a person or entity to have actual knowledge of the statutes or a specific intent to violate them. Moreover, the ACA provides that the government may assert that a claim that includes items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act. Furthermore, on January 31, 2019, the Department of Health and Human Services (HHS) and HHS Office of Inspector General (OIG) proposed an amendment to one of the existing Anti-Kickback safe harbors (42 C.F.R. 1001.952(h)) which would prohibit certain pharmaceutical manufacturers from offering rebates to pharmacy benefit managers ("PBMs") in the Medicare Part D and Medicaid managed care programs. The proposed amendment would remove protection for "discounts" from Anti-Kickback enforcement action, and would include criminal and civil penalties for knowingly and willfully offering, paying, soliciting, or receiving remuneration to induce or reward the referral of business reimbursable under federal health care programs. At the same time, HHS also proposed to create a new safe harbor to protect point-of-sale discounts that drug manufacturers provide directly to patients, and adds another safe harbor to protect certain administrative fees paid by manufacturers to PBMs. If this proposal is adopted, in whole or in part, it could affect the pricing and reimbursement for any products for which we receive approval in the future. 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.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal, and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. Such reforms could have an adverse effect on anticipated revenues from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop product candidates.

Additional regulation

In addition to the foregoing, state, and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservation and Recovery Act, and the Toxic Substances Control Act, affect our business. These and other laws govern the use, handling, and disposal of various biologic, chemical, and radioactive substances used in, and wastes generated by, operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. Equivalent laws have been adopted in third countries that impose similar obligations.

Employees

As of March 1, 2019, we had 49 full-time employees, including 11 employees with Ph.D. or M.D. degrees. 40 of our employees are engaged in research and development activities and 9 are engaged in general and administrative activities. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Facilities

We occupy approximately 7,795 square feet of office space in Newton, MA under a lease that expires in December of 2020. In addition, we occupy approximately 7,564 square feet of office and laboratory space in Sudbury, MA under a lease that expires in February 2021. We do not own any real property. We believe that this office and laboratory space is sufficient to meet our current needs and that suitable additional space will be available as and when needed.

Legal Proceedings

From time to time, we may become involved in litigation relating to claims arising from the ordinary course of business. Our management believes that there are currently no claims or actions pending against us, the ultimate disposition of which could have a material adverse effect on our results of operations or financial condition.

Corporate Information

We were incorporated under the laws of the State of Delaware and commenced business operations in 2011. Our principal executive offices are located at One Newton Executive Park, Suite 202, Newton, MA 02462 and our telephone number is (617) 467-4577. Our website address is www.allenapharma.com. The information contained on our website, or that can be accessed through our website, is not a part of this prospectus and is not incorporated by reference into this prospectus. You should not rely on any such information in deciding whether to purchase our common stock.

We are an “emerging growth company” as defined in the Jumpstart Our Business Startups Act of 2012. We will remain an emerging growth company until the earlier of: (i) the last day of the fiscal year (a) following the fifth anniversary of the completion of the IPO, (b) in which we have total annual gross revenue of at least $1.07 billion, or (c) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700.0 million as of the prior June 30th, and (ii) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period.

Financial Information and Segments

The financial information required under this Item 1 is incorporated herein by reference to the section of this Annual Report titled “Part II-Item 8-Financial Statements and Supplementary Data.” We operate in one business segment. See Note 2 to our consolidated audited financial statements included in this Annual Report. For financial information regarding our business, see “Part II-Item 7-Management’s Discussion and Analysis of Financial Condition and Results of Operations” of this Annual Report and our consolidated audited financial statements and related notes included elsewhere in this Annual Report.

Available Information

Our Internet address is www.allenapharma.com. Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, including exhibits, proxy and information statements and amendments to those reports filed or furnished pursuant to Sections 13(a), 14, and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, are available through the "Investors" portion of our website free of charge as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Information on our website is not part of this Annual Report on Form 10-K or any of our other securities filings unless specifically incorporated herein by reference. The public may read and copy these materials at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. The public may obtain information on the operation of the Public Reference Room by calling the Securities and Exchange Commission, or the SEC, at 1-800-SEC-0330. In addition, our filings with the SEC may be accessed through the SEC's Interactive Data Electronic Applications system at http://www.sec.gov. All statements made in any of our securities filings, including all forward-looking statements or information, are made as of the date of the document in which the statement is included, and we do not assume or undertake any obligation to update any of those statements or documents unless we are required to do so by law.

ITEM 1A. RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks described below, as well as the other information in this Annual Report on Form 10-K and in our other public filings before making an investment decision. Our business, prospects, financial condition, or operating results could be harmed by any of these risks, as well as other risks not currently known to us or that we currently consider immaterial. If any such risks or uncertainties actually occur, our business, financial condition or operating results could differ materially from the plans, projections and other forward-looking statements included in the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere in this report and in our other public filings. The trading price of our common stock could decline due to any of these risks, and as a result, you may lose all or part of your investment.

Risks Related to Drug Development, Regulatory Approval and Commercialization

We are heavily dependent on the regulatory approval of reloxaliase (formerly referred to as ALLN-177) in the United States and Europe, and subsequent commercial success of reloxaliase, both of which may never occur.

We are a late-stage biopharmaceutical company with no products approved by regulatory authorities or available for commercial sale. We have generated no revenue to date and do not expect to do so for the foreseeable future. As a result, our future success is currently dependent upon the clinical trial results, regulatory approval and commercial success of reloxaliase in one or more of the indications for which we seek approval. Our ability to generate revenues in the near term will depend on our ability to obtain regulatory approval and successfully commercialize reloxaliase on our own in the United States, if approved. We may experience delays in obtaining regulatory approval in the United States for reloxaliase, if it is approved at all, and our stock price may be negatively impacted. Even if we receive regulatory approval, the timing of the commercial launch of reloxaliase in the United States is dependent upon a number of factors, including, but not limited to, hiring sales and marketing personnel, pricing and reimbursement timelines, the production of sufficient quantities of commercial drug product and implementation of marketing and distribution infrastructure.

In addition, we have incurred and expect to continue to incur significant expenses as we continue to pursue the approval of reloxaliase in the United States, Europe and elsewhere. We plan to devote a substantial portion of our effort and financial resources in order to continue to grow our operational capabilities. This represents a significant investment in the clinical and regulatory success of reloxaliase, which is uncertain. The success of reloxaliase, if approved, and revenue from commercial sales, will depend on several factors, including:

- execution of an effective sales and marketing strategy for the commercialization of reloxaliase;
- acceptance by patients, the medical community and third-party payors;
- our success in educating physicians and patients about the benefits, administration and use of reloxaliase;
- the incidence and prevalence of patient populations with enteric hyperoxaluria in those markets in which reloxaliase is approved;
- the prevalence and severity of side effects, if any, experienced by patients treated with reloxaliase;

- the availability, perceived advantages, cost, safety and efficacy of alternative treatments, including potential alternate treatments that may currently be available or in development or may later be available or in development or regulatory approval or marketing of a generic, biosimilar, or any other version of oxalate decarboxylase, the active enzyme in reloxaliase;

- successful implementation of our manufacturing processes that are included in our new biologics license application, or BLA, and production of sufficient quantities of commercial drug product;

- maintaining compliance with regulatory requirements, including current good manufacturing practices, or cGMPs, good laboratory practices, or GLP, and good clinical practices, or GCPs; and

- obtaining and maintaining patent, trademark and trade secret protection and regulatory exclusivity and otherwise protecting our rights in our intellectual property portfolio.

We may also fail in our efforts to develop and commercialize future product candidates, including ALLN-346 for patients with hyperuricemia and chronic kidney disease, or CKD. If this were to occur, we would continue to be heavily dependent on the regulatory approval and successful commercialization of reloxaliase, our development costs may increase and our ability to generate revenue or profits, or to raise additional capital, could be impaired.

Results of earlier studies may not be predictive of future clinical trial results, and planned or ongoing studies may not establish an adequate safety or efficacy profile for reloxaliase and other product candidates that we may pursue to justify proceeding to an application for regulatory approval or be worthy of regulatory approval if such an application is made.

The results of preclinical studies and clinical trials of reloxaliase conducted to date and future studies and trials of reloxaliase, including our pivotal Phase 3 clinical trials, and other product candidates that we may pursue, may not be predictive of the results of subsequent clinical trials. Additionally, interim results of a clinical trial do not necessarily predict final results. Data, our interpretation of data and results from our Phase 2 clinical trials of reloxaliase in adults with enteric hyperoxaluria do not ensure that we will achieve similar results in our ongoing pivotal Phase 3 clinical trials in enteric hyperoxaluria or in clinical trials of reloxaliase in other patient populations, including patients being treated in our ongoing Study 206. In addition, preclinical and clinical data are often susceptible to various interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and early-stage clinical trials have nonetheless failed to replicate results in later-stage clinical trials and subsequently failed to obtain marketing approval. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy despite having progressed through nonclinical studies and earlier clinical trials.

In particular, as is common with Phase 2 clinical trials, particularly clinical trials first conducted in a patient population with disease, we explored numerous endpoints and analyzed the data from our Phase 2 clinical trials of reloxaliase in a number of ways. Prior to obtaining approval for reloxaliase, we expect that the results of our URIROX-1 and URIROX-2 trials will have to demonstrate statistically significant improvement in the percent change from baseline in 24-hour urinary oxalate, or UOx, during Weeks 1-4, comparing reduction in the average UOx excretion across Weeks 1-4 with reloxaliase to placebo, the primary efficacy endpoint of both of our Phase 3 clinical trials. To date, two of our randomized Phase 2 clinical trials of reloxaliase (Study 713 and Study 649) did not demonstrate statistically significant results in the pre-specified primary endpoints. The design of our later-stage clinical trials differs in significant ways from our Phase 2 clinical trials of reloxaliase, which we believe may cause the outcome of these later-stage trials to differ from what we observed in our Phase 2 clinical trials. These differences include changes to inclusion and exclusion criteria, efficacy endpoints and statistical design.

Product candidates in Phase 3 clinical trials, such as reloxaliase in our pivotal Phase 3 clinical program, may fail to demonstrate sufficient efficacy despite having progressed through initial clinical trials, even if certain analyses of primary or secondary endpoints in those early trials showed potential treatment effects. Some of the data we present on the use of reloxaliase for the treatment of enteric hyperoxaluria is drawn from pre-specified analyses and other data is from post-hoc analyses. While we believe all the data from the Phase 2 program were useful in informing the design of our pivotal Phase 3 program, and will remain useful for clinical trials evaluating reloxaliase, the post-hoc analyses involve the inherent bias of post-hoc rendering of data and choice of analytical methods. Further, while Study 713 was the largest randomized, controlled trial ever conducted in hyperoxaluria, only 18 subjects with enteric hyperoxaluria, the indication we intend to evaluate in our pivotal Phase 3 program, enrolled in the trial. Thus, we have limited data on the activity or safety of reloxaliase in the target population for our ongoing Phase 3 clinical program.

The primary efficacy endpoint in our pivotal Phase 3 program is percent change from baseline in 24-hour urinary oxalate, which is a biochemical measurement of the daily amount of oxalate handling by the kidney and therefore its reduction would indicate lessening of potential kidney damage by oxalate. However, based on published scientific literature and data generated in our own clinical trials, daily urinary oxalate excretion is a biomarker that demonstrates significant variability between patients and day-to-day for the same patient. This variability in 24 hour urinary oxalate excretion, especially in enteric hyperoxaluria patients, can be attributed to changes in diet, metabolic activity, hydration status or other factors. It can also be attributed to the manner in which these measurements are taken. In our completed Phase 2 clinical trials, we relied heavily on the efforts and contributions of investigative clinical sites and study patients to comply with accurate timing of 24 hour urine collection, with the complete collection of all of the patient's urine during a given 24 hour period and with the proper handling of collected urine specimens, including storage, documentation, sample handling and shipping to the testing laboratory. Following our completed Phase 2 clinical trials, we conducted a post-hoc review of these collection procedures. Although we are not aware of any case where the data reported in our prior clinical trials was inaccurate, due to the variability inherent in these data collection techniques, we cannot provide assurance that in all cases the data reported in our clinical trials accurately reflect the actual biochemical responses experienced by patients in these trials. We believe that capturing multiple measurements of 24 hour a time-weighted average of daily urinary oxalate excretion over the course of a clinical trial mitigates the risks of inherent variability, dietary change and sample handling associated with the testing of each individual 24 hour urine specimen, but no assurance can be given that any such variability will be fully addressed by this approach.

A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier studies, and we cannot be certain that we will not face similar setbacks. Even if early stage clinical trials are successful, we may need to conduct additional clinical trials for product candidates in additional patient populations or under different treatment conditions before we are able to seek approvals from the U.S. Food and Drug Administration, or FDA, and comparable foreign regulators to market and sell these product candidates. Our failure to demonstrate the required characteristics to support marketing approval for reloxaliase or any other product candidate we may choose to develop in any ongoing or future clinical trials would substantially harm our business, prospects, financial condition and results of operations.

Although we have reached alignment with the FDA on the design of URIROX-2, our second pivotal Phase 3 trial of reloxaliase in patients with enteric hyperoxaluria, and our strategy to pursue a BLA submission for reloxaliase using the accelerated approval regulatory pathway, the clinical data we generate from our Phase 3 clinical program and/or the data we derive from third party datasets may not be sufficient to meet the FDA requirements for filing and obtaining marketing authorization via the accelerated approval regulatory pathway. If we are unable to obtain accelerated approval, we may be required to conduct additional preclinical studies or clinical trials beyond those that we contemplate, which could increase the expense of obtaining, reduce the likelihood of obtaining and/or delay the timing of obtaining, necessary marketing approvals. Even if we receive accelerated approval from the FDA, if our confirmatory trials do not verify clinical benefit, or if we do not comply with rigorous post-marketing requirements, the FDA may seek to withdraw accelerated approval.

We may seek an accelerated approval development pathway for our product candidates, and we intend to do so for reloxaliase. Under the accelerated approval provisions of the Federal Food, Drug, and Cosmetic Act and the FDA's implementing regulations, the FDA may grant accelerated approval to a product designed to treat a serious or life-threatening condition that provides meaningful therapeutic advantage over available therapies and demonstrates an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. The FDA considers a clinical benefit to be a positive therapeutic effect that is clinically meaningful in the context of a given disease. For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. The accelerated approval development pathway may be used in cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage, but is a clinically important improvement from a patient and public health perspective. If granted, accelerated approval is contingent on the sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug's clinical profile or risks and benefits for accelerated approval. The FDA may require that any such confirmatory study be initiated or substantially underway prior to the submission of an application for accelerated approval. If such post-approval studies fail to confirm the drug's clinical profile or risks and benefits, the FDA may withdraw its approval of the drug.

We have reached alignment with the FDA on the design of URIROX-2, our second pivotal Phase 3 clinical trial of reloxaliase in patients with enteric hyperoxaluria, and the FDA has advised us that they agree with our overall strategy to obtain accelerated approval for this product candidate. The data generated from the URIROX-1 and URIROX-2 trials could thus potentially form the basis of an accelerated approval of reloxaliase using reduction in UOx as a surrogate endpoint, with

the final results from the URIROX-2 trial used to confirm clinical benefit post-approval. We believe 24 hour urinary oxalate excretion is an appropriate metric of the therapeutic effect of reloxaliase because 24 hour urinary oxalate excretion is a biochemical measurement of the daily amount of oxalate handling by the kidney and therefore its reduction would indicate lessening of potential kidney damage by oxalate. However, the data generated in our clinical trials may not be sufficient to support an accelerated approval of reloxaliase, or any approval.

The FDA has advised us that part of its assessment of the adequacy of the URIROX-2 trial to support accelerated approval will be both the size of the effect seen on UOx in this trial and the predictive model from this UOx reduction effect that further supports a relationship between UOx levels and stone formation rates, which model can be informed by data generated in the URIROX-2 trial or other data sources. This approach is consistent with the FDA's published guidance on the accelerated approval pathway, which provides that clinical data from a single clinical trial can be used to both support accelerated approval and verify the clinical benefit. This guidance also stipulates that the protocol and statistical analysis plan should clearly account for an analysis of the surrogate endpoint data to provide support for accelerated approval, with continuation of the randomized trial(s) to obtain data on the clinical endpoint that will be the basis for verifying the clinical benefit. In light of this guidance, URIROX-2 incorporates adaptive design elements that, through sample size re-estimations, will, if necessary, allow for increases in sample size and duration of treatment, based on accrued kidney stone disease progression rates and the conditional probability of achieving ultimate statistical success in the long-term follow-up phase of the trial as reviewed by the FDA. However, the data generated in our clinical trials may not be sufficient to provide additional support for the relationship between UOx levels and stone formation rates or to demonstrate the conditional probability of achieving ultimate statistical success. Based on the interim data we generate in the URIROX-2 trial, we may be required to increase the number of patients treated and/or extend the follow-up period before we are able to submit a BLA for reloxaliase seeking accelerated approval, if ever. If we are required to increase the number of patients treated and/or extend the follow-up period in our clinical trials, it could have a material adverse effect on our expected clinical and regulatory timelines, business, prospects, financial condition and results of operations.

We expect that our data package for accelerated approval would include a conditional power estimate based on the effect of reloxaliase on reducing kidney stone disease progression as assessed with interim data from the URIROX-2 trial, the effects of reloxaliase on reduction of UOx in the URIROX-1 and URIROX-2 trials, and further support for the model relating UOx levels to kidney stone disease progression, including but not limited to available data obtained in the URIROX-2 trial. We expect we will continue to work with scientific experts to identify additional third-party datasets to further substantiate the relationship between urinary oxalate levels and the risk of kidney stones and kidney dysfunction. The FDA has advised us that we have not yet provided sufficient data regarding UOx excretion necessary to support its use as a surrogate endpoint for these clinical trials and questioned whether changes in UOx of the magnitude expected would be reasonably likely to predict clinical benefit. We have provided the FDA with the details of analyses we conducted using available data collected from a third-party clinical database, in order to demonstrate an increased probability of kidney stone events in patients with enteric hyperoxaluria and increasing UOx levels. The FDA has advised us that it remains concerned about the strength of this relationship, based in part on the limited clinical data currently available and whether other factors may play a role in the production of kidney stones. The data we generate from the URIROX-1 and URIROX-2 trials, together with additional data we identify from third-party datasets, may not be sufficient to satisfy the FDA that we have generated a model that supports a relationship between UOx levels and stone formation rates and as necessary to use the accelerated approval regulatory pathway for reloxaliase. If we are unable to reach consensus with the FDA on the magnitude of UOx reduction significant enough to predict clinical benefit, we may be required to demonstrate effectiveness by showing an effect on stone formation directly, or conduct one or more additional clinical trials to demonstrate this effect, prior to the submission of a BLA for reloxaliase.

Furthermore, even if we generate clinical data sufficient to support a BLA submission seeking accelerated approval, there can be no assurance that such application will be accepted or that approval will be granted on a timely basis, or at all. For example, the FDA may require demonstration that we have initiated or made substantial progress in our clinical follow-up of trial subjects, or any such clinical outcomes trial, prior to the submission of our BLA for accelerated approval of reloxaliase. The FDA notes in its guidance that when the same trial is used to support accelerated approval and verify clinical benefit, the data to verify the clinical benefit may be, in some cases, nearly complete by the time of accelerated approval. In addition, if another company receives full approval from the FDA to market a product for treatment of enteric hyperoxaluria, our ability to seek and obtain accelerated approval for reloxaliase in the same or similar indication may be materially adversely affected. The FDA or foreign regulatory authorities also could require us to conduct further studies or trials prior to considering our application or granting approval of any type. We might not be able to fulfill the FDA's requirements in a timely manner, which would cause delays, or approval might not be granted because our submission is deemed incomplete by the FDA. A failure to obtain accelerated approval or any other form of expedited development, review or approval for a product candidate would result in a longer time period to obtain approval for and commercialize such product candidate, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace.

Even if we receive accelerated approval from the FDA for reloxilase or any of our other product candidates, we will be subject to rigorous post-marketing requirements, including the completion of confirmatory post-market clinical trial(s) to verify the clinical benefit of the product, and submission to the FDA of all promotional materials prior to their dissemination. The FDA could seek to withdraw accelerated approval for multiple reasons, including if we fail to conduct any required post-market study with due diligence, a post-market study does not confirm the predicted clinical benefit, other evidence shows that the product is not safe or effective under the conditions of use, or we disseminate promotional materials that are found by the FDA to be false and misleading. We anticipate that whether the reduction in kidney stone reduction we observe in our Phase 3 clinical program for reloxilase is sufficient to demonstrate a clinical benefit will ultimately be a review issue with FDA.

A failure to obtain accelerated approval or any other form of expedited development, review or approval for a product candidate that we may choose to develop would result in a longer time period prior to commercializing such product candidate, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace.

Foreign regulators may not agree with our proposed Phase 3 clinical program for reloxaliase, in which case we may be required to modify our planned clinical trials, or run additional clinical trials, before we can submit foreign applications for marketing approval for reloxaliase.

In January 2019 we announced that we had reached alignment with the FDA on both the design of URIROX-2, our second pivotal Phase 3 trial of reloxaliase in patients with enteric hyperoxaluria, and our strategy to pursue a BLA submission for reloxaliase using the accelerated approval regulatory pathway. However, our planned Phase 3 program may not be sufficient to support the submission of applications for marketing approval in foreign jurisdictions, including the European Union. Although our preliminary discussions with regulatory authorities in select countries within the European Union lead us to believe our planned Phase 3 program, if successful, may be sufficient to support the submission of an MAA in Europe via the conditional approval pathway, which is similar to the FDA's accelerated approval pathway, these discussions are not binding on such authorities or the EMA. Accordingly, no assurance can be given that our planned Phase 3 program will be sufficient to support the submission of an MAA in Europe, and we may be required to modify the design of these planned trials, or run additional clinical trials, before seeking marketing approval. Any of these decisions could have a material adverse effect on our expected clinical and regulatory timelines, business, prospects, financial condition and results of operations.

Because we are developing product candidates for the treatment of diseases in which there is little clinical trial experience and, in some cases, using new endpoints or methodologies, there is increased risk that the FDA or other regulatory authorities may not consider the endpoints of our clinical program to provide clinically meaningful results and that these results may be hard to analyze.

There are no pharmacologic therapies approved to treat the underlying causes of hyperoxaluria. In addition, it should be noted that no therapeutic agents have previously been approved by the FDA on the basis of a biochemical measurement of 24 hour urinary oxalate excretion, endpoints used in our Phase 2 clinical program and for our pivotal Phase 3 clinical program. The FDA retains discretion to reserve judgment on whether our clinical endpoints and the results we obtain in our pivotal Phase 3 clinical program sufficiently demonstrate clinical meaningfulness until the FDA reviews the data included in our planned BLA submission, which will not occur for several years from now, if at all. As a result, the design and conduct of clinical trials for the treatment of hyperoxaluria, and the underlying conditions and disorders that drive the metabolic disease, are subject to increased risk.

Moreover, even if the FDA does find our success criteria to be sufficiently validated and clinically meaningful, we may not achieve the pre-specified endpoint to a degree of statistical significance, in either or both of the Phase 3 clinical trials that we believe will be necessary for approval. Further, even if we do achieve the pre-specified criteria, we may produce results that are unpredictable or inconsistent with the results of the secondary efficacy endpoints in the trials. The FDA also could give overriding weight to other efficacy endpoints, even if we achieve statistically significant results on the primary endpoint, if we do not achieve statistically significant or clinically meaningful results on any of our secondary efficacy endpoints. The FDA also weighs the benefits of a product against its risks and the FDA may view the efficacy results in the context of safety as not being supportive of regulatory approval. Other regulatory authorities in the EU and other countries may take similar positions.

In addition, we are conducting a Phase 2 clinical trial of reloxaliase utilizing an open-label, basket trial design that will enroll subsets of patients suffering from complications of severe hyperoxaluria, including adolescents and adults with primary hyperoxaluria or severe forms of secondary hyperoxaluria, both of which can lead to systemic oxalosis. We have not yet evaluated reloxaliase in patients with primary hyperoxaluria and as such we have not yet demonstrated proof-of-concept in this patient population. Basket trial designs permit the exploration of a study drug in patient populations with common biochemical markers, such as patients afflicted with different forms of cancer, but the same genetic mutation. Although all patients enrolled in our planned Phase 2 trials will have elevated urinary oxalate levels, the underlying cause of their hyperoxaluria may be

different. We cannot predict whether the design of our pivotal Phase 3 clinical program, Study 206 or any other future trials that we may conduct may successfully demonstrate reloxaliase or any future product candidate's safety and efficacy.

If clinical trials of our product candidates fail to satisfactorily demonstrate safety and efficacy to the FDA and other comparable foreign regulators, we, or any future collaborators, may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of these product candidates.

We, and any future collaborators, are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining marketing approval from the FDA. Comparable foreign regulators, such as the European Medicines Agency, or EMA, impose similar restrictions. We, and any future collaborators, may never receive such approvals. We, and any future collaborators, must complete extensive preclinical development and clinical trials to demonstrate the safety and efficacy of our product candidates in humans before we, or they, will be able to obtain these approvals.

Clinical testing is expensive, difficult to design and implement, can take many years to complete and is inherently uncertain as to outcome. We have not previously submitted a BLA to the FDA or similar drug approval applications to comparable foreign regulators for any of our product candidates. Any inability to complete preclinical and clinical development successfully could result in additional costs to us, or any future collaborators, and impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. Moreover, if (1) we, or any future collaborators, are required to conduct additional clinical trials or other testing of our product candidates beyond the trials and testing that we, or they contemplate, (2) we, or any future collaborators, are unable to successfully complete clinical trials of our product candidates or other testing, (3) the results of these trials or tests are unfavorable, uncertain or are only modestly favorable, or (4) there are unacceptable safety concerns associated with our product candidates, we, or any future collaborators, may:

- incur additional unplanned costs;
- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or significant safety warnings, including boxed warnings;
- be subject to additional post-marketing testing or other requirements; or
- be required to remove the product from the market after obtaining marketing approval.

Our failure to successfully complete clinical trials of our product candidates and to demonstrate the efficacy and safety necessary to obtain regulatory approval to market any of our product candidates would significantly harm our business, prospects, financial condition and results of operations.

Clinical drug development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

Our Phase 3 clinical program for reloxaliase consists of two Phase 3 clinical trials of reloxaliase in adult patients with enteric hyperoxaluria. We have also conducted scientific advisory meetings with regulatory authorities in three countries within the European Union, or the EU. Even though we have received and incorporated guidance from these regulatory authorities, foreign regulators could disagree that we have satisfied their requirements to commence our clinical trials in those jurisdictions. Further, the FDA or other regulatory authorities could change their position on the acceptability of our trial designs or the clinical endpoints selected, which may require us to complete additional preclinical studies or clinical trials or impose stricter approval conditions than we currently expect. We may need to conduct additional clinical trials or other testing for, among other things, drug-drug interactions, the generation of formate (i.e. a metabolic byproduct resulting from the degradation of oxalate by reloxaliase) and increased dosages of our product candidates. Successful completion of our clinical trials is a prerequisite to submitting a BLA to the FDA and a Marketing Authorization Application, or MAA, in Europe for each product candidate and, consequently, the ultimate approval and commercial marketing of reloxaliase, ALLN-346 and any product

candidates we may develop in the future. We do not know whether any of our clinical trials will be completed on schedule, if at all.

We may experience delays in initiating or completing our planned clinical trials or additional preclinical studies or clinical trials in the future, and we may experience numerous unforeseen events during, or as a result of, any future clinical trials that we conduct that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

- regulators or institutional review boards, or IRBs, or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable terms with prospective trial sites and prospective contract research organizations, or CROs, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- we may experience delays in recruiting, or be unable to recruit, a sufficient number of suitable patients to participate in our clinical trials;
- the patients and sites who participate in our trials may not comply with protocols, such as compliance with the capsule and timing regimen and urine collection requirements, rendering the results insufficient or uninterpretable;
- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional preclinical studies or clinical trials or we may decide to abandon drug development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials or fail to return for post-treatment follow-up at a higher rate than we anticipate;
- our third party contractors may fail to comply with regulatory or legal requirements or meet their contractual obligations to us in a timely manner, or at all, or may deviate from the clinical trial protocol or drop out of the trial, which may require that we add new clinical trial sites or investigators;
- we may elect to, or regulators or IRBs or ethics committees may require that we or our investigators, suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;
- the occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits;
- any changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or IRBs or ethics committees to suspend or terminate the trials, or reports may arise from preclinical or clinical testing of other therapies that raise safety or efficacy concerns about our product candidates; and
- the FDA or other comparable foreign regulators may require us to submit additional data or impose other requirements before permitting us to initiate a clinical trial.

We could encounter delays if a clinical trial is suspended or terminated by us, by the IRBs of the institutions in which such trials are being conducted, by the Data Safety Monitoring Board for such trial or by the FDA or other comparable foreign regulators. Such authorities may impose such a suspension or termination due to a number of factors, including failure to

conduct the clinical trial in accordance with regulatory requirements, GCP or our clinical protocols, inspection of the clinical trial operations or trial sites by the FDA or other comparable foreign regulators resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. 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. Further, the FDA may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials.

Our drug development costs will also increase if we experience delays in testing or regulatory approvals. We do not know whether any of our clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant preclinical study or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations. Any delays in our preclinical or clinical development programs may significantly harm our business, prospects, financial condition and results of operations.

The regulatory approval processes of the FDA and comparable foreign regulators are lengthy, time-consuming and inherently unpredictable. If we are ultimately unable to obtain regulatory approval for reloxaliase or our other product candidates, our business will be substantially harmed.

We are not permitted to market reloxaliase or any of our other product candidates in the United States or the EU, until we receive approval of a BLA from the FDA or an MAA from the EMA, respectively. Prior to submitting a BLA to the FDA or an MAA to the EMA for approval of any of our product candidates for a specific indication, we are required to complete preclinical studies and clinical trials.

Successfully initiating and completing our clinical program and obtaining approval of a BLA or an MAA is a complex, lengthy, expensive and uncertain process, and the FDA, the EMA or other comparable foreign regulators may delay, limit or deny approval of any of our candidates for many reasons, including, among others:

- we may not be able to demonstrate that our product candidates are safe and effective to the satisfaction of the FDA or the EMA;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA or the EMA for marketing approval;
- the FDA or the EMA may disagree with the number, design, size, conduct or implementation of our clinical trials;
- the FDA or the EMA may require that we conduct additional clinical trials;
- the FDA or the EMA or other applicable foreign regulators may not approve the formulation, labeling or specifications of reloxaliase or our other product candidates;
- the CROs that we retain to conduct our clinical trials may take actions outside of our control that materially adversely impact our clinical trials;
- the FDA or the EMA may find the data from preclinical studies and clinical trials insufficient to demonstrate that the clinical and other benefits of reloxaliase and our other product candidates outweigh their safety risks;
- the FDA or the EMA may disagree with our interpretation of data from our preclinical studies and clinical trials, including our characterization of observed toxicities;
- the FDA or the EMA may not accept data generated at our clinical trial sites;
- if our BLAs or MAAs, if and when submitted, are reviewed by the FDA or the EMA, as applicable, the regulatory agency may have difficulties scheduling the necessary review meetings in a timely manner, may recommend against approval of our application or may recommend that the FDA or the EMA, as applicable, require, as a condition of approval, additional preclinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;

- the FDA may require development of a Risk Evaluation and Mitigation Strategy as a condition of approval or post-approval, and the EMA may grant only conditional approval or impose specific obligations as a condition for marketing authorization, or may require us to conduct post-authorization safety studies;

- the FDA, the EMA or other applicable foreign regulators may find deficiencies with or not approve the manufacturing processes or facilities of third-party manufacturers with which we contract; or

- the FDA or the EMA may change their approval policies or adopt new regulations.

Any of these factors, many of which are beyond our control, could jeopardize our ability to obtain regulatory approval for and successfully market reloxaliase or any of our other product candidates. Any such setback in our pursuit of regulatory approval would have a material adverse effect on our business and prospects.

In addition to the United States and Europe, we or potential collaborators intend to market our product candidates, if approved, in other international markets. Such marketing will require separate regulatory approvals in each market and compliance with numerous and varying regulatory requirements. The approval procedures vary from country-to-country and may require additional testing. Moreover, the time required to obtain approval may differ from that required to obtain FDA or EMA approval. In addition, in many countries, a product candidate must be approved for reimbursement before it can be approved for sale in that country, even if regulatory approval has been obtained. Approval by the FDA or the EMA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA or the EMA. The regulatory approval process in other international markets may include all of the risks associated with obtaining FDA or EMA approval.

Changes in regulatory requirements and guidance may also occur and we may need to amend clinical trial protocols submitted to applicable regulatory authorities to reflect these changes. Amendments may require us to resubmit clinical trial protocols to IRBs or ethics committees for re-examination, which may impact the costs, timing or successful completion of a clinical trial.

The FDA's and other comparable foreign regulators' policies may change, and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of reloxaliase and any future product candidates we may develop. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action in the United States, the EU or other countries or jurisdictions. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, and we may not achieve or sustain profitability, which would harm our business, prospects, financial condition and results of operations.

If we are required to conduct additional clinical trials or other studies with respect to reloxaliase or any future product candidates we may develop beyond those that we currently contemplate, or if we are unable to successfully complete our clinical trials or other studies, we may be delayed in obtaining regulatory approval of reloxaliase and any future product candidates we may develop, we may obtain approval of indications that are not as broad as intended or we may not be able to obtain regulatory approval at all. Our product development costs will also increase if we experience delays in testing or approvals, and we may not have sufficient funding to complete the testing and approval process for reloxaliase or any future product candidates we may develop. Significant clinical trial delays could allow our competitors to bring products to market before we do and impair our ability to commercialize our products if and when approved. If any of this occurs, our business would be harmed.

If we experience delays or difficulties in the enrollment or continuation of patients in our clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or comparable foreign regulators, or if a significant number of patients withdraw of our clinical trials. In particular, because we are focused on patients with enteric hyperoxaluria with respect to our Phase 3 development of reloxaliase, our ability to enroll eligible patients may be limited or may result in slower enrollment than we anticipate.

Patient enrollment may be affected by other factors including, but not limited to:

- the severity of the disease under investigation;

- the design of the clinical trial;

- the size and nature of the patient population;
- the eligibility criteria for the clinical trial in question;
- the availability of appropriate screening tests for study subjects;
- the perceived risks and benefits of the product candidate under study;
- availability of competing therapies and clinical trials;
- clinicians' and patients' perceptions as to the potential advantages of the drug being studied in relation to other available therapies or treatment approaches;
- the efforts to facilitate timely enrollment in clinical trials;
- the ability to obtain and maintain patient consents and the risk that patients enrolled in clinical trials will not complete a clinical trial;
- the patient referral practices of physicians;
- the ability of patients to comply with the protocol, including capsule and timing regimen and urine collection requirements;
- the ability to monitor patients adequately during and after treatment;
- the proximity and availability of clinical trial sites for prospective patients; and
- the extent to which our competitors have ongoing clinical trials for product candidates that treat the same indications as our product candidates.

In addition, patients may withdraw from our clinical trials prematurely, which could also have a negative effect on our ability to complete our clinical trials or obtain and retain regulatory approvals. For example, both of our Phase 3 clinical trials for reloxaliase are randomized, double-blind and placebo controlled, and our URIROX-2 trial is intended to potentially enable a BLA submission using the accelerated approval pathway, following which patients would continue in the study for a minimum treatment period of two years to confirm clinical benefit post-approval. Patients enrolled in our Phase 3 clinical trials may elect to withdraw from the trial prematurely, particularly in the event we are able to obtain an accelerated approval. If a significant number of patients withdraw from the trial prematurely it could potentially jeopardize the interpretability of the results from our clinical trials, which could have a material adverse effect on our ability to obtain, or retain, regulatory approval for reloxaliase.

Our product candidates may cause undesirable side effects that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

Undesirable side effects caused by our product candidates could cause us to interrupt, delay or halt preclinical studies or could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign regulators. Results of our trials could reveal a high and unacceptable severity and prevalence of these or other side effects. Although the incidences of adverse events that were considered related to study drug in our Phase 2 trials were low and no drug-related serious or severe adverse events were observed, it is possible that our Phase 3 clinical program or future clinical trials we conduct may not demonstrate a favorable safety profile. In addition, while we have not observed reloxaliase to be absorbed into the bloodstream in our clinical trials to date, it is possible absorption could occur in our Phase 3 clinical trials, particularly with a target population of patients with enteric hyperoxaluria, who are predisposed to chronic hyperabsorption. We may also need to conduct additional clinical trials or other testing for, among other things, drug-drug interactions, the generation of formate and increased dosages of our product candidates. In the event of adverse safety issues, our trials could be suspended or terminated and the FDA or comparable foreign regulator could order us to cease further development of or deny approval of reloxaliase for any or all targeted indications. Any drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial

or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

Further, clinical trials by their nature utilize a sample of the potential patient population. With a limited number of patients and limited duration of exposure, rare and severe side effects of our product candidates may only be uncovered with a significantly larger number of patients exposed to the product candidate. If reloxaliase or our other product candidates receive marketing approval and we or others identify undesirable side effects caused by such product candidates (or any other similar drugs) after such approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw or limit their approval of such product candidates;
- regulatory authorities may require the addition of labeling statements, such as a "boxed" warning or a contraindication;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- we may be required to change the way such product candidates are distributed or administered, conduct additional clinical trials or change the labeling of the product candidates;
- regulatory authorities may require a Risk Evaluation and Mitigation Strategy 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;
- we may be subject to regulatory investigations and government enforcement actions;
- we may decide to remove such product candidates from the marketplace;
- we could be sued and held liable for injury caused to individuals exposed to or taking our product candidates; and
- our reputation may suffer.

We believe that any of these events could prevent us from achieving or maintaining market acceptance of the affected product candidates and could substantially increase the costs of commercializing our product candidates, if approved, and significantly impact our ability to successfully commercialize our product candidates and generate revenues.

Even if we receive regulatory approval for any of our product candidates, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense. Additionally, our product candidates, if approved, could be subject to labeling and other restrictions and market withdrawal and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our drugs.

If the FDA, the EMA or a comparable foreign regulator approves any of our product candidates, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the drug will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs and GCPs for any clinical trials that we conduct post-approval. Any regulatory approvals that we receive for our product candidates may also be subject to limitations on the approved indicated uses for which the drug may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the safety and efficacy of the drug. Later discovery of previously unknown problems with a drug, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of the drug, withdrawal of the drug from the market, or voluntary or mandatory drug recalls;
- fines, warning letters or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us, or suspension or revocation of drug approvals;

- drug seizure or detention, or refusal to permit the import or export of the drug; and
- injunctions or the imposition of civil or criminal penalties.

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, which would adversely affect our business, prospects and ability to achieve or sustain profitability.

Accordingly, assuming we, or any collaborators we may have, receive marketing approval for one or more product candidates we develop, we, and such collaborators, and our and their contract manufacturers will continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance, and quality control. If we and such collaborators are not able to comply with post-approval regulatory requirements, we and such collaborators could have the marketing approvals for our products withdrawn by regulatory authorities and our, or such collaborators', ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our business, operating results, financial condition, and prospects.

We face substantial competition, which may result in others discovering, developing or commercializing drugs before or more successfully than we do, and reducing or eliminating our commercial opportunity.

Our industry is highly competitive and subject to rapid and significant technological change as researchers learn more about diseases and develop new technologies and treatments. Our potential competitors include primarily large pharmaceutical, biotechnology companies and specialty pharmaceutical companies. Key competitive factors affecting the commercial success of reloxaliase, ALLN-346 and any other product candidates we may develop are likely to be efficacy, safety and tolerability profile, reliability, convenience of administration, price and reimbursement.

There is no approved pharmacologic therapy for the reduction of urinary oxalate excretion in patients with hyperoxaluria, either primary or secondary. Existing treatment options for hyperoxaluria generally are non-specific and include high fluid intake to increase urine output to more than two to three liters per day, a diet low in salt and oxalate, oral citrate and/or calcium and/or magnesium supplementation and orthophosphate and Vitamin B6, exclusively for the specific subset of responsive patients with the most severe form of primary hyperoxaluria (PH1).

We are aware of other companies pursuing oxalate reduction in both primary and secondary hyperoxaluria. For example, Alnylam is conducting an ongoing pivotal Phase 3 study under the Accelerated Approval pathway for the treatment of patients with primary hyperoxaluria Type 1. Dicerna is conducting ongoing clinical development for the treatment of primary hyperoxaluria Types 1-3. Oxthera AB (Sweden) and Captozyme (U.S.) are developing orally delivered products to degrade oxalate in the stomach and GI tract. Oxthera is conducting Phase 3 clinical trials for Oxabact, *Oxalobacter formigenes*, indicated for the treatment of primary hyperoxaluria.

Several of our existing or potential competitors have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a small number of our competitors. Accordingly, our competitors may be more successful than we may be in obtaining FDA approval of drugs and achieving widespread market acceptance. Our competitors' drugs, or drugs they may develop in the future, may be more effective, or more effectively marketed and sold, than any drug we may commercialize and may render reloxaliase or any future product candidates we may develop obsolete or non-competitive before we can recover the expenses of developing and commercializing reloxaliase or any future product candidates we may develop. Our competitors may also obtain FDA or other regulatory approval of their products more rapidly than we may obtain approval of ours. Our competitors could develop and the FDA could approve a generic or biosimilar version of oxalate decarboxylase, the active enzyme in reloxaliase. We anticipate that we will face intense and increasing competition as new drugs enter the market and more advanced technologies become available. If we are unable to compete effectively, our opportunity to generate revenue from the sale of reloxaliase or any future product candidates we may develop, if approved, will be adversely affected.

The incidence and prevalence for target patient populations of our product candidates have not been established with precision. If the market opportunities for our product candidates are smaller than we believe they are, our revenue may

be adversely affected, and our business may suffer. Our ability to successfully identify patients and acquire a significant market share will be necessary for us to achieve profitability and growth.

We focus our research and product development on treatments for hyperoxaluria and hyperuricemia. The precise incidence and prevalence for these diseases are unknown. 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 estimates. For example, we estimate there are approximately 200,000 to 250,000 patients in the United States with enteric hyperoxaluria and kidney stones. In addition, an estimated 375,000 patients in the United States have refractory gout and CKD, the target population for our ALLN-346 product candidate. These estimates have been derived from a variety of sources, including the scientific literature and market research projects with third-party consultants, and may prove to be incorrect. Further, new studies and future developments in patient care or treatment paradigms may change the estimated incidence or prevalence of this disorder. The number of patients may turn out to be lower than expected. 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. Further, even if we obtain significant market share for one or more of our product candidates, because certain of our potential target populations are small, including our target populations for which reloxaliase has received orphan drug designation, we may never achieve profitability despite obtaining such significant market share.

Even if one of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success and the market opportunity for such product candidate may be smaller than we estimate.

We have never obtained marketing approval for a product candidate or commercialized a product. Even if one of our product candidates is approved by the appropriate regulatory authorities for marketing and sale, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. For example, physicians are often reluctant to switch their patients from existing therapies even when new and potentially more effective or convenient treatments enter the market. Further, patients often acclimate to the therapy that they are currently taking and do not want to switch unless their physicians recommend switching products or they are required to switch therapies due to lack of reimbursement for existing therapies.

Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may not be successful. If any one of our product candidates is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues and we may not become profitable. The degree of market acceptance of any of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the potential advantages of the product compared to alternative treatments;
- the prevalence and severity of any side effects;
- the clinical indications for which the product is approved;
- the potential absence of the results of a late-stage clinical trial with a clinically meaningful primary endpoint;
- whether the product is designated under physician treatment guidelines as a first-line therapy or as a second- or third-line therapy;
- limitations or warnings, including distribution or use restrictions, contained in the product's approved labeling;
- our ability, or the ability of any future collaborators, to offer the product for sale at competitive prices;
- the product's convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try, and of physicians to prescribe, the product;
- the strength of our sales, marketing and distribution support;
- the approval of other new products for the same indications;

- changes in the standard of care for the targeted indications for the product;
- the timing of market introduction of our approved products as well as competitive products;
- availability and amount of reimbursement from government payors, managed care plans and other third-party payors;
- adverse publicity about the product or favorable publicity about competitive products; and
- potential product liability claims.

The potential market opportunities for our product candidates are difficult to estimate precisely. Our estimates of the potential market opportunities are predicated on many assumptions, including industry knowledge and publications, third-party research reports and other surveys. While we believe that our internal assumptions are reasonable, these assumptions involve the exercise of significant judgment on the part of our management, are inherently uncertain and the reasonableness of these assumptions has not been assessed by an independent source. If any of the assumptions proves to be inaccurate, the actual markets for our product candidates could be smaller than our estimates of the potential market opportunities, which would adversely affect our results of operations and our business.

Our proprietary technological approach is a new approach to the design and development of stable, non-absorbable oral enzyme therapies and may not result in any additional product candidates or ultimately any products of commercial value.

We have developed our proprietary know-how in enzyme technology which allows us to design, formulate and deliver non-absorbed and stable enzymes orally and in sufficient doses for activity in the GI tract. While the general therapeutic approach of deploying a non-absorbed drug into the GI tract to reduce metabolic disease burden in patients with kidney disease has been proven successful in several therapeutic categories, we cannot assure you that our technological approach will ultimately work for reloxaliase, ALLN-346, or any other product candidates we may develop. In addition, while we believe our enzyme therapeutic candidates will not be absorbed, future clinical trials may find this not to be true. We also cannot guarantee that any other aspects of our proprietary technological approach will yield product candidates that could receive regulatory approval, enter clinical development and, ultimately, be commercially valuable.

We only have a limited number of employees to manage and operate our business.

As of March 1, 2019, we had 49 full-time, part-time, or short-term employees. Our focus on the development of reloxaliase and ALLN-346 requires us to optimize cash utilization and to manage and operate our business in a highly efficient manner. We will need to hire and retain a significant number of new employees to execute our clinical development and manufacturing plans. We cannot provide assurance that we will be able to hire and/or retain adequate staffing levels to develop reloxaliase, or ALLN-346 or run our operations and/or to accomplish all of the objectives that we otherwise would seek to accomplish.

We currently have no sales and marketing organization and, as a company, have not commercialized any products. If we are unable to establish effective sales and marketing capabilities in the United States and access them in Europe and other international markets, we may not succeed in commercializing our product candidates.

At present, we have no sales or marketing employees and we rely on part-time consultants. We cannot guarantee that we will be successful in marketing reloxaliase for enteric hyperoxaluria in the United States, if approved. We may not be able to establish a direct sales force in a cost-effective manner or realize a positive return on this investment. In addition, we will have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain sales and marketing personnel. Factors that may inhibit our efforts to commercialize reloxaliase in the United States without strategic partners or licensees include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of our planned relatively small sales force to obtain access to or inform adequate numbers of nephrologists, urologists or other practitioners at kidney stone clinics;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines;

- the inability of market-access personnel to obtain sufficient levels of pricing and reimbursement in each jurisdiction; and
- unforeseen costs, expenses and delays associated with creating a commercial organization.

If we are not successful in timely recruiting of sales and marketing personnel or in building a sales and marketing infrastructure or if we do not successfully enter into appropriate collaboration arrangements, we will have difficulty commercializing reloxaliase, which could harm our business, operating results and financial condition. Expansion of our business into the EU and other international markets will require significant management attention and additional financial resources. We currently intend to explore commercializing reloxaliase, if approved, in Europe and other international markets by entering into collaboration agreements with other biopharmaceutical companies, and we may not be successful in entering into these collaboration agreements. In the event that we do enter into such agreements, we may have limited or no control over the sales, marketing and distribution activities of these third parties. Additional factors and risks that may inhibit our efforts to commercialize reloxaliase in foreign markets include:

- our inability to directly control commercial activities because we are relying on third parties, should we enter into third-party collaborations;
- varying pricing in different foreign markets, which could adversely affect pricing in the United States or other countries;
- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- import or export licensing requirements;
- longer collection times for accounts receivable;
- longer lead times for shipping;
- language barriers for technical training;
- reduced protection of intellectual property rights in some foreign countries, and related prevalence of generic alternatives to therapeutics;
- the imposition of governmental price controls, political and economic instability, trade restrictions and changes in tariffs;
- foreign currency exchange rate fluctuations;
- our customers' ability to obtain adequate reimbursement for reloxaliase in foreign markets at all, either at all or at prices that exceed our costs; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

Our future revenues may depend heavily on the success of the efforts of these third parties. We may not be able to establish a commercial operation in a cost-effective manner or realize a positive return on this investment, even with the assistance of one or more third-party collaborators, should we choose to enter into such an arrangement. In addition, we will have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain sales and marketing personnel.

If we or third-party collaborators are not successful in recruiting sales and marketing personnel or in building a sales and marketing infrastructure or if we do not successfully enter into additional collaboration arrangements with third parties, we may not be able to successfully commercialize reloxaliase and any future product candidates we may develop in foreign markets, which could impair our business, operating results and financial condition.

Even with the potential assistance of third-party collaborators, we may not be successful in establishing a commercial operation in foreign markets for numerous reasons, including, but not limited to, failing to attract, retain and motivate the necessary skilled personnel and failing to develop a successful marketing strategy. Failure to establish a commercial operation in foreign markets will have a negative outcome on our ability to commercialize reloxaliase and generate revenue.

Additionally, if approved for marketing in one or more countries, we and/or our potential third-party collaborators may encounter unexpected or unforeseen delays in establishing our commercial operations that delay the commercial launch in these countries. These delays may increase the cost of and the resources required for successful commercialization of reloxaliase internationally. We do not have any experience in a commercial launch in Europe or elsewhere.

We expect to expand our development, regulatory, and future sales and marketing capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of clinical development, manufacturing, regulatory affairs, and sales and marketing. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational, and financial systems, expand our facilities, and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expected expansion of our operations or recruit and train additional qualified personnel. Moreover, the expected physical expansion of our operations may lead to significant costs and may divert our management and business development resources and attention. Any inability to manage growth could delay the execution of our business plans or disrupt our operations, which could affect our ability to generate revenue.

The manufacture and packaging of pharmaceutical products such as reloxaliase is subject to FDA requirements and those of similar foreign regulatory bodies. If we or our third-party manufacturers fail to satisfy these requirements, our product development and commercialization efforts may be harmed.

The manufacture and packaging of pharmaceutical products, such as reloxaliase, if approved, is regulated by the FDA and similar foreign regulatory bodies and must be conducted in accordance with the FDA's cGMP and comparable requirements of foreign regulatory bodies. There are a limited number of manufacturers that operate under these cGMP regulations who are both capable of manufacturing reloxaliase and willing to do so. We may not be able to identify or secure contracts with manufacturers with suitable capability to manufacture reloxaliase according to FDA requirements on favorable terms or at all. Failure by us or our third-party manufacturers to comply with applicable regulations or requirements could result in sanctions being imposed on us, including fines, injunctions, civil penalties, failure of regulatory authorities to grant marketing approval of our products, delays, suspension or withdrawal of approvals, seizures or voluntary or mandatory recalls of product, operating restrictions and criminal prosecutions, any of which could harm our business. The same requirements and risks are applicable to the suppliers of the key raw material used to manufacture reloxaliase, including the specific bacterial strains that are used to manufacture the oxalate decarboxylase enzyme, which is an active ingredient in reloxaliase.

Changes in the manufacturing process or procedure, including a change in the location where the product is manufactured or a change of a third-party manufacturer, may require prior FDA review and approval of the manufacturing process and procedures in accordance with the FDA's cGMPs. Any new facility is subject to a pre-approval inspection by the FDA and would again require us to demonstrate product comparability to the FDA. There are comparable foreign requirements. This review may be costly and time consuming and could delay, constrain or prevent the launch or supply of a product.

Furthermore, in order to obtain approval of our product candidates, including reloxaliase, by the FDA and foreign regulatory agencies, we will be required to consistently produce the drug substance and the finished product in commercial quantities and of specified quality on a repeated basis and document our ability to do so. This requirement is referred to as process validation. We have not yet met with the FDA or foreign regulatory agencies to understand the complete manufacturing requirements which must be met for reloxaliase to receive regulatory approval. Each of our potential suppliers will likely use a different method to manufacture drug substance, which has the potential to increase the risk to us that our manufacturers will fail to meet applicable regulatory requirements. We also need to complete process validation on the finished product in the packaging we propose for commercial sales. This includes testing of stability, measurement of impurities and testing of other product specifications by validated test methods. If the FDA or foreign regulatory agencies do not consider the result of the process validation or required testing to be satisfactory, we may not obtain approval to launch the product or approval, launch or availability of commercial supply after launch may be delayed.

The FDA and similar foreign regulatory bodies may also implement new requirements, or change their interpretation and enforcement of existing requirements, for manufacture, packaging or testing of products at any time. If we are unable to comply, we may be subject to regulatory, civil actions or penalties which could harm our business.

Manufacture and supply of drug substance, drug product and finished drug product is a complex and technically challenging undertaking, particularly for oral biologics, and there is potential for failure at many points in the manufacturing, testing, quality assurance and distribution supply chain, as well as the potential for latent defects after a product has been manufactured and distributed.

Manufacture and supply of drug substance, drug product and finished drug product is technically challenging, particularly for oral biologics. Changes that may be made outside the purview of our direct control can have an impact on the success of our processes, on quality, and on successful delivery of finished drug product. Mistakes and mishandling could affect successful production and supply. Some of these risks include:

- failure to follow cGMP requirements or mishandling of our product while in production or in preparation for transit;
- delays in analytical results or failure of analytical techniques that we depend on for quality control and release of drug product;
- natural disasters, labor disputes, lack of raw material supply, issues with facilities and equipment or other forms of disruption to business operations at our manufacturing facilities; and
- latent defects that may become apparent after drug product has been released and which may result in recall or required destruction of drug product.

If any of these risks materialize, it would have a material and adverse impact on our ability to develop, obtain regulatory approval for and market reloxaliase, if approved.

The longer term growth of our business depends on our ability to expand our portfolio of product candidates, which may require substantial financial resources and may ultimately be unsuccessful.

The longer term growth of our business depends upon our ability to develop and commercialize multiple product candidates. In addition to the development and commercialization of reloxaliase for hyperoxaluria, we intend to pursue development of ALLN-346 for hyperuricemia and CKD as well as other product candidates. We may never be able to identify other developmental prospects that we can successfully develop into product candidates, let alone receive regulatory approval of or successfully commercialize such product candidates.

A significant portion of the research that we are conducting involves new technologies. Research programs to identify new disease targets and product candidates require substantial technical, financial and human resources whether or not we ultimately identify any product candidates. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including, but not limited to:

- the research methodology used may not be successful in identifying potential product candidates; or
- potential product candidates may on further study be shown to have harmful side effects or other characteristics that indicate they are unlikely to be effective drugs.

There are a number of FDA requirements that we must satisfy before we can commence a clinical trial in the United States. If we are able to identify additional potential product candidates, satisfaction of these regulatory requirements will entail substantial time, effort and financial resources. We may never satisfy these requirements. Any time, effort and financial resources we expend on development of other product candidates may impair our ability to continue efforts to develop and commercialize reloxaliase for the treatment of enteric hyperoxaluria and other indications, and we may never commence clinical trials of such development programs despite expending significant resources in pursuit of their development. If we do commence clinical trials of other product candidates, those product candidates may never demonstrate sufficient safety and efficacy to be approved by the FDA or other comparable foreign regulators. If any of these events occur, we may be forced to abandon our development efforts for such program or programs, which would harm our business. If we do not successfully develop and commercialize product candidates based upon our approach, we will not be able to obtain drug revenues in future periods, which likely would result in significant harm to our financial position and adversely affect our stock price.

We may fail to obtain and maintain orphan drug designations from the FDA for our current and future product candidates, as applicable. Even for reloxaliase for which we have received such designation for treatment of primary hyperoxaluria and pediatric hyperoxaluria, we may be unable to maintain the benefits associated with orphan drug designation, including the potential for market exclusivity.

Our strategy includes seeking orphan drug designation where available for our product candidates. Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug or biologic intended to treat a rare disease or condition, which is defined as one occurring in a patient population of fewer than 200,000 in the 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 or biologic will be recovered from sales in the United States. 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 that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications, including a full new drug application, or NDA, or BLA, to market the same drug or biologic for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or where the original manufacturer is unable to assure sufficient product quantity.

The FDA has granted separate orphan drug designations for reloxaliase for treatment of primary hyperoxaluria and for the treatment of pediatric hyperoxaluria. In addition, the European Commission has granted orphan designation for reloxaliase for the treatment of primary hyperoxaluria. Even where we have obtained such designations, we may not be the first to obtain regulatory approval of a product candidate for the orphan-designated indication due to the uncertainties associated with developing pharmaceutical products. We may also fail to meet requirements to maintain orphan drug designation during our continued development of reloxaliase, which is primarily focused on enteric hyperoxaluria. In addition, exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan-designated indication or may be lost if the FDA later determines that the request for designation was materially defective or if we are unable to assure sufficient quantities of the product to meet the needs of patients with the orphan-designated disease or condition. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties may receive and be approved for the same condition, and only the first applicant to receive approval will receive the benefits of marketing exclusivity. Even after an orphan-designated product is approved, the FDA can subsequently approve a later drug with the same active moiety for the same condition if the FDA concludes that the later drug is clinically superior if it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug, nor gives the drug any advantage in the regulatory review or approval process. In addition, while we may seek orphan drug designation for our product candidates, we may never receive such designations.

Our relationships with customers and third-party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to penalties, including criminal sanctions, civil penalties, exclusion from government healthcare programs, contractual damages, reputational harm and diminished profits and future earnings.

Although we do not currently have any drugs on the market, once we begin commercializing our product candidates, we will be subject to additional healthcare statutory and regulatory requirements and enforcement by the federal government and the states, foreign governments and other jurisdictions in which we conduct our business. Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our product candidates for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federal and state healthcare programs such as Medicare and Medicaid. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Although there are several statutory exceptions and regulatory safe harbors protecting certain common activities from prosecution, they are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exception or safe harbor. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- the federal civil False Claims Act imposes criminal and civil penalties and authorizes civil whistleblower or qui tam actions against individuals or entities for: knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent; or making a false statement or record material to a false or fraudulent claim or obligation to pay or transmit money or property to the federal government; or knowingly concealing or knowingly and improperly avoiding or decreasing an obligation to pay money to the federal government. In addition, the government may assert that a claim including items and services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;

- the anti-inducement law prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary’s selection of a particular supplier of items or services reimbursable by a federal or state governmental program;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- the federal physician payment transparency requirements, sometimes referred to as the "Sunshine Act" under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the Affordable Care Act, require manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children's Health Insurance Program to report to the Department of Health and Human Services information related to physician payments and other transfers of value and the ownership and investment interests of such physicians and their immediate family members;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 and its implementing regulations, which also imposes obligations on certain covered entity healthcare providers, health plans, and healthcare clearinghouses as well as their business associates that perform certain services involving the use or disclosure of individually identifiable health information, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information; and

- analogous state laws and regulations, such as state anti-kickback and false claims laws that may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers; and some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care 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 often are not preempted by HIPAA, thus complicating compliance efforts.

Ensuring that our future business arrangements with third parties comply with applicable healthcare laws and regulations could involve substantial costs. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations, including anticipated activities to be conducted by our sales team, were to be found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. Any of these occurrences may significantly harm our business, financial condition, prospects and results of operations and adversely affect our stock price.

The risk of us being found in violation of these laws is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. For example, the definition of the “remuneration” under the federal Anti-Kickback Statute has been interpreted to include anything of value. Further, courts have found that if “one purpose” of remuneration is to induce referrals, the federal Anti-Kickback Statute is violated.

Additionally, recent healthcare reform legislation has strengthened federal and state healthcare fraud and abuse laws. For example, the ACA amends the intent requirement of the federal Anti-Kickback Statute and criminal healthcare fraud statutes to clarify that liability under these statutes does not require a person or entity to have actual knowledge of the statutes or a specific intent to violate them. Moreover, the ACA provides that the government may assert that a claim that includes items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act. Furthermore, on January 31, 2019, the Department of Health and Human Services (HHS) and HHS Office of Inspector General (OIG) proposed an amendment to one of the existing Anti-Kickback safe harbors (42 C.F.R. 1001.952(h)) which would prohibit certain pharmaceutical manufacturers from offering rebates to pharmacy benefit managers, or PBMs, in the Medicare Part D and Medicaid managed care programs. The proposed amendment would remove protection for "discounts" from Anti-Kickback enforcement action, and would include criminal and civil penalties for knowingly and willfully offering, paying, soliciting, or receiving remuneration to induce or reward the referral of business reimbursable under federal health care programs. At the same time, HHS also proposed to create a new safe harbor to protect point-of-sale discounts that drug manufacturers provide directly to patients, and adds another safe harbor to protect certain administrative fees paid by manufacturers to PBMs. If this proposal is adopted, in whole or in part, it could affect the pricing and reimbursement for any products for which we receive approval in the future. 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.

Legislative or regulatory reform of the health care system in the United States and foreign jurisdictions may adversely impact our business, operations or financial results.

Our industry is highly regulated and changes in law may adversely impact our business, operations or financial results. In particular, in March 2010, the Affordable Care Act and a related reconciliation bill were signed into law. This legislation changes the current system of healthcare insurance and benefits intended to broaden coverage and control costs. The law also contains provisions that will affect companies in the pharmaceutical industry and other healthcare related industries by

imposing additional costs and changes to business practices. Provisions affecting pharmaceutical companies include the following:

- mandatory rebates for drugs sold into the Medicaid program have been increased, and the rebate requirement has been extended to drugs used in risk-based Medicaid managed care plans;
- the definition of "average manufacturer price" was revised for reporting purposes, which could increase the amount of Medicaid drug rebates by state;
- the 340B Drug Pricing Program under the Public Health Service Act has been extended to require mandatory discounts for drug products sold to certain critical access hospitals, cancer hospitals and other covered entities;
- pharmaceutical companies are required to offer discounts on brand-name drugs to patients who fall within the Medicare Part D coverage gap, commonly referred to as the "donut hole"; and
- pharmaceutical companies are required to pay an annual non-tax deductible fee to the federal government based on each company's market share of prior year total sales of branded products to certain federal healthcare programs. Since we expect our branded pharmaceutical sales to constitute a small portion of the total federal health program pharmaceutical market, we do not expect this annual assessment to have a material impact on our financial condition.

In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. On August 2, 2011, the Budget Control Act of 2011 among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013, which will remain in effect until 2027 unless additional congressional action is taken. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, increased the statute of limitations period for the government to recover overpayments to providers from three to five years. We expect that additional federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, and in turn could significantly reduce the projected value of certain development projects and reduce our profitability.

In addition, in September 2007, the Food and Drug Administration Amendments Act of 2007 was enacted giving the FDA enhanced post-marketing authority including the authority to require post-marketing studies and clinical trials, labeling changes based on new safety information and compliance with risk evaluations and mitigation strategies approved by the FDA. The FDA's exercise of this authority could result in delays or increased costs during product development, clinical trials and regulatory review, increased costs to ensure compliance with post-approval regulatory requirements and potential restrictions on the sale and/or distribution of approved products. Other legislative and regulatory initiatives have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. For example, the Drug Supply Chain Security Act of 2013 imposes new obligations on manufacturers of certain pharmaceutical products related to product tracking and tracing. We do not know whether additional legislative changes will be enacted, or whether the FDA regulations, guidance documents or interpretations will be changed, or what the impact of such changes on the marketing approvals of reloxaliase, if any, may be. In addition, increased scrutiny by Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

The current presidential administration and U.S. Congress have also recently attempted to repeal or "repeal and replace" the Affordable Care Act. Although those efforts did not succeed, we the presidential administration may continue to seek to modify, repeal, or otherwise invalidate all, or certain provisions of, the Affordable Care Act. There is still uncertainty with respect to the impact President Trump's administration and the U.S. Congress may have on the Affordable Care Act, if any, and any changes will likely take time to unfold. Additionally, since its enactment, there have been judicial and Congressional challenges to certain aspects of the Affordable Care Act. For example, on December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, or Texas District Court Judge, ruled that the entire Affordable Care Act is invalid based primarily on the fact that the Tax Cuts and Jobs Act of 2017 repealed the tax-based shared responsibility payment imposed by the Affordable Care Act, on certain individuals who fail to maintain qualifying health coverage for all or part of a year, which is commonly referred to as the "individual mandate". While the Texas District Court Judge, as well as the current presidential administration and the Centers for Medicare and Medicaid Services, have stated that this ruling will have no immediate effect, it is unclear how this decision and subsequent appeals will impact the law and the effect such impact could have on coverage and reimbursement for healthcare items and services covered by plans that were authorized by the Affordable Care Act.

However, we cannot predict the ultimate content, timing or effect of any healthcare reform legislation or the impact of potential legislation on us.

Moreover, we cannot predict what healthcare reform initiatives may be adopted in the future. Further, federal and state legislative and regulatory developments are likely, and 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 reloxaliase and any other product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop product candidates.

We may fail to comply with evolving European and other privacy laws.

Since we conduct clinical trials in the European Economic Area, or the EEA, we are subject to additional European data privacy laws. The General Data Protection Regulation, (EU) 2016/679, or GDPR, became effective on May 25, 2018, and deals with the processing of personal data and on the free movement of such data. The GDPR imposes a broad range of strict requirements on companies subject to the GDPR, including requirements relating to having legal bases for processing personal information relating to identifiable individuals and transferring such information outside the EEA, including to the United States, providing details to those individuals regarding the processing of their personal information, keeping personal information secure, having data processing agreements with third parties who process personal information, responding to individuals' requests to exercise their rights in respect of their personal information, reporting security breaches involving personal data to the competent national data protection authority and affected individuals, appointing data protection officers, conducting data protection impact assessments, and record-keeping. The GDPR increases substantially the penalties to which we could be subject in the event of any non-compliance, including fines of up to 10,000,000 Euros or up to 2% of our total worldwide annual turnover for certain comparatively minor offenses, or up to 20,000,000 Euros or up to 4% of our total worldwide annual turnover for more serious offenses. Given the limited enforcement of the GDPR to date, we face uncertainty as to the exact interpretation of the new requirements on our trials and we may be unsuccessful in implementing all measures required by data protection authorities or courts in interpretation of the new law.

In particular, national laws of member states of the EU are in the process of being adapted to the requirements under the GDPR, thereby implementing national laws which may partially deviate from the GDPR and impose different obligations from country to country, so that we do not expect to operate in a uniform legal landscape in the EEA. Also, as it relates to processing and transfer of genetic data, the GDPR specifically allows national laws to impose additional and more specific requirements or restrictions, and European laws have historically differed quite substantially in this field, leading to additional uncertainty. Further, the impact of the impending "Brexit", (whereby the United Kingdom is planning to leave the EEA in March of 2019), either with or without a "deal" is uncertain and cannot be predicted at this time.

In the event we continue to conduct clinical trials in the EEA, we must also ensure that we maintain adequate safeguards to enable the transfer of personal data outside of the EEA, in particular to the United States, in compliance with European data protection laws. We expect that we will continue to face uncertainty as to whether our efforts to comply with our obligations under European privacy laws will be sufficient. If we are investigated by a European data protection authority, we may face fines and other penalties. Anype1 such investigation or charges by European data protection authorities could have a negative effect on our existing business and on our ability to attract and retain new clients or pharmaceutical partners. We may also experience hesitancy, reluctance, or refusal by European or multi-national clients or pharmaceutical partners to continue to use our products and solutions due to the potential risk exposure as a result of the current (and, in particular, future) data protection obligations imposed on them by certain data protection authorities in interpretation of current law, including the GDPR. Such clients or pharmaceutical partners may also view any alternative approaches to compliance as being too costly, too burdensome, too legally uncertain, or otherwise objectionable and therefore decide not to do business with us. Any of the foregoing could materially harm our business, prospects, financial condition and results of operations

If successful product liability claims are brought against us, we may incur substantial liability and costs. If the use of our product candidates harms patients, or is perceived to harm patients even when such harm is unrelated to our product candidates, our regulatory approvals could be revoked or otherwise negatively impacted and we could be subject to costly and damaging product liability claims.

The use of our product candidates in clinical trials and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, participants in our clinical trials, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. There is a risk that our product candidates may induce adverse events. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation;
- withdrawal of clinical trial participants;
- costs due to related litigation;
- distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- increased FDA warnings on product labels;
- the inability to commercialize our product candidates; and
- decreased demand for our product candidates, if approved for commercial sale.

We carry product liability insurance in amounts that we believe are sufficient in light of our current clinical programs; however, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

During the course of treatment, patients may suffer adverse events, including death, for reasons that may or may not be related to our product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market our product candidates, if approved, or require us to suspend or abandon our commercialization efforts of any approved product candidates. Even in a circumstance in which we do not believe that an adverse event is related to our products, the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our sales efforts, delay our regulatory approval process in other countries, or impact and limit the type of regulatory approvals our product candidates receive or maintain. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

We depend heavily on the success of our most advanced program, reloxaliase. Our only other product development program, ALLN-346, is at the preclinical stage. Preclinical testing and clinical trials of product candidates may not be successful. If we are unable to commercialize any product candidates we may develop or experience significant delays in doing so, our business will be materially harmed.

We have invested substantially all of our efforts and financial resources in the identification and development of our most advanced product program, reloxaliase for the treatment of hyperoxaluria. Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of reloxaliase and our future product candidates. The success of reloxaliase, ALLN-346 and future product candidates we may identify and develop will depend on many factors, including the following:

- sufficiency of our financial and other resources to complete the necessary preclinical studies and clinical trials for our most advanced program;
- successful completion of preclinical studies;
- successful enrollment in, and completion of, clinical trials;
- receipt of marketing approvals from applicable regulatory authorities in our target indications and potential additional indications;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and non-patent exclusivity for our medicines;
- launching commercial sales of the medicines, if and when approved, whether alone or in collaboration with others;
- acceptance of the medicines, if and when approved, by patients, the medical community, and third-party payors;
- effectively competing with other therapies and treatment options;
- a continued acceptable safety profile of the medicines following approval;
- enforcing and defending intellectual property and proprietary rights and claims; and
- achieving desirable medicinal properties for the intended indications.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our most advanced program or any other product candidates we may develop, which would materially harm our business.

Of the large number of biologics and drugs in development in the pharmaceutical industry, only a small percentage result in the submission of a BLA or NDA to the FDA or an MAA to the EMA. Not all BLAs, NDAs or MAAs that are submitted to a regulatory agency are approved for commercialization. reloxaliase is an oral biologic product candidate, which is a less common formulation in the biotech industry. Accordingly, there are few oral biologic therapeutics that have achieved regulatory approval. Furthermore, even if we do receive regulatory approval to market our most advanced program or any other product candidates that we may identify and develop, any such approval may be subject to limitations on the indicated uses for which we may market the product. Accordingly, even if we are able to obtain the requisite financing to continue to fund our research programs, we cannot assure you that we will successfully develop or commercialize our most advanced program, or any of our other research programs. If we or any of our future development partners are unable to develop, or obtain regulatory approval for, or, if approved, successfully commercialize, our most advanced program or any product candidates we may identify and develop, we may not be able to generate sufficient revenue to continue our business.

Even if we are able to commercialize any product candidates, such products may become subject to unfavorable pricing regulations, third-party reimbursement practices, or healthcare reform initiatives, which would harm our business.

The regulations that govern marketing approvals, pricing, and reimbursement for new medicines vary widely from country to country. Some countries require approval of the sale price of a medicine before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets,

prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a medicine in a particular country, but then be subject to price regulations that delay our commercial launch of the medicine, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the medicine in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if any product candidates we may develop obtain marketing approval.

Our ability to commercialize any medicines successfully also will depend in part on the extent to which reimbursement for these medicines and related treatments will be available from government health administration authorities, private health insurers, and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that reimbursement will be available for any medicine that we commercialize and, if reimbursement is available, the level of reimbursement. Reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

There may be significant delays in obtaining reimbursement for newly approved medicines, and coverage may be more limited than the purposes for which the medicine is approved by the FDA or comparable foreign regulators. Moreover, eligibility for reimbursement does not imply that any medicine will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale, marketing and distribution. Interim reimbursement levels for new medicines, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the medicine and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost medicines and may be incorporated into existing payments for other services. Net prices for medicines may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of medicines 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 policies. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved medicines we may develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize medicines, and our overall financial condition.

Due to the novel nature of our product candidates and the potential for any product candidates we may develop to offer therapeutic benefit, we face uncertainty related to pricing and reimbursement for these product candidates.

Our initial target patient populations are relatively small, as a result of which the pricing and reimbursement of any product candidates we may develop, if approved, must be adequate to support the necessary commercial infrastructure. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell any such product candidates will be adversely affected. The manner and level at which reimbursement is provided for services related to any product candidates we may develop (e.g. for administration of our product to patients) is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our products. In addition, it may be necessary for us to develop new reimbursement models in order to realize adequate value. Payors may not be able or willing to adopt such new models, and patients may be unable to afford that portion of the cost that such models may require them to bear. If we determine such new models are necessary but we are unsuccessful in developing them, or if such models are not adopted by payors, our business, financial condition, results of operations, and prospects could be adversely affected.

We expect that coverage and reimbursement by government and private payors will be essential for most patients to be able to afford our product candidates. Accordingly, sales of any such product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of any product candidates we may develop will be paid by health maintenance, managed care, pharmacy benefit, and similar healthcare management organizations, or will be reimbursed by government authorities, private health coverage insurers, and other third-party payors. Coverage and reimbursement by a third-party payor may depend upon several factors, including the third-party payor’s determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective, and medically necessary;
- appropriate for the specific patient;

- cost-effective; and
- neither experimental nor investigational.

Obtaining coverage and reimbursement for a product from third-party payors is a time-consuming and costly process that could require us to provide to the payor supporting scientific, clinical, and cost-effectiveness data. There is significant uncertainty related to third-party coverage and reimbursement of newly approved products. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If coverage and reimbursement are not available, or are available only at limited levels, we may not be able to successfully commercialize any product candidates we may develop. Even if coverage is provided, the approved reimbursement amount may not be adequate to realize a sufficient return on our investment.

Moreover, the downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become intense. As a result, increasingly high barriers are being erected to the entry of new products such as ours. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell any product candidates we may develop will be harmed.

In light of the large population of patients with hyperoxaluria who reside outside the United States, our ability to generate meaningful revenues in those jurisdictions may be limited due to the strict price controls and reimbursement limitations imposed by governments outside of the United States.

In some countries, particularly those in the EU, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a drug. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. If reimbursement of our product candidates is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially, if we are not able to market our product to the large population of patients with hyperoxaluria who reside in outside the United States.

Currently we plan to seek regulatory approval to market reloxaliase solely for the treatment of enteric hyperoxaluria in adults and, unless we seek regulatory approval for additional indications, we will be prohibited from marketing reloxaliase for any other indication.

We intend to initially seek approval to market reloxaliase for the treatment of enteric hyperoxaluria in adults. Even if we obtain regulatory approval to market reloxaliase in this indication, we will likely be prohibited from marketing reloxaliase for any other indications. The FDA strictly regulates the promotional claims that may be made about prescription products. While reloxaliase has been studied in patients beyond the enteric subgroup, reloxaliase may not be promoted for uses that are not approved by the FDA as reflected in its approved labeling. Under applicable regulations, the ability of a company to make marketing statements about the effectiveness of its drug outside of the statements made in the label, referred to as “off-label” marketing, is prohibited. If we are found to have promoted such off-label uses, we may become subject to significant liability.

If we fail to comply or are found to have failed to comply with FDA and other regulations prohibiting the promotion of reloxaliase for unapproved uses, we could be subject to criminal penalties, substantial fines or other sanctions and damage awards.

The regulations prohibiting the promotion of products for unapproved uses are complex and subject to substantial interpretation by the FDA and other government agencies. If we receive marketing approval for reloxaliase for the treatment of enteric hyperoxaluria in adults, physicians may nevertheless prescribe it to their patients in a manner that is inconsistent with the approved label. We intend to implement compliance and training programs designed to ensure that our sales and marketing practices comply with applicable regulations. Notwithstanding these programs, the FDA or other government agencies may allege or find that our practices constitute prohibited promotion of reloxaliase for unapproved uses. We also cannot be sure that our employees will comply with company policies and applicable regulations regarding the promotion of products for unapproved uses.

Over the past several years, a significant number of pharmaceutical and biotechnology companies have been the target of inquiries and investigations by various federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of products for unapproved uses and other sales practices, including the Department of Justice and various U.S. Attorneys’ Offices, the Office of Inspector General of the Department of Health and Human Services, the FDA, the Federal Trade Commission and various state Attorneys General offices. These investigations have alleged violations of various federal and state laws and regulations, including claims asserting antitrust violations, violations of the Federal Food, Drug, and Cosmetic Act, the False Claims Act, the Prescription Drug Marketing Act, anti-kickback laws, and other alleged

violations in connection with the promotion of products for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. Many of these investigations originate as "qui tam" actions under the False Claims Act. Under the False Claims Act, any individual can bring a claim on behalf of the government alleging that a person or entity has presented a false claim, or caused a false claim to be submitted, to the government for payment. The person bringing a qui tam suit is entitled to a share of any recovery or settlement. Qui tam suits, also commonly referred to as "whistleblower suits," are often brought by current or former employees. In a qui tam suit, the government must decide whether to intervene and prosecute the case. If it declines, the individual may pursue the case alone.

If the FDA or any other governmental agency initiates an enforcement action against us or if we are the subject of a qui tam suit and it is determined that we violated prohibitions relating to the promotion of products for unapproved uses, we could be subject to substantial civil or criminal fines or damage awards and other sanctions such as consent decrees and corporate integrity agreements pursuant to which our activities would be subject to ongoing scrutiny and monitoring to ensure compliance with applicable laws and regulations. Any such fines, awards or other sanctions would have an adverse effect on our revenue, business, financial prospects and reputation.

Inadequate funding for the FDA, the SEC and other government agencies could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the FDA, the SEC and other government agencies on which our operations may rely, including those that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new therapies to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, upon completion of this offering and in our operations as a public company, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Risks Related to Our Dependence on Third Parties

The third parties upon whom we rely for the supply of the drug product and drug substance used in our lead product candidate are our sole source of supply, and the loss of any of these suppliers could significantly harm our business.

We do not currently operate manufacturing facilities for clinical or commercial production of any product candidates. We have limited personnel experienced in drug manufacturing and formulation, and we lack the resources and the capabilities to manufacture reloxaliase on a clinical or commercial scale. We do not intend to develop facilities for the manufacture of drug product candidates for clinical trials or products for commercial purposes in the foreseeable future. The drug product and drug substance used in reloxaliase are supplied to us from single-source suppliers. Our ability to successfully develop our product candidates, to supply the drug required for our planned clinical trials, and to ultimately supply our commercial drugs in quantities sufficient to meet the market demand, depends in part on our ability to obtain the drug product and drug substance for these drugs in accordance with regulatory requirements and in sufficient quantities for commercialization and clinical testing. We do not currently have arrangements in place for a redundant or second-source supply of any such drug product or drug substance in the event any of our current suppliers of such drug product and drug substance cease their operations for any reason.

For all of our product candidates, we intend to identify and qualify additional manufacturers to provide such drug product and drug substance prior to submission of a BLA to the FDA and/or an MAA to the EMA. We are not certain, however, that our single-source suppliers will be able to meet our demand for their products, either because of the nature of our agreements with those suppliers, our limited experience with those suppliers or our relative importance as a customer to those suppliers. It may be difficult for us to assess their ability to timely meet our demand in the future based on past performance. While our suppliers have generally met our demand for their products on a timely basis in the past, they may subordinate our needs in the future to their other customers.

Establishing additional or replacement suppliers for the drug product and drug substance used in our product candidates, if required, may not be accomplished quickly. If we are able to find a replacement supplier, such replacement supplier would

need to be qualified and may require additional regulatory approval, which could result in further delay. While we seek to maintain adequate inventory of the drug product and drug substance used in our product candidates, any interruption or delay in the supply of components or materials, or our inability to obtain such drug product and drug substance from alternate sources at acceptable prices in a timely manner could impede, delay, limit or prevent our development efforts, which could harm our business, results of operations, financial condition and prospects.

We plan to continue to rely upon contract manufacturers and, potentially, collaboration partners to manufacture commercial quantities of our product candidates if and when approved for marketing by the applicable regulatory authorities. We have not secured commercial supply agreements with any contract manufacturers for reloxaliase and can give no assurance that we will enter commercial supply agreements with any contract manufacturers on favorable terms or at all or that we will be able to manufacture our product candidates at commercial scale at the cost we expect. Our contract manufacturers' failure to achieve and maintain high manufacturing standards, in accordance with applicable regulatory requirements, or the incidence of manufacturing errors, could result in patient injury or death, product shortages, product recalls or withdrawals, delays or failures in product testing or delivery, cost overruns or other problems that could seriously harm our business. Contract manufacturers often encounter difficulties involving production yields, quality control and quality assurance, as well as shortages of qualified personnel.

An element of our strategy is to enter into licensing or collaboration agreements with respect to reloxaliase and future product candidates in certain territories. We may not be able to identify suitable collaborators and, even if we do, our dependence on such relationships may adversely affect our business.

Because we have limited resources, we may seek to enter into collaboration agreements with other pharmaceutical or biotechnology companies. Our strategy for commercializing reloxaliase and any future product candidates we may develop outside of the United States may depend on our ability to enter into agreements with collaborators to obtain assistance and funding for the development and potential commercialization of our product candidates in the territories in which we may seek to partner. Despite our efforts, we may be unable to secure collaborative licensing or other arrangements that are necessary for us to further develop and commercialize our product candidates. Supporting diligence activities conducted by potential collaborators and negotiating the financial and other terms of a collaboration agreement are long and complex processes with uncertain results. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities ourselves, we may not be able to further develop our product candidates or bring them to market or continue to develop our technology platforms, and our business may be materially and adversely affected. Even if we are successful in entering into one or more collaboration agreements, collaborations may involve greater uncertainty for us, as we may have less control over certain aspects of our collaborative programs than we do over our proprietary development and commercialization programs. All of the risks relating to product development, regulatory approval and commercialization described in this Annual Report on Form 10-K also apply to the activities of any of our future program collaborators.

Any future collaborations that we enter into may not be successful. Any failure by our partners to perform their obligations or any decision by our partners to terminate these agreements could negatively impact our ability to successfully develop, obtain regulatory approvals for and commercialize our product candidates. In addition, partners may not properly obtain, maintain or, defend or enforce our intellectual property rights, may infringe, misappropriate or otherwise violate third-party intellectual property rights, may misappropriate our trade secrets or may otherwise use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to litigation and potential liability. In the event we grant exclusive rights to such partners, we could be precluded from potential commercialization of our product candidates within the territories in which we have a partner. Furthermore, any termination of our collaboration agreements will terminate any funding we may receive under the relevant collaboration agreement and may impair our ability to fund further development efforts and our progress in our development programs.

Further, our potential future collaborators may develop alternative products or pursue alternative technologies either on their own or in collaboration with others, including our competitors, and the priorities or focus of our collaborators may shift such that our product candidates receive less attention or resources than we would like, or they may be terminated altogether. Any such actions by our potential future collaborators may harm our business prospects and ability to earn revenues. In addition, we could have disputes with our potential future collaborators, such as the interpretation of terms in our agreements. Any such disagreements could lead to delays in the development or commercialization of our product candidates or could result in time-consuming and expensive litigation or arbitration, which may not be resolved in our favor.

We have relied, and will rely in the future, on third parties to conduct our nonclinical studies and clinical trials. If these third parties do not appropriately carry out their contractual duties, fail to conduct high-quality studies or meet expected deadlines, regulatory approval and commercialization of reloxaliase or any future candidates we may develop could be delayed or not obtained at all.

We do not have the ability to conduct all of our clinical trials independently. We have relied will continue to rely on third parties, including clinical investigators, third-party CROs, patients and consultants, to monitor, manage data for, participate in and execute our ongoing nonclinical and planned clinical programs for reloxaliase and other product candidates, and we control only some aspects of their activities. For example, in both our completed Phase 2 clinical trials and ongoing Phase 3 clinical trials we relied and are relying heavily on the efforts and contributions of investigative clinical sites and study patients to comply with a strict treatment regimen (e.g. three capsules per day with meals) and accurate timing of 24 hour urine collection, with the complete collection of all of the patient's urine during a given 24 hour period and with the proper handling of collected urine specimens, including storage, documentation, sample handling and shipping to the testing laboratory. Any failure of these third parties to meet their obligations has had or may in the future have an adverse effect on the results of clinical trials we have conducted or will conduct.

Because we rely on third parties, our internal capacity to perform these functions is limited. We currently have a small number of employees, which limits the internal resources we have available to identify and monitor our third-party providers. Nevertheless, we are responsible for ensuring that each of our nonclinical studies and clinical trials is conducted in accordance with the applicable protocol and legal, regulatory and scientific requirements and standards, including, for example, GLP, the Animal Welfare Act and GCPs. Our reliance on third parties does not relieve us of our regulatory responsibilities. Regulatory authorities enforce GCPs through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of these third parties fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the relevant regulatory authorities may require us to perform additional clinical trials in support of our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP requirements. We are also required to register clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to comply with these regulations may require us to repeat nonclinical studies and clinical trials, which would delay the regulatory approval process.

The third parties conducting our nonclinical studies and clinical trials on our behalf are not our employees, and except for remedies available to us under our agreements with such contractors, we cannot control whether or not they devote sufficient time, skill and resources to our ongoing clinical and nonclinical programs. To the extent we are unable to identify and successfully manage the performance of third-party service providers in the future, our business may be adversely affected. If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, 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 nonclinical studies and clinical trials may be extended, delayed or terminated and we may not be able to obtain, or may be delayed in obtaining, regulatory approval of or successfully commercialize reloxaliase and any other product candidates we may develop. As a result, our results of operations and the commercial prospects for our product candidates could be harmed, our costs could increase and our ability to generate revenues could be delayed, impaired or foreclosed.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties to manufacture reloxaliase and conduct other aspects of our clinical development activities, we must, at times, share trade secrets and other confidential information with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with any collaborators, CROs, manufacturers and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets. However, we cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or other confidential information. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets and confidential information become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's or other third party's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of certain collaborators, CROs, manufacturers and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are notified in advance and may delay publication for a specified time in order to secure our intellectual property rights arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in

some cases we may share these rights with other parties. Despite our efforts to protect our trade secrets, our competitors or other third parties may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets in cases where we do not have proprietary or otherwise protected rights at the time of publication. Discovery of our trade secrets by a competitor or other third party would impair our competitive position and have an adverse impact on our business.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since inception, expect to incur significant and increasing losses for at least the next several years, have not generated any revenue, may never generate any revenue, and may never achieve or maintain profitability.

We have incurred significant annual net operating losses in every year since our inception. We expect to continue to incur significant and increasing net operating losses for at least the next several years. Our net losses were $35.6 million and $21.7 million for the years ended December 31, 2018 and 2017, respectively. As of December 31, 2018, we had an accumulated deficit of $117.6 million. We have not generated any revenue, have not completed the development of any product candidate and may never have a product candidate approved for commercialization. We have financed our operations to date primarily through private placements of convertible preferred stock, our initial public offering, or IPO, in November 2017 and our credit facilities. We have devoted substantially all of our financial resources and efforts to research and development of reloxaliase and general and administrative expense to support such research and development. Our net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' (deficit) equity and working capital.

We anticipate that our expenses will increase substantially if and as we:

- conduct future clinical trials of our lead product candidate, reloxaliase, including our planned pivotal Phase 3 clinical program in adult patients with enteric hyperoxaluria;
- manufacture additional material for these potential future clinical trials;
- scale up our manufacturing process for reloxaliase to prepare for the submission of a potential BLA and commercialization if our clinical development program is successful;
- advance the development of ALLN-346;
- seek to identify and develop additional product candidates;
- seek regulatory and marketing approvals for our product candidates that successfully complete clinical trials, if any;
- establish sales, marketing, distribution and other commercial infrastructure in the future to commercialize various products for which we may obtain marketing approval, if any;
- obtain, maintain, expand and protect our intellectual property portfolio;
- hire and retain additional personnel, such as clinical, manufacturing, quality control and scientific personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development and help us comply with our obligations as a public company; and
- add equipment and physical infrastructure to support our research and development programs.

Our ability to become and remain profitable depends on our ability to generate revenue. We do not expect to generate significant revenue unless and until we are, or any future collaborator is, able to obtain marketing approval for, and successfully commercialize, one or more of our product candidates. Successful commercialization will require achievement of key milestones, including initiating and successfully completing clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those products for which we, or any of our future collaborators, may obtain marketing approval, satisfying any post-marketing requirements and obtaining reimbursement for our products from private insurance or government payors. Because of the uncertainties and risks associated with these activities, we are unable to accurately predict the timing and amount of revenues, if any, and if or when we might achieve profitability.

We and any future collaborators may never succeed in these activities and, even if we do, or any future collaborators do, we may never generate revenues that are large enough for us to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our pipeline of product candidates or continue our operations and cause a decline in the value of our stock price.

We have a limited operating history, no products approved for sale and no history of commercializing pharmaceutical products, which may make it difficult to evaluate the prospects for our future viability.

We commenced operations in 2011. Our operations to date have been limited to financing and staffing our company and developing our product candidates. We have not yet demonstrated an ability to obtain marketing approvals, manufacture a commercial-scale product or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Accordingly, you should consider our prospects in light of the costs, uncertainties, delays and difficulties frequently encountered by companies in the early stages of development, especially clinical stage biopharmaceutical companies such as ours. Any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing pharmaceutical products.

We may encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives. We will eventually need to transition from a company with a development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

We expect our financial condition and operating results to continue to fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

We will require substantial additional financing to achieve our goals, and a failure to obtain this necessary capital when needed on acceptable terms, or at all, could force us to delay, limit, reduce or terminate our product development, other operations or commercialization efforts.

Since our inception, most of our resources have been dedicated to the nonclinical and clinical development of our lead product candidate, reloxaliase. As of December 31, 2018, we had working capital of $58.7 million and capital resources consisting of cash and cash equivalents of $61.6 million. We believe that we will continue to expend substantial resources for the foreseeable future as we continue clinical development, seek regulatory approval, and prepare for the commercialization of reloxaliase and develop ALLN-346 and any other product candidates we may choose to pursue. These expenditures will include costs associated with research and development, conducting nonclinical studies and clinical trials, obtaining regulatory approvals, sales and marketing, and manufacturing and supply. In addition, other unanticipated costs may arise. Because the outcome of any clinical trial and/or regulatory approval process is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development, regulatory approval process and commercialization of reloxaliase and any future product candidates.

We believe that our existing cash and cash equivalents as of December 31, 2018 will enable us to fund our operating plan through at least the first half of 2020. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity, debt financings or other sources, such as strategic collaborations. Such financing may result in dilution to stockholders, imposition of debt covenants and repayment obligations, or other restrictions that may affect our business. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans.

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

- the time and cost necessary to complete our planned pivotal Phase 3 clinical program and obtain regulatory approvals for reloxaliase and the costs of post-marketing studies that could be required by regulatory authorities;
- the costs of manufacturing clinical trial supplies of reloxaliase;
- our ability to successfully commercialize reloxaliase;

- the selling and marketing costs associated with reloxaliase, including the cost and timing of building our sales and marketing capabilities;
- the amount of sales and other revenues from reloxaliase, including the sales price and the availability of adequate third-party reimbursement;
- the cash requirements of any future acquisitions or discovery of product candidates;
- the progress, timing, scope and costs of our nonclinical studies and clinical trials, including the ability to enroll patients in a timely manner for potential future clinical trials;
- our ability to comply with the covenants under our current and future credit facilities;
- the time and cost necessary to respond to technological and market developments; and
- the costs of filing, prosecuting, maintaining, defending and enforcing any patent claims and other intellectual property rights.

Additional funds may not be available when we need them, on terms that are acceptable to us, or at all. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce or terminate:

- clinical trials or other development activities for reloxaliase, ALLN-346 or any other product candidate;
- our preclinical research and development activities; or
- our establishment of sales and marketing capabilities or other activities that may be necessary to commercialize reloxaliase or any future product candidate.

Our existing and any future indebtedness could adversely affect our ability to operate our business.

As of December 31, 2018, we had $10.0 million of outstanding borrowings under our credit facility with Pacific Western Bank, or PWB. We currently make monthly interest payments. Beginning January 2020, we will be required to make payments of principal and interest on these borrowings in monthly installments through June 2022. Subject to the restrictions in this existing credit facility, we could in the future incur additional indebtedness beyond our borrowings from PWB.

Our outstanding indebtedness, including any additional indebtedness beyond our borrowings from PWB, combined with our other financial obligations and contractual commitments could have significant adverse consequences, including:

- requiring us to dedicate a portion of our cash resources to the payment of interest and principal, reducing money available to fund working capital, capital expenditures, product development and other general corporate purposes;
- increasing our vulnerability to adverse changes in general economic, industry and market conditions;
- subjecting us to restrictive covenants that may reduce our ability to take certain corporate actions or obtain further debt or equity financing;
- limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we compete; and
- placing us at a competitive disadvantage compared to our competitors that have less debt or better debt servicing options.

We intend to satisfy our current and future debt service obligations with our existing cash and cash equivalents. However, we may not have sufficient funds, and may be unable to arrange for additional financing, to pay the amounts due under our existing credit facility or any other debt instruments. Failure to make payments or comply with other covenants under our existing credit facility or such other debt instruments could result in an event of default and acceleration of amounts due. Under our loan and security agreement with PWB, the occurrence of an event that would reasonably be expected to have a material adverse effect on our business, operations, assets or condition is an event of default. If an event of default occurs and PWB accelerates the amounts due, we may not be able to make accelerated payments, and the lenders could seek to enforce security interests in the collateral securing such indebtedness, which includes substantially all of our assets other than our

intellectual property. In addition, the covenants under our existing credit facility, the pledge of our assets as collateral and the negative pledge with respect to our intellectual property could limit our ability to obtain additional debt financing.

Risks Related to Our Business and Industry

We depend on the knowledge and skill of our senior management and other key employees, and if we are unable to retain or if we fail to recruit additional highly skilled personnel, our business will be harmed.

Our ability to compete in the highly competitive pharmaceuticals industry depends in large part upon our ability to attract and retain highly qualified managerial, commercial, scientific and medical personnel. We are highly dependent on our management, commercial, scientific and medical personnel. In order to induce valuable employees to remain with us, we have provided employees with stock options that vest over time. The value to employees of stock options that vest over time is significantly affected by movements in our stock price that we cannot control and, together with our other compensation programs and benefits, may at any time be insufficient to counteract more lucrative offers from other companies.

We are highly dependent upon the principal members of our management team, including Louis Brenner, M.D., our President and Chief Executive Officer and Edward Wholihan, our Chief Financial Officer, as well as the other principal members of our management, scientific and clinical team. Although we have entered into employment agreements with our executive officers, each of them may terminate their employment with us at any time. The loss of any executive or other principal member of our management team would impair our ability to identify, develop and market new products and conduct successful operations.

In addition, our growth will require us to hire a significant number of qualified technical, commercial and administrative personnel. There is intense competition from other companies and research and academic institutions for qualified personnel in the areas of our activities. Other biopharmaceutical companies with which we compete for qualified personnel may have greater financial and other resources, different risk profiles, and a longer history in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high-quality candidates than what we have to offer. If we are unable to continue to attract and retain high-quality personnel, the rate and success at which we can develop and commercialize reloxaliase and any other product candidates we may develop would be impaired and could adversely affect our growth and financial performance.

Our employees, principal investigators, CROs and consultants may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk that our employees, principal investigators, CROs and consultants may engage in fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violate the regulations of the FDA and other comparable foreign regulators, including those laws requiring the reporting of true, complete and accurate information to such authorities; healthcare fraud and abuse laws and regulations in the United States and abroad; or laws that require the reporting of financial information or data accurately. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, 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. Activities subject to these laws also involve the improper use of information obtained in the course of clinical trials or creating fraudulent data in our preclinical studies or clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. Prior to completing our IPO, we adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. Additionally, we are subject to the risk that a person could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

We are subject to U.S. and foreign anti-corruption and anti-money laundering laws with respect to our operations and non-compliance with such laws can subject us to criminal and/or civil liability and harm our business.

We are subject to the U.S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and possibly other state and national anti-

bribery and anti-money laundering laws in countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, third-party intermediaries, joint venture partners and collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or benefits to recipients in the public or private sector. We may have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. In addition, we may engage third-party intermediaries to promote our clinical research activities abroad and/or to obtain necessary permits, licenses, and other regulatory approvals. We can be held liable for the corrupt or other illegal activities of these third-party intermediaries, our employees, representatives, contractors, partners, and agents, even if we do not explicitly authorize or have actual knowledge of such activities.

In connection with our IPO, we adopted a Code of Business Conduct and Ethics, and expect to prepare and implement policies and procedures to ensure compliance with such code. The Code of Business Conduct and Ethics mandates compliance with the FCPA and other anti-corruption laws applicable to our business throughout the world. However, we cannot assure you that our employees and third-party intermediaries will comply with this code or such anti-corruption laws. Noncompliance with anti-corruption and anti-money laundering laws could subject us to whistleblower complaints, investigations, sanctions, settlements, prosecution, other enforcement actions, disgorgement of profits, significant fines, damages, other civil and criminal penalties or injunctions, suspension and/or debarment from contracting with certain persons, the loss of export privileges, reputational harm, adverse media coverage, and other collateral consequences. If any subpoenas, investigations, or other enforcement actions are launched, or governmental or other sanctions are imposed, or if we do not prevail in any possible civil or criminal litigation, our business, results of operations and financial condition could be materially harmed. In addition, responding to any action will likely result in a materially significant diversion of management's attention and resources and significant defense and compliance costs and other professional fees. In certain cases, enforcement authorities may even cause us to appoint an independent compliance monitor which can result in added costs and administrative burdens.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. 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.

Our business and operations would suffer in the event of computer system failures, cyber-attacks on our systems or deficiency in our cyber security.

Despite the implementation of security measures, our internal computer systems, and those of third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, malware, natural disasters, fire, terrorism, war and telecommunication, electrical failures, cyber-attacks or cyber-intrusions over the Internet, attachments to emails, persons inside our organization, or persons with access to systems inside our organization. The risk of a security breach or disruption, particularly through cyber-attacks or cyber intrusion, including by computer hackers, foreign governments, and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. In addition, our systems safeguard important confidential personal data regarding patients enrolled in our clinical trials. If a disruption event were to occur and cause interruptions in our operations, it could result in a disruption of our drug development programs. For example, the loss of clinical trial data from completed, ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of reloxaliase and any other product candidates we may develop could be delayed.

Risks Related to Intellectual Property

If we are unable to obtain and maintain sufficient patent protection for our product candidates, or if the scope of the patent protection is not sufficiently broad, our competitors could develop and commercialize products similar or identical to ours, and our ability to commercialize our product candidates successfully may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary product candidates. If we do not adequately protect or enforce our intellectual property, competitors may be able to erode or negate any competitive advantage we may have, which could harm our business and ability to achieve profitability. To protect our proprietary position, we file patent applications in the United States and abroad related to our novel product candidates that are important to our business. The patent application and approval process is expensive, complex and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the United States or in many foreign jurisdictions. In addition, the determination of patent rights with respect to biological and pharmaceutical products commonly involves complex legal and factual questions, which has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent. However, prior to March 16, 2013, in the United States, the first to invent was entitled to the patent. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions.

Moreover, because the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, our patents or pending patent applications may be challenged in the courts or patent offices in the United States and abroad. For example, we may be subject to a third party preissuance submission of prior art to the U.S. Patent and Trademark Office, or USPTO, or become involved in post-grant review procedures, oppositions, derivations, reexaminations, *inter partes* review or interference proceedings, in the United States or elsewhere, challenging our patent rights or the patent rights of others. An adverse determination in any such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized.

Our pending and future patent applications may not result in patents being issued which protect our product candidates, in whole or in part, or which effectively prevent others from commercializing competitive products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, the laws of foreign countries may not protect our rights to the same extent or in the same manner as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. Our competitors may also seek approval to market their own products similar to or otherwise competitive with our products, for example, reloxaliase. Alternatively, our competitors may seek to market generic versions of any approved products by submitting abbreviated BLAs to the FDA during which process they may claim that patents owned or licensed by us are invalid, unenforceable or not infringed. In these circumstances, we may need to defend or assert our patents, or both, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid or unenforceable, or that our competitors are competing in a non-infringing manner. Thus, even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

We heavily rely on certain in-licensed patents and other intellectual property rights in connection with our development of reloxaliase and, if we fail to comply with our obligations under our existing and any future intellectual property licenses with third parties, we could lose license rights that are important to our business.

Our ability to develop and commercialize our lead product candidate, reloxaliase, is heavily dependent on licenses to patent rights and other intellectual property granted to us by third parties. For example, we are party to a license agreement with Althea Technologies, Inc. (now known as Ajinomoto Althea, Inc.), or Althea, under which we received an exclusive, worldwide, royalty-bearing, sublicensable, and, except under certain circumstances, non-transferable license under certain of the patent rights to develop, use, make, have made, market, offer to sell, sell, have sold, distribute, import or otherwise exploit reloxaliase. We may enter into additional license agreements in the future. Our license agreement with Althea imposes, and we expect that future license agreements will impose, various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with our obligations under these licenses, our licensors, including Althea, may have the right to terminate these license agreements, in which event we might not be able to market our lead product candidate, reloxaliase. Similarly, other licensors may convert an exclusive license to a non-exclusive license, which could adversely affect the value of a product candidate developed under a given license agreement. Termination of any of our license agreements or reduction or elimination of our licensed rights may also result in our having to negotiate new or reinstated licenses with less favorable terms.

Further, in some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. For example, pursuant to our license agreement with Althea, Althea controls such activities for certain patents licensed to us under such agreement. Therefore, we cannot be certain that these patents will be prosecuted, maintained and enforced in a manner consistent with the best interests of our business. If our current or future licensors or collaboration partners fail to obtain, maintain or protect any patents or patent applications licensed to us, our rights to such patents and patent applications may be reduced or eliminated and our right to develop and commercialize any of our product candidates that are the subject of such licensed rights could be adversely affected.

Patent term may be inadequate to protect our competitive position on our products for an adequate amount of time.

Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984 permits a patent term extension of up to five years beyond the normal expiration of the patent, which is limited to the approved indication (or any additional indications approved during the period of extension). However, a patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of the product's approval by the FDA, only one patent applicable to an approved drug is eligible for the extension, and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. In the future, if and when our product candidates, for example, reloxaliase, receive FDA approval, we intend to apply for patent term extensions on patents covering those products in any jurisdiction where these are available. However, the applicable authorities, including the FDA and the USPTO in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. Moreover, we may not receive an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. If this occurs, our competitors may be able to take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case.

We may become involved in lawsuits to protect or enforce our patents and other intellectual property rights, which could be expensive, time consuming and unsuccessful.

Competitors and other third parties may infringe, misappropriate or otherwise violate our patents and other intellectual property rights. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming and divert the time and attention of our management, business and scientific personnel. In addition, many of our adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we can.

A court may disagree with our allegations and may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the third-party technology in question. Furthermore, the other party could counterclaim that we infringe their intellectual property or counterclaim that a patent we have asserted against them is invalid or unenforceable, or both. In patent litigation in the United States, counterclaims challenging the validity, enforceability or scope of asserted patents are commonplace. Similarly, third parties may initiate legal proceedings against us seeking a

declaration that certain of our intellectual property rights are non-infringed, invalid, or unenforceable. The outcome of any such proceeding is generally unpredictable.

Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, non-enablement, or written description. In addition, validity challenges may, under certain circumstances, be based upon non-statutory obviousness-type double patenting and associated rules related to common ownership, which, if successful, could result in a finding that the patent claims at issue are invalid and unenforceable or a loss of patent term, including a patent term adjustment granted by the USPTO. Furthermore, patents may be held unenforceable if someone connected with prosecution of the patent in question withheld relevant information from the USPTO or made a misleading statement during prosecution of the patent. It is possible that prior art of which we and the patent examiner were unaware during prosecution exists, which could render our patents invalid. It is also possible that prior art may exist that we are aware of but do not believe is relevant to our current or future patents, but that could nevertheless be determined to render our patents invalid.

An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. If a defendant were to prevail on a legal assertion of invalidity or unenforceability of our patents covering one of our product candidates, we would lose at least part, and perhaps all, of the patent protection covering such product candidate. Competing drugs may also be sold in other countries in which our patent coverage might not exist or be as strong. If we lose a foreign patent lawsuit, alleging our infringement of a competitor's patents, we could be prevented from marketing our drugs in one or more foreign countries. Any of these outcomes would have a material adverse effect on our business.

Because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public announcements of the results of hearing, motions, or other interim developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of shares of our common stock. Even if we ultimately prevail, a court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may not be an adequate remedy. Furthermore, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our business.

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

Filing, prosecuting and defending patents on our product candidates in all countries throughout the world would be prohibitively expensive. The requirements for patentability may differ in certain countries, particularly in developing countries.

Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. Additionally, the patent laws of some foreign countries do not afford intellectual property protection to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, for example, India and China, do not favor the enforcement of patents and other intellectual property rights. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, certain foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States.

Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, if our ability to enforce our patents to stop infringing activities is inadequate. These products may compete with our product candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business. Furthermore, while we intend to protect our intellectual property rights in the major markets for our product candidates, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our product candidates. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate.

Obtaining and maintaining patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In addition, periodic maintenance fees on issued patents often must be paid to the USPTO and foreign patent agencies over the lifetime of the patent. While an unintentional lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we fail to maintain the patents and patent applications covering our drugs or procedures, we may not be able to stop a competitor from marketing drugs that are the same as or similar to our product candidates, which would have a material adverse effect on our business.

If we are sued for infringing intellectual property of third parties, such litigation could be costly and time consuming and could prevent or delay us from developing or commercializing our product candidates.

Our commercial success depends, in part, upon our ability to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the proprietary rights and intellectual property of third parties. We may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates and technologies we use in our business. Our competitors or other third parties may assert infringement claims against us, alleging that our product candidates are covered by their patents. We cannot be certain that we do not infringe existing patents or that we will not infringe patents that may be granted in the future. For example, we are aware of companies that have filed patent applications directed to oxalate and uric acid degrading enzymes, some of which have already been allowed or issued, and others may issue in the future. It is possible that additional patent applications are filed and additional patents directed to these enzymes are granted in the future. Furthermore, because patent applications can take many years to issue and may be confidential for 18 months or more after filing, and because patent claims can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use or sale of our product candidates. If a patent holder believes our product candidate infringes its patent rights, the patent holder may sue us even if we have received patent protection for our technology. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant drug revenue and against whom our own patent portfolio may thus have no deterrent effect.

If we were sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable. However, proving invalidity and unenforceability is difficult. In the United States, for example, providing invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could significantly harm our business and operating results. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our product candidates and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain such a license, it could be granted on non-exclusive terms, thereby providing our competitors and other third parties access to the same technologies licensed to us. Without such a license, we could be forced, including by court order, to cease developing and commercializing the infringing technology or product candidates. In addition, we could be found liable for significant monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed such third-party patent rights. A finding of infringement could significantly harm our business and operating results.

Changes to the patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.

As is the case with other biotechnological and pharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnological and pharmaceutical industries involve both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Recent patent reform legislation in the United States and other countries, including the Leahy-Smith America Invents Act, or Leahy-Smith Act, signed into law on September 16, 2011, could increase those uncertainties and costs. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications

are prosecuted, redefine prior art and provide more efficient and cost-effective avenues for competitors to challenge the validity of patents. In addition, the Leahy-Smith Act has transformed the U.S. patent system into a "first to file" system. The first-to-file provisions, however, only became effective on March 16, 2013. It is still not yet clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could make it more difficult to obtain patent protection for our inventions and increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could harm our business, results of operations and financial condition.

In addition, the U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. Additionally, there have been recent proposals for additional changes to the patent laws of the United States and other countries that, if adopted, could impact our ability to obtain patent protection for our proprietary technology or our ability to enforce our proprietary technology. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

Although we have obtained composition of matter patents covering reloxaliase and its use in therapy, we also rely on trade secrets, including confidential and unpatented know-how important to the maintenance of our competitive position. We protect our trade secrets and confidential and unpatented know-how, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to such knowledge, such as our employees, outside scientific collaborators, advisors, contractors, contract manufacturers and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants that obligate them to maintain confidentiality and assign their inventions to us. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts in the United States and certain foreign jurisdictions are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be harmed.

We may be subject to claims by third parties asserting that our employees or we have misappropriated or otherwise violated their intellectual property rights, or claiming ownership of what we regard as our own intellectual property.

Many of our consultants, advisors and employees, including our senior management, were previously employed at other biotechnology or pharmaceutical companies. Some of these individuals, including certain members of our senior management, may have executed proprietary rights, non-disclosure and non-competition agreements, or similar agreements, in connection with such previous employment. Although we try to ensure that our consultants, advisors and employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these individuals have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such third party. Litigation may be necessary to defend against such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel or sustain damages. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products. Such a license may not be available on commercially reasonable terms or at all. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while we typically require our employees, consultants and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, develops intellectual property that we regard as our own, which may result in claims by or against us related to the ownership of such intellectual property. The assignment of intellectual property rights may not be self-executing, or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our senior management and scientific personnel. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Risks Related to Our Common Stock

The price of our common stock may be volatile and fluctuate substantially.

On November 6, 2017, we completed the sale of 5,333,333 shares of our common stock in our IPO, at a price to the public of $14.00 per share. Since our common stock began trading on The NASDAQ Global Select Market on November 6, 2017, our stock has traded at prices as low as $5.11 per share and as high as $16.60 per share through March 1, 2019. There has been a public market for our common stock for only a short period of time. Although our common stock is listed on The NASDAQ Global Select Market, an active public market for our common stock may not emerge or be sustained.

In addition, the market price for our common stock may fluctuate significantly in response to a number of factors, including:

- the success of competitive drugs or technologies;
- regulatory actions with respect to our product candidates or our competitors' products and product candidates;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures,
- collaborations or capital commitments;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates or drugs;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts, and our performance in relation to such estimates;
- variations in our financial results or those of companies that are perceived to be similar to us;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or other stockholders;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover our stock;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this "Risk Factors" section.

We will incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to compliance initiatives and corporate governance practices.

As a public company, and particularly after we are no longer an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, we will incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The Nasdaq Stock Market and other applicable securities

rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. We expect that we will need to hire additional accounting, finance and other personnel in connection with our becoming, and our efforts to comply with the requirements of being, a public company and our management and other personnel will need to devote a substantial amount of time towards maintaining compliance with these requirements. These requirements will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. We are currently evaluating these rules and regulations, and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404 of the Sarbanes-Oxley Act, or SOX Section 404, we will be required to furnish a report by our management on our internal control over financial reporting beginning with our second filing of an Annual Report on Form 10-K with the Securities and Exchange Commission, or the SEC. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with SOX Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by SOX Section 404. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

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

The trading market for our common stock will likely depend, in part, on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. There can be no assurance that analysts will cover us, or provide favorable coverage. If one or more analysts downgrade our stock or change their opinion of our stock, our share price would likely decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

Our directors, executive officers and principal stockholders exercise significant control over our company, which will limit your ability to influence corporate matters.

As of March 1, 2019, our executive officers, directors and principal stockholders collectively controlled approximately 78.1% of our outstanding common stock, excluding any shares of common stock that such persons may have the right to acquire upon exercise of outstanding options or warrants. As a result, these stockholders, if they act together, will be able to influence our management and affairs and all matters requiring stockholder approval, including the election of directors and approval of significant corporate transactions. As a result, these stockholders, if they act together, will be able to influence our management and affairs and all matters requiring stockholder approval, including the election of directors and approval of significant corporate transactions.

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our restated certificate of incorporation and amended and restated by-laws may delay or prevent an acquisition of us or a change in our management. These provisions include a classified board of directors, a prohibition on actions by written consent of our stockholders and the ability of our board of directors to issue preferred stock without stockholder approval. In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us. Although we believe these provisions collectively provide for an opportunity to obtain greater value for stockholders by requiring potential acquirors to negotiate with our board of directors, they would apply even if an offer rejected by our board were considered beneficial by some stockholders. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult

for stockholders to replace members of our board of directors, which is responsible for appointing the members of our management.

A significant portion of our total outstanding shares are restricted from immediate resale but may be sold into the market in the near future, which could cause the market price of our common stock to drop significantly, even if our business is otherwise doing well.

If our existing stockholders sell, or indicate an intent to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline significantly. As of March 1, 2019, we had 20,815,014 outstanding shares of common stock, assuming no exercise of outstanding options or warrants. In addition, the 2,141,527 shares subject to outstanding options under our stock option plans as of December 31, 2018, the 2,120,814 shares reserved for future issuance under our stock option plans, the 405,742 shares reserved for future issuance under our employee stock purchase plan and the shares subject to outstanding warrants will become eligible for sale in the public market in the future, subject to certain legal and contractual limitations. If our existing stockholders sell substantial amounts of our common stock in the public market, or if the public perceives that such sales could occur, this could have an adverse impact on the market price of our common stock, even if there is no relationship between such sales and the performance of our business.

We are an "emerging growth company," and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an "emerging growth company," as defined in the JOBS Act, and may remain an emerging growth company for up to five years. For so long as we remain an emerging growth company, we are permitted and plan to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include not being required to comply with the auditor attestation requirements of SOX Section 404, not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements, reduced disclosure obligations regarding executive compensation, 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. As a result, the information we provide stockholders will be different than the information that is available with respect to other public companies. In our Annual Report on Form 10-K for the year ended December 31, 2018, we did not include all of the executive compensation related information that would be required if we were not an emerging growth company. We cannot predict whether investors will find our common stock less attractive if we 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.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to 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 exemption from new or revised accounting standards, and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We do not intend to pay dividends on our common stock and, consequently, your ability to achieve a return on your investment will depend on appreciation in the price of our common stock.

We have never declared or paid any cash dividend on our common stock and do not currently intend to do so in the foreseeable future. Our credit facility with PWB also prohibits us from paying cash dividends without the prior written consent of PWB. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends in the foreseeable future. Therefore, the success of an investment in shares of our common stock will depend upon any future appreciation in their value. There is no guarantee that shares of our common stock will appreciate in value or even maintain the price at which you purchased them.

The effects of recently enacted tax legislation and other legislative, regulatory and administrative developments to our business are uncertain. Increased costs related to such developments could adversely affect our financial condition and results of operations.

On December 22, 2017, the President of the United States signed into law H.R. 1, informally titled the Tax Cuts and Jobs Act, or the TCJA. The TCJA makes major changes to the taxation of corporations, including reduction of the corporate tax rate from 35% to 21%, limitation of the tax deduction for interest expense to 30% of adjusted taxable income (except for certain small businesses), limitation of the deduction for net operating losses to 80% of annual taxable income and elimination of net operating loss carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions

and credits. The effect of the significant changes made by the TCJA is highly uncertain, and administrative guidance will be required in order to fully evaluate the effect of many provisions on our business and stockholders.

Our ability to utilize our net operating loss carryforwards and certain other tax attributes may be limited.

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change" (generally defined as a greater than 50% change (by value) in the ownership of its equity over a three year period), the corporation's ability to use its pre-change net operating loss carryforwards and certain other pre-change tax attributes to offset its post-change income may be limited. We may have experienced such ownership changes in the past, and we may experience ownership changes as a result of our IPO or subsequent shifts in our stock ownership, some of which are outside our control. As of December 31, 2018, we had federal net operating loss carryforwards of approximately $111.1 million, and our ability to utilize those net operating loss carryforwards could be limited by an "ownership change" as described above, which could result in increased tax liability to us. The reduction of the corporate tax rate under the TCJA may cause a reduction in the economic benefit of our net operating loss carryforwards and other deferred tax assets available to us. Under the TCJA, net operating losses generated after December 31, 2017 are not subject to expiration.

Volatility in our share price could subject us to securities class action litigation.

Securities class action litigations have often been brought against companies following a decline in the market price of their securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant share price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, would result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

We will need additional capital in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

Pursuant to our 2017 Stock Option and Incentive Plan, or the 2017 Plan, we are authorized to grant stock options and other equity-based awards to our employees, directors and consultants. The number of shares available for future grant under the 2017 Plan will automatically increase each year by up to 4% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our board of directors or compensation committee to take action to reduce the size of the increase in any given year. Currently, we plan to register the increased number of shares available for issuance under the 2017 Plan each year. If our board of directors elects to increase the number of shares available for future grant by the maximum amount each year, our stockholders may experience additional dilution, and our stock price may fall.

As a public reporting company, we are subject to rules and regulations established from time to time by the SEC and the Public Company Accounting Oversight Board, or PCAOB, regarding our internal control over financial reporting. We may not complete improvements to our internal control over financial reporting in a timely manner, or these internal controls may not be determined to be effective, which may adversely affect investor confidence in our company and, as a result, the market price of our common stock could decline and you could lose all or part of your investment.

Upon completion of our IPO, we became a public reporting company subject to the rules and regulations established from time to time by the SEC and the PCAOB. These rules and regulations require, among other things that we establish and periodically evaluate procedures with respect to our internal controls over financial reporting. These reporting obligations are likely to place a considerable strain on our financial and management systems, processes and controls, as well as on our personnel.

In addition, we will be required to document and test our internal controls over financial reporting pursuant to SOX Section 404, so that our management can certify as to the effectiveness of our internal controls over financial reporting by the time our annual report for the year ending December 31, 2018 is due and thereafter, which will require us to document and make significant changes to our internal controls over financial reporting. Likewise, our independent registered public accounting firm will be required to provide an attestation report on the effectiveness of our internal control over financial reporting at such time as we cease to be an "emerging growth company," as defined in the JOBS Act, although, as described in the preceding risk factor, we could potentially qualify as an "emerging growth company" for more than five years. At such

time, our independent registered public accounting firm may issue a report that is adverse in the event it is not satisfied with the level at which our controls are documented, designed or operating.

If our senior management is unable to conclude that we have effective internal control over financial reporting, or to certify the effectiveness of such controls, or if our independent registered public accounting firm cannot render an unqualified opinion on management's assessment and the effectiveness of our internal control over financial reporting once we cease to be an emerging growth company, or if material weaknesses in our internal controls are identified, we could be subject to regulatory scrutiny and a loss of public confidence, which could have a material adverse effect on our business and our stock price. In addition, if we do not maintain adequate financial and management personnel, processes and controls, we may not be able to manage our business effectively or accurately report our financial performance on a timely basis, which could cause a decline in our common stock price and adversely affect our results of operations and financial condition.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to the periodic reporting requirements of the Exchange Act of 1934, as amended, or the Exchange Act. Our disclosure controls and procedures are designed to reasonably ensure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management and recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures as well as internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are and will be met. These inherent limitations include the realities that judgments in decision-making can be faulty and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements due to error or fraud may occur and not be detected.

Our restated certificate of incorporation and amended and restated bylaws provide that the Court of Chancery of the State of Delaware is the exclusive forum for certain litigation that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our restated certificate of incorporation and amended and restated bylaws provide that the Court of Chancery of the State of Delaware is the exclusive forum for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim for breach of a fiduciary duty owed by any of our directors, officers or other employee to us or our stockholders, (iii) any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law, our restated certificate of incorporation or our amended and restated bylaws or (iv) any action asserting a claim 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 restated certificate of incorporation and amended and restated bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

We occupy approximately 7,795 square feet of office space in Newton, MA under a lease that expires in December of 2020. In addition, we occupy approximately 7,564 square feet of office and laboratory space in Sudbury, MA under a lease that expires in February 2021. We do not own any real property. We believe that this office and laboratory space is sufficient to meet our current needs and that suitable additional space will be available as and when needed.

ITEM 3. LEGAL PROCEEDINGS

From time to time, we may become involved in litigation relating to claims arising from the ordinary course of business. Our management believes that there are currently no claims or actions pending against us, the ultimate disposition of which could have a material adverse effect on our results of operations or financial condition.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

PART II

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

Market Information

Our common stock commenced trading under the symbol "ALNA" on the NASDAQ Global Select Market on November 2, 2017. Prior to that time, there was no public market for our common stock. Our common stock in our initial public offering priced at $14.00 per share on November 1, 2017. The following table sets forth on a per share basis, for the periods indicated, the low and high close prices of our common stock as reported by the NASDAQ Global Select Market for our fiscal years ended December 31, 2018 and 2017 since our initial public offering.

Year ended December 31, 2018	High	Low
First Quarter	$ 11.56	$ 6.13
Second Quarter	$ 17.56	$ 11.80
Third Quarter	$ 13.98	$ 9.45
Fourth Quarter	$ 11.82	$ 4.80

Year ended December 31, 2017	High	Low
Fourth Quarter (from November 2, 2017)	$ 15.40	$ 8.66

On March 1, 2018, the last reported sales price of our common stock on the Nasdaq Global Select Market was $6.83 and as of March 1, 2018, there were approximately 22 holders of record of our common stock. However, because many of our outstanding shares are held in accounts with brokers and other institutions, we believe we have more beneficial owners.

Dividend Policy

We have never declared or paid any dividends on our capital stock. We currently intend to retain all available funds and any future earnings, if any, to fund the development and expansion of our business and we do not anticipate paying any cash dividends in the foreseeable future. In addition, pursuant to our loan and security agreement with SVB, we are prohibited from paying cash dividends without the prior written consent of SVB. Moreover, any future indebtedness that we may incur could preclude us from paying dividends. Any future determination to pay dividends will be made at the discretion of our board of directors. Investors should not purchase our common stock with the expectation of receiving cash dividends.

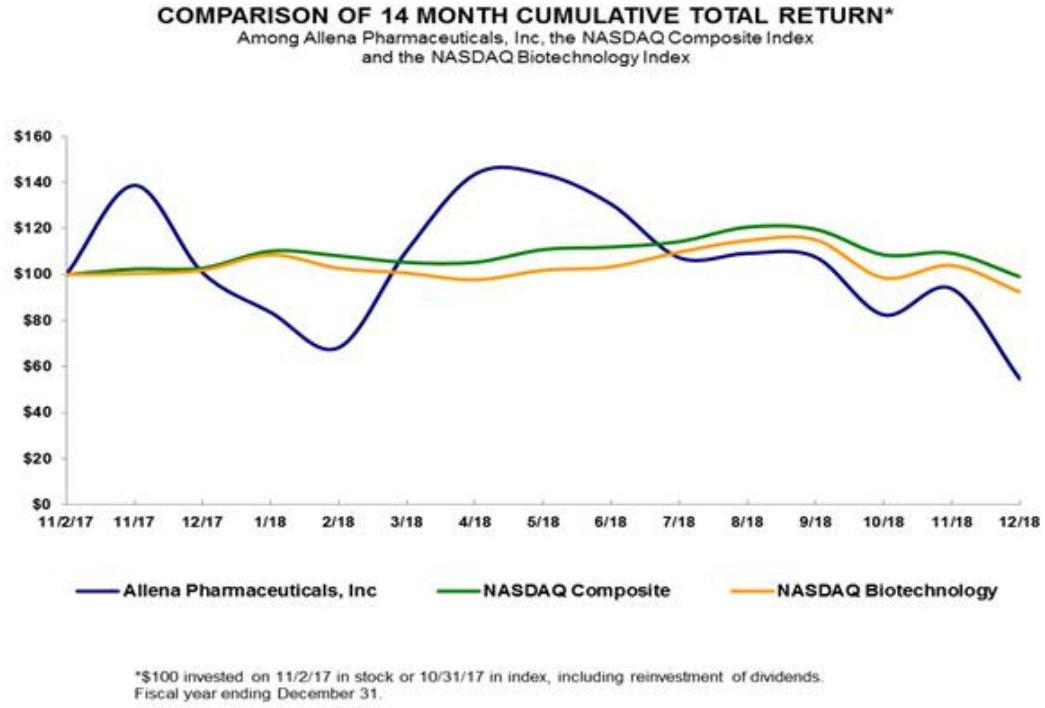
Equity Compensation Plan Information

For information regarding securities authorized for issuance under equity compensation plans, see Part III "Item 12—Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters."

Stock Performance Graph

The following performance graph and related information shall not be deemed to be "soliciting material" or to be "filed" with the SEC, for purposes of Section 18 of the Exchange Act, nor shall such information be incorporated by reference into any future filing under the Exchange Act or Securities Act, except to the extent that we specifically incorporate it by reference into such filing.

The following graph compares the performance of our common stock to the NASDAQ Composite Index and to the NASDAQ Biotechnology Index from November 2, 2017 (the first date that shares of our common stock were publicly traded) through December 31, 2018. The comparison assumes $100 was invested in our common stock and in each of the foregoing indices after the market closed on November 2, 2017, and it assumes reinvestment of dividends, if any. The stock price performance included in this graph is not necessarily indicative of future stock price performance.



Unregistered Sales of Equity Securities and Use of Proceeds

Recent Sales of Unregistered Equity Securities

None.

Use of Proceeds from Initial Public Offering

On November 6, 2017, we completed the sale of 5,333,333 shares of our common stock in our IPO at a price to the public of $14.00 per share. The underwriters partially exercised their over-allotment option on December 1, 2017, and purchased an additional 16,969 shares of our common stock. We received approximately $67.0 million in net proceeds from our IPO after deducting $7.9 million of underwriting discounts, commissions and offering costs. The offer and sale of the shares in our IPO was registered under the Securities Act pursuant to registration statements on Form S-1 (File No. 333-220857), which was filed with the SEC on October 6, 2017 and amended subsequently and declared effective by the SEC on November 1, 2017. Following the sale of the shares in connection with the closing of our IPO, the offering terminated. The offering did not terminate before all the securities registered in the registration statements were sold. Credit Suisse Securities, LLC (USA), Jefferies LLC and Cowen and Company, LLC acted as lead book-running managers for the offering. Wedbush PacGrow acted as the co-manager for the offering.

We raised approximately $67.0 million in net proceeds after deducting underwriting discounts and commissions and offering expenses payable by us. None of these expenses consisted of direct or indirect 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. There has been no material change in the planned use of proceeds from our IPO as described in our final prospectus filed with the SEC on November 6, 2017. As of December 31, 2017, the funds received were held as cash equivalents.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

ITEM 6. SELECTED FINANCIAL DATA

You should read the following selected consolidated financial data together with our consolidated financial statements and the related notes appearing elsewhere in this Annual Report on Form 10-K and the information under the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations." We have derived the consolidated statements of operations data for the years ended December 31, 2018, 2017 and 2016 and the balance sheet data as of December 31, 2018 and 2017 from our audited consolidated financial statements included elsewhere in this Annual Report on Form 10-K. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period and are not necessarily indicative of results to be expected for a full year or any other interim period.

	Years Ended December 31,		
	2018	2017	2016
	(in thousands, except share and per share data)		
Consolidated Statement of Operations Data:			
Operating expenses:			
Research and development	$ 26,376	$ 15,519	$ 20,103
General and administrative	9,217	5,431	4,083
Total operating expenses	35,593	20,950	24,186
Other income (expense):			
Interest income (expense), net	575	(443)	(200)
Other income (expense), net	(13)	(257)	(121)
Loss on extinguishment of debt	(617)	—	—
Other income (expense), net	(55)	(700)	(321)
Net loss	$ (35,648)	$ (21,650)	$ (24,507)
Net loss per share attributable to common stockholders — basic and diluted (1)	$ (1.72)	$ (4.80)	$ (18.35)
Weighted-average common shares outstanding — basic and diluted	20,741,226	4,520,337	1,339,254

(1) See Note 2 within the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for a description of the method used to calculate basic and diluted net loss per share of common stock.

	December 31,		
	2018	2017	2016
	(in thousands)		
Consolidated Balance Sheet Data:			
Cash, cash equivalents and investments	$ 61,643	$ 94,494	$ 48,755
Working capital (1)	58,706	88,490	46,025
Total assets	65,229	96,249	49,479
Loan payable, net of current portion and discount	9,980	5,516	9,409
Convertible preferred stock	—	—	95,727
Total stockholders' equity (deficit)	49,456	82,870	(59,277)

(1) We define working capital as current assets less current liabilities. See our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for further details regarding our current assets and current liabilities.

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

Overview

You should read the following discussion and analysis of our financial condition and results of operations together with our "Selected Consolidated Financial Data" and our consolidated financial statements and the related notes included elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this Annual Report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a late-stage, clinical biopharmaceutical company dedicated to developing and commercializing first-in-class, oral enzyme therapeutics to treat patients with rare and severe metabolic and kidney disorders. We are focused on metabolic disorders that result in excess accumulation of certain metabolites that can cause kidney stones, damage the kidney, and potentially lead to chronic kidney disease, or CKD, and end-stage renal disease. Our lead product candidate, reloxaliase (formerly known as ALLN-177), is a first-in-class, oral enzyme therapeutic that we are developing for the treatment of hyperoxaluria, a metabolic disorder characterized by markedly elevated urinary oxalate levels and commonly associated with kidney stones, CKD and other serious kidney diseases. There are currently no approved therapies for the treatment of hyperoxaluria.

We have conducted a robust clinical development program of reloxaliase, including three Phase 2 clinical trials, which demonstrated reductions of urinary oxalate excretion in patients with secondary hyperoxaluria, particularly in patients with enteric hyperoxaluria. Reloxaliase has also been well tolerated in clinical trials to date. Based on these data, the high unmet medical need, the enzyme's specific mechanism of action, and the significant market opportunity, we are initially developing reloxaliase for adult patients with enteric hyperoxaluria.

In March 2018, we initiated URIROX-1™ (URIROX-1) (formerly Study 301), the first of our two anticipated Phase 3 clinical trials in support of our planned Biologic License Application, or BLA, for reloxaliase in patients with enteric hyperoxaluria. Based on our enrollment progress to date, we expect to announce topline data from this trial in the second half of 2019. In the fourth quarter of 2018, we initiated URIROX-2 (formerly Study 302), our second pivotal Phase 3 trial of reloxaliase in patients with enteric hyperoxaluria. The FDA has advised us that it agrees with our strategy to pursue a BLA submission for reloxaliase using the accelerated approval regulatory pathway. We expect to submit a BLA filing to the FDA after 400 patients have been randomized and followed for six months in URIROX-2. For the long-term follow-up phase of the trial, subjects would continue in URIROX-2 for a minimum treatment period of two years to confirm clinical benefit post-approval.

In addition to our Phase 3 program of reloxaliase for enteric hyperoxaluria, we are also evaluating reloxaliase in Study 206, a Phase 2 basket trial in adults and adolescents with primary hyperoxaluria or enteric hyperoxaluria with hyperoxalemia, which we initiated in March 2018. We expect to announce interim data from Study 206 in the second quarter of 2019 and topline data from this trial in the second half of 2019.

In addition, we have designed our second product candidate, ALLN-346, an orally administered, novel, urate degrading enzyme, for patients with hyperuricemia and gout in the setting of advanced CKD. Hyperuricemia, or elevated levels of uric acid in the blood, results from overproduction or insufficient excretion of urate, or often a combination of the two. ALLN-346 has demonstrated a robust reduction in both plasma and urine uric acid levels in an established urate oxidase knock-out mouse model, a severe animal model of hyperuricemia with advanced CKD and kidney damage due to urate crystal deposition. We presented preclinical data for ALLN-346 in October at the 2018 American College of Rheumatology (ACR/ARHP) Annual Meeting. We are advancing our preclinical program for ALLN-346 and scaling our manufacturing processes for clinical studies. Subject to the successful completion of these activities, we expect to file an IND for ALLN-346 with the FDA in the second half of 2019 and to initiate our first clinical trial of ALLN-346 in patients with hyperuricemia in the first half of 2020.

On November 6, 2017, we completed our IPO, in which we issued and sold 5,333,333 shares of our common stock at a public offering price of $14.00 per share, for aggregate gross proceeds of $74.7 million. The underwriters partially exercised their over-allotment option on December 1, 2017, and purchased 16,969 shares of our common stock, for aggregate gross

proceeds of $0.2 million. As a result of the IPO, we received approximately $67.0 million in net proceeds after deducting $7.9 million of underwriting discounts and commissions and offering costs.

Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, developing our technology, identifying potential product candidates, producing drug substance and drug product material for use in preclinical studies and clinical trials, conducting preclinical studies of our product candidates and clinical trials for our lead product candidate, reloxaliase. We do not have any products approved for sale and have not generated any revenue to date. As of December 31, 2018, we had cash and cash equivalents totaling $61.6 million.

We have incurred significant net operating losses in every year since our inception and expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. Our net losses may fluctuate significantly from quarter to quarter and year to year. Our net losses were $35.6 million, $21.7 million and $24.5 million for the years ended December 31, 2018, 2017 and 2016, respectively. As of December 31, 2018, we had an accumulated deficit of $117.6 million. We anticipate that our expenses will increase significantly as we:

- conduct future clinical trials of our lead product candidate, reloxaliase;
- manufacture additional material for our pivotal Phase 3 clinical program and potential future clinical studies we might conduct for our product candidates;
- scale up our manufacturing process for reloxaliase to prepare for the filing of a potential Biologics License Application, or BLA, and commercialization if our clinical development program is successful;
- advance the development of ALLN-346;
- conduct research on the discovery and development of additional product candidates;
- seek regulatory and marketing approvals for product candidates that successfully complete clinical trials, if any;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain regulatory approval in geographies in which we plan to commercialize our products ourselves;
- maintain, expand and protect our intellectual property portfolio;
- hire additional staff, including clinical, scientific, technical, operational, and financial personnel, to execute our business plan; and
- add clinical, scientific, operational, financial and management information systems to support our product development and potential future commercialization efforts, and to enable us to operate as a public company.

We do not expect to generate revenue from product sales unless and until we successfully complete development and obtain regulatory approval for a product candidate. Additionally, we currently use contract research organizations, or CROs, and contract manufacturing organizations, or CMOs, to carry out our preclinical and clinical development activities. We do not yet have a sales organization. If we obtain regulatory approval for our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Furthermore, we expect to incur additional costs associated with operating as a public company. Accordingly, we may seek to fund our operations through public or private equity or debt financings or other sources, including strategic collaborations. We may, however, be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all. Our failure to raise capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop our current product candidates, or any additional product candidates, if developed.

Financial Operations Overview

Revenue

To date, we have not generated any revenue from product sales or any other source and do not expect to generate any revenue from the sale of products for the foreseeable future. If our development efforts for reloxaliase or other product candidates that we may develop in the future are successful and result in marketing approval or collaboration or license

agreements with third parties, we may generate revenue in the future from a combination of product sales or payments from such collaboration or license agreements.

Research and Development Expenses

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:

- employee-related expenses, including salaries, benefits and stock-based compensation expense;
- costs incurred under agreements with third parties, including CROs, that conduct research and development, preclinical studies and clinical trials on our behalf;
- costs related to production of preclinical and clinical materials, including fees paid to CMOs;
- consulting, licensing and professional fees related to research and development activities;
- costs of purchasing laboratory supplies and non-capital equipment used in our research and development activities;
- costs related to compliance with clinical regulatory requirements; and
- facility costs and other allocated expenses, which include expenses for rent and maintenance of facilities, insurance, depreciation and other supplies.

We expense research and development costs as incurred. We recognize costs for certain development activities, such as clinical trials, based on an evaluation of the progress to completion of specific tasks using data such as clinical site activations, patient enrollment, or information provided to us by our vendors and our clinical investigative sites. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and may be reflected in our consolidated financial statements as prepaid or accrued research and development expenses. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are deferred and capitalized, even when there is no alternative future use for the research and development. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

The following summarizes our most advanced current research and development programs:

- reloxaliase is our lead product candidate which we are developing for the treatment of hyperoxaluria. Substantially all of our research and development costs to date have been used to fund this program.
- ALLN-346 is our second product candidate which we are developing for patients with hyperuricemia and CKD. We began incurring external research and development costs for this program in 2016.

We typically use our employee and infrastructure resources across our development programs. We track outsourced development costs by product candidate or development program, but we do not allocate personnel costs and other internal costs to specific product candidates or development programs.

The following table summarizes our research and development expenses by program (in thousands):

	For the Year Ended December 31,		
	2018	2017	2016
Reloxaliase external costs	$ 15,651	$ 9,764	$ 16,057
ALLN-346 external costs	1,489	611	312
Employee compensation and benefits	7,167	4,218	3,074
Other	2,069	926	660
Total research and development expenses	$ 26,376	$ 15,519	$ 20,103

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages, primarily due to the increased size and duration of later-stage clinical trials. Since inception, we have incurred $65.0 million of external research and development

costs for reloxaliase and $2.4 million of external research and development costs for ALLN-346. We expect that our research and development costs will continue to increase for the foreseeable future as we initiate additional clinical trials of reloxaliase, scale our manufacturing processes and advance development of ALLN-346.

The successful development of reloxaliase, ALLN-346 and other potential future product candidates is highly uncertain. Accordingly, at this time, we cannot reasonably estimate or know the nature, timing and costs of the efforts that will be necessary to complete the development of these product candidates. We are also unable to predict when, if ever, we will generate revenue and material net cash inflows from the commercialization and sale of any of our product candidates for which we may obtain marketing approval. We may never succeed in achieving regulatory approval for any of our product candidates. The duration, costs and timing of preclinical studies, clinical trials and development of our product candidates will depend on a variety of factors, including:

- successful enrollment in, and completion of, clinical trials for reloxaliase;
- successful data from our clinical program of reloxaliase that supports an acceptable benefit-risk profile of reloxaliase in the intended populations;
- establishing an appropriate safety profile for ALLN-346 and any potential future product candidate with studies to enable the filing of an investigational new drug application;
- approval of INDs for ALLN-346 and any potential future product candidate to commence planned or future clinical trials;
- significant and changing government regulation and regulatory guidance;
- timing and receipt of marketing approvals from applicable regulatory authorities;
- making arrangements with CMOs for third-party commercial manufacturing of our product candidates;
- obtaining and maintaining patent and other intellectual property protection and regulatory exclusivity for our product candidates;
- commercializing the product candidates, if and when approved, whether alone or in collaboration with others;
- acceptance of the product, if and when approved, by patients, the medical community and third-party payors; and
- maintenance of a continued acceptable safety profile of the drugs following approval.

A change in the outcome of any of these variables with respect to the development, manufacture or commercialization enabling activities of any of our product candidates could mean a significant change in the costs, timing and viability associated with the development of that product candidate.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in executive, finance, accounting, business development and human resources functions. Other significant costs include facility costs not otherwise included in research and development expenses, legal fees relating to patent and corporate matters and professional fees for accounting, auditing, tax and consulting services.

We expect that our general and administrative expenses will increase in the future to support continued research and development activities and potential commercialization of our product candidates. These increases will likely include increased costs related to the hiring of additional personnel and fees to outside consultants, attorneys and accountants, among other expenses.

Interest Income (Expense), Net

Interest income (expense), net, primarily consists of interest income earned on our cash and cash equivalents, interest expense incurred on our credit facilities, amortized debt discount related to the fair value of the warrants issued in conjunction with the advances under our former credit facility with Silicon Valley Bank, or SVB related debt issuance costs.

Other Income (Expense), Net

Other income (expense), net, primarily consists of gain (loss) on foreign currency transactions and non-cash changes in the fair value of warrants issued in connection with our former credit facility with SVB. The warrants converted upon the closing of our IPO and therefore became exercisable into common stock instead of convertible preferred stock. The warrants for the purchase of common stock met the criteria to be classified in stockholders' equity and the fair value of the warrant liability as of the IPO date was reclassified to stockholders' equity (deficit). As a result, we will no longer recognize any changes to the fair value of the warrants through other income (expense).

Critical Accounting Policies and Use of Estimates

Our management's discussion and analysis of financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States, or GAAP. The preparation of these 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 during the reporting periods. These items are monitored and analyzed by us for changes in facts and circumstances, and material changes in these estimates could occur in the future. We base our estimates on historical experience, known trends and events, and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Changes in estimates are reflected in reported results for the period in which they become known. Actual results may differ materially from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K, we believe the following accounting policies used in the preparation of our financial statements require the most significant judgments and estimates.

Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing purchase orders and open contracts, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the services when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met; however, some require advance payments. We make estimates of our accrued expenses as of each balance sheet date in our consolidated financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. The significant estimates in our accrued research and development expenses include the costs incurred for services performed by CROs and CMOs in connection with research and development activities for which we have not yet been invoiced.

We contract with CROs and CMOs to conduct clinical and manufacturing and other research and development services on our behalf. We base our expenses related to CROs and CMOs on our estimates of the services received and efforts expended pursuant to quotes and contracts with them. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our CROs or CMOs will exceed the level of services provided and result in a prepayment of the research and development expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or amount of prepaid expense accordingly. Non-refundable advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received rather than when the payment is made.

Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in us reporting amounts that are too high or too low in any particular period. To date, there have been no material differences between our estimates of such expenses and the amounts actually incurred.

Stock-Based Compensation

We apply the fair value recognition provisions of ASC 718, *Compensation—Stock Compensation*, or ASC 718, for stock-based awards granted to employees and directors for their services on the board of directors. We account for stock-based awards to non-employees in accordance with ASC 505-50, *Equity-Based Payments to Non-Employees*, or ASC 505-50. Determining the amount of stock-based compensation to be recorded requires us to develop estimates of the fair value of stock

options as of their grant date. We estimate the fair value of each stock option grant using the Black-Scholes option-pricing model. Calculating the fair value of stock-based awards requires that we make subjective assumptions.

Pursuant to ASC 718, we measure stock-based awards granted to employees and members of the board of directors at fair value on the date of grant and recognize the corresponding stock-based compensation expense of those awards on a straight-line basis over the requisite service period, which is generally the vesting period of the respective award. We have historically granted stock options with exercise prices equivalent to the fair value of our common stock as of the date of grant.

Pursuant to ASC 505-50, we measure stock-based awards granted to consultants at fair value as the awards vest and recognize the resulting value as expense during the period the related services are rendered, which is typically the vesting period. At the end of each financial reporting period prior to completion of the service, we re-measure the unvested portion of these awards using the then-current fair value of our common stock and updated assumption inputs in the Black-Scholes option-pricing model.

The Black-Scholes option-pricing model uses the following inputs: the fair value of our common stock, the expected volatility of our common stock, the expected term of our stock options, the risk-free interest rate for a period that approximates the expected term of our stock options and our expected dividend yield. Due to the lack of a public market for our common stock prior to our IPO and a lack of company-specific historical and implied volatility data, we have based our computation of expected volatility on the historical volatility of a representative group of public companies with similar characteristics to us, including stage of product development, life science industry focus, length of trading history and similar vesting provisions. The historical volatility data is calculated based on a period of time commensurate with the expected term assumption. We will continue to apply this process until a sufficient amount of historical information regarding the volatility of our own stock price becomes available or until circumstances change, such that the identified entities are no longer representative companies. In the latter case, more suitable, similar entities whose share prices are publicly available would be utilized in the calculation. We use the simplified method as prescribed by the SEC Staff Accounting Bulletin No. 107, *Share-Based Payment*, to calculate the expected term for options granted to employees as we do not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. Under this approach, the weighted-average expected option term is presumed to be the average of the contractual term (ten years) and the vesting term (generally four years) of our stock options. We utilize this method due to lack of historical exercise data and the "plain-vanilla" nature of our stock-based awards. The expected term is applied to the stock option grant group as a whole, as we do not expect substantially different exercise or post-vesting termination behavior among our employee population. For options granted to non-employees, we utilize the contractual term of the arrangement as the basis for the expected term assumption. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected term of the stock options. The expected dividend yield is assumed to be zero as we have never paid dividends and have no current plans to pay any dividends on our common stock.

The fair value of stock options granted to employees and directors was estimated on the date of grant using the Black-Scholes option-pricing model, with the following range of assumptions for the years ended December 31, 2018, 2017 and 2016:

	Years Ended December 31,		
	2018	2017	2016
Risk-free interest rate	2.3% – 3.1%	1.9% – 2.3%	1.3% – 1.7%
Expected dividend yield	—%	—%	—%
Expected term (in years)	5.5 – 6.1	5.6 – 6.3	5.4 – 6.4
Expected volatility	81% – 89%	81% – 87%	77% – 84%

The fair value of stock options granted to consultants was estimated on the date of grant and as the grants are remeasured over the vesting period using the Black-Scholes option-pricing model, with the following range of assumptions for the year ended December 31, 2016:

	Year Ended December 31, 2016
Risk-free interest rate	1.9% – 2.4%
Expected dividend yield	—%
Expected term (in years)	8.9 – 10.0
Expected volatility	89% – 96%

We did not grant any stock options to consultants during the years ended December 31, 2018 and 2017. These assumptions represented our best estimates, but the estimates involve inherent uncertainties and the application of our

judgment. As a result, if factors change and we use significantly different assumptions or estimates, our stock-based compensation expense could be materially different.

In the first quarter of the year ended December 31, 2017, we made an accounting policy election to recognize forfeitures as they occur upon adoption of guidance per ASU No. 2016-09, *Compensation—Stock Compensation*, or ASU 2016-09. The adoption of ASU 2016-09 did not have a material impact on our consolidated financial statements. In reporting periods prior to the year ended December 31, 2017, we estimated forfeitures at the time of grant and revised the forfeiture rate in subsequent periods as necessary if actual forfeitures differed from estimates.

Through December 31, 2016, the amount of stock-based compensation expense recognized in our consolidated financial statements was based on awards that were ultimately expected to vest. Forfeitures were estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differed from those estimates. The term "forfeitures" is distinct from "cancellations" or "expirations" and represents only the unvested portion of the surrendered option.

The following table summarizes the classification of our stock-based compensation expense recognized in our statements of operations and comprehensive loss (in thousands):

	Years Ended December 31,		
	2018	2017	2016
Research and development	$ 584	$ 147	$ 68
General and administrative	1,465	370	183
Total	$ 2,049	$ 517	$ 251

As of December 31, 2018, we had $4.4 million of unrecognized compensation expense related to stock option awards, which is expected to be recognized over weighted-average remaining vesting periods of approximately 2.8 years. In future periods, we expect stock-based compensation expense to increase, due in part to our existing unrecognized stock-based compensation expense, potential increases in the value of our common stock and expected additional stock-based awards to continue to attract and retain our employees.

Determination of Fair Value of Common Stock

As a private company with no active public market for our common stock prior to the completion of our IPO, our board of directors historically determined the fair value of our common stock on each date of grant, with input from management. Our board of directors periodically determined the estimated per share fair value of our common stock at various dates using contemporaneous valuations performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, or the Practice Aid. Once a public trading market for our common stock had been established in connection with the completion of our IPO, it is no longer be necessary for us to estimate the fair value of our common stock in connection with our accounting for stock options, as the fair value of our common stock will be its trading price on The Nasdaq Stock Market.

We performed contemporaneous valuations, with the assistance of a third-party specialist, as of November 6, 2014, February 15, 2016, December 31, 2016, April 30, 2017 and August 31, 2017, which resulted in valuations of our common stock of $1.17, $1.59, $4.01, $4.88 and $5.72 per share, respectively. In conducting the valuations, we considered all objective and subjective factors that we believed to be relevant for each valuation conducted, including our best estimate of our business condition, prospects and operating performance at each valuation date. Within the valuations performed, a range of factors, assumptions and methodologies were used. The significant factors included:

- the lack of an active public market for our common stock and convertible preferred stock;
- the prices at which we sold shares of our convertible preferred stock in arm's length transactions and the superior rights, preferences and privileges of the convertible preferred stock relative to our common stock, including the liquidation preferences of our preferred stock;
- our results of operations and financial condition, including cash on hand and borrowings under our credit facility;
- the material risks related to our business;
- our stage of development and business strategy;

- the composition of, and changes to, our management team and board of directors;
- the market performance of publicly traded companies in the life sciences and biotechnology sectors, as well as recently completed initial public offerings, or IPOs, of companies in the life sciences and biotechnology sectors; and
- the likelihood of achieving a liquidity event such as an IPO given prevailing market conditions.

Historically, the dates of our contemporaneous valuations have not coincided with the dates of our stock-based compensation grants. In determining the exercise prices of the stock options granted, our board of directors considered, among other things, the most recent contemporaneous valuations of our common stock and our assessment of additional objective and subjective factors we believed were relevant as of the grant date. The additional factors considered when determining any changes in fair value of our common stock between the most recent contemporaneous valuation and the grant dates included the status of our stage of research and development, our operating and financial performance and current business conditions.

There were significant judgments and estimates inherent in the determination of the fair value of our common stock. These judgments and estimates were management's best estimates and included assumptions regarding our future operating performance, the time to completing an IPO or other liquidity event, the related company valuations associated with such events and the determinations of the appropriate valuation methods. If we had made different assumptions, our stock-based compensation expense, net loss and net loss per common share could have been different.

Warrant Valuation

We issued warrants to purchase shares of our Series A and Series C convertible preferred stock in conjunction with the advances made under our former credit facility with SVB. These warrants were classified as liabilities as they either conditionally or unconditionally obligated us to transfer assets regardless of the timing of the redemption feature or price of the underlying convertible preferred stock. The warrants were initially recorded at their grant date fair value and were subject to revaluation at each balance sheet date. Changes in the fair value of the warrants were recorded as a component of other income (expense) in the statements of operations and comprehensive loss, until the earlier of their exercise or expiration or the completion of a liquidation event, at which time the warrant liability may be reclassified to stockholders' (deficit) equity if the criteria for recording the warrant as an equity instrument were met.

The fair value of the warrants was estimated using the Black-Sholes model, which incorporated assumptions and estimates to value these warrants. We assessed these assumptions and estimates on a periodic basis based on information available to us on each valuation date. Such assumptions and estimates include: the fair value of the Series A and Series C convertible preferred stock, the remaining contractual term of the warrants, the risk-free interest rate applicable to the remaining contractual term, the expected dividend yield and the expected volatility of the price of the underlying common stock into which the preferred stock is convertible. We estimated the fair value of our Series A and Series C convertible preferred stock upon the issuance of the warrants and at each reporting period based upon our common stock valuations which included a derived fair value for such shares of preferred stock. We have historically been a private company and lacked company-specific historical and implied volatility information of our stock. Therefore, we estimated expected stock volatility based on the historical volatility of publicly traded comparable companies for a term equal to the remaining contractual term of the warrants. The risk-free interest rate was determined by reference to the U.S. Treasury yield curve for time periods that were approximately equal the remaining contractual term of the warrants at each reporting period. We assumed no dividend yield based on the fact that we have never paid or declared dividends, and do not expect to pay or declare dividends in the future.

Upon completion of the IPO, all outstanding shares of our preferred stock were converted to common stock. The convertible preferred warrants therefore became exercisable into common stock instead of convertible preferred stock and the warrants met the criteria to be classified in stockholders' equity and the fair value of the warrant liability as of the IPO date was reclassified to stockholders' equity (deficit).

Results of Operations

Comparison of Years Ended December 31, 2018 and 2017

The following table summarizes our results of operations for the years ended December 31, 2018 and 2017 (in thousands):

	For the Year Ended December 31, 2018	2017	Dollar Change
Operating expenses:			
Research and development	$ 26,376	$ 15,519	$ 10,857
General and administrative	9,217	5,431	3,786
Total operating expenses	35,593	20,950	14,643
Loss from operations	(35,593)	(20,950)	(14,643)
Other income (expense):			
Interest income (expense), net	575	(443)	1,018
Other income (expense), net	(13)	(257)	244
Loss on extinguishment of debt	(617)	—	(617)
Other income (expense), net	(55)	(700)	645
Net loss	$ (35,648)	$ (21,650)	$ (13,998)

Research and Development Expenses

Research and development expense increased by $10.9 million from $15.5 million for the year ended December 31, 2017 to $26.4 million for the year ended December 31, 2018. The following table summarizes our research and development expenses for the years ended December 31, 2018 and 2017 (in thousands):

	For the Year Ended December 31, 2018	2017	Dollar Change
Clinical development external costs	$ 10,708	$ 4,059	$ 6,649
Manufacturing external costs	5,699	3,846	1,853
Employee compensation and benefits	7,167	4,218	2,949
Other	2,802	3,396	(594)
Total research and development expenses	$ 26,376	$ 15,519	$ 10,857

The $10.9 million increase in research and development expense was primarily attributable to the following:

- Our clinical development external costs increased by $6.6 million from $4.1 million for the year ended December 31, 2017 to $10.7 million for the year ended December 31, 2018:
  - We initiated our URIROX-1 Study during the first quarter of 2018. Expenses for this study were $6.6 million for the year ended December 31, 2018;
  - We also initiated our 206 Study during the first quarter of 2018 and incurred $1.6 million of costs for this study during the year ended December 31, 2018;
  - We initiated our URIROX-2 Study during the fourth quarter of 2018. We began preparation and start-up activities for this study during the second quarter of 2018 and incurred $1.5 million of costs relating to this study during the year ended December 31, 2018; and
  - The increase in costs due to our URIROX-1 Study, URIROX-2 Study and 206 Study was partially offset by costs incurred during the year ended December 31, 2017, for which there were no comparable costs during the year ended December 31, 2018. We incurred $1.9 million of costs during the year ended December 31, 2017 on the closeout of our 713 and 649 Studies and $0.4 million of costs as we completed our 204 Study.

- Our manufacturing external costs increased by $1.9 million from $3.8 million for the year ended December 31, 2017 to $5.7 million for the year ended December 31, 2018.
    - Included in manufacturing costs for the year ended December 31, 2018 was $1.8 million of costs incurred at our CMOs for the production of engineering and clinical batches of drug substance for our Phase 3 clinical program and $0.7 million of drug product costs for our Phase 3 clinical program;
    - We purchased consumables and raw materials required for engineering and clinical batches. Our costs for consumables and raw materials were $0.9 million and $1.0 million for the years ended December 31, 2018 and 2017, respectively;
    - Also included in manufacturing costs for the year ended December 31, 2018 was $0.8 million of costs incurred for ALLN-346 formulation and development activities, an increase of $0.2 million in costs from the year ended December 31, 2017; and
    - Included in manufacturing costs for the year ended December 31, 2017 was $0.9 million of costs incurred at our CMO for the production of engineering batches, $1.0 million for consumables and raw materials, $0.6 million of drug product costs and $0.2 of costs for modifications of equipment at our CMO.
- Our employee compensation and benefits costs increased by $2.9 million for the year ended December 31, 2018, primarily due to an increase in headcount from 22 employees at December 31, 2017 to 37 employees at December 31, 2018 as we grew our clinical and technical operations teams in preparation for our Phase 3 program.

We expect that our research and development expenses will increase in future periods as we continue our clinical development of reloxaliase, scale our manufacturing processes for reloxaliase and advance development of ALLN-346.

General and Administrative Expenses

General and administrative expense increased by $3.8 million from $5.4 million for the year ended December 31, 2017 to $9.2 million for the year ended December 31, 2018. The following table summarizes our general and administrative expenses for the years ended December 31, 2018 and 2017 (in thousands):

	For the Year Ended December 31,		Dollar
	2018	2017	Change
Employee compensation and benefits	$ 4,317	$ 2,616	$ 1,701
Consulting and professional services	2,764	1,616	1,148
Market research and commercialization planning	576	445	131
Other	1,560	754	806
Total general and administrative expenses	$ 9,217	$ 5,431	$ 3,786

The $3.8 million increase in general and administrative expense was primarily attributable to the following:

- Our employee compensation and benefits costs increased by $1.7 million for the year ended December 31, 2018, primarily due to an increase in employee salaries, wages, benefit costs and stock-based compensation. Our stock-based compensation expense increased from $0.4 million for the year ended December 31, 2017 to $1.5 million for the year ended December 31, 2018;
- Our consulting and professional services costs increased by $1.2 million for the year ended December 31, 2018. The increase was primarily related to increased consulting costs, recruiting costs, accounting and tax costs and other costs incurred as a public company, partially offset by a decrease in legal costs;
- Our market research and commercialization planning costs increased by $0.1 million for the year ended December 31, 2018. During the year ended December 31, 2018 we incurred costs of $0.2 million as we engaged an independent third party to conduct a study to assess the market opportunities for reloxaliase in Europe and Asia; and
- Our other costs increased by $0.8 million for the year ended December 31, 2018, due primarily to a $0.5 million increase in corporate insurance premiums. Our insurance premiums increased as a result of being a public company.

We expect that our general and administrative expense will increase in future periods as we expand our operations and incur additional costs in connection with being a public company.

Interest Income (Expense), net

Interest income (expense), net consists of interest income earned on our cash and cash equivalents, interest expense charged on our outstanding debt, and amortization of our debt discount. We had net interest income of $0.6 million for the year ended December 31, 2018 and net interest expense of $0.4 million for the year ended December 31, 2017. The increase was primarily attributable to interest earned from higher average balances of cash and cash equivalents for the year ended December 31, 2018 due to the net proceeds received from our IPO in November 2017.

Loss On Extinguishment of Debt

On June 29, 2018, we terminated our loan agreement with SVB. As a result we recorded a loss on extinguishment of debt of $0.6 million representing the unamortized debt discount and the final payment fee associated with the loan.

Comparison of the Years Ended December 31, 2017 and 2016

The following table summarizes our results of operations for the years ended December 31, 2016 and 2015 (in thousands):

	For the Year Ended December 31, 2017	2016	Dollar Change
Operating expenses:			
Research and development	$ 15,519	$ 20,103	$ (4,584)
General and administrative	5,431	4,083	1,348
Total operating expenses	20,950	24,186	(3,236)
Loss from operations	(20,950)	(24,186)	3,236
Other income (expense):			
Interest income (expense), net	(443)	(200)	(243)
Other income (expense), net	(257)	(121)	(136)
Other income (expense), net	(700)	(321)	(379)
Net loss	$ (21,650)	$ (24,507)	$ 2,857

Research and Development Expense

Research and development expense decreased by $4.6 million from $20.1 million for the year ended December 31, 2016 to $15.5 million for the year ended December 31, 2017. The following table summarizes our research and development expenses for the years ended December 31, 2017 and 2016 (in thousands):

	For the Year Ended December 31, 2017	2016	Dollar Change
Clinical development external costs	$ 4,059	$ 7,275	$ (3,216)
Manufacturing external costs	3,846	7,068	(3,222)
Employee compensation and benefits	4,218	3,074	1,144
Other	3,396	2,686	710
Total research and development expenses	$ 15,519	$ 20,103	$ (4,584)

The decrease in research and development expense was primarily attributable to the following:

- Our clinical development external costs decreased by $3.2 million from $7.3 million for the year ended December 31, 2016 to $4.1 million for the year ended December 31, 2017.
    - Study 649 expense decreased by $2.0 million from $2.2 million for the year ended December 31, 2016 to $0.2 million for the year ended December 31, 2017. We enrolled our first subject into the trial in September 2015, and completed enrollment in June 2016. The majority of enrollment and CRO expenses were incurred during the year ended December 31, 2016;

- Study 713 expense decreased by $1.3 million from $3.0 million for the year ended December 31, 2016 to $1.7 million for the year ended December 31, 2017. We enrolled our first subject into this trial in December 2015 and completed enrollment in early 2017. We incurred significant enrollment, CRO, and associated site costs during the year ended December 31, 2016, and incurred expenses related to the completion of this trial, finalization of the database, analysis of the data, and closeout of the trial during the year ended December 31, 2017;

- Consulting expense decreased by $0.3 million from $1.1 million for the year ended December 31, 2016 to $0.8 million for the year ended December 31, 2017. We required increased consulting services during the year ended December 31, 2016 to support Studies 649 and 713, and less consulting services during the year ended December 31, 2017, as the majority of the work for each study was completed during 2016; and

- The decrease in clinical development external costs was partially offset by $0.6 million of start-up expenses associated with URIROX-1, during the year ended December 31, 2017, of which we did not have similar expense for the year ended December 31, 2016.

- Our manufacturing external costs decreased by $3.2 million from $7.1 million for the year ended December 31, 2016 to $3.8 million for the year ended December 31, 2017.

  - We entered into a contract manufacturing agreement with a new CMO for the manufacturing of our reloxaliase drug substance in June 2015. We incurred significant costs setting up the new CMO in the second half of 2015 and the duration of 2016. These start-up costs incurred at this CMO were $0.2 million and $1.7 million during the years ended December 31, 2017 and 2016, respectively;

  - Our costs for consumables and raw materials were $1.0 million and $1.7 million for the years ended December 31, 2017 and 2016, respectively. During the year ended December 31, 2016, we purchased consumables and raw materials to supply our planned pre-engineering, engineering and clinical batches. These consumables and raw materials were expensed at the time of purchase. During the year ended December 31, 2017, we purchased additional consumables and raw materials required for engineering and clinical batches; and

  - During the years ended December 31, 2017 and 2016, we conducted considerable process development and manufactured several pre-engineering and engineering batches of product for reloxaliase as we scaled our manufacturing process and manufactured material for our clinical trials. Costs associated with these activities were $1.0 million and $1.8 million for the years ended December 31, 2017 and 2016, respectively.

- Our research and development employee compensation and benefits costs increased by $1.1 million from $3.1 million for the year ended December 31, 2016 to $4.2 million for the year ended December 31, 2017. The increase is primarily due to an overall increase in research and development headcount. We had 22 employees in research and development at December 31, 2017 compared to 18 employees in research and development at December 31, 2016. Further, of the 18 employees in research and development at December 31, 2016, eight were hired during the year ended December 31, 2016 but were employed during the entire year ended December 31, 2017.

- Other costs increased by $0.7 million from $2.7 million for the year ended December 31, 2016 to $3.4 million for the year ended December 31, 2017.

    - Our costs associated with the development of ALLN-346, increased by $0.3 million from $0.3 million for the year ended December 31, 2016 to $0.6 million for the year ended December 31, 2017 as we continue to advance the development of this program.

    - Our regulatory costs increased by $0.3 million from $0.2 million during the year ended December 31, 2016 to $0.5 million for the year ended December 31, 2017. The increase in costs is primarily attributable to increased consulting services during 2017 to assist us with our communications with the FDA and various regulatory agencies in the European Union.

General and Administrative Expenses

General and administrative expense increased by $1.3 million from $4.1 million for the year ended December 31, 2016 to $5.4 million for the year ended December 31, 2017. The following table summarizes our general and administrative expenses for the years ended December 31, 2016 and 2017 (in thousands):

	For the Year Ended December 31,		Dollar
	2017	2016	Change
Employee compensation and benefits	$ 2,616	$ 1,939	$ 677
Consulting and professional services	1,616	843	773
Market research and commercialization planning	445	674	(229)
Other	754	627	127
Total general and administrative expenses	$ 5,431	$ 4,083	$ 1,348

The increase in general and administrative expense was primarily attributable the following:

- Our employee compensation and benefits costs increased by $0.7 million. The increase was primarily related to an increase in the number of employees, including the addition of our Chief Financial Officer, who joined us in June 2016. We had eight general and administrative employees at December 31, 2017 compared to seven employees at December 31, 2016. Our stock-based compensation expense also increased $0.2 million from $0.2 million for the year ended December 31, 2016 to $0.4 million for the year ended December 31, 2017;

- Our consulting and professional services costs increased by $0.8 million. The increase is primarily related to increased legal costs for general corporate purposes and intellectual property legal costs associated with ALLN-346; and

- Our market research and commercialization planning costs decreased by $0.2 million during the year ended December 31, 2017. During the year ended December 31, 2016, we engaged an independent third party to conduct a study to assess the market opportunity for reloxaliase.

Interest Income (Expense), net

Interest income (expense), net consists of interest income earned on our cash, cash equivalents and short-term investments, interest expense charged on our outstanding debt, and amortization of our debt discount related to the fair value of the warrants and other debt issuance costs. Interest income (expense) net increased $(0.2) million from $(0.2) million for the year ended December 31, 2016 to $(0.4) million for the year ended December 31, 2017. The increase in net expense was attributable to the amortization of debt issuance costs associated with the refinancing of our credit facility in May 2016, as well as a decrease in interest income during the period due to a decrease in average cash, cash equivalents and investment balances prior to the completion of our IPO.

Other Income (Expense), net

Other income (expense), net consists primarily of non-cash changes in the fair value of warrants issued in connection with our credit facility.

Liquidity and Capital Resources

Sources of Liquidity

We have funded our operations from inception through December 31, 2018 through gross proceeds of $96.0 million from sales of our convertible preferred stock, borrowings of $10.0 million under our credit facilities and net proceeds from our IPO of $67.0 million which was completed in November 2017. Our total cash and cash equivalents was $61.6 million and $94.5 million at December 31, 2018 and 2017, respectively.

On June 29, 2018, we entered into a loan and security agreement with Pacific Western Bank, or the PWB Loan Agreement. The PWB Loan Agreement provides up to $12.0 million principal in term loans, $10.0 million of which was funded at the time we entered into the agreement, of which we utilized approximately $8.5 million to repay the outstanding indebtedness under our existing loan and security agreement with SVB. The borrowings under the PWB Loan Agreement have an interest rate equal to the greater of 5.0% or the prime rate then in effect.

The repayment schedule provides for interest only payments for 18 months, beginning in July 2018, pursuant to the terms of the PWB Loan Agreement. The PWB Loan Agreement provides for extension of the aforementioned 18 month period to 24 months following receipt by us of at least $50 million in gross proceeds from the sale of equity securities or an upfront payment from a strategic partnership by December 31, 2019. Following the interest only period, the loan repayment schedule provides for 30 or 24 equal monthly payments of principal plus interest, as the case may be. We have the option to prepay the outstanding balance of the term loan in full, subject to a prepayment fee of 0% to 2% depending upon when the prepayment occurs. In addition, in the event we close one or more financings pursuant to which we receive aggregate gross proceeds in the amount of at least $25.0 million, the PWB Loan Agreement requires us to pay to Pacific Western Bank, or PWB, a one-time fee equal to (a) $200,000, if such fee is paid on or before June 30, 2019 or (b) $300,000, if such fee is paid after June 30, 2019. This obligation survives the termination of the PWB Loan Agreement. The term loan facility matures on June 29, 2022.

The borrowings under the PWB Loan Agreement are secured by a lien on all of our assets except intellectual property. The PWB Loan Agreement contains customary representations, warranties and covenants by us, including negative covenants restricting our activities, such as disposing of our business or certain assets, incurring additional debt or liens or making payments on other debt, making certain investments and declaring dividends, acquiring or merging with another entity, engaging in transactions with affiliates or encumbering intellectual property, among others. The obligations under the PWB Loan Agreement are subject to acceleration upon occurrence of specified events of default, including a material adverse change in our business, operations or financial or other condition.

Cash Flows

The following table provides information regarding our cash flows for the years ended December 31, 2018, 2017 and 2016 (in thousands):

	For the Year Ended December 31,		
	2018	2017	2016
Net cash used in operations	$ (31,839)	$ (21,065)	$ (23,394)
Net cash (used in) provided by investing activities	(318)	23,417	(23,762)
Net cash (used in) provided by financing activities	(694)	66,892	3,395
Net increase (decrease) in cash and cash equivalents	$ (32,851)	$ 69,244	$ (43,761)

Net Cash Used in Operating Activities

The cash used in operating activities resulted primarily from our net losses adjusted for non-cash charges and changes in components of working capital.

Net cash used in operating activities was $31.8 million for the year ended December 31, 2018 compared to $21.1 million for the year ended December 31, 2017. The increase in cash used in operating activities of $10.7 million was attributable to:

- An increase in net loss of $14.0 million;
- an increase in non-cash items of $1.7 million resulting primarily from increases in stock-based compensation expense and our loss on extinguishment of debt; and
- an increase of $1.6 million in changes in the components of working capital, including increases in accounts payable and accrued expenses partially offset by decreases in prepaid expenses and other current assets.

Net cash used in operating activities was $21.1 million for the year ended December 31, 2017 compared to $23.4 million for the year ended December 31, 2016. The decrease in cash used in operating activities of $2.3 million was attributable to:

- A decrease in net loss of $2.9 million;
- An increase in non-cash items of $0.4 million resulting primarily from increases in stock-based compensation expense, non-cash interest expense and the change in the fair market value of the warrant liability, partially offset by a decrease in amortization of premium on investments; and
- A decrease of $1.0 million in changes in the components of working capital, including an decrease in prepaid expenses and other current assets.

Net Cash (Used In) Provided by Investing Activities

Net cash used by investing activities was $0.3 million for the year ended December 31, 2018 compared to net cash provided by investing activities of $23.4 million for the year ended December 31, 2017. The decrease in cash flows from investing activities of $23.7 million was attributable to maturities of short term investments of $24.7 million for the year ended December 31, 2017, partially offset by $1.2 million of purchases of investments during the period, as we converted short-term investments to cash and cash equivalents to fund our operations. We did not have any maturities or purchases of short term investments during the year ended December 31, 2018.

Net cash provided by investing activities was $23.4 million for the year ended December 31, 2017 compared to net cash used in investing activities of $23.8 million for the year ended December 31, 2016. The increase in cash flows from investing activities of $47.2 million was attributable to a decrease in purchases of short-term investments of $52.0 million and an increase in maturities of short-term investments of $4.8 million, as we converted short-term investments to cash and cash equivalents to fund our operations.

Net Cash (Used In) Provided by Financing Activities

Net cash used in financing activities was $0.7 million for the year ended December 31, 2018 compared to net cash provided by financing activities of $66.9 million for the year ended December 31, 2017. The net cash used in financing activities for the year ended December 31, 2018 included $10.5 million used to pay off our credit facility with SVB and $0.2 million for payments of initial public offering costs that were included in accounts payable and accrued expenses at December 31, 2017. These payments were partially offset by $10.0 million of proceeds received under our new credit facility with PWB and $0.1 million received from the exercises of stock options. The net cash provided by financing activities for the year ended December 31, 2017 was attributable to net proceeds of $67.0 million received from our IPO in November 2017, partially offset by debt repayments of $0.3 million.

Net cash provided by financing activities was $66.9 million for the year ended December 31, 2017 compared to $3.4 million for the year ended December 31, 2016. The increase in cash provided by financing activities of $63.5 million was attributable to net proceeds of $67.0 million received from our IPO in November 20017, partially offset by debt repayments of $0.3 million.

Funding Requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development for, initiate later stage clinical trials for, and seek marketing approval for, our product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts.

We believe that our cash and cash equivalents as of December 31, 2018 will enable us to fund our operating expenses and capital expenditure requirements through at least the first half of 2020. We have based this estimate on assumptions that may prove to be wrong, and we may use our available capital resources sooner than we currently expect. Our future capital requirements will depend on many factors, including:

- the costs of conducting future clinical trials of reloxaliase;
- the costs of manufacturing additional material for our planned pivotal Phase 3 clinical program, planned Phase 2 basket clinical trial and potential future clinical studies we might conduct for reloxaliase;
- the costs of scaling up our manufacturing process for reloxaliase to prepare for the filing of a potential BLA and commercialization if our clinical development program is successful;
- the advancement of ALLN-346;
- the scope, progress, results and costs of discovery, preclinical development, laboratory testing and clinical trials for other potential product candidates we may develop, if any;
- the costs, timing and outcome of regulatory review of our product candidates;
- our ability to establish and maintain collaborations on favorable terms, if at all;
- the achievement of milestones or occurrence of other developments that trigger payments under any collaboration agreements we might have at such time;
- the costs and timing of future commercialization activities, including product sales, marketing, manufacturing and distribution, for any of our product candidates for which we receive marketing approval;
- the amount of revenue, if any, received from commercial sales of our product candidates, should any of our product candidates receive marketing approval;
- the costs of preparing, filing and prosecuting patent applications, obtaining, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- our headcount growth and associated costs as we expand our business operations and our research and development activities; and
- the costs of operating as a public company.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products that we do not expect to be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. With the exception of our credit facility, we do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interests may be diluted, and the terms of these securities may include liquidation or other preferences that could adversely affect your rights as a common stockholder. Additional debt financing, if available, may involve agreements that include restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends, that could adversely impact our ability to conduct our business.

If we raise funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings

when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Contractual Obligations

The following table summarizes our significant contractual obligations as of payment due date by period at December 31, 2018 (in thousands):

	Total	Less than 1 year	1 to 3 years	3 to 5 years	More than 5 years
Credit facility (1)	$ 11,261	$ 550	$ 8,679	$ 2,032	$ —
Operating lease obligations (2)	1,056	487	569	—	—
Total	$ 12,317	$ 1,037	$ 9,248	$ 2,032	$ —

(1) Consists of repayment obligations under our credit facility with PWB, including interest.

(2) Represents future minimum lease payments under our non-cancelable operating leases which expire through February 2021. The minimum lease payments above do not include any related common area maintenance charges or real estate taxes.

Under a license agreement with Althea Technologies, Inc. (now known as Ajinomoto Althea, Inc.), or Althea, which we entered into in March 2012, as amended in March 2016, we reimbursed Althea for patent-related fees of $0.1 million and issued 88,186 shares of common stock to Althea. In addition, we are obligated to pay milestone payments and royalties of a mid-single digit percentage of net sales. Milestone payments are triggered upon the achievement of specified regulatory milestones that could total up to $31.0 million and sales-based milestones that could total up to $25.0 million. The milestone payments are not creditable against royalties. Actual amounts due under the agreement will vary depending on the number of products developed, the type and development path of the products, and other related factors. As of December 31, 2018, we were unable to estimate the timing or likelihood of achieving these milestones or generating future product sales. We have the right to terminate the agreement for convenience upon 60 days prior written notice to Althea. As a result, no amounts are included in the table above. See “Business—Althea License Agreement” for a more detailed description of this agreement.

We enter into agreements in the normal course of business with CROs for clinical trials, CMOs for clinical supply manufacturing, professional consultants for expert advice and other vendors for other services for operating purposes. We have not included these payments in the table of contractual obligations above since the contracts do not contain any minimum purchase commitments and are cancelable at any time by us, generally upon 30 days prior written notice, therefore we believe that our non-cancelable obligations under these agreements are not material.

Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under applicable SEC rules.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to market risk related to changes in interest rates. As of December 31, 2018, our cash equivalents consisted of primarily of short-term money market funds. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates. Due to the short-term nature of the cash equivalents in our portfolio and the low risk profile of our cash equivalents, an immediate 10% change in interest rates would not have a material effect on the fair market value of our financial position or results of operations.

We are not currently exposed to significant market risk related to changes in foreign currency exchange rates; however, we have contracted with and may continue to contract with foreign vendors that are located in Europe. Our operations may be subject to fluctuations in foreign currency exchange rates in the future.

Inflation generally affects us by increasing our cost of labor and clinical trial costs. We do not believe that inflation had a material effect on our business, financial condition or results of operations during the years ended December 31, 2018, 2017 and 2016.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

Our consolidated financial statements, together with the reports of our independent registered public accounting firms, appear at pages F-1 through F-23 of this Annual Report on Form 10-K for the year ended December 31, 2018.

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

We maintain "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, that are designed to ensure that information required to be disclosed in the reports that we file or submit under the Exchange Act is (1) recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission's rules and forms and (2) accumulated and communicated to our management, including our principal executive and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Our disclosure controls and procedures are designed to provide reasonable assurance of achieving their control objectives.

Our management, with the participation of our principal executive officer and principal financial and accounting officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2018. Based upon such evaluation, our principal executive officer and principal financial and accounting officer have concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of such date.

Management's Annual Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting as such term is defined in Exchange Act Rule 13a–15(f) or 15d-15(f). Our internal control system was designed to provide reasonable assurance to our management and our board of directors regarding the preparation and fair presentation of published financial statements. All internal control systems, no matter how well designed have inherent limitations. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation. Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2018. In making this assessment, our management used the criteria set forth in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission in 2013 (COSO criteria). Based on this assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2018. This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm 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 was no change in our internal control over financial reporting that occurred during the year ended December 31, 2018 that has materially affected, or is 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 under this item is incorporated herein by reference to the Company's definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company's fiscal year ended December 31, 2018.

ITEM 11. EXECUTIVE COMPENSATION

The information required under this item is incorporated herein by reference to the Company's definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company's fiscal year ended December 31, 2018.

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

The information required under this item is incorporated herein by reference to the Company's definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company's fiscal year ended December 31, 2018.

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

The information required under this item is incorporated herein by reference to the Company's definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company's fiscal year ended December 31, 2018.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

The information required under this item is incorporated herein by reference to the Company's definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company's fiscal year ended December 31, 2018.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

(a) 1. **Financial Statements.**

For a list of the financial statements included herein, see Index to the Financial Statements on page F-1 of this Annual Report on Form 10-K.

2. Financial Statement Schedules.

No financial statement schedules have been submitted because they are not required or are not applicable or because the information required is included in the financial statements or the notes thereto.

3. List of Exhibits.

See the Exhibit Index in Item 15(b) below.

(b) **Exhibit Index.**

Exhibit Number	Description
3.1*	Amended and Restated Certificate of Incorporation of Allena Pharmaceuticals, Inc. (Incorporated by reference to Exhibit 3.1 to the Registrant's Form 8-K filed on November 6, 2017)
3.2*	Amended and Restated By-Laws of Allena Pharmaceuticals, Inc. (Incorporated by reference to Exhibit 3.1 to the Registrant's Form 8-K filed on November 6, 2017)
4.1*	Form of Common Stock certificate (Incorporated by reference from Exhibit 4.1 to the Registrant's Amendment No. 1 to Form S-1 filed on October 23, 2017)
4.2*	Second Amended and Restated Investor Rights Agreement, by and between the Registrant and the Investors named therein, dated as November 25, 2015 (Incorporated by reference from Exhibit 4.2 to the Registrant's Form S-1 filed on October 6, 2017)
4.3*	Warrant to Purchase Stock issued to Silicon Valley Bank, dated May 2, 2016 (Incorporated by reference from Exhibit 4.3 to the Registrant's Form S-1 filed on October 6, 2017)
4.4*	Warrant to Purchase Stock issued to Silicon Valley Bank, dated August 18, 2014 (Incorporated by reference from Exhibit 4.4 to the Registrant's Form S-1 filed on October 6, 2017)
10.1*†	2011 Stock Incentive Plan and forms of agreements thereunder (Incorporated by reference from Exhibit 10.1 to the Registrant's Form S-1 filed on October 6, 2017)
10.2*†	2017 Stock Option and Incentive Plan and forms of agreement thereunder (Incorporated by reference from Exhibit 10.2 to the Registrant's Amendment No. 1 to Form S-1 filed on October 23, 2017)
10.3*†	2017 Employee Stock Purchase Plan (Incorporated by reference from Exhibit 10.3 to the Registrant's Amendment No. 1 to Form S-1 filed on October 23, 2017)
10.4*†	Senior Executive Cash Incentive Bonus Plan (Incorporated by reference from Exhibit 10.4 to the Registrant's Form S-1 filed on October 6, 2017)
10.5*†	Employment Agreement by and between the Registrant and Alexey Margolin (Incorporated by reference from Exhibit 10.5 to the Registrant's Amendment No. 1 to Form S-1 filed on October 23, 2017)
10.6*†	Employment Agreement by and between the Registrant and Edward Wholihan (Incorporated by reference from Exhibit 10.6 to the Registrant's Amendment No. 1 to Form S-1 filed on October 23, 2017)
10.7*†	Employment Agreement by and between the Registrant and Louis Brenner (Incorporated by reference from Exhibit 10.7 to the Registrant's Amendment No. 1 to Form S-1 filed on October 23, 2017)
10.8*	Form of Indemnification Agreement, to be entered into between the Registrant and its directors and officers (Incorporated by reference from Exhibit 10.8 to Form S-1 filed on October 6, 2017)
10.9*	Lease Agreement, by and between the Registrant and Newton Executive Park Limited Partnership, dated August 29, 2011, as amended
10.10*	Commercial Lease, by and between the Registrant and Cummings Properties, LLC, dated August 18, 2016, as amended (Incorporated by reference from Exhibit 10.10 to the Registrant's Form S-1 filed on October 6, 2017)
10.11*#	License Agreement dated March 22, 2012, as amended, by and between the Registrant and Ajinomoto Althea, Inc. (f/k/a Althea Technologies, Inc.) (Incorporated by reference from Exhibit 10.11 to the Registrant's Form S-1 filed on October 6, 2017)

10.12*	Loan and Security Agreement by and between the Registrant and Silicon Valley Bank, dated August 18, 2014, as amended (Incorporated by reference from Exhibit 10.12 to the Registrant's Form S-1 filed on October 6, 2017)
10.13*†	Non-Employee Director Compensation Policy (Incorporated by reference from Exhibit 10.13 to Amendment No. 1 to the Registrant's Form S-1 filed on October 23, 2017)
21.1*	Subsidiaries (Incorporated by reference from Exhibit 10.8 to the Registrant's Form S-1 filed on October 6, 2017)
23.1**	Consent of Ernst & Young LLP
31.1**	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2**	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1***	Certification of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101	Interactive Data Files regarding (a) our Consolidated Balance Sheets as of December 31, 2018 and 2017, (b) our Consolidated Statements of Operations and Comprehensive Loss for the Years Ended December 31, 2018, 2017 and 2016, (c) our Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit) for the Years Ended December 31, 2018, 2017 and 2016, (d) our Consolidated Statements of Cash Flows for the Years Ended December 31, 2018, 2017 and 2016, and (e) the Notes to Consolidated Financial Statements

* Previously filed.
** Filed herewith.
*** Furnished herewith.
† Indicates management contract or compensation plan.
# Application has been made to the Securities and Exchange Commission for confidential treatment of certain provisions. Omitted material for which confidential treatment has been requested has been filed separately with the Securities and Exchange Commission.

ITEM 16. FORM 10-K SUMMARY

None.

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 7, 2019

ALLENA PHARMACEUTICALS, INC.

By: /s/ Louis Brenner, M.D.
Louis Brenner, M.D.
Chief Executive Officer and Director

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/ Louis Brenner, M.D. Louis Brenner, M.D.	Chief Executive Officer and Director (Principal Executive Officer)	March 7, 2019
/s/ Edward Wholihan Edward Wholihan	Chief Financial Officer (Principal Financial and Accounting Officer)	March 7, 2019
/s/ Alexey Margolin, Ph.D. Alexey Margolin, Ph.D.	Chairman	March 7, 2019
/s/ Axel Bolte Axel Bolte	Director	March 7, 2019
/s/ Andrew A. F. Hack, M.D., Ph.D. Andrew A. F. Hack, M.D., Ph.D.	Director	March 7, 2019
/s/ Gino Santini Gino Santini	Director	March 7, 2019
/s/ Robert Tepper, M.D. Robert Tepper, M.D.	Director	March 7, 2019
/s/ James N. Topper, M.D., Ph.D. James N. Topper, M.D., Ph.D.	Director	March 7, 2019
/s/ Robert Alexander, Ph.D. Robert Alexander, Ph.D.	Director	March 7, 2019

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Shareholders and the Board of Directors of
Allena Pharmaceuticals, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Allena Pharmaceuticals, Inc. (the Company) as of December 31, 2018 and 2017, and the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit) and cash flows for each of the three years in the period ended December 31, 2018, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting 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.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2012.

Boston, Massachusetts
March 7, 2019

Allena Pharmaceuticals, Inc.

Consolidated Balance Sheets
(in thousands, except share and per share data)

	December 31,	
	2018	2017
Assets		
Current assets:		
Cash and cash equivalents	$ 61,643	$ 94,494
Prepaid expenses and other current assets	2,826	1,539
Total current assets	64,469	96,033
Property and equipment, net	514	127
Other assets	246	89
Total assets	$ 65,229	$ 96,249
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 2,138	$ 1,724
Loan payable, net of discount	—	3,870
Accrued expenses	3,625	1,949
Total current liabilities	5,763	7,543
Loan payable, net of current portion and discount	9,980	5,516
Other liabilities	30	320
Total liabilities	15,773	13,379
Commitments and contingencies (Note 11)		
Stockholders' equity:		
Common stock, $0.001 par value; 125,000,000 shares authorized; 20,809,025 and 20,694,658 shares issued and outstanding at December 31, 2018 and 2017, respectively	21	20
Undesignated preferred stock, $0.001 par value; 5,000,000 shares authorized; no shares issued or outstanding	—	—
Additional paid-in capital	167,040	164,807
Accumulated deficit	(117,605)	(81,957)
Total stockholders' equity	49,456	82,870
Total liabilities and stockholders' equity	$ 65,229	$ 96,249

See accompanying notes.

Allena Pharmaceuticals, Inc.

Consolidated Statements of Operations and Comprehensive Loss
(in thousands, except share and per share data)

	Years Ended December 31,		
	2018	2017	2016
Operating expenses:			
Research and development	$ 26,376	$ 15,519	$ 20,103
General and administrative	9,217	5,431	4,083
Total operating expenses	35,593	20,950	24,186
Other income (expense):			
Interest income (expense), net	575	(443)	(200)
Other income (expense), net	(13)	(257)	(121)
Loss on extinguishment of debt	(617)	—	—
Other income (expense), net	(55)	(700)	(321)
Net loss	$ (35,648)	$ (21,650)	$ (24,507)
Net loss per share attributable to common stockholders — basic and diluted	$ (1.72)	$ (4.80)	$ (18.35)
Weighted-average common shares outstanding — basic and diluted	20,741,226	4,520,337	1,339,254
Comprehensive loss:			
Net loss	$ (35,648)	$ (21,650)	$ (24,507)
Other comprehensive income (loss):			
Unrealized loss on investments	—	—	(2)
Total other comprehensive loss	—	—	(2)
Comprehensive loss	$ (35,648)	$ (21,650)	$ (24,509)

See accompanying notes.

Allena Pharmaceuticals, Inc.

Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit)
(in thousands, except share amounts)

	Series A convertible preferred stock		Series B convertible preferred stock		Series C convertible preferred stock		Common stock		Additional paid-in capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Total stockholders' equity (deficit)
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount				
Balance at December 31, 2015	18,367,344	$ 17,959	19,841,270	$ 24,913	20,000,000	$ 52,786	1,315,940	$ 1	$ 830	$ —	$ (35,800)	$ (34,969)
Exercise of common stock options	—	—	—	—	—	—	24,770	0	19	—	—	19
Vesting of restricted common stock	—	—	—	—	—	—	675	—	—	—	—	—
Accretion of convertible preferred stock to redemption value	—	8	—	18	—	43	—	—	(69)	—	—	(69)
Stock-based compensation	—	—	—	—	—	—	—	—	251	—	—	251
Change in unrealized gain (loss) on available for sale investments	—	—	—	—	—	—	—	—	—	(2)	—	(2)
Net loss	—	—	—	—	—	—	—	—	—	—	(24,507)	(24,507)
Balance at December 31, 2016	18,367,344	17,967	19,841,270	24,931	20,000,000	52,829	1,341,385	1	1,031	(2)	(60,307)	(59,277)
Issuance of common stock, net of issuance costs	—	—	—	—	—	—	5,350,302	5	66,994	—	—	66,999
Exercise of common stock options	—	—	—	—	—	—	33,061	—	28	—	—	28
Exercise of common stock warrants	—	—	—	—	—	—	24,401	—	—	—	—	—
Accretion of convertible preferred stock to redemption value	—	7	—	15	—	36	—	—	(58)	—	—	(58)
Conversion of preferred stock into common stock	(18,367,344)	(17,974)	(19,841,270)	(24,946)	(20,000,000)	(52,865)	13,945,509	14	95,771	—	—	95,785
Conversion of warrant liability to equity	—	—	—	—	—	—	—	—	524	—	—	524
Stock-based compensation	—	—	—	—	—	—	—	—	517	—	—	517
Change in unrealized gain (loss) on available for sale investments	—	—	—	—	—	—	—	—	—	2	—	2
Net loss	—	—	—	—	—	—	—	—	—	—	(21,650)	(21,650)
Balance at December 31, 2017	—	—	—	—	—	—	20,694,658	20	164,807	—	(81,957)	82,870
Exercise of common stock options	—	—	—	—	—	—	106,879	1	138	—	—	139
Issuance of common stock through employee stock purchase plan ("ESPP")	—	—	—	—	—	—	7,488	—	34	—	—	34
Stock-based compensation	—	—	—	—	—	—	—	—	2,049	—	—	2,049
Issuance costs related to initial public offering	—	—	—	—	—	—	—	—	12	—	—	12
Net loss	—	—	—	—	—	—	—	—	—	—	(35,648)	(35,648)
Balance at December 31, 2018	—	—	—	—	—	—	20,809,025	21	167,040	—	(117,605)	49,456

See accompanying notes.

Allena Pharmaceuticals, Inc.

Consolidated Statements of Cash Flows
(in thousands)

	Years Ended December 31,		
	2018	2017	2016
Cash flows from operating activities:			
Net loss	$ (35,648)	$ (21,650)	$ (24,507)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	2,049	517	251
Depreciation expense	78	73	46
Non-cash interest expense	161	351	204
Amortization of premium on investments	—	33	153
Loss on extinguishment of debt	617	—	—
Change in fair value of warrant liability	—	257	132
Changes in assets and liabilities:			
Prepaid expenses and other current assets	(1,287)	(984)	343
Other assets	(34)	(89)	—
Accounts payable	441	199	(525)
Accrued expenses	1,764	228	689
Other liabilities	20	—	(180)
Net cash used in operating activities	(31,839)	(21,065)	(23,394)
Cash flows from investing activities:			
Purchases of property and equipment	(318)	(57)	(102)
Purchases of investments	—	(1,247)	(53,210)
Maturities of investments	—	24,721	29,550
Net cash (used in) provided by investing activities	(318)	23,417	(23,762)
Cash flows from financing activities:			
Proceeds from (payments of issuance costs) the issuance of common stock, net of issuance costs	(309)	67,197	—
Proceeds from exercise of stock options	139	28	19
Proceeds from issuance of stock through ESPP	34	—	—
Proceeds from loan payable	10,000	—	10,000
Repayment of loan payable	(10,492)	(333)	(6,256)
Debt issuance costs paid	(33)	—	(368)
Other	(33)	—	—
Net cash (used in) provided by financing activities	(694)	66,892	3,395
Net (decrease) increase in cash and cash equivalents	(32,851)	69,244	(43,761)
Cash and cash equivalents, beginning of period	94,494	25,250	69,011
Cash and cash equivalents, end of period	$ 61,643	$ 94,494	$ 25,250
Supplemental disclosure of non-cash activities:			
Cash paid for interest	$ 906	$ 452	$ 472
Property and equipment purchases included in accounts payable	$ 72	$ 11	$ 38
Initial public offering costs included in accounts payable and accrued expenses	$ —	$ 199	$ —
Issuance of warrants in connection with loan payable	$ —	$ —	$ 67
Accretion of convertible preferred stock to redemption value	$ —	$ 58	$ 69

See accompanying notes.

1. Organization and Basis of Presentation

Allena Pharmaceuticals, Inc. (the "Company") is a clinical stage company focused on developing non-absorbed oral enzyme therapeutics to treat metabolic conditions including hyperoxaluria and hyperuricemia. The Company was incorporated under the laws of the State of Delaware on June 24, 2011. The Company's headquarters are in Newton, Massachusetts.

The Company is subject to risks common to companies in the biotechnology industry, including but not limited to, risks of failure of preclinical studies and clinical trials, the need to obtain marketing approval for any drug product candidate that it may identify and develop, the need to successfully commercialize and gain market acceptance of its product candidates, dependence on key personnel, protection of proprietary technology, compliance with government regulations, development by competitors of technological innovations, reliance on third party manufacturers, ability to transition from pilot-scale manufacturing to large-scale production of products and the need to obtain adequate additional financing to fund the development of its product candidates.

The Company has an accumulated deficit of $117.6 million at December 31, 2018, and will require substantial additional capital to fund operations. The future success of the Company is dependent on its ability to identify and develop its product candidates and ultimately upon its ability to attain profitable operations. At December 31, 2018, the Company had $61.6 million of cash and cash equivalents.

The Company believes its cash and cash equivalents as of December 31, 2018 will be sufficient to fund the Company's operating plan for a period of at least one year from the issuance date of the consolidated financial statements. Thereafter, the Company will be required to obtain additional funding in the future to achieve its operating plan. There can be no assurances, however, that the current operating plan will be achieved or that additional funding will be available on terms acceptable to the Company, or at all.

Basis of Presentation

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP"). Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standard Codification ("ASC") and Accounting Standards Updates ("ASU") of the Financial Accounting Standards Board ("FASB").

2. Summary of Significant Accounting Policies

Principles of Consolidation

The consolidated financial statements include the accounts of Allena Pharmaceuticals, Inc. and its wholly owned subsidiaries Allena Pharmaceuticals Security Corporation ("Security Corporation"), which was incorporated in December 2014, and Allena Pharmaceuticals Ireland Limited, which was incorporated in March 2017. All intercompany transactions and balances have been eliminated.

Use of Estimates

The preparation of the Company's consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities, expenses and related disclosure of contingent assets and liabilities at the date of the financial statements and reported amounts of expenses during the reporting period. On an ongoing basis, the Company's management evaluates its estimates, which include but are not limited to management's judgments of prepaid and accrued research and development expenses, fair value of common stock prior to the closing of the Company's IPO, valuation of share-based awards and the fair value of warrants prior to the conversion into warrants for the purchase of common stock upon the closing of the IPO. Actual results could differ from those estimates.

The Company utilized significant estimates and assumptions in determining the fair value of its common stock prior to the Company's IPO. The Company utilized various valuation methodologies in accordance with the framework

of the American Institute of Certified Public Accountants Technical Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation* (the "Practice Aid"), to estimate the fair value of its common stock. Each valuation methodology includes estimates and assumptions that require the Company's judgment. These estimates and assumptions include a number of objective and subjective factors, including external market conditions, the prices at which the Company sold shares of preferred stock, the superior rights and preferences of securities senior to the Company's common stock at the time of, and the likelihood of, achieving a liquidity event, such as an initial public offering or sale. Significant changes to the key assumptions used in the valuations could result in different fair values of common stock at each valuation date.

Segment Information

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision-maker in deciding how to allocate resources and assess performance. The Company's chief operating decision-maker, the Company's chief executive officer, views the Company's operations and manages its business as a single operating segment, which is the business of discovering and developing non-absorbed oral enzyme therapeutics.

Comprehensive Income (Loss)

Comprehensive income (loss) is defined as the change in equity of a business enterprise during a period from transactions and other events and circumstances from non-owner sources. Comprehensive loss equaled net loss for the years ended December 31, 2018 and 2017. The Company recognized other comprehensive loss of $2,000 for the year ended December 31, 2016 related to unrealized loss on available-for-sale investments.

Cash and Cash Equivalents

The Company considers all highly liquid investments with an original maturity of three months or less to be cash equivalents. Cash and cash equivalents include cash held in banks and amounts held in money market funds. Cash equivalents are stated at cost, which approximates market value.

Cash and cash equivalents consist of the following at December 31, 2018 and 2017 (in thousands):

	December 31,	
	2018	2017
Cash and cash equivalents:		
Cash	$ 228	$ 749
Money market funds	61,415	93,745
	$ 61,643	$ 94,494

Investments

The Company invests available cash primarily in U.S. and foreign corporate debt securities and United States government treasury securities. The Company classifies its investments in debt securities as available-for-sale. Available-for-sale investments are carried at fair value with unrealized gains and losses included in stockholders' (deficit) equity. Any premium or discount arising at purchase is amortized and/or accreted to interest income and/or expense. The cost of securities sold is determined on a specific identification basis, and realized gains and losses are included in interest income (expense) within the statement of operations and comprehensive loss. The Company did not hold any investments at December 31, 2018 and 2017.

The Company evaluates its available-for-sale investments with unrealized losses for other-than-temporary impairment. When assessing investments for other-than-temporary declines in value, the Company considers such factors as, among other things, how significant the decline in value is as a percentage of the original cost, how long the market value of the investment has been less than its original cost, the Company's ability and intent to retain the investment for a period of time sufficient to allow for any anticipated recovery in fair value and market conditions in general. If any adjustment to fair value reflects a decline in the value of the investment that the Company considers to be "other than temporary", the Company reduces the investment to fair value through a charge to the statement of operations and comprehensive loss. No such adjustments were necessary during the periods presented.

Concentration of Credit Risk and Off-Balance Sheet Risk

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents and investments. The Company maintains all of its cash and cash equivalents at a single accredited financial institution, in amounts that exceed federally insured limits. The Company generally invests its excess cash in money market funds that are subject to minimal credit and market risk. Management has established guidelines relative to credit ratings and maturities intended to safeguard principal balances and maintain liquidity. The investment portfolio is maintained in accordance with the Company's investment policy, which defines allowable investments, specifies credit quality standards and limits the credit exposure of any single issuer.

The Company has no significant off-balance sheet risk such as foreign exchange contracts, option contracts, or other foreign hedging arrangements.

Significant Suppliers

The Company is dependent on third-party manufacturers to supply products for research and development activities of its programs, including preclinical and clinical testing. In particular, the Company relies and expects to continue to rely on a small number of manufacturers to supply it with its requirements for the active pharmaceutical ingredients and formulated drugs related to these programs. These programs could be adversely affected by a significant interruption in the supply of active pharmaceutical ingredients and formulated drugs.

Fair Value of Financial Instruments

Fair value is defined as the price that would be received upon sale of an asset or paid to transfer a liability between market participants at measurement dates. ASC Topic 820, *Fair Value Measurement* ("ASC 820"), establishes a three-level valuation hierarchy for instruments measured at fair value. The hierarchy is based on the transparency of inputs to the valuation of an asset or liability as of the measurement date. The hierarchy defines three levels of valuation inputs, of which the first two are considered observable and the last is considered unobservable:

Level 1 inputs:	Quoted prices in active markets for identical assets or liabilities.
Level 2 inputs:	Inputs other than quoted prices included within Level 1 that are either directly or indirectly observable, such as quoted market prices, interest rates and yield curves.
Level 3 inputs:	Unobservable inputs developed using estimates or assumptions developed by the Company, which reflect those that a market participant would use in pricing the asset or liability.

To the extent that the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

Property and Equipment

Property and equipment consists of laboratory equipment, computer equipment, software and leasehold improvements recorded at cost. These amounts are depreciated using the straight-line method over the estimated useful lives of the assets as follows:

Laboratory equipment	4 years
Computer equipment	3 years
Software	5 years
Leasehold improvements	Shorter of useful life or remaining term of related lease

Upon retirement or sale, the cost of the assets disposed of and the related accumulated depreciation are eliminated from the balance sheet and related gains or losses are reflected in the statement of operations and comprehensive loss. Repairs and maintenance costs are expensed as incurred and costs of significant improvements are capitalized.

Impairment of Long-Lived Assets

The Company continually evaluates long-lived assets for potential impairment when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparing the book values of the assets to the expected future net undiscounted cash flows that the assets are expected to generate. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the book values of the assets exceed their fair value. The Company did not recognize any impairment losses for the years ended December 31, 2018, 2017 and 2016.

Warrants to Purchase Shares Subject to Redemption

Prior to the closing of the IPO, the Company accounted for warrant instruments that either conditionally or unconditionally obligate the issuer to transfer assets as liabilities regardless of the timing of the redemption feature or price, even though the underlying shares may be classified as equity. These warrants were subject to revaluation at each balance sheet date, and any changes in fair value were recorded as a component of other income (expense) in the statements of operations and comprehensive loss. Upon the closing of the IPO, the warrants met the criteria to be classified in stockholders' equity and the fair value of the warrant liability as of the IPO date was reclassified to stockholders' equity (deficit).

Research and Development

The Company expenses all costs incurred in performing research and development activities. Research and development expenses include salaries and benefits, materials and supplies, preclinical and clinical trial expenses, manufacturing expenses, stock-based compensation expense, depreciation of equipment, contract services and other outside expenses. Costs of certain development activities, such as manufacturing, are recognized based on an evaluation of the progress to completion of specific tasks. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the consolidated financial statements as prepaid or accrued research and development costs. Nonrefundable 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.

Patent Costs

The Company expenses patent application and related legal costs as incurred and classifies such costs as general and administrative expenses in the accompanying consolidated statements of operations and comprehensive loss.

Accounting for Stock-Based Compensation

The Company accounts for its stock-based compensation in accordance with ASC Topic 718, *Compensation—Stock Compensation* ("ASC 718"). ASC 718 requires all share-based payments to employees and directors to be recognized as expense in the statements of operations and comprehensive loss based on their grant date fair values. The Company accounts for share-based payments to non-employees in accordance with ASC Topic 505, *Equity-Based Payments to Non-Employees* ("ASC 505"). ASC 505 requires that the expense related to share-based payments to non-employees be recognized in the statement of operations and comprehensive loss based on the awards' vesting date fair values. The Company estimates the fair value of options granted using the Black-Scholes option pricing model for stock option grants to both employees and non-employees. The Company believes the fair value of the stock options granted to non-employees is more reliably determinable than the fair value of the services provided.

The Black-Scholes option pricing model requires inputs based on certain subjective assumptions, including (a) the expected stock price volatility, (b) the expected term of the award, (c) the risk-free interest rate and (d) expected dividends. Due to the lack of a public market for the Company's common stock and a lack of company-specific historical and implied volatility data, the Company has based its computation of expected volatility on the historical volatility of a representative group of public companies with similar characteristics to the Company, including stage of product development and life science industry focus. The historical volatility is calculated based on a period of

time commensurate with the expected term assumption. The Company uses the simplified method as prescribed by the SEC Staff Accounting Bulletin No. 107, *Share-Based Payment*, to calculate the expected term for options granted to employees as it does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. The expected term is applied to the stock option grant group as a whole, as the Company does not expect substantially different exercise or post-vesting termination behavior among its employee population. For options granted to non-employees, the Company utilizes the contractual term of the share-based payment as the basis for the expected term assumption. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected term of the stock options. The expected dividend yield is assumed to be zero as the Company has never paid dividends and has no current plans to pay any dividends on its common stock.

In the first quarter of 2017, the Company made an accounting policy election to recognize forfeitures as they occur upon adoption of guidance per ASU No. 2016-09, *Compensation – Stock Compensation*. The adoption of ASU No. 2016-09 did not have a material impact on the Company's financial statements. In reporting periods prior to 2017, the Company estimated forfeitures at the time of grant and revised the forfeitures rate in subsequent periods as necessary if actual forfeitures differed from estimates. The Company used historical data to estimate pre-vesting forfeitures and recorded stock-based compensation expense only for those awards that were expected to vest.

The Company expenses the fair value of its share-based compensation awards to employees on a straight-line basis over the requisite service period, which is generally the vesting period. Stock-based compensation awards to non-employees are adjusted through stock-based compensation expense at each reporting period end to reflect the current fair value of such awards and are expensed on a straight-line basis.

Income Taxes

The Company accounts for income taxes using the liability method in accordance with ASC Topic 740, *Income Taxes* (“ASC 740”). The difference between the financial statement and tax basis of the assets and liabilities is determined annually. Deferred income tax assets and liabilities are computed using the tax laws and rates that are expected to apply for periods in which such differences reverse. Valuation allowances are established, if necessary, to reduce the deferred tax asset to the amount that will more likely than not be realized.

The Company recognizes the effect of income tax positions only if those positions are more likely than not of being sustained. Recognized income tax positions are measured at the largest amount that is greater than 50% likely of being realized. Changes in recognition or measurement are reflected in the period in which the change in judgment occurs.

Net Loss Per Share

The Company has reported losses since inception and has computed basic net loss per share attributable to common stockholders by dividing net loss attributable to common stockholders by the weighted-average number of common shares outstanding for the period, without consideration for potentially dilutive securities. The Company has computed diluted net loss per common share after giving consideration to all potentially dilutive common shares, including options to purchase common stock, restricted common stock, convertible preferred stock and warrants to purchase convertible preferred stock, outstanding during the period determined using the treasury-stock and if-converted methods, except where the effect of including such securities would be anti-dilutive. Because the Company has reported net losses since inception, these potential common shares have been anti-dilutive and basic and diluted loss per share have been the same.

Basic and diluted net loss per share attributable to common stockholders was calculated as follows (in thousands, except share and per share data):

	Years Ended December 31,		
	2018	2017	2016
Numerator:			
Net loss	$ (35,648)	$ (21,650)	$ (24,507)
Accretion of convertible preferred stock	—	(58)	(69)
Net loss attributable to common stockholders	$ (35,648)	$ (21,708)	$ (24,576)
Denominator:			
Weighted-average common shares – basic and diluted	20,741,226	4,520,337	1,339,254
Net loss per share attributable to common stockholders –basic and diluted	$ (1.72)	$ (4.80)	$ (18.35)

The following table sets forth the potentially dilutive securities that have been excluded from the calculation of diluted net loss per share because to include them would be anti-dilutive (in common stock equivalent shares):

	Years Ended December 31,		
	2018	2017	2016
Series A convertible preferred stock	—	—	4,400,410
Series B convertible preferred stock	—	—	4,753,536
Series C convertible preferred stock	—	—	4,791,563
Warrants	9,040	9,040	43,265
Stock options	2,141,527	1,508,124	1,348,845
Total	2,150,567	1,517,164	15,337,619

Loss Contingencies

In accordance with ASC 450, *Contingencies*, the Company accrues anticipated costs of settlement, damages, and losses for loss contingencies based on historical experience or to the extent specific losses are probable and estimable. Otherwise, the Company expenses these costs as incurred. If the estimate of a probable loss is a range, and no amount within the range is more likely, the Company accrues the minimum amount of the range.

Guarantees

The Company has identified the guarantees described below as disclosable, in accordance with ASC 460, *Guarantees*.

As permitted under Delaware law, the Company indemnifies its officers and directors for certain events or occurrences while the officer or director is, or was, serving at the Company's request in such capacity. The maximum potential amount of future payments the Company could be required to make is unlimited; however, the Company has directors' and officers' insurance coverage that should limit its exposure and enable it to recover a portion of any future amounts paid.

The Company is a party to a number of agreements entered into in the ordinary course of business that contain typical provisions that obligate the Company to indemnify the other parties to such agreements upon the occurrence of certain events. Such indemnification obligations are usually in effect from the date of execution of the applicable agreement for a period equal to the applicable statute of limitations. The aggregate maximum potential future liability of the Company under such indemnification provisions is uncertain.

The Company leases office space under several noncancelable operating leases. The Company has standard indemnification arrangements under these leases that require it to indemnify the landlord against all costs, expenses, fines, suits, claims, demands, liabilities, and actions directly resulting from any breach, violation, or nonperformance of any covenant or condition of the respective lease.

As of December 31, 2018 and 2017, the Company had not experienced any losses related to these indemnification obligations, and no material claims with respect thereto were outstanding. The Company does not expect significant claims related to these indemnification obligations and, consequently, concluded that the fair value of these obligations is negligible, and no related reserves have been established.

Recently Adopted Accounting Pronouncements

From time to time, new accounting pronouncements are issued by the FASB or other standard setting bodies and adopted by the Company as of the specified effective date. Unless otherwise discussed, the Company believes that the impact of recently issued standards that are not yet effective will not have a material impact on its consolidated financial position or results of operations upon adoption.

In August 2016, the FASB issued ASU No. 2016-15, *Statement of Cash Flows: Classification of Certain Cash Receipts and Cash Payments* ("ASU No. 2016-15"). This guidance addresses the presentation and classification of certain cash receipts and cash payments in the statement of cash flows. The Company adopted ASU No. 2016-15 effective January 1, 2018. The adoption of ASU No. 2016-15 did not have a material impact on the Company's financial statements.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash*. This standard requires that a statement of cash flows explain the change during the period in the total of cash, cash equivalents and amounts generally described as restricted cash or restricted cash equivalents. Therefore, amounts generally described as restricted cash and restricted cash equivalents should be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. The Company adopted this standard effective January 1, 2018. The adoption did not have a material impact on the Company's financial statements.

In May 2017, the FASB issued ASU No. 2017-09, *Compensation-Stock Compensation (Topic 718): Scope of Modification Accounting* ("ASU No. 2017-09"). This update clarifies the changes to terms or conditions of a share-based payment award that require an entity to apply modification accounting. The Company adopted ASU No. 2017-09 effective January 1, 2018. The adoption of ASU No. 2017-09 did not have a material impact on the Company's financial statements.

In May 2014, the FASB issued ASU 2014-09, *Revenue from Contracts with Customers (Topic 606)*, which supersedes all existing revenue recognition requirements, including most industry-specific guidance. The new standard requires a company to recognize revenue when it transfers goods or services to customers in an amount that reflects the consideration that the company expects to receive for those goods or services. The Company adopted ASC 606 on January 1, 2018 under the modified retrospective method. The modified retrospective method requires that the cumulative effect of initially applying ASC 606 be recognized as an adjustment to the opening balance of retained earnings or accumulated deficit of the annual period that includes the date of initial application. The Company did not have any arrangements that were in the scope of ASC 606 and thus there was no impact to the Company's financial statements as a result of the adoption.

Recently Issued Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* ("ASU 2016-02"). The standard requires that all lessees recognize the assets and liabilities that arise from leases on the balance sheet and disclose qualitative and quantitative information about its leasing arrangements. In July 2018, the FASB issued ASU No. 2018-11, *Leases (Topic 842): Targeted Improvements* ("ASU 2018-11"), which offers a transition option to entities adopting ASC 842. Under ASU 2018-11 entities can elect to apply ASC 842 using a modified-retrospective adoption approach resulting in a cumulative effect adjustment to accumulated deficit at the beginning of the year in which the new lease standard is adopted, rather than adjustments to the earliest comparative period presented in their financial statements. Pursuant to the guidance under ASU 2016-02, the Company elected the optional package of practical expedients, which allow the Company to not reassess: (i) whether expired or existing contracts contain leases; (ii) lease classification for any expired or existing leases; and (iii) initial direct costs for any existing leases. The standard also allows entities to make certain policy elections, some of which the Company also plans to elect, including: (i) a policy to not record short-term leases on the balance sheet and (ii) a policy to not separate lease and non-lease components for certain classes of underlying assets. The Company adopted ASC 842 on January 1, 2019 using the modified-retrospective method and expects to record right-of-use assets of approximately $1.0 million and

corresponding liabilities of approximately $1.0 million related to its real estate leases with terms of more than 12 months that are not treated as financing leases under ASC 842, accordingly. These adjustments will have no impact on the Company's consolidated statement of operations and no impact on the Company's accumulated deficit.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation-Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting*. The new standard largely aligns the accounting for share-based payment awards issued to employees and nonemployees by expanding the scope of ASC 718 to apply to nonemployee share-based transactions, as long as the transaction is not effectively a form of financing. The new guidance will be effective for the Company on January 1, 2019. The Company is in the process of finalizing the potential impact that ASU No. 2018-07 may have on its financial statements.

In 2018, the FASB issued ASU 2018-15, *Intangibles—Goodwill and Other—Internal-Use Software (Subtopic 350-40): Customer's Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That Is a Service Contract* ("ASU 2018-15"), which clarifies the accounting for implementation costs in cloud computing arrangements. The new guidance will become effective for the Company on January 1, 2020. Early adoption is permitted. The Company is currently evaluating the impact the adoption of ASU 2018-15 will have on its consolidated financial statements.

In 2018, the FASB issued ASU 2018-13, *Fair Value Measurement (Topic 820): Disclosure Framework-Changes to the Disclosure Requirements for Fair Value Measurement* ("ASU 2018-13"), which modifies the disclosure requirements on fair value measurements. The new guidance will become effective for the Company on January 1, 2020. Early adoption is permitted. The Company currently is evaluating the impact the adoption of ASU 2018-13 will have on its disclosures.

3. Fair Value Measurements

The following tables present information about the Company's financial assets and liabilities that have been measured at fair value at December 31, 2018 and 2017 and indicates the fair value hierarchy of the valuation inputs utilized to determine such fair value (in thousands):

Description	December 31, 2018	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Assets:				
Money market funds, included in cash and cash equivalents	$ 61,415	$ 61,415	$ —	$ —
Total assets	$ 61,415	$ 61,415	$ —	$ —

Description	December 31, 2017	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Assets:				
Money market funds, included in cash and cash equivalents	$ 93,745	$ 93,745	$ —	$ —
Total assets	$ 93,745	$ 93,745	$ —	$ —

At December 31, 2018 and 2017, all of the Company's cash equivalents were comprised of money market funds.

There have been no changes to the valuation methods used during the years ended December 31, 2018 and 2017. There were no transfers within the fair value hierarchy during the years ended December 31, 2018 and 2017.

The carrying amounts reflected in the consolidated balance sheets for cash and cash equivalents, prepaid expenses and other current assets, accounts payable and accrued expenses approximate their carrying values. The Company

believes the terms of the loan payable reflect current market conditions for an instrument with similar terms and maturity, therefore the carrying value of the Company's debt approximates its fair value based on Level 3 of the fair value hierarchy.

Warrants to Purchase Shares Subject to Redemption

Prior to the Company's IPO, the Company had warrants outstanding for the purchase of shares of convertible preferred stock (the "Warrants") that were measured at fair value at each reporting period. The estimated fair value of the Warrants was determined using the Black-Scholes option-pricing model. A significant input to the fair value of the warrants is the fair value of the Series A and C Convertible Preferred Stock which was determined based upon the Company's common stock valuations. The fair value of the Warrants was remeasured at each reporting date through the date of the IPO using then-current assumptions with changes in fair value charged to other income (expense) on the statements of operations and comprehensive loss.

The following table sets forth a summary of changes in the fair value of the Warrants, which represented a recurring measurement classified within Level 3 of the fair value hierarchy, wherein fair value was estimated using significant unobservable inputs (in thousands, except share data):

Balance at December 31, 2016	$	267
Change in fair value of Warrants through the date of the IPO included in other income (expense)		257
Fair value of Warrants reclassified to stockholders' equity (deficit) upon conversion to warrants for the conversion of common stock		(524)
Balance at December 31, 2017	$	—

An entity may choose to measure many financial instruments and certain other items at fair value at specified election dates. Subsequent unrealized gains and losses on items for which the fair value option has been elected will be reported in earnings. The Company did not elect to measure any financial instruments or other items at fair value.

4. Property and Equipment, Net

Property and equipment includes the following at December 31, 2017 and 2016 (in thousands):

	December 31,	
	2018	**2017**
Property and equipment:		
Laboratory equipment	$ 728	$ 263
Computer equipment	6	6
Software	39	39
	773	308
Less: Accumulated depreciation	(259)	(181)
Property and equipment, net	$ 514	$ 127

The Company recognized $78,000, $73,000 and $46,000 of depreciation expense for the years ended December 31, 2018, 2017 and 2016, respectively.

5. Accrued Expenses

Accrued expenses consist of the following (in thousands):

	December 31,	
	2018	2017
Payroll and employee-related expenses	$ 1,690	$ 1,132
Third-party research and development expenses	1,514	135
Professional fees	299	420
Loan interest	46	40
IPO-related costs	—	111
Other	76	111
Total accrued expenses	$ 3,625	$ 1,949

6. Loan and Security Agreement

At December 31, 2017, the Company had $9.7 million outstanding under a loan agreement with SVB, as amended ("Amended SVB Loan Agreement"). The borrowings were secured by a lien on all Company assets, excluding intellectual property. The May 2016 and December 2016 advances had a floating per annum interest rate of the greater of 4.0% or 0.5% above the prime rate. Principal payments were due through May 2020. At its option, the Company could prepay all, but not less than all, of the outstanding borrowings subject to a prepayment premium as defined in the Amended SVB Loan Agreement. The Company was also required to make a final payment equal to 8.25% of the total borrowings ("Final Payment") on the earliest of the loan maturity date, an acceleration of the loan as defined in the Amended SVB Loan Agreement or at the time of prepayment.

On June 29, 2018, the Company terminated the Amended SVB Loan Agreement and repaid the $7.7 million outstanding principal balance and the Final Payment to SVB. The Company recorded a loss on extinguishment of debt of $0.6 million in the Statement of Operations, accordingly.

On June 29, 2018 the Company also entered into a loan agreement with Pacific Western Bank ("PWB Loan Agreement") providing up to $12.0 million of borrowings, of which $10.0 million was advanced on June 29, 2018. The remaining $2.0 million of borrowings available under the PWB Loan Agreement are available to the Company through one additional advance request until the end of the interest only period as defined below. Borrowings are secured by a lien on all Company assets, excluding intellectual property, and amounts borrowed have a floating per annum interest rate of the greater of 5.0% or the prime rate. The PWB Loan Agreement has a term of 48 months and an initial interest only period of 18 months. If the Company receives at least $50M of gross proceeds from the sale of its equity securities or upfront cash payment from a strategic partnership prior the expiration of the initial interest only period, the interest only period will be extended an additional six months. Upon the expiration of the initial interest only period on December 31, 2019, amounts borrowed will be repaid over 30 equal monthly payments of principal plus accrued but unpaid interest. If the interest only period is extended an additional six months, amounts borrowed will be repaid over 24 equal monthly payments of principal plus accrued but unpaid interest beginning July 1, 2020. At its option, the Company may prepay all, but not less than all, of the outstanding borrowings subject to a prepayment premium as defined in the Loan Agreement. Upon the closing of one or more financings, in which the Company receives aggregate gross proceeds of at least $25 million, a success fee will be paid to the Lender. If the gross proceeds are received on or before June 30, 2019, the Success Fee is $200,000, and if the gross proceeds are received after June 30, 2019, the Success Fee is $300,000. The Company's obligation to pay this Success Fee survives termination of the Agreement.

The PWB Loan Agreement contains negative covenants restricting the Company's activities, including limitations on dispositions, mergers or acquisitions, incurring indebtedness or liens, paying dividends or making investments and certain other business transactions. There are no financial covenants associated with the PWB Loan Agreement. The obligations under the PWB Loan Agreement are subject to acceleration upon the occurrence of specified events of default, including a material adverse change in the Company's business, operations or financial or other condition. The Company has determined that the risk of subjective acceleration under the material adverse events clause is remote and therefore has classified the outstanding principal based on scheduled principal payments.

The Company evaluated the PWB Loan Agreement for embedded features that require bifurcation, noting certain features were required to be bifurcated, but were concluded to be de minimis in value at December 31, 2018.

The minimum aggregate future loan and interest payments at December 31, 2018 are as follows (in thousands):

Years Ending December 31,	
2019	$ 550
2020	4,450
2021	4,229
2022	2,032
Total minimum payments	11,261
Less: Amount representing interest	(1,261)
Less: Discount	(20)
Less: Current portion	—
Loan payable, net of current portion	$ 9,980

7. Stockholders' Equity

On November 6, 2017, the Company completed an initial public offering ("IPO"), in which the Company issued and sold 5,333,333 shares of its common stock at a public offering price of $14.00 per share, for aggregate gross proceeds of $74.7 million. The underwriters partially exercised their over-allotment option on December 1, 2017, and purchased an additional 16,969 shares of our common stock for aggregate gross proceeds of $0.2 million. As a result of the IPO, the Company received approximately $67.0 million in net proceeds after deducting $7.9 million of underwriting discounts and commissions and offering costs.

Upon the closing of the IPO, all of the outstanding shares of convertible preferred stock automatically converted into 13,945,509 shares of common stock.

Common Stock

The holders of common stock are entitled to one vote for each share held. Common stockholders are not entitled to receive dividends, unless declared by the Board of Directors.

The Company has reserved for future issuances the following shares of common stock as of December 31, 2018 and 2017:

	December 31, 2018	December 31, 2017
Warrants	9,040	9,040
Stock options	4,262,341	3,538,345
Employee stock purchase plan	405,742	206,284
Total	4,677,123	3,753,669

Warrants

At December 31, 2018 and 2017, the Company has 9,040 warrants outstanding for the purchase of shares of common stock at an exercise price of $11.06. The warrants expire on May 1, 2026.

8. Stock Incentive Plans

Stock Option Plans

The Company adopted the 2017 Stock Option and Incentive Plan ("2017 Plan") on October 31, 2017. Upon adoption of the 2017 Plan, no further grants were made under the 2011 Stock Incentive Plan ("2011 Plan"). The 2017 Plan initially provided for the grant of awards for 2,038,021 shares of common stock. In addition to the shares available for grant under the 2017 Plan, any awards outstanding under the 2011 Plan as of the October 31, 2017 that

are cancelled, forfeited or otherwise terminated without being exercised, the number of shares underlying such awards are available for future grant under the 2017 Plan. The 2017 Plan also provides that an additional number of shares will automatically be added to the shares authorized for issuance under the 2017 Plan on January 1 of each year. The number of shares added each year will be equal to the lesser of: (i) 4% of the outstanding shares on the immediately preceding December 31 or (ii) such amount as determined by the Compensation Committee of the registrant's Board of Directors. On January 1, 2018 and 2019, the shares available for grant under the 2017 Plan was automatically increased by 827,786 and 832,361 shares, respectively.

All of the Company's employees, officers, directors, consultants and advisors are eligible to be granted options, restricted stock units ("RSUs"), and other share-based awards under the terms of the 2017 Plan. As of December 31, 2018, 2,120,814 shares of common stock were available for future grant under the 2017 Plan.

All stock option grants are nonstatutory stock options except option grants to employees (including officers and directors) intended to qualify as incentive stock options under the Internal Revenue Code of 1986, as amended. Incentive stock options may not be granted at less than the fair market value of the Company's common stock on the date of grant. Nonqualified stock options may be granted at an exercise price established by the Board of Directors at its sole discretion (which has not been less than fair market value on the date of grant) and the vesting periods may vary. Vesting periods are generally four years and are determined by the Board of Directors or a delegated subcommittee. Stock options become exercisable as they vest. Stock options granted under the 2017 and 2011 Plans expire no more than 10 years from the date of grant.

Stock-based compensation expense included in the Company's statements of operations and comprehensive loss is as follows (in thousands):

	Years Ended December 31,		
	2018	2017	2016
Research and development	$ 584	$ 147	$ 68
General and administrative	1,465	370	183
Total	$ 2,049	$ 517	$ 251

The fair value of each stock option granted to employees and directors was estimated on the date of grant using the Black-Scholes option-pricing model, with the following range of assumptions for the years ended December 31, 2018, 2017 and 2016:

	Years Ended December 31,		
	2018	2017	2016
Risk-free interest rate	2.3% – 3.1%	1.9% – 2.3%	1.3% – 1.7%
Expected dividend yield	—%	—%	—%
Expected term (in years)	5.5 – 6.1	5.6 – 6.3	5.4 – 6.4
Expected volatility	81% – 89%	81% – 87%	77% – 84%

The expense related to awards granted to employees and directors for their service on the Board of Directors was $1.9 million, $0.5 million, and $0.2 million for the years ended December 31, 2018, 2017 and 2016, respectively.

The Company did not grant any stock options to non-employees during the years ended December 31, 2018 or 2017.The fair value of each stock option granted to non-employees was estimated on the date of grant using the Black-Scholes option-pricing model. The expense related to awards granted to non-employees was $0.1 million, $65,000 and $24,000 for the years ended December 31, 2018 and 2017 and 2016, respectively.

A summary of the stock option activity under the 2017 and 2011 Plans is as follows:

	Shares	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Life (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2017	1,508,124	$ 1.89	7.9	$ 12,328
Granted	801,474	8.57		
Exercised	(106,879)	1.29		
Cancelled	(61,192)	5.73		
Outstanding at December 31, 2018	2,141,527	$ 4.32	7.7	$ 4,959
Exercisable at December 31, 2018	1,163,352	$ 2.07	6.9	$ 4,115

The weighted-average fair value of options granted to employees and directors for their service on the Board of Directors during the years ended December 31, 2018, 2017 and 2016 was $6.21, $6.16 and $1.13 per share, respectively. The weighted-average fair value of options granted to non-employees during the year ended December 31, 2016 was $1.38 per share.

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the stock options and the fair value of the Company's common stock for those stock options that had exercise prices lower than the fair value of the Company's common stock. The total intrinsic value of options exercised during the years ended December 31, 2018, 2017 and 2016 was $1.2 million, $276,000 and $21,000, respectively.

As of December 31, 2018, total unrecognized stock-based compensation expense relating to unvested stock options was $4.4 million. This amount is expected to be recognized over a weighted-average period of 2.8 years.

Employee Stock Purchase Plan

The Company adopted the 2017 Employee Stock Purchase Plan ("ESPP") on October 31, 2017. The ESPP permits eligible employees to enroll in six-month offering periods. Participants may purchase shares of the Company's common stock, through payroll deductions, at a price equal to 85% of the fair market value of the common stock on the first or last day of the applicable six-month offering period, whichever is lower. Purchase dates under the ESPP occur on or about January 1 and July 1 each year. The ESPP initially reserved 206,284 shares of common stock for issuance. The ESPP also provides that an additional number of shares will automatically be added to the shares authorized for issuance under the ESPP on January 1 of each year. The number of shares added each year will be equal to the lesser of: (i) 1% of the outstanding shares on the immediately preceding December 31 or (ii) such amount as determined by the Compensation Committee of the registrant's Board of Directors. On January 1, 2018 the shares available for grant under the ESPP was automatically increased by 206,946 shares. No shares were added to the ESPP on January 1, 2019.

During the year ended December 31, 2018, $35,000 was withheld from employees, on an after-tax basis, in order to purchase 7,488 shares of the Company's common stock. As of December 31, 2018, 405,742 shares of Company's common stock remained available for issuance under the ESPP.

9. Income Taxes

New Tax Legislation

On December 22, 2017, the President of the United States signed into law the Tax Cuts and Jobs Act ("TCJA"). This legislation reduced the U.S. corporate tax rate from the current rate of 34% to 21% for tax years beginning after

December 31, 2017. As a result of the enacted law, the Company was required to revalue deferred tax assets and liabilities existing as of December 31, 2017 from the 34% federal rate in effect through the end of 2017, to the new 21% rate. The Company has recognized the impact of the Tax Reform Act in these consolidated financial statements and related disclosures. Due to the complexities involved in accounting for the enactment of the Tax Reform Act, the SEC staff issued Staff Accounting Bulletin No. 118 ("SAB 118"), which allows a registrant to record provisional amounts during a measurement period not to extend beyond one year of the enactment date. In accordance with SAB 118, the Company recorded provisional amounts reflecting the impact of the Tax Reform Act in these consolidated financial statements and related disclosures. The impact of the remeasurement of the Company's U.S. deferred tax assets and liabilities to 21% resulted in the reduction of deferred tax assets of approximately $9.3 million, which is offset by a full valuation allowance. There was no impact to the Company's income statement due to the reduction in the U.S. corporate tax rate.

Income Taxes

The Company records a provision or benefit for income taxes on pre-tax income or loss based on its estimated effective tax rate for the year. During the year ended December 31, 2018, the Company recorded a net loss of approximately $35.6 million and, since it maintains a full valuation allowance on its deferred tax assets, the Company did not record an income tax benefit for the year ended December 31, 2018.

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The significant components of the Company's deferred tax assets are comprised of the following (in thousands):

	December 31,	
	2018	2017
Deferred tax assets:		
Net operating loss carryforwards	$ 30,294	$ 21,190
Research and development credits	5,843	4,732
Licenses	21	24
Stock based compensation	369	70
Other	418	300
Total gross deferred tax asset	36,945	26,316
Less: Valuation allowance	(36,945)	(26,316)
Net deferred tax asset	$ —	$ —

ASC 740 requires a valuation allowance to reduce the deferred tax assets reported if, based on the weight of the evidence, it is more likely than not that some portion or all of the deferred tax assets will not be realized. After consideration of all the evidence, both positive and negative, the Company has recorded a valuation allowance against its deferred tax assets at December 31, 2018 and 2017, respectively, because the Company's management has determined that it is more likely than not that the Company will not recognize the benefits of its federal and state deferred tax assets primarily due to its cumulative loss position and, as a result, a valuation allowance of $36.9 million and $26.3 million has been established at December 31, 2018 and 2017, respectively. The valuation allowance increased by approximately $10.6 million during the year ended December 31, 2018 due primarily to the generation of net operating losses and decreased by approximately $0.3 million in the year ended December 31, 2017 due primarily to the revaluation of the deferred tax assets at a 21% Federal tax rate.

A reconciliation of income tax expense computed at the statutory federal income tax rate to income taxes reflected in the financial statements is as follows:

	2018	2017	2016
Income tax computed at federal statutory tax rate	21.0%	34.0%	34.0%
Permanent differences	—%	(1.9)%	(0.2)%
State taxes, net of federal benefit	6.2%	4.8%	5.1%
Research and development and other tax credits	3.1%	5.0%	6.1%
Stock based compensation	(0.5)%	(0.5)%	(0.3)%
Federal rate change	—%	(42.7)%	—%
Change in deferred tax asset valuation allowance	(29.8)%	1.3%	(44.7)%
	—%	—%	—%

As of December 31, 2018 and 2017, the Company had U.S. federal net operating loss carryforwards of approximately $111.1 million and $77.9 million, respectively, which may be available to offset future income tax liabilities and expire at various dates through 2037. As of December 31, 2018 and 2017, the Company also had U.S. state net operating loss carryforwards of approximately $110.3 million and $76.5 million, respectively, which may be available to offset future income tax liabilities and expire at various dates through 2038.

As of December 31, 2018 and 2017, the Company had federal research and development tax credit carryforwards of approximately $4.0 million and $3.3 million, respectively, available to reduce future tax liabilities which expire at various dates through 2038. As of December 31, 2018 and 2017, the Company had state research and development tax credit carryforwards of approximately $2.2 million and $1.9 million, respectively, available to reduce future tax liabilities which expire at various dates through 2033. The Company has generated research credits but has not conducted a study to document the qualified activity. This study may result in an adjustment to the Company's research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the deferred tax asset established for the research and development credit carryforwards and the valuation allowance.

Under the provisions of the Internal Revenue Code, the net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed several financings since its inception which resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code.

Ownership changes, as defined in the Internal Revenue Code, including those resulting from the issuance of common stock in connection with our public offerings, may limit the amount of net operating loss and tax credit carryforwards that can be utilized to offset future taxable income or tax liability. The amount of the limitation is determined in accordance with Section 382 of the Internal Revenue Code. We have performed an analysis of ownership changes through December 31, 2018. Based on this analysis, we do not believe that any of our tax attributes will expire unutilized due to Section 382 limitations.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2018 and 2017, the Company had no accrued interest or penalties related to uncertain tax positions and no such amounts have been recognized in the Company's statements of operations and comprehensive loss.

10. Related Party Transactions

From September 2015 to June 2017, the Company received consulting and management services from one of its investors, Third Rock Ventures LLP ("Third Rock Ventures"). The Company paid Third Rock Ventures $2,000 and

$69,000 for these services during the years ended December 31, 2017 and 2016, respectively. No amounts were payable to Third Rock Ventures at December 31, 2018 and 2017.

11. Commitments and Contingencies

In August 2011 and October 2013, the Company and an independent third party entered into operating leases for approximately 6,055 square feet of office space in Newton, MA ("Newton Lease") and approximately 3,170 square feet of laboratory space in Natick, MA, respectively. Base rent for the office space during the initial rent period was approximately $0.1 million per year and increased annually. Base rent for the lab space was approximately $59,000 annually. Rent expense, inclusive of the escalating rent payments and free rent period, was recognized on a straight-line basis over the term of each lease agreement. The Company and the independent third party were each jointly and severally liable for the obligations under both leases. In October 2016, the Newton lease was amended to extend the term one year to May 2018 and, effective June 1, 2017 removed the independent third party from the lease and all related obligations of the lease. In December 2017, the Newton lease was amended again to increase the amount of office space to approximately 7,795 square feet and extend the term to December 31, 2020. The amended lease for laboratory space expired October 31, 2017.

In August 2016, the Company entered into an operating lease for approximately 3,890 square feet of laboratory space in Sudbury, MA. This lease was to expire in August 2017. In February 2017, the Company amended this lease to extend the term to February 2019 and increase the amount of rentable space to approximately 5,133 square feet, with an option to lease another 2,029 square feet. In March 2018, this lease was amended again to reduce rentable space to approximately 4,636 square feet and extend the term to February 2021. The Company accounted for these amendments as modifications to the original lease agreement. In August 2018, this lease was again amended to add approximately 2,928 square feet of office space. Base rent for this space is approximately $0.2 million annually.

Rent expense includes the Company's allocated portion of rental obligations under the leases. The Company recorded $0.5 million, $0.4 million and $0.2 million, of rent expense for the years ended December 31, 2018, 2017 and 2016, respectively.

The minimum aggregate future operating lease commitments at December 31, 2018 are as follows (in thousands):

	December 31, 2018
2019	$ 487
2020	539
2021	30
	$ 1,056

12. License Agreement

In March 2012, the Company entered into an exclusive license agreement ("License Agreement") with Althea Technologies, Inc. ("Althea") for certain intellectual property. The Company reimbursed Althea for patent related fees and costs incurred by Althea totaling $0.1 million in the aggregate and issued a total of 88,186 shares of common stock to Althea. Under the terms of the License Agreement, the Company agreed to pay annual license maintenance fees, milestone payments and royalties as a percentage of net sales. Annual license maintenance fees are creditable against royalties earned during the same calendar year and are not material to the financial statements. Milestone payments are triggered upon the achievement of specified development, regulatory and commercialization milestones and are not creditable against royalties. Actual amounts due under the License Agreement will vary depending on the number of products developed, the type and development path of the products, and other related factors. Milestone payments could total up to $56.0 million. The Company may terminate the agreement at any time with 60 days prior written notice.

13. Employee Benefit Plan

Effective January 2012, employees of the Company are eligible to participate in the Company's 401(k) retirement plan ("401(k) Plan"). Participants may contribute up to 100% of their annual compensation to the 401(k) Plan, subject to statutory limitations. Through December 31, 2018, the 401(k) Plan did not allow the Company to make matching contributions. Effective January 1, 2019, the Company amended the 401(k) Plan to allow the Company to

make matching contributions. The 401(k) Plan will match 100% of employee contributions up to a maximum of 4% of employees' salary. Matching contributions are fully vested at the time of contribution.

14. Selected Quarterly Financial Data (Unaudited)

The following table contains quarterly financial information for 2018 and 2017. The Company believes that the following information reflects all normal recurring adjustments necessary for the fair statement of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

	2018				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
	(in thousands, except per share amounts)				
Total operating expenses	$ 7,973	$ 8,135	$ 9,705	$ 9,780	$ 35,593
Loss from operations	(7,973)	(8,135)	(9,705)	(9,780)	(35,593)
Net loss	(7,880)	(8,647)	(9,510)	(9,611)	(35,648)
Net loss attributable to common stockholders - basic and diluted	$ (0.38)	$ (0.42)	$ (0.46)	$ (0.46)	$ (1.72)

	2017				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
	(in thousands, except per share amounts)				
Total operating expenses	$ 5,542	$ 4,475	$ 4,362	$ 6,571	$ 20,950
Loss from operations	(5,542)	(4,475)	(4,362)	(6,571)	(20,950)
Net loss	(5,671)	(4,632)	(4,670)	(6,677)	(21,650)
Net loss attributable to common stockholders - basic and diluted	$ (4.24)	$ (3.46)	$ (3.49)	$ (0.48)	$ (4.80)

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

1. Registration Statement (Form S-8, File No. 333-221306) pertaining to the 2011 Stock Incentive Plan, the 2017 Stock Option and Incentive Plan, and the 2017 Employee Stock Purchase Plan of Allena Pharmaceuticals, Inc.,

2. Registration Statement (Form S-8, File No. 333-223939) pertaining to the 2017 Stock Option and Incentive Plan and the 2017 Employee Stock Purchase Plan of Allena Pharmaceuticals, Inc., and

3. Registration Statement (Form S-3, File No. 333-228656) and related Prospectus of Allena Pharmaceuticals, Inc. for the registration of common stock, preferred stock, debt securities, warrants, and units;

of our report dated March 7, 2019, with respect to the consolidated financial statements of Allena Pharmaceuticals, Inc., included in this Annual Report (Form 10-K) for the year ended December 31, 2018.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 7, 2019

Exhibit 31.1

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Louis Brenner, certify that:

1. I have reviewed this annual report on Form 10-K for the year ended December 31, 2018 of Allena Pharmaceuticals, 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)) 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. (Paragraph omitted pursuant to SEC Release Nos. 33-8238/34-47986 and 33-8392/34-49313);

   c. 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

   d. 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 my 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.

March 7, 2019

By: /s/ Louis Brenner
Louis Brenner
Chief Executive Officer and Director
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Edward Wholihan, certify that:

1. I have reviewed this quarterly report on Form 10-K for the year ended December 31, 2018 of Allena Pharmaceuticals, 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)) 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. (Paragraph omitted pursuant to SEC Release Nos. 33-8238/34-47986 and 33-8392/34-49313);

   c. 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

   d. 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 my 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.

March 7, 2019

By: /s/ Edward Wholihan
Edward Wholihan
Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report on Form 10-K of Allena Pharmaceuticals, Inc. (the "Company") for the year ended December 31, 2018, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), each of the undersigned officers hereby certify, pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, 18 U.S.C. Section 1350, that to his knowledge:

1) the Report which this statement accompanies fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

March 7, 2019

By: /s/ Louis Brenner
Louis Brenner
Chief Executive Officer and Director
(Principal Executive Officer)

March 7, 2019

By: /s/ Edward Wholihan
Edward Wholihan
Chief Financial Officer
(Principal Financial and Accounting Officer)