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 001-38560

Aerpio Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its Charter)

Delaware	**EIN 61-1547850**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
9987 Carver Road, Cincinnati, OH	**45242**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (513) 985-1920

Securities registered pursuant to Section 12(b) of the Act: Common Stock, Par Value $0.0001 Per Share; Common stock traded on Nasdaq Capital Market.

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

Indicate by check mark if the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES ☐ NO ☒

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or 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 required 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 (§229.405) is not contained herein, and will not be contained, to the best of Registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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 aggregate market value of the registrant's voting and non-voting common stock held by non-affiliates (without admitting that any person whose shares are not included in such calculation is an affiliate) computed by reference to the price at which the common stock was last sold on June 29, 2018 was approximately $101,488,694.

As of March 1, 2019, there were 40,588,004 shares of common stock, $0.0001 par value per share, outstanding.

Portions of the Registrant's Definitive Proxy Statement relating to the Annual Meeting of Shareholders are incorporated by reference into Part III of this Report. Such Proxy Statement will be filed with the Securities and Exchange Commission within 120 days of the Registrant's fiscal year ended December 31, 2018.

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Forward-Looking Statements

This Annual Report on Form 10-K contains "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. These forward-looking statements may be identified by forward-looking words such as "may," "could," "should," "would," "will," "plans," "intend," "expect," "anticipate," "predicts," "potential," "believe," "continue" or similar words, although not all forward-looking statements contain these identifying words. Forward-looking statements include, but are not limited to, statements regarding the progress and timing of our product development programs and related trials; our future opportunities; our strategy, future operations, anticipated financial position, future revenues and projected costs; our management's prospects, plans and objectives; and any other statements about management's future expectations, beliefs, goals, plans or prospects constitute forward-looking statements.

Readers should not place undue reliance on these forward-looking statements. Our actual results may differ materially from such forward-looking statements as a result of numerous factors, some of which we may not be able to predict and may not be within our control. Factors that could cause such differences include, but are not limited to, the accuracy of our estimates regarding expense, future revenues, uses of cash, capital requirements and the need for additional financing; the initiation, cost, timing, progress and results of our development activities, preclinical studies and clinical trials; the timing of and our ability to obtain and maintain regulatory approval of our existing product candidates, any product candidates that we may develop, and any related restrictions, limitations, and/or warnings in the label of any approved product candidates; our plans to research, develop and commercialize our current and future product candidates; our ability to attract collaborators with development, regulatory and commercialization expertise; our ability to obtain and maintain intellectual property protection for our product candidates; our ability to successfully commercialize our product candidates; the size and growth of the markets for our product candidates and our ability to serve those markets; the success of competing drugs that are or become available; our ability to obtain additional financing; our ability to attract and retain key personnel, as well as those risks discussed elsewhere in this report, including under the heading "Risk Factors." All forward-looking statements are made as of the date of this report and we do not undertake any obligation to update our forward-looking statements, except as required by applicable law.

PART I

Item 1. Business.

Overview

Aerpio is a biopharmaceutical company focused on advancing first-in-class treatments for ocular disease. Our lead product candidate, AKB-9778, a small molecule activator of the Tie2 pathway, is being developed for the treatment of non-proliferative diabetic retinopathy, or NPDR, a disease characterized by progressive compromise of blood vessels in the back of the eye. The Tie2 receptor is expressed almost exclusively in endothelial cells (cells that line the inside of blood vessels) and its activity is essential for regulating vascular stability and preventing blood vessel compromise associated with diabetes. We have completed a Phase 2a trial of AKB-9778 in 144 patients with diabetic eye disease. Based on the results from this trial, we believe AKB-9778 has the potential to slow down or possibly reverse the damage to blood vessels caused by diabetes. In contrast to marketed treatments for NPDR that are administered by a physician via intraocular injection, we intend to deliver AKB-9778 systemically by self-administered subcutaneous injection, similar to insulin. We believe this delivery method provides an opportunity to treat diabetic eye disease at an earlier stage and reduces the likelihood of developing vision-threatening complications.

In June 2017, we initiated a 48-week, double-masked, Phase 2b clinical trial, which we refer to as TIME-2b, in patients with NPDR who have not developed more serious complications such as diabetic macular edema, or DME or proliferative diabetic retinopathy, or PDR. The TIME-2b study is a double-masked, placebo-controlled multi-center trial that is currently on-going and has enrolled 167 patients randomized evenly to receive either AKB-9778 15 mg subcutaneously once daily, AKB-9778 15 mg subcutaneously twice daily or placebo for a 48-week treatment period. The primary endpoint of the TIME-2b study is the percentage of patients who improve by at least 2 steps in Diabetic Retinopathy Severity Score, or DRSS, in the study eye. We expect to report top line results of this trial in March 2019.

According to the World Health Organization's Global Report of Diabetes as of 2014, there are an estimated 422 million individuals living with diabetes worldwide. An estimated 34.6% of these individuals, or 146 million people, have Diabetic Retinopathy, or DR, 6.81%, or 28 million, have DME and 6.96%, or 29.7 million, have PDR. The underlying problem in diabetic complications is damage to the blood vessels, commonly referred to as diabetic vasculopathy, which is caused by chronic hyperglycemia. This damage causes blood vessels to leak fluid and proteins into the surrounding tissue, leading to complications. In the eyes, this damage leads to DR which can progress to DME and/or PDR. In other parts of the body such as the kidney, the damage leads to diabetic nephropathy and in the lower extremities, the damage leads to non-healing foot ulcers, peripheral artery disease and critical limb ischemia. These diabetic complications lead to life- and sight-threatening conditions including kidney dialysis, amputations and blindness that are costly to treat. Diabetic patients with complications are estimated to cost the health care system 3.5 times more than patients without complications. If approved, we believe that systemic treatment with AKB-9778 could have the potential to change the treatment paradigm for diabetics in the future and potentially address a major societal problem by lowering the cost of care associated generally with diabetes.

Diabetic eye disease is one of the most common and debilitating complications of diabetes. Over time, diabetes damages blood vessels in the back of the eye. When this happens, a patient is said to have DR. Eventually, these damaged blood vessels can leak blood proteins and fluid into the central portion of the retina, called the macula, which is responsible for high resolution central vision. The leakage of protein and fluid into the macula causes swelling, a condition called DME. The more progressive stages of DR, referred to as PDR, are characterized by the growth of abnormal new blood vessels. These new blood vessels can bleed into the eye and if left untreated can result in decreased visual acuity and eventual blindness. The likelihood of a person developing these sight-threatening complications increases as DR progresses.

AKB-9778 is a small molecule activator of the Tie2 pathway that we believe helps to stabilize blood vessel walls and prevent vascular compromise in the eye, and based on pre-clinical models, potentially elsewhere in the body. Such vascular compromise in the eye may eventually lead to DME or PDR and, in many cases, to loss of vision or even blindness. We believe AKB-9778's mechanism of action reduces vascular damage and restores vascular integrity. In contrast to current therapies for diabetic eye disease, which are all administered by a physician via repeated injections into the eye, AKB-9778 is being developed as a self-administered subcutaneous injection that allows for treatment of both eyes.

Compromise of the Tie2 function is also implicated in other vascular complications of diabetes. We believe systemic treatment with AKB-9778 may address some of the most debilitating of the complications, including diabetic nephropathy. If we are successful in developing and commercializing AKB-9778 for NPDR, we may conduct clinical trials to evaluate AKB-9778's potential to reduce or delay the need for kidney dialysis. In post-hoc analysis of Aerpio's TIME-2b clinical trial, there was a 21% reduction (geometric mean) in urine albumin-to-creatinine ration (UACR) from baseline in the AKB-9778 treatment arms, but an overall increase in UACR in the placebo arm. The study suggests potential beneficial activity from Tie2 activation in diabetic kidney disease.

In addition to diabetic vascular disease, existing preclinical and clinical evidence suggest the potential of AKB-9778 for reducing intraocular pressure in primary open angle glaucoma, or POAG, and ocular hypertension. We plan to initiate a Phase 1b clinical trial in the second quarter of 2019 to evaluate AKB-9778, administered via topical eye drops, and, if we observe positive results, we expect to initiate a Phase 2 program for this indication.

In June 2018, we licensed AKB-4924, a selective stabilizer of hypoxia-inducible factor-1 alpha, or HIF-1 alpha to Gossamer Bio, Inc. ("Gossamer"). AKB-4924, (now called GB004), is being developed for the treatment of inflammatory bowel disease (IBD). HIF-1 alpha is involved in mucosal wound healing and the reduction of inflammation in the gastrointestinal tract. We have completed a single ascending dose clinical trial in healthy volunteers for AKB-4924 and Gossamer is currently conducting a multiple ascending dose, or MAD, study and is responsible for all remaining development and commercial activities for GB004.

ARP-1536, our humanized monoclonal antibody directed at the same target as AKB-9778, is in preclinical development. We are evaluating development options for ARP-1536, including subcutaneous injection for the treatment of diabetic vascular complications and intravitreal injection for the treatment of advanced diabetic eye disease such as DME or PDR.

Our Strategy

Our objective is to become the leader in the development of Tie2-targeted therapeutics for the treatment of vascular disorders. We are taking the following critical steps to achieve this goal:

- **Advance the development of AKB-9778 for treatment of diabetic retinopathy**

In June 2017, we initiated a 48-week, double-masked, Phase 2b clinical trial, TIME-2b, in patients with DR who have not developed more serious complications such as DME or PDR. We expect to report top line data in March 2019.

- **If approved for treatment of DR, establish collaborations to commercialize AKB-9778 globally**

If approved, we intend to independently pursue the approval and commercialization of AKB-9778 for treatment of DR in the U.S. We believe that many health care providers, including general ophthalmologists, endocrinologists, and primary care physicians have the potential to treat early diabetic eye disease with AKB-9778, and we plan on utilizing a multi-faceted strategy that will engage these various health care providers. Outside of the U.S., we intend to pursue the approval and commercialization of AKB-9778 for treatment of DR through strategic collaborations. We may develop and commercialize AKB-9778 for other indications independently or through collaborations with third parties.

- **Advance the development of AKB-9778 for primary open angle glaucoma**

We plan to evaluate a topical formulation of AKB-9778 for POAG into a proof-of-concept Phase 1b study in the second quarter of 2019. If we observe positive results from this study, we expect to initiate a Phase 2 program to evaluate AKB-9778 for POAG.

- **Investigate the potential of AKB-9778 in other indications**

The downregulation of Tie2 activity occurs in the vasculature of diabetics systemically, particularly in the kidney. While we are initially focused on the development of AKB-9778 for treatment of DR, our ongoing Phase 2b trial includes exploratory endpoints to study the effects of AKB-9778 on diabetic kidney disease. If we observe positive signals in these exploratory endpoints, we will consider clinical development of AKB-9778 in diabetic nephropathy.

- **Advance the development of ARP-1536**

We are evaluating development options for ARP-1536, including subcutaneous injection for the treatment of diabetic vascular complications and intravitreal injection for the treatment of advanced diabetic eye disease (DME/PDR).

- **Explore strategic collaborations with leading organizations for the development and commercialization of promising product candidates in our pipeline**

We may explore strategic collaborations with leading biopharmaceutical companies and organizations to develop and commercialize product candidates in our pipeline. In June 2018, we licensed AKB-4924 to Gossamer for the development of this candidate for the treatment of inflammatory bowel disease. We may consider additional collaborations in the future to apply our technology to areas of unmet medical need.

AKB-9778 for Diabetic Retinopathy

We believe that AKB-9778, if approved, has the potential to be a market leader for the treatment of early stage diabetic eye disease, DR that has not yet developed vision-threatening complications. There are currently approximately 146 million individuals globally with DR, and this number is projected to continue to grow over the next 30 years. AKB-9778 is designed to eliminate intraocular injections, reduce physician visit burden, simultaneously treat both eyes, of which an estimated 65-70% of diabetic eye disease patients have bilateral disease, reduce or slow progression to development of vision-threatening events, such as DME and PDR, and protect other vascular beds affected by diabetes.

We have completed a Phase 2a trial of AKB-9778 in 144 patients with DR complicated by DME. We observed the following results in this trial:

- We observed promising signs of reduction in the severity of DR when AKB-9778 was used as monotherapy.
- These improvements in diabetic retinopathy severity were seen bilaterally, in the study and fellow eye.
- AKB-9778 monotherapy had fewer ocular and non-ocular adverse events than either Lucentis (ranibizumab) monotherapy or combination therapy.

Diabetic Retinopathy and Diabetic Macular Edema Overview

DR is a frequent complication of diabetes and is a leading cause of visual impairment and blindness among working-age individuals. Patients with DR have a progressive compromise of microvasculature which eventually manifests as leaky blood vessels that allow fluid and blood to leak into surrounding tissues. This leakage presents problems in areas of the body that are highly vascularized such as the retina and the kidney. Fluid leakage in the eye can distort vision directly and the loss of blood flow to other parts of the retina can result in local oxygen deprivation or hypoxia. This hypoxia then triggers the formation of new blood vessels; however, these new vessels are often not well-formed and leaky, leading to further deterioration of vision. In some cases, there is excessive accumulation of fluid or edema near the center of the retina or macula that has severe effects on vision. This accumulation is referred to as DME. This edema leads to thickening of the macula region of the retina and loss of visual acuity. The various features of DR vascular dysfunction are illustrated in the following graphic.

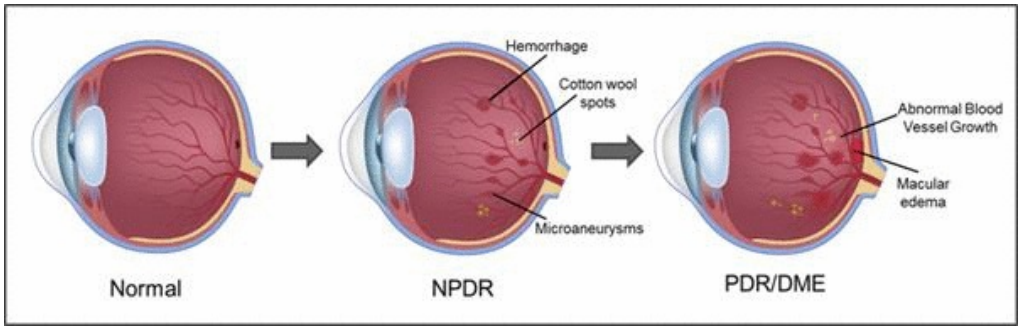

Figure 1: Progression of diabetic eye disease is characterized by worsening vascular compromise.

The severity of DR is evaluated using the Early Treatment Diabetic Retinopathy Study, or ETDRS, severity scale. This scale is divided into 11-discreet steps with less severe disease having lower step scores and more advanced disease having higher step scores. The natural history of DR in most patients is a progressive worsening that can be captured in photographs of the retina, shown below. In its initial stages, DR is characterized by vascular changes in the retina that are detectable by color photography of the back of the eye, or fundus. In these early stages, visual function can remain intact even in the presence of profound vascular compromise. The progression of DR severity is associated with increased risk for vision loss due to the growth of abnormal blood vessels, typical in DME and PDR.

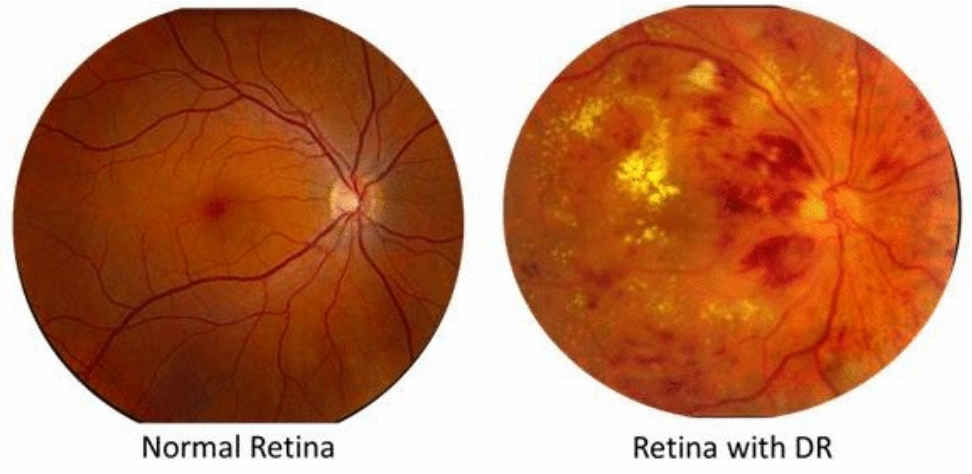

Figure 2. Fundus photographs or a normal retina (left) and a retina with advanced DR (right).

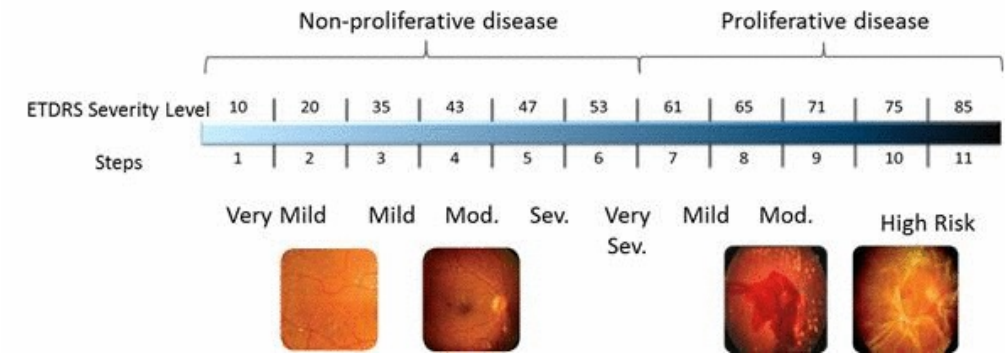

Figure 3: Early Treatment of Diabetic Retinopathy Study scale used to grade fundus images of the retina and measure the progression and regression of diabetic retinopathy.

The majority of diabetic patients will eventually develop DR. By 20 years after disease diagnosis, nearly 100% of type 1 diabetics and 60% of type 2 diabetics will have developed DR. Among an estimated 19.8 million US adults forty years and older known to have diabetes (Types 1 and 2), prevalence rates for DR and DME were 23.7% (4.7 million) and 3.8% (746,000), respectively. We believe both DR and DME are likely to persist as public health problems due to both the aging of the global population and increasing prevalence of diabetes over time.

Current Treatments for DR

Laser photocoagulation is sometimes used to treat DR prior to the development of vision-threatening events. This treatment entails using a high-energy laser to destroy diseased retinal tissue and cauterize leaking blood vessels. While this therapy prevents further vision loss, it does not address the pathology of constant and prolonged vascular damage that happens in the diabetic retina and is therefore not considered a disease-modifying therapy. In addition

to destroying retinal tissue, laser photocoagulation can be associated with several adverse events including transient decreases in central vision, black spots in the center or around the center of a patient's vision, delayed or impaired adaption of vision in dark settings, visual field defects or proliferation of abnormal blood vessels leading to macular edema.

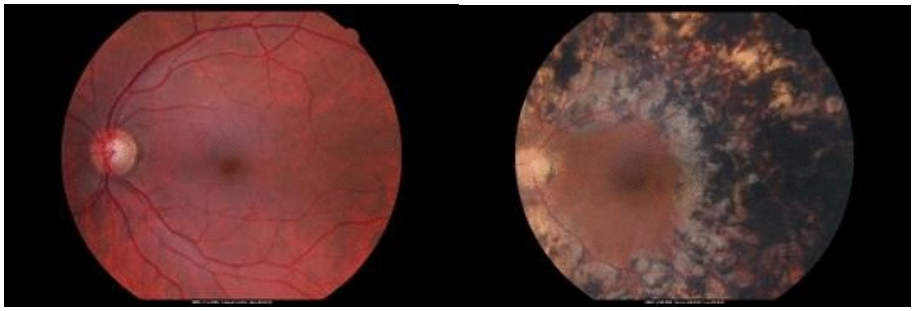

Figure 4: Normal retina (left). Retina after panretinal laser photocoagulation (right).

Lucentis is approved for the treatment of DR. This approval is based on the ability of monthly intraocular injections of Lucentis to improve underlying diabetic retinopathy by two or more steps on the ETDRS DRSS scale compared to placebo at the end of one year of treatment. Improved rates of 2-step improvement in DRSS has also recently been demonstrated with repeated Eylea intraocular injection compared to sham injection. Based on these results, Regeneron has submitted a sBLA for the indication treatment of DR. However, Lucentis and Eylea require intraocular injections and frequent visits to the ophthalmologist which could create patient burden and discomfort. Furthermore, if the patient presents with bilateral disease (approximately 70% of DR patients have bilateral disease), the patient must undergo separate intraocular injections in each eye.

If we are successful in developing and obtaining approval of AKB-9778 for the treatment of DR we believe that we can be market leaders in the space due to the potential advantages of AKB-9778, including the potential to eliminate intraocular injections, reduce physician visit burden, simultaneously treat both eyes, of which approximately 65-70% of diabetic eye disease patients have bilateral disease, reduce or slow progression to development of vision-threatening events, such as DME and PDR, and possibly protect other vascular beds affected by diabetes.

Role of Tie2 in Diabetic Disease

Tie2 is a receptor that is normally activated in healthy blood vessels. When active, Tie2 is a key regulator of vascular stability and function. In its active state, Tie2 maintains blood vessel stability by several mechanisms, including tightening the junctions between the cells that line blood vessels, maintaining support cell coverage of blood vessels, and resisting growth signaling from proliferative cytokines. In diabetic patients, an upregulation of vascular endothelial protein tyrosine phosphatase, or VE-PTP, an enzyme that inactivates Tie2, contributes to vascular destabilization.

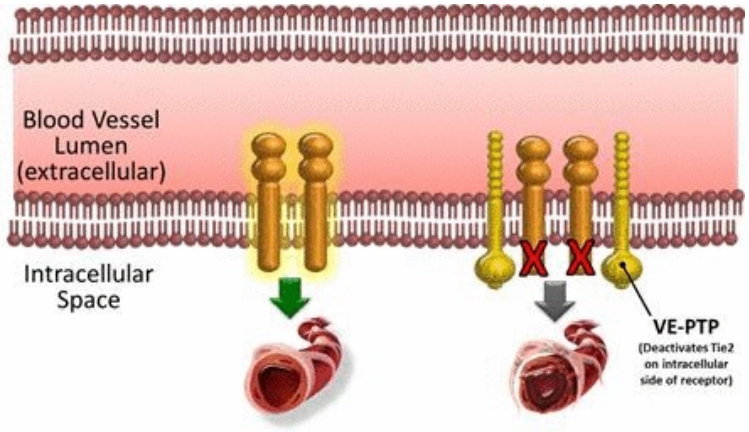

Figure 5. VE-PTP is upregulated in diabetic vasculature and leads to deactivation of the Tie2 receptor.

Our Solution AKB-9778

AKB-9778 works by inhibiting VE-PTP, an enzyme that is upregulated in diabetic eye disease and that is responsible for inactivating Tie2. AKB-9778 was developed using modern drug discovery techniques such as structure-based drug design to selectively target and inhibit VE-PTP at sub-nanomolar concentrations and has a high degree of selectivity. The potency and selectivity of AKB-9778 minimize the potential for off-target side effects. Inhibition of the inhibitor, VE-PTP, by AKB-9778 leads to activation of Tie2.

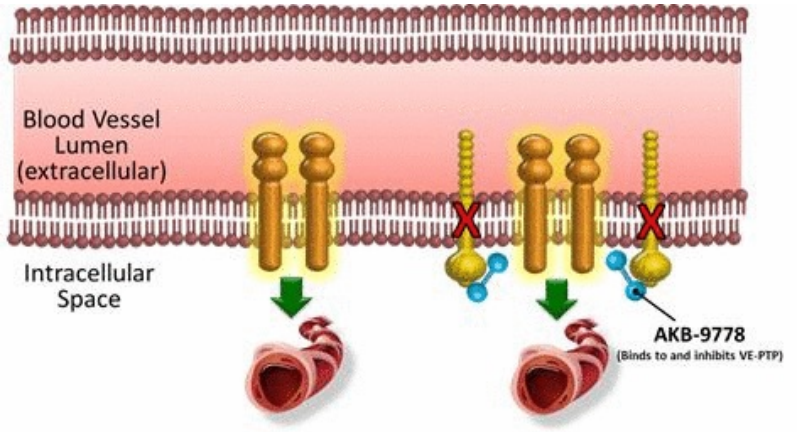

Figure 6. AKB-9778 binds to and inhibits the active site of VE-PTP, resulting in Tie2 activation.

We believe that AKB-9778 may hold a competitive advantage versus other product candidates that are currently in development that target other aspects of the Tie2 pathway. We are aware that two other companies, Roche and Regeneron, are developing agents that inhibit Ang-2, a natural antagonist of Tie2. Ang-2 can bind to Tie2 and

prevent Ang-1 dependent activation. However, simply reducing the levels of Ang-2 has no effect on the activity of VE-PTP, which inactivates Tie2 further downstream of Ang-2 binding.

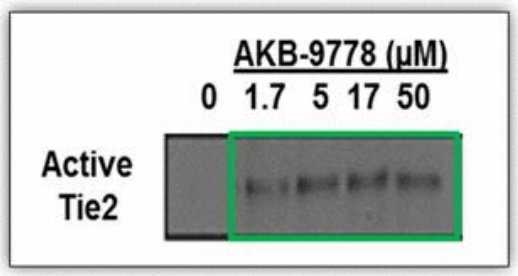

Figure 7. Inhibiting VE-PTP with AKB-9778 robustly activates Tie2 in human endothelial cells in pre-clinical experiments (Shen et al. JCI 124:4564-76, 2014).

Clinical Results in DME

We completed a double-masked Phase 2a trial of AKB-9778 in 144 patients with DR complicated by DME. In this trial 15 mg of AKB-9778 was administered by subcutaneous injection twice daily (BID) for three months either as monotherapy or in combination with intravitreal injections of Lucentis. Patients were randomized to receive subcutaneous AKB-9778 + sham intravitreal injections, subcutaneous AKB-9778 + Lucentis intravitreal injections, or subcutaneous placebo + Lucentis intravitreal injections. Only one eye, designated as the study eye, received the intravitreal injections. In addition to efficacy measures based on parameters related to DME, the efficacy of these agents on DR severity was also pre-defined.

Efficacy in DME was evaluated by measuring the thickness of the macula using a standard criterion called central subfield thickness, or CST. As edema, or fluid leak from blood vessels, increases, the macula layer becomes distended, and rather than having a normal thickness of less than 300 μm, the DME patients in this trial had an average CST (baseline) of approximately 500 μm. The retinal thickness was measured using optical coherence tomography or OCT, an imaging technology providing high resolution images showing changes in retinal thickness.

In our completed Phase 2a study the cohort of patients treated with the combination of AKB-9778 and Lucentis showed a significantly greater reduction in macular edema (mean reduction = 164.4 μm) compared to that achieved by Lucentis monotherapy (mean reduction = 110.4 μm; with p=0.008, ANCOVA using baseline values as covariate). The mean CST at end of treatment was 340.0 μm with 29.2% of eyes achieving a CST less than 300 μm in the AKB-9778 combination group versus 392.1 μm with 17.0% of eyes achieving a CST less than 300 μm in the Lucentis monotherapy group. The improvement in CST when AKB-9778 was used in combination increased between the second and third months of treatment. Based on this pattern, we believe that longer treatments with the combination of AKB-9778 and Lucentis have the potential to further reduce CST. AKB-9778 monotherapy did not show efficacy in reducing macular edema. The long standing DME in the TIME-2 study, duration of DME roughly 5 years, is characterized by large vascular endothelial growth factor, or VEGF loads. Anti-VEGF therapy is required to reduce the VEGF load and the resultant permeability. In animal models, therapy with AKB-9778 activates the Tie2 receptor, which has been shown to reduce the endothelial response to VEGF and normalize vasculature, improve blood flow and oxygenation potentially leading to reduced VEGF production. These findings explain, in part, why combination therapy may produce greater clinical activity than anti-VEGF alone and provide a hypothesis as to why Tie2 therapy alone has minimal benefit as it relates to VEGF-driven vascular permeability. In earlier disease, where vascular compromise has not progressed far enough to stimulate a VEGF response, we believe AKB-9778 may be able to positively remodel vasculature and reverse early diabetic eye disease delaying or preventing the onset of DME and PDR.

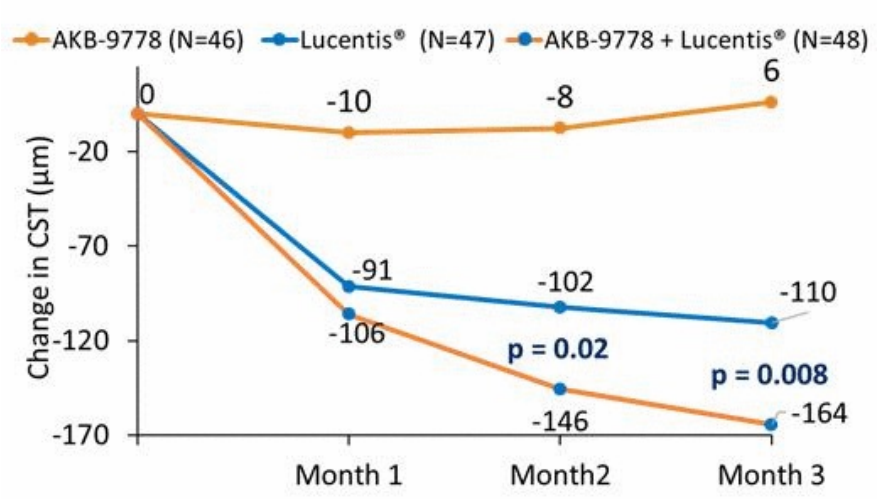

Figure 8. Aggregate Data for Reduction in CST in Phase 2a trial in patients with DME.

Clinical Results in DR

The DR efficacy in the study eyes was assessed in 118 patients with study eyes having DRSS scores of less than seven, which represents mild to severe disease severity, a level of disease that we believe may be reversible. Because AKB-9778 was dosed systemically we were also able to assess the potential efficacy of AKB-9778 in both the study eye and fellow eyes with underlying DR. Of the 144 patients in this trial, 94 of them had DR in fellow eye, with a DRSS score of less than seven and had not received other treatments during the study treatment period. The severity of DR was assessed using the ETDRS grading of standard retinal photographs. Grading is based on an 11-point scale whose progression is measured through a series of discrete steps. These steps are referred to as the DRSS.

Improvement in diabetic retinopathy severity in study eyes was similar across groups at three months with approximately 10% of patients in each group achieving a two or more-step improvement in DRSS. Importantly, in the study eye, AKB-9778 was associated with approximately the same response rate as Lucentis, which is approved for the treatment of DR. A key difference between these two agents is that Lucentis was administered by an injection into the eye by a clinician while AKB-9778 was administered by subcutaneous injection by the patient, which we believe may result in greater patient compliance due to ease of administration.

The activity of AKB-9778 in the fellow eye was assessed using the same criteria. None of the fellow eyes received any intravitreal injections of Lucentis or sham. Out of the 94 patients with fellow eyes with previously untreated DR, 24 of them received subcutaneous placebo and 70 of them received subcutaneous AKB-9778. In the placebo group, 4.2% of fellow eyes showed 2 or more-step improvement in diabetic retinopathy severity score after three months of treatment, compared to 11.4% of fellow eyes in the AKB-9778 group. The systemic nature of this treatment approach allows AKB-9778 to reach the vasculature of both eyes, potentially treating both eyes with one treatment.

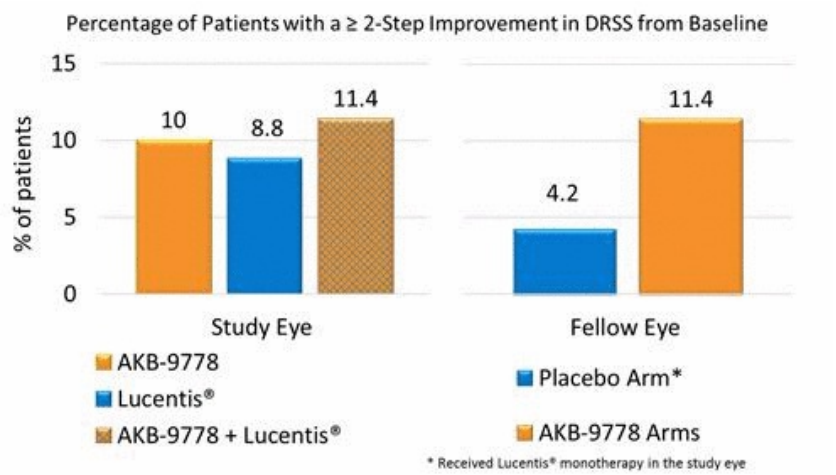

Figure 9. Percent of patients with a 2 or more-step improvement in diabetic retinopathy from baseline to three months in the Phase 2a, TIME-2 trial.

Because the likelihood of development of macular edema or proliferative diabetic retinopathy increases as DR severity increases, which is supported by other contemporaneous studies of diabetic eye disease, we believe improvement of underlying DR or prevention of its progression could reduce visual disability associated with diabetes.

Safety

There was a total of fifteen severe adverse events in the three-month treatment period of the Phase 2a trial with four considered to be treatment-related. Three of these treatment-related events occurred in a single patient who was enrolled in the Lucentis monotherapy arm and who experienced two severe headaches and one migraine event. A second patient in the AKB-9778 combination therapy group reported a severe treatment-related hypoglycemia event.

Ongoing Phase 2b Clinical Trial in Diabetic Retinopathy

In June 2017, we initiated a Phase 2b clinical trial called TIME-2b. TIME-2b is a double-masked, placebo-controlled multi-center trial that has enrolled 167 patients randomized evenly to receive either AKB-9778 15 mg subcutaneously once daily, AKB-9778 15 mg twice daily or placebo for 48-weeks. The primary endpoint of the TIME-2b study is the percentage of patients who improve by at least 2 steps in DRSS in the study eye. We expect to report topline data from this trial in March 2019.

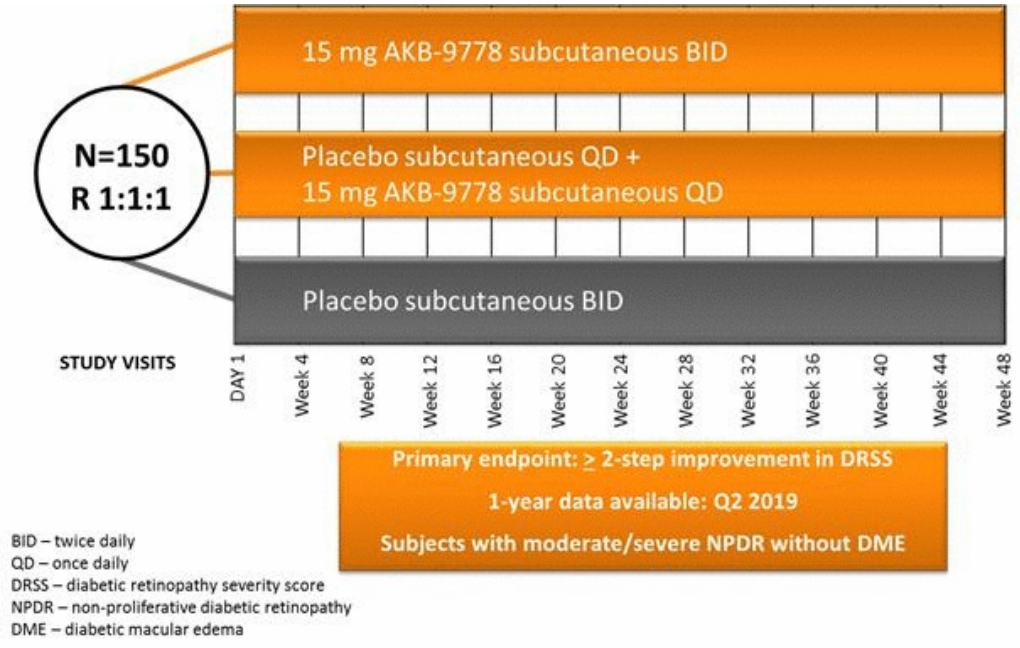

Figure 10. Trial design for Phase 2b trial in DR with AKB-9778.

Rationale for Selecting Treatment of Diabetic Retinopathy as Development Indication

We have chosen to focus our development of AKB-9778 in NPDR for several reasons:

- Preliminary evidence of efficacy in Phase 2a setting that is similar to FDA-approved treatment (i.e. Lucentis)
- Consistent bilateral improvement in study and fellow eye
- Lack of improvement in placebo-treated eyes without active therapeutic is consistent with results from control arm of contemporaneous diabetic retinopathy studies
- Established regulatory path for the treatment of diabetic retinopathy by previous therapeutic approaches (i.e. Lucentis): proportion of patients achieving a two or more-step improvement in diabetic retinopathy severity score compared to placebo at one year
- Patient compliance and convenience benefit of subcutaneous method of administration compared to intra-vitreal injection: reduction of visit and treatment burden
- Potential ability to benefit disease in both eyes
- Potential ability to benefit other vascular beds
- Opportunity to treat diabetic eye disease at an earlier stage
- High unmet medical need and market potential

Treating patients earlier in the disease process, before the onset of vision-threatening pathology, represents a market opportunity with significant unmet need. Currently, no disease modifying therapy exists for earlier stage DR with the same convenience of AKB-9778. We believe systemic treatment with AKB-9778 has the potential to reverse or prevent vascular damage that is the hallmark of early diabetic eye disease potentially resulting in the delay or

prevention of development of advanced complications such as DME and PDR. Lucentis, the only approved therapy for DR, is administered by repeat injections into the eye, and patients with bilateral disease require separate injections in each eye. Furthermore, treatment with Lucentis requires monthly visits to the ophthalmologist. Our internal market research indicates intraocular injections for DR are not favored by patients with early stage disease which is typically bilateral and minimally symptomatic.

We believe AKB-9778 monotherapy provides a promising opportunity for the treatment of early stage DR. As a patient self-administered therapy, AKB-9778 could potentially reduce the burden of treatment and office visits associated with other treatments for diabetic eye disease. This is of importance given emerging evidence that even patients with more advanced disease whose vision is at risk from diabetic eye disease do not visit ophthalmologists and receive treatment on a regular basis. A treatment that does not require an office visit could potentially be a solution to this problem. A majority of patients with early DR will have bilateral disease with fairly well-preserved visual acuity. We believe these patients are more likely to accept a therapy based on subcutaneous injections, a delivery method that is already familiar to most diabetics, than an injection into the eye. The systemic nature of this treatment approach allows AKB-9778 to reach the vasculature of both eyes, treating bilateral disease.

If approved by the FDA, AKB-9778 will, to our knowledge, be the only patient self-administered drug to treat non-proliferative diabetic retinopathy with subcutaneous injections, a delivery method that, according to market research we have conducted, is preferred by patients compared to injections into the eye. In addition, AKB-9778 has the potential to decrease the need for the anti-VEGF drugs if it delays or prevents disease progression to DME and/or PDR, an effect we intend to investigate in post marketing studies.

Prevalence studies estimate that roughly one in every three diabetics has underlying diabetic retinopathy while one in every fifteen diabetics has underlying DME. This translates into the DR market being roughly five times larger than the DME market.

The approval of Lucentis for all forms of diabetic retinopathy and aflibercept for the treatment of DR in the setting of DME as well as the agreed upon special protocol assessment between Regeneron and the FDA on the Phase III PANORAMA study has established a regulatory path in DR. Our ongoing Phase 2b clinical trial of AKB-9778 is powered to show a statistically significant difference between AKB-9778 and placebo in the proportion of patients improving by 2 or more-steps on the ETDRS diabetic retinopathy severity scale.

Other Potential Systemic Indications

Systemic therapy with AKB-9778 could also provide therapeutic benefits in other areas of the body affected by diabetes, including in the kidneys and other organ systems. Treatment that could affect vascular compromise in these tissues could potentially prevent or delay the need for more extreme interventions such as kidney dialysis or amputation. We have included exploratory endpoints in our on-going Phase 2b trial of AKB-9778 in early-stage DR to study the effects of AKB-9778 on parameters of diabetic kidney disease, including but not limited to urine albumin creatinine ratio. If approved for such indications, we believe that systemic treatment with AKB-9778 has the potential to change the treatment paradigm for diabetics and solve a major societal problem by lowering the cost of care associated with diabetic complications. This societal cost is significant as diabetic complications are estimated to cost the health care system 3.5 times more than patients without complications.

AKB-9778 in Primary Open Angle Glaucoma

Unmet medical need:

POAG is a leading cause of blindness affecting approximately 64.3 million people worldwide in 2013 with an expected increase to 76.0 million in 2020 and 118.0 million by 2040. POAG is characterized by optic nerve and neuroretina anomalies and progressive visual field defects. Elevated intraocular pressure, or IOP, is the primary modifiable risk factor and reducing IOP is the only clinical approach shown to slow or prevent vision loss. Despite the availability of effective IOP lowering drugs, many patients require multiple agents to control IOP that together often fail to achieve target IOP. The conventional outflow pathway, consisting of the trabecular meshwork and a specialized vessel called Schlemm's canal, controls IOP and has been identified as the site of increased resistance to aqueous humor outflow in POAG. Importantly, most current POAG therapies do not target conventional outflow, and reduce IOP by either decreasing the formation of aqueous humor or facilitating non-conventional outflow pathways. The failure of most current therapies to modify conventional outflow has been hypothesized to contribute to continued deterioration of conventional outflow and progressive increases in IOP over time. We believe that developing agents that target

conventional outflow pathology directly will likely have improved therapeutic potential alone or in combination with approved glaucoma agents and may prevent progression of POAG that often occurs despite current therapy.

Emerging role of the Tie2 Pathway in the maintenance of conventional outflow:

Recently, two independent groups have shown that Tie2 is expressed and activated in Schlemm's canal endothelial cells during development and in the mature vessel. Disruption of the Tie2 pathway in mice by conditional knockout early in postnatal development results in failure of the formation of Schlemm's canal, associated with increased IOP and with retinal and optic nerve pathology resembling human congenital glaucoma. Tie2 pathway disruption later in postnatal development results in degeneration of Schlemm's canal with development of increased IOP and retinal and optic pathology reminiscent of POAG. Tie2 is most highly expressed in mature Schlemm's canal inner wall endothelium and disruption of the Tie2 pathway results in increased cell death, or apoptosis, and reduced formation of giant vacuoles consistent with compromised conventional outflow. Supporting these preclinical findings, Tie2 loss of function variants were identified in 10 of 189 unrelated primary congenital glaucoma families, and SNPs in the Ang-1 promoter region were significantly associated with the risk of POAG. We believe that these preclinical findings along with human genetic evidence provides a sound scientific premise that activation of the Tie2 pathway in Schlemm's canal could provide a novel conventional outflow-targeted POAG therapy.

Role of VE-PTP in Signaling Pathways and Relevance to Glaucoma

Aerpio has developed first-in-class, potent and selective small molecule inhibitors of the catalytic domain of VE-PTP. In vascular endothelial cells, AKB-9778, Aerpio's lead VE-PTP inhibitor, activates Tie2 and triggers signaling pathways downstream of Tie2 that have been implicated in modulation of conventional outflow facility. These include endothelial nitric oxide synthase, or eNOS, activation and Rho pathway inhibition via Rac1.

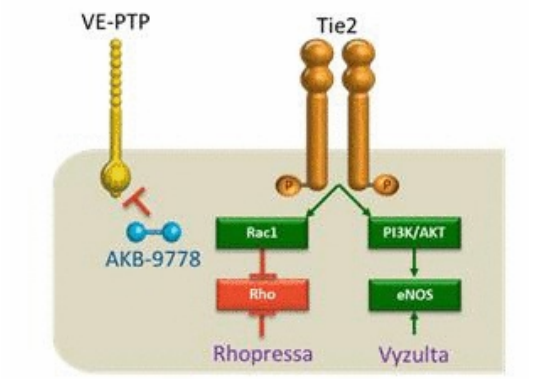

Figure 11. VE-PTP inhibition as a novel conventional outflow targeted approach for glaucoma treatment.

Activation of Tie2, with AKB-9778, affects pathways commonly associated with reduction of intraocular pressure. Rhopressa and Vyzulta are recently approved glaucoma drugs which block the Rho pathway and stimulate the eNOS pathway, respectively. Inhibition of VE-PTP should provide both benefits, blocking Rho and stimulating eNOS.

Evidence Supporting Tie2 Activation as a Conventional Outflow Glaucoma Target:

In a completed Phase 2a clinical trial, patients receiving subcutaneous AKB-9778 demonstrated a statistically significant reduction from baseline in IOP compared to those receiving subcutaneous placebo injections. These IOP reductions were detected in individuals with normal ocular pressure in a study not designed to measure IOP changes and were of the same magnitude as reductions seen in individuals with normal ocular pressure on oral β-blocker therapy. Moreover, patients with baseline IOP greater than or equal to 16 mmHg had larger reductions in IOP than those with baseline IOP less than 16 mmHg, consistent with effects on pressure dependent conventional outflow.

	AKB-9778 Monotherapy		AKB-9778 + Lucentis®		Lucentis® monotherapy	
	SE	FE	SE	FE	SE	FE
Mean Baseline IOP (mmHG)	15.8	15.4	15.9	16.1	15.2	15.8
Mean Δ from BL (mmHG)	**-1.4**	**-1.4**	**-1.0**	**-1.5**	0.1	-0.1
t-test Δ BL-Mo 3 (p-value)	**<0.01**	**<0.01**	**<0.05**	**<0.01**	0.88	0.84

BL = baseline; SE = study eye; FE = Fellow eye; SD = standard deviation

Figure 12. Subcutaneous administration of AKB-9778 significantly reduces IOP in patients with normal ocular pressure.

Preclinical Data Supporting Topical Ocular Delivery of AKB-9778:

Based on preliminary clinical proof-of-concept by subcutaneous administration of AKB-9778, Aerpio is advancing a topical ocular program for AKB-9778 as a conventional outflow-targeted approach to the treatment of patients with POAG or ocular hypertension. AKB-9778 is soluble in aqueous solution and preliminary topical ocular studies in rabbits have demonstrated good tolerability, superior aqueous humor exposure and IOP lowering compared to subcutaneous administration. The AKB-9778 topical formulation was well tolerated, and exposure was demonstrated in the aqueous humor following two days of three times a day 30 µL topical ocular administration to both eyes of New Zealand White rabbits. These data suggest that a topical ocular formulation of AKB-9778 may be sufficient to deliver AKB-9778 to target ocular tissues with acceptable tolerability.

The AKB-9778 topical ocular formulation was also well tolerated following seven days of once daily, or QD, and twice daily, or BID, 30 μL topical ocular administration to both eyes in New Zealand White Rabbits with normal ocular pressure and demonstrated a dose-dependent and statistically significant reduction in IOP of both QD and BID topical ocular dosing at the highest dose level, as shown in the figure below. Reduction in IOP persisted for at least 24 hours following the last dosing period and the treatment was well-tolerated with no visible irritation or hyperemia seen.

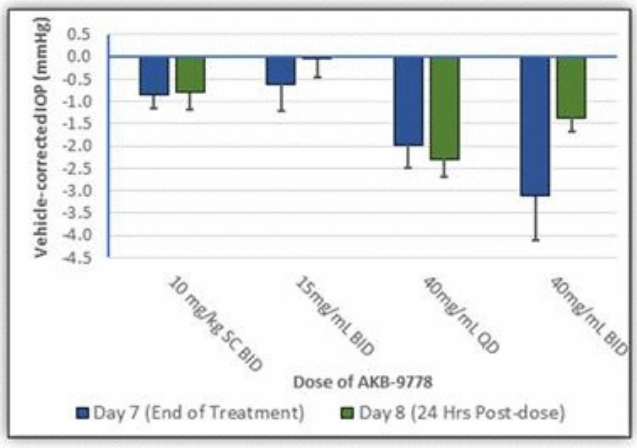

Figure 13. IOP effects of topical ocular compared to subcutaneous AKB-9778 in male rabbits. High dose topical ocular (40 mg/ml) AKB-9778 administered either QD or BID reduced IOP more than low dose topical (15 mg/ml) or subcutaneous (10 mg/kg) administration BID (Day 7). IOP effects persisted 24 hours post dose (Day 8).

We plan to initiate a Phase 1b study to evaluate the potential of topical AKB-9778 to lower IOP in the first half of 2019, with top-line results expected to be available by the third quarter of 2019.

ARP-1536

ARP-1536 is a humanized monoclonal antibody currently in preclinical development that is directed at the same target as AKB-9778. ARP-1536 binds the extracellular domain of VE-PTP inhibiting its ability to interact with Tie2. Our preclinical development program has shown that inhibiting VE-PTP with an antibody results in an activity profile similar to AKB-9778 in a number of different models of retinopathy. We are evaluating development options for ARP-1536, including subcutaneous injection for the treatment of diabetic vascular complications and intravitreal injection for advanced diabetic eye disease, such as DME and PDR.

AKB-4924 for Inflammatory Bowel Disease

AKB-4924 (now called GB004), a selective stabilizer of hypoxia-inducible factor-1 alpha, or HIF-1 alpha, works by inhibiting HIF prolyl-hydroxylase enzymes. Unlike other compounds currently in development that act broadly against all forms of HIF, GB004 selectively stabilizes a specific form of HIF, HIF-1 alpha. HIF-1 alpha has an effect on innate immunity and epithelial barrier function. However, HIF-1alpha differs from HIF-2, in that it does not stimulate the formation of new red blood cells. We have tested GB004 in multiple preclinical models of IBD and also completed a Phase 1a single-ascending dose trial in healthy volunteers with orally administered GB004. Gossamer is currently conducting a multiple ascending dose, or MAD study.

License Agreement

In June 2018, we entered into a license agreement with a wholly-owned subsidiary of Gossamer under which we granted Gossamer an exclusive, sublicensable license to develop and commercialize AKB-4924 and other structurally related products worldwide, with initial development expected in the indications of induction and maintenance in ulcerative colitis and Crohn's Disease ("Gossamer License"). Gossamer is responsible for the further

development and commercialization of the licensed products, and a joint development committee has been formed to oversee the development and manufacturing activities related to the licensed products.

Pursuant to the terms of the agreement, Gossamer paid an upfront payment to us of $20 million. We are also eligible to receive up to $55 million in development milestone payments, up to $85 million in commercial milestone payments, and up to $260 million in sales milestone payments, with such payments contingent on the achievement of specified milestones with respect to the first licensed product for each of the first two initial indications. We are also eligible to receive tiered royalties on sales of licensed products at percentages ranging from a high-single-digit to mid-teens, subject to certain customary reductions. In addition, under certain circumstances, in lieu of receiving the foregoing milestone payments and royalties, we may elect to receive a specified percentage of payments received by Gossamer and its stockholders (with some exclusions) in connection with Gossamer's grant of a sublicense or other rights to the licensed products or if Gossamer undergoes a change of control and the value of the transaction exceeds a certain value (provided that Gossamer can prevent us from exercising this option if the parent company of Gossamer is the entity undergoing the change of control). Conversely, we could be required to accept such a specified percentage of those payments, if Gossamer agrees to pay us a certain minimum upon Gossamer and its stockholders being paid. Such amount may be reduced if the subject transaction includes pharmaceutical candidates or products or other named asset categories in addition to the licensed products.

The agreement expires on a licensed product-by-licensed product and country-by-country basis on the later of fifteen years from the date of first commercial sale or when there is no longer a valid patent claim covering such licensed product in such country. Either party may terminate the agreement for an uncured material breach by the other party or upon the bankruptcy or insolvency of the other party. Gossamer may terminate the agreement in the event Gossamer determines there is a potential safety or efficacy issue with the licensed products. We may terminate the agreement if Gossamer institutes certain actions related to the licensed patents. Under certain termination circumstances, we would have worldwide rights to the terminated program.

Intellectual Property

As of December 31, 2018, we owned at least 28 U.S. patents, at least 21 pending U.S. provisional or non-provisional patent applications, at least 235 foreign patents and at least 111 pending foreign applications, with claims directed toward various aspects of our product candidates and research programs, not counting patents and patent applications that have been licensed to a third party. Specifically, the claims of these patents and patent applications include compositions of matter, methods of use, drug product formulations, and methods of manufacture. Such patents and patent applications, if issued, are expected to expire on various dates from 2027 to 2039, without taking into account any possible patent term adjustments or extensions. Within the foregoing patent portfolio, as of December 31, 2018, we owned at least 5 U.S. patents, at least 8 pending U.S. provisional or non-provisional patent applications, at least 37 foreign patents and at least 25 pending foreign applications that are directed toward ARP-1536 and formulations or uses thereof. As of December 31, 2018, within the foregoing patent portfolio, we owned at least 23 U.S. patents, at least 13 pending U.S. provisional or non-provisional patent applications, at least 199 foreign patents and at least 86 pending foreign applications that are directed toward AKB-9778 and formulations, medicinal chemistry variants or uses thereof. Such patents claiming compositions of matter directed toward ARP-1536 are set to expire in 2027, without taking into account any possible patent term adjustments or extensions. Such patents claiming compositions of matter directed toward AKB-9778 are set to expire in 2027, without taking into account any possible patent term adjustments or extensions.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technologies, knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

There are a number of currently marketed products and product candidates in preclinical research and clinical development by third parties to treat the various diseases that we are targeting. If AKB-9778 and our other product candidates are approved for the indications that we are targeting, they will compete with the products and product candidates discussed below.

DR—Lucentis was recently approved to treat patients with DR. In addition, laser photocoagulation is sometimes used to treat DR prior to the onset of DME and temporarily prevent further vision loss. The anti-VEGF agent, Eylea (aflibercept), which is injected into the eye, is in a Phase 3 study for DR without DME, entitled PANORAMA. 24-week and 52-week results demonstrated an improved rate of 2-step improvement in DRSS with repeated Eylea intraocular injections compared to sham injections. Regeneron has submitted a sBLA supplement for the indication treatment of diabetic retinopathy based on these results (PDUFA date May 13, 2019). In addition, we are aware that there are a number of other companies that are actively developing product candidates for the treatment of DR without DME.

DME—The principal competitors for our program in DME are the anti-Ang-2 antibodies REGN-910 (nesvacumab, from Regeneron) and RG7716 (bi-specific antibody which targets VEGF-A and Ang-2, from Roche/Genentech). Nesvacumab development was recently discontinued by Regeneron, while RG7716 recently initiated Phase 3 clinical development for the treatment of DME.

Sales and Marketing

We hold worldwide commercialization rights to all of our product candidates. Subject to receiving marketing approval, we intend to independently pursue the commercialization of AKB-9778 in the United States for DR by building a focused sales and marketing organization. We believe that such an organization will be able to address the community of physicians who are key specialists in treating the patient populations for which our product candidates are being developed.

We also plan to build a marketing and sales management organization to create and implement marketing strategies for any products that we market through our own sales organization and to oversee and support our sales force. The responsibilities of the marketing organization would include developing educational initiatives with respect to approved products and establishing relationships with researchers and practitioners in relevant fields of medicine.

Outside of the United States, we intend to pursue the approval and commercialization of AKB-9778 for DR through strategic collaborations. We may develop and commercialize AKB-9778 for other indications either independently or through collaborations with third parties. We may also develop and commercialize ARP-1536, subject to receiving additional funding, which may be from a collaboration with a strategic or commercial partner.

Manufacturing

We do not currently own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates. We have relied on and intend to continue to rely on qualified third-party contract manufacturers to produce our product candidates, including clinical supplies to support our clinical trials. We expect that commercial quantities of any compound and materials for our product candidates, if approved, will be manufactured in facilities and by processes that comply with FDA and other regulations. At the appropriate time in the product development process, we will determine whether to establish manufacturing facilities or continue to rely on third parties to manufacture commercial quantities of any products that we may successfully develop.

Government Regulation

Government authorities in the United States, including federal, state, and local authorities, and in other countries, extensively regulate, among other things, the manufacturing, research and clinical development, marketing, labeling and packaging, storage, distribution, post-approval monitoring and reporting, advertising and promotion, and export and import of pharmaceutical and biological products, such as those we are developing. In addition, some government authorities regulate the pricing of such products. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources.

U.S. Government Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations, and biologics under the FDCA and the Public Health Service Act, or PHSA, and its implementing regulations. FDA approval is required before any new unapproved drug or biologic or dosage form, including a new use of a previously approved drug, can be marketed in the United States. Drugs and biologics are also subject to other federal, state, and local statutes and regulations. If we fail to comply with applicable FDA or other requirements at any time during the product development process, clinical testing, the approval process or after approval, we may become subject to administrative or judicial sanctions. These sanctions could include the FDA's

refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, untitled or warning letters, voluntary or mandatory product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution. Any FDA enforcement action could have a material adverse effect on us.

The process required by the FDA before product candidates may be marketed in the United States generally involves the following:

- completion of extensive nonclinical laboratory tests and nonclinical animal studies, all performed in accordance with the Good Laboratory Practices, or GLP, regulations;
- submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical trials may begin and must be updated annually;
- approval by an independent institutional review board, or IRB, or ethics committee representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with Good Clinical Practices, or GCPs, to establish the safety and efficacy of the product candidate for each proposed indication;
- preparation of and submission to the FDA of a biologics license application, or BLA, or a new drug application, or NDA, after completion of all pivotal clinical trials;
- review of the product application by an FDA advisory committee, where appropriate and if applicable;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities where the proposed product is produced to assess compliance with current Good Manufacturing Practices, or cGMP;
- satisfactory completion of any FDA audits of the clinical study sites to assure compliance with GCPs, and the integrity of clinical data in support of the BLA or NDA; and
- FDA review and approval of a BLA for a biologic drug candidate that is safe, pure, and potent or an NDA for a drug candidate that is safe and effective prior to any commercial marketing or sale of the product in the United States.

The nonclinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

An IND is a request for authorization from the FDA to administer an investigational new drug or biological product to humans in clinical trials. The central focus of an IND submission is on the general investigational plan, the protocol(s) for human trials and the safety of study participants. The IND also includes results of animal and in vitro studies assessing the toxicology, pharmacokinetics, pharmacology and pharmacodynamic characteristics of the product; chemistry, manufacturing and controls information; and any available human data or literature to support the use of the investigational new drug. An IND must become effective before human clinical trials may begin. An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to the proposed clinical trials. In such a case, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before clinical trials can begin. Accordingly, submission of an IND may or may not result in the FDA allowing clinical trials to commence. The FDA may impose a clinical hold at any time during clinical trials and may impose a partial clinical hold that would limit trials, for example, to certain doses or for a certain length of time.

Clinical Trials

Clinical trials involve the administration of the investigational new drug or biological product to human subjects under the supervision of qualified investigators in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the inclusion and exclusion criteria, the parameters to be used in monitoring safety and the efficacy 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. Additionally, approval must also be obtained from each clinical trial site's IRB, before the trials may be initiated and the IRB must monitor the trial until completed. There are also requirements governing the reporting of ongoing clinical trials and clinical trial results to public registries.

The clinical investigation of a drug or biological product is generally divided into three or four phases. Although the phases are usually conducted sequentially, they may overlap or be combined.

- *Phase 1*. The drug or biological product is initially introduced into healthy human subjects or patients with the target disease or condition. These studies are designed to evaluate the safety, dosage tolerance, metabolism and pharmacologic actions of the investigational product in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness.
- *Phase 2*. The investigational product is administered to a limited patient population to evaluate dosage tolerance and optimal dosage, identify possible adverse side effects and safety risks, and preliminarily evaluate efficacy.
- *Phase 3*. The investigational product is administered to an expanded patient population, generally at geographically dispersed clinical trial sites to generate enough data to statistically evaluate dosage, clinical effectiveness and safety (or safety, purity, and potency for biological products), to evaluate the overall benefit-risk profile of the investigational product, and to provide an adequate basis for physician labeling.
- *Phase 4*. In some cases, the FDA may condition approval of a BLA or NDA for a product candidate on the sponsor's agreement to conduct additional clinical trials after approval. In other cases, a sponsor may voluntarily conduct additional clinical trials after approval to gain more information about the drug or biological product. Such post-approval studies are typically referred to as Phase 4 clinical trials.

Sponsors must also report to the FDA, within certain timeframes, serious and unexpected adverse reactions, any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator's brochure, or any findings from other studies or animal or in vitro testing that suggest a significant risk in humans exposed to the product candidate. The FDA, the IRB, or the clinical trial sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. 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 provides authorization for whether or not a trial may move forward at designated check points based on access to certain data from the trial. We may also suspend or terminate a clinical trial based on evolving business objectives or competitive climate.

Submission of a BLA or NDA to the FDA

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, detailed investigational new drug product information is submitted to the FDA in the form of a BLA or NDA requesting approval to market the product for one or more indications. Under federal law, the submission of most BLAs and NDAs is subject to an application user fee. For fiscal year 2019, the application user fee is $2,588,478, and the sponsor of an approved BLA or NDA is also subject to an annual program fee of $309,915 for each approved prescription drug or biological product on the market. These fees are typically increased annually. Applications for orphan drug products are exempted from the BLA and NDA user fees and may be exempted from program fees, unless the application includes an indication for other than a rare disease or condition.

A BLA or NDA must include all relevant data available from pertinent nonclinical studies and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls, and proposed labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including trials initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational new drug product to the satisfaction of the FDA.

The FDA conducts a preliminary review of all NDAs and BLAs within the first 60 days after submission before accepting them for filing to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an application for filing. Once a BLA or NDA has been accepted for filing, the FDA's goal for novel drug and biological products generally is to review the application within ten months after it accepts the application for filing, or, if the application relates to an unmet medical need in a serious or life-threatening indication, six months after the FDA accepts the application for filing. The review process is often significantly extended by the FDA's requests for additional information or clarification.

Before approving a BLA or NDA, 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 compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving a BLA or NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

The FDA is required to refer an application for a novel drug or biological product to an advisory committee or explain why such referral was not made. 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.

The FDA's Decision on a BLA or NDA

After the FDA evaluates the BLA or NDA and conducts relevant inspections, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response Letter will identify the deficiencies that prevent the FDA from approving the application and may require additional clinical data or an additional Phase 3 clinical trial(s), or other significant, expensive and time-consuming requirements related to clinical trials, nonclinical studies or manufacturing. Even if such additional information is submitted, the FDA may ultimately decide that the BLA or NDA does not satisfy the criteria for approval and issue a denial.

The FDA could also approve the BLA or NDA with a Risk Evaluation and Mitigation Strategy, or REMS, plan to mitigate risks, which could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling, development of adequate controls and specifications, or a commitment to conduct one or more post-market studies or clinical trials. Such post-market testing may include Phase 4 clinical trials and surveillance to further assess and monitor the product's safety and effectiveness after commercialization.

New government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

Expedited Review and Accelerated Approval Programs

A sponsor may seek approval of its product candidate under programs designed to accelerate FDA's review and approval of BLAs and NDAs. For example, Fast Track Designation may be granted to a drug intended for treatment of a serious or life-threatening disease or condition that has potential to address unmet medical needs. The key benefits of fast track designation are more frequent interactions with the FDA during development and testing, the eligibility for priority review, and rolling review, which is submission of portions of an application before the complete marketing application is submitted.

Based on results of the Phase 3 clinical trial(s) submitted in a BLA or NDA, the FDA may grant the BLA or NDA a priority review designation, which sets the target date for FDA action on the application for a novel product at six months after the FDA accepts the application for filing. Priority review is granted where there is evidence that the proposed product would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. If criteria are not met for priority review, the application is subject to the standard FDA review period of ten months after FDA accepts the application for filing. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Under the accelerated approval program, the FDA may approve a BLA or NDA on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Post-marketing trials or completion of ongoing trials after marketing approval are generally required to verify the drug's clinical benefit in relationship to the surrogate endpoint or ultimate outcome in relationship to the clinical benefit.

In addition, a sponsor may seek FDA designation of its product candidate as a breakthrough therapy if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or

condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval.

Drug manufacturers are subject to periodic unannounced inspections by the FDA and state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

We rely, and expect to continue to rely, on third parties for the production of clinical quantities of our product candidates and expect to rely in the future on third parties for the production of commercial quantities. Future FDA and state inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production, or distribution, or may require substantial resources to correct. In addition, discovery of previously unknown problems with a product or the failure to comply with applicable requirements may result in restrictions on a product, manufacturer or holder of an approved BLA or NDA, including withdrawal or recall of the product from the market or other voluntary, FDA-initiated or judicial action that could delay or prohibit further marketing.

The FDA may withdraw 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 restrictions 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 or warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending BLAs or NDAs or supplements to approved BLAs or NDAs, 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. Drugs 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.

Pediatric Trials and Exclusivity

A sponsor who is planning to submit a marketing application for a drug that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration must submit an initial Pediatric Study Plan, or PSP, within sixty days of an end of Phase 2 meeting or as may be agreed between the sponsor and FDA. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. Development

program candidates designated as orphan drugs are exempt from the above requirements. FDA and the sponsor must reach agreement on the PSP. A sponsor can submit amendments to an agreed upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from nonclinical studies, early phase clinical trials, and/or other clinical development programs.

Pediatric exclusivity is another type of non-patent 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 five-year and three-year non-patent and orphan exclusivity. This six-month exclusivity may be granted if a BLA or NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of FDA-requested pediatric trials are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection covering 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 accept or approve another application relying on the BLA or NDA sponsor's data.

Patent Term Restoration

Depending upon the timing, duration, and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA or NDA, plus the time between the submission date and the approval of that application. 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 and within 60 days of the product's approval. The U.S. Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant BLA or NDA.

Biosimilars and Exclusivity

The Patient Protection and Affordable Care Act, or Affordable Care Act, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCI Act, which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHSA attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the proposed biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical trial or trials. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, 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. A reference biologic is granted twelve years of exclusivity from the time of first licensure of the reference product.

Abbreviated New Drug Applications, or ANDA for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. In support of such applications, a generic manufacturer may rely on the nonclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is the same as the RLD with respect to the active ingredient(s), the route of administration, the dosage form, the strength of the drug and the labeling (with certain exceptions). At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to an RLD if "the rate and

extent of absorption of the [generic] drug do not show a significant difference from the rate and extent of absorption of the listed drug."

Upon approval of an ANDA, the FDA assigns a therapeutic equivalence rating to the approved generic drug in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider an "A" therapeutic equivalence rating to mean that a generic drug is fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of an "A" rating often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

The FDCA provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity. In cases where such exclusivity has been granted, an ANDA (or a 505(b)(2) NDA, which is a marketing application in which sponsors may rely on investigations that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted) may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, discussed below, in which case the applicant may submit its application four years following the original product approval. The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or a method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA or 505(b)(2) applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA or 505(b)(2) applicant is not seeking approval.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge a listed patent, the ANDA or 505(b)(2) application will not be approved until the listed patent expires (unless the patent claims only a method-of-using the referenced product and the ANDA or 505(b)(2) applicant indicates that it is not seeking approval of the claimed method of use).

If the applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA or 505(b)(2) application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA or 505(b)(2) application until the earlier of expiration of the patent, a decision in the infringement case that is favorable to the ANDA or 505(b)(2) applicant, or 30 months after the receipt of the Paragraph IV notice (which can be extended if the reference product has 5-year exclusivity and the ANDA or 505(b)(2) application is submitted between 4 and 5 years after approval of the reference product).

European Union/Rest of World Government Regulation

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products. The cost of establishing a regulatory compliance system for numerous varying jurisdictions can be very significant. Although many of the issues discussed above with respect to the United States apply similarly in the context of the European Union and in other jurisdictions, the approval process varies between countries and jurisdictions and can involve additional

product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the European Union, for example, a clinical trial authorization application, or CTA, must be submitted for each clinical protocol to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is accepted in accordance with a country's requirements, the clinical trial may proceed.

The requirements and process governing the conduct of clinical trials vary from country to country. In all cases, the clinical trials are conducted in accordance with GCP, the applicable regulatory requirements, and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational medicinal product under European Union regulatory systems, we must submit a marketing authorization application. The content of the BLA or NDA filed in the United States is similar to that required in the European Union, with the exception of, among other things, country-specific document requirements.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing product licensing, pricing, and reimbursement vary from country to country.

Countries that are part of the European Union, as well as countries outside of the European Union, have their own governing bodies, requirements, and processes with respect to the approval of pharmaceutical and biologic products. If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Authorization Procedures in the European Union

Medicines can be authorized in the European Union by using either the centralized authorization procedure or national authorization procedures.

- *Centralized procedure.* The European Medicines Agency, or EMA, implemented the centralized procedure for the approval of human medicines to facilitate marketing authorizations that are valid throughout the European Economic Area, or EEA, which is comprised of the 28-member states of the European Union plus Norway, Iceland, and Lichtenstein. This procedure results in a single marketing authorization issued by the EMA that is valid across the EEA. The centralized procedure is compulsory for human medicines that are: derived from biotechnology processes, such as genetic engineering, contain a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions, and officially designated orphan medicines.
- For medicines that do not fall within these categories, an applicant has the option of submitting an application for a centralized marketing authorization to the European Commission following a favorable opinion by the EMA, as long as the medicine concerned is a significant therapeutic, scientific or technical innovation, or if its authorization would be in the interest of public health.
- *National authorization procedures.* There are also two other possible routes to authorize medicinal products in several European Union countries, which are available for investigational medicinal products that fall outside the scope of the centralized procedure:
- *Decentralized procedure.* Using the decentralized procedure, an applicant may apply for simultaneous authorization in more than one European Union country of medicinal products that have not yet been authorized in any European Union country and that do not fall within the mandatory scope of the centralized procedure.
- *Mutual recognition procedure.* In the mutual recognition procedure, a medicine is first authorized in one European Union Member State, in accordance with the national procedures of that country. Following this, further marketing authorizations can be sought from other European Union countries in

a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization.

In some cases, a Pediatric Investigation Plan, or PIP, or a request for waiver or deferral, is required for submission prior to submitting a marketing authorization application. A PIP describes, among other things, proposed pediatric trials and their timing relative to clinical trials in adults.

New Chemical Entity Exclusivity

In the European Union, new chemical entities, sometimes referred to as new active substances, qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application for eight years, after which generic marketing authorization can be submitted, and the innovator's data may be referenced, but not approved for two years. 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 their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

Accelerated Review

Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of a marketing authorization application is 210 days (excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the EMA's Committee for Medicinal Products for Human Use, or CHMP). Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, particularly from the point of view of therapeutic innovation. In this circumstance, EMA ensures that the opinion of the CHMP is given within 150 days, excluding clock stops.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any products for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend in part on the availability of coverage and reimbursement from third-party payors. Third-party payors include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor will pay for the product. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication. Moreover, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third- party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. In order to obtain coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain regulatory approvals. Our product candidates may not be considered medically necessary or cost-effective. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit.

The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. By way of example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively, the Affordable Care Act, or ACA, contains provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs.

Some of the provisions of the Affordable Care Act have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. For example, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the Affordable Care Act to waive, defer, grant exemptions from, or delay the implementation of any provision of the Affordable Care Act that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices.

Other legislative changes have been proposed and adopted since the ACA was enacted. While Congress has not passed comprehensive repeal legislation, it has enacted laws that modify certain provisions of the ACA, including eliminating a tax-based shared responsibility payment imposed 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. 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, the remaining provisions of the ACA are invalid as well. The Trump administration and the Center for Medicare and Medicaid Services, or 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. Thus, the full impact of the Affordable Care Act, or any law replacing elements of it, on our business remains unclear. Adoption of government controls and measures and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals.

Further, the Trump administration's budget proposal for fiscal year 2019 contained further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. Additionally, the Trump administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. In response to the Blueprint, on November 30, 2018, CMS announced a proposed rule that would amend the Medicare Advantage and Medicare Part D prescription drug benefit regulations to reduce out of pocket costs for plan enrollees and allow Medicare plans to negotiate lower rates for certain drugs. Among other things, the proposed rule changes would allow Medicare Advantage plans to use pre-authorization (PA) and step therapy (ST) for six protected classes of drugs, with certain exceptions, permit plans to implement PA and ST in Medicare Part B drugs, changes the definition of "negotiated prices" in the regulations and adds a definition of "price concession" to the regulation. It is unclear whether these proposed changes will be accepted, and if so, what effect such changes will have on our business and our ability to receive adequate reimbursement for our future products.

In the European Community, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed to by the government. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, an increasing emphasis on cost containment measures in the United States and other countries has increased and we expect will continue to increase the pressure on pharmaceutical pricing. 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 we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Other Healthcare Laws and Compliance Requirements

If we obtain regulatory approval for any of our product candidates, we may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. These laws may impact, among other things, our proposed sales, marketing and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;
- the federal 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 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;
- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- the federal Physician Payment Sunshine Act, that requires drug and biologics manufacturers to disclose payments and other transfers of value provided to physicians and teaching hospitals;
- HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and its implementing regulations, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information; and
- state and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws that may apply to items or services reimbursed by any third-party payor, including commercial insurers, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

The Affordable Care Act broadened the reach of the fraud and abuse laws by, among other things, amending the intent requirement of the federal Anti-Kickback Statute and the applicable criminal healthcare fraud statutes contained within 42 U.S.C. § 1320a-7b. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act or the civil monetary penalties statute. Many states have adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs.

We are also subject to the U.S. Foreign Corrupt Practices Act, or FCPA, which prohibits improper payments or offers of payments to foreign governments and their officials for the purpose of obtaining or retaining business and requires companies to maintain accurate books and records and a system of internal accounting controls. Safeguards we implement to discourage improper payments or offers of payments by our employees, consultants, and others may be ineffective, and violations of the FCPA and similar laws may result in severe criminal or civil sanctions, or other liabilities or proceedings against us, any of which would likely harm our reputation, business, financial condition and result of operations.

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

Employees

As of December 31, 2018, we had 27 full-time or part-time employees, including 11 employees with doctorate level degrees. Of these employees, 17 employees are engaged in research and development activities and 10 employees are engaged in general and administrative activities. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider the relationship with our employees to be good.

Our Corporate Information

We were originally incorporated in the State of Delaware in November 2007 under the name "Zeta Acquisition Corp. II." Prior to our merger in March 2017, Zeta Acquisition Corp. II was a "shell" company registered under the Exchange Act with no specific business plan or purpose until it began operating the business of Aerpio through the merger on March 15, 2017, or the Merger. Aerpio was incorporated in the State of Delaware in November 2011 to focus primarily on advancing first-in-class treatments for ocular disease. Effective upon the Merger, a wholly-owned subsidiary of Zeta Acquisition Corp. II merged with and into Aerpio, and Aerpio continued as the operating subsidiary of Zeta Acquisition Corp. II. Immediately following the Merger, Aerpio converted into a Delaware limited liability company with the name Aerpio Therapeutics LLC.

Our corporate headquarters are located at 9987 Carver Road, Cincinnati, Ohio 45242, and our telephone number is (513) 985-1920. We maintain a website at www.aerpio.com, to which we regularly post copies of our press releases as well as additional information about us. Our filings with the Securities and Exchange Commission, or SEC, will be available free of charge through the website as soon as reasonably practicable after being electronically filed with or furnished to the SEC. Information contained in our website does not constitute a part of this prospectus or our other filings with the SEC.

Item 1A. Risk Factors.

The following risk factors and other information included in this Annual Report on Form 10-K should be carefully considered. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Please see page 2 of this Annual Report on Form 10-K for a discussion of some of the forward-looking statements that are qualified by these risk factors. If any of the following risks actually occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since inception and anticipate that we will continue to incur significant losses for the foreseeable future and may never achieve or maintain profitability.

We have incurred net losses each year since our inception, including net losses of $10.4 million and $21.4 million for the years ended December 31, 2018 and 2017, respectively. As of December 31, 2018, we had an accumulated deficit of $119.0 million. To date, we have not commercialized any products or generated any revenues from the sale of products, and we do not expect to generate any product revenues in the foreseeable future. We do not know whether or when we will generate revenue or become profitable.

We have devoted most of our financial resources to research and development, including our clinical and preclinical development activities. The amount of our future net losses will depend, in part, on the rate of our future expenditures, and our financial position will depend, in part, on our ability to obtain funding through equity or debt financings, strategic collaborations or grants. Our lead product candidate, AKB-9778, completed a proof of concept Phase 2 clinical trial in April 2015, and we initiated a Phase 2b clinical trial in June 2017. Our other product candidates, including ARP-1536, are in preclinical development. As a result, we expect that it will be several years, if ever, before we have a product candidate ready for commercialization. Even if we obtain regulatory approval to market AKB-9778 or any of our other product candidates, our future revenues will depend upon the size of any markets in which AKB-9778 or any of our other product candidates has received approval, our ability to achieve sufficient market acceptance, reimbursement from third-party payors and other factors.

We expect to continue to incur significant expenses and operating losses for the foreseeable future. We anticipate that our expenses will likely increase significantly if and as we:

- continue our Phase 2 program and prepare for and conduct a future Phase 3 development program of AKB-9778 for the treatment of diabetic retinopathy, including as we continue our ongoing TIME-2b clinical trial.
- seek regulatory approvals for our product candidates that successfully complete clinical trials;
- have our product candidates manufactured for clinical trials and for commercial sale;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- initiate additional preclinical, clinical or other studies for AKB-9778, ARP-1536 and other product candidates that we may develop or acquire;
- seek to discover and develop additional product candidates;
- acquire or in-license other commercial products, product candidates and technologies;
- make royalty, milestone or other payments under any future in-license agreements;
- maintain, protect and expand our intellectual property portfolio;
- attract and retain skilled personnel; and
- create additional infrastructure to support our operations as a public company.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, if at all, we will be able to achieve profitability. If we are required by the United States Food and Drug Administration, or FDA, the European Medicines Agency, or EMA, or other regulatory authorities to perform studies in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates, our expenses could increase.

The net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance. In any

particular quarter or quarters, our operating results could be below the expectations of securities analysts or investors, which could cause our stock price to decline.

To become and remain profitable, we must succeed in developing and commercializing our product candidates, which must generate significant revenue. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, discovering additional product candidates, obtaining regulatory approval for these product candidates and manufacturing, marketing and selling any products for which we may obtain regulatory approval. We are only in the preliminary stages of most of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough 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 could depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could cause you to lose all or part of your investment.

We will require substantial additional financing. A failure to obtain this necessary capital when needed could force us to delay, limit, reduce or terminate our product development or commercialization efforts.

As of December 31, 2018, our cash and cash equivalents were $62.6 million. We believe that we will continue to expend substantial resources for the foreseeable future developing AKB-9778 for diabetic retinopathy and any other indications that we may pursue, such as primary open angle glaucoma. Additionally, we expect to expend substantial resources to further develop ARP-1536. We may also expend substantial resources to develop any other product candidates that we may develop or acquire. These expenditures will include costs associated with research and development, potentially obtaining regulatory approvals and having our products manufactured, as well as marketing and selling products approved for sale, if any. In addition, other unanticipated costs may arise. Because the outcome of our current and anticipated clinical trials is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of our product candidates.

Our future capital requirements depend on many factors, including:

- the rate of progress, results and cost of completing our Phase 2 program of AKB-9778 and our operating costs incurred as we conduct these trials and through our end of Phase 2 meeting with the FDA, and equivalent meetings with the EMA and other regulatory authorities;
- assuming AKB-9778 advances to Phase 3 clinical trials, the scope, size, rate of progress, results and costs of initiating and completing our Phase 3 development program of AKB-9778;
- assuming favorable clinical results, the cost, timing and outcome of our efforts to obtain marketing approval for AKB-9778 in the United States, Europe and in other jurisdictions, including to fund the preparation and filing of regulatory submissions for AKB-9778 with the FDA, the EMA and other regulatory authorities;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials that we may undertake for ARP-1536 and any other product candidates that we may develop or acquire;
- the timing of, and the costs involved in, obtaining regulatory approvals for ARP-1536 if clinical trials of this product candidate are successful;
- the cost and timing of future commercialization activities for our products, if any of our product candidates are approved for marketing, including product manufacturing, marketing, sales and distribution costs;
- the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;
- the cost of having our product candidates manufactured for clinical trials in preparation for regulatory approval and in preparation for commercialization;
- our ability to establish and maintain strategic collaborations, licensing or other arrangements and the financial terms of such agreements; and
- the costs involved in preparing, filing, prosecuting patent applications, maintaining, defending and enforcing our intellectual property rights, including litigation costs and the outcome of such litigation.

Based on our current operating plan, and absent any future financings or strategic partnerships, we believe that our existing cash and cash equivalents will be sufficient to fund our projected operating expenses and capital expenditure requirements at least into the second quarter of 2020. However, our operating plan may change as a result of many factors currently unknown to us, and we may need additional funds sooner than planned. 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. 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 preclinical studies, clinical trials or other development activities for AKB-9778, ARP-1536 or any other product candidates that we develop or acquire, or delay, limit, reduce or terminate our establishment of sales and marketing capabilities or other activities that may be necessary to commercialize our product candidates.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to product candidates on unfavorable terms to us.

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 and license, development and commercialization agreements with collaborators. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms may include liquidation or other preferences and anti-dilution protections that adversely affect your rights as a stockholder. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take certain actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through strategic collaborations with third parties, we may have to relinquish valuable rights to our product candidates, future revenue streams, research programs or product candidates or grant licenses on terms that are not favorable to us. For example, in June 2018, we entered into a license agreement with a wholly-owned subsidiary of Gossamer Bio, Inc. (including its affiliates, "Gossamer") for the development and commercialization of AKB-4924. If we are unable to raise additional funds through equity or debt financing when needed, we may be required to delay, limit, reduce or terminate our product development or commercialization efforts for AKB-9778, ARP-1536 or any other product candidates that we develop or acquire, or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We commenced active operations in 2011, and our operations to date have been limited to organizing and staffing our company, business planning, raising capital, identifying potential product candidates, undertaking preclinical studies and conducting clinical trials. We currently have two product candidates that we are developing internally, one of which is in preclinical development. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. Only a small fraction of biopharmaceutical development programs ultimately results in commercial products or even product candidates and a number of events could delay our development efforts and negatively impact our ability to obtain regulatory approval for, and to manufacture, market and sell, a product. We have not yet demonstrated our ability to successfully complete later stage clinical trials, obtain regulatory 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. Consequently, 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.

In addition, as a young business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to expand our capabilities to support commercial activities. We may not be successful in adding such capabilities.

Risks Related to Our Business and the Clinical Development, Regulatory Review and Approval of Product Candidates

We depend heavily on the success of our lead product candidate, AKB-9778, which is currently in Phase 2 clinical development. Even if we obtain favorable clinical results, we may not be able to obtain regulatory approval for, or successfully commercialize, AKB-9778.

We rely on our lead product candidate, AKB-9778, which is currently in Phase 2 clinical development, and our business depends almost entirely on the successful clinical development, regulatory approval and commercialization of that product candidate, which may never occur. We currently have no products for sale, generate no revenues from sales of any drugs, and may never be able to develop marketable products. AKB-9778, which completed a proof of concept Phase 2 clinical trial in April 2015, will require substantial additional clinical development, testing, manufacturing process development, and regulatory approval before we are permitted to commence its commercialization. In June 2017, we announced the initiation of patient dosing in our ongoing Phase 2b clinical trial of AKB-9778 in patients with DR. Additionally, in July 2017 we announced the completion of a single-center study of the safety and efficacy of treatment with concomitant anti-VEGF therapy. We are currently evaluating development options for ARP-1536, which is our other product candidate that we are developing internally. None of our product candidates has advanced into a pivotal trial, and it may be years before such trial is initiated, if ever. The clinical trials of our product candidates are, and the manufacturing and marketing of our product candidates will be, subject to extensive and rigorous review and regulation by numerous government authorities in the United States and in other countries where we intend to test and, if approved, market any product candidates. Before obtaining regulatory approval for the commercial sale of any product candidate, we must demonstrate through extensive preclinical testing and clinical trials that any drug candidate is safe and effective and any biological product candidate is safe, pure, and potent for use in each target indication. This process can take many years. Of the large number of drugs in development in the United States, only a small percentage successfully complete the FDA regulatory approval process and are commercialized. Accordingly, even if we are able to obtain the requisite capital to continue to fund our development and clinical programs, we may be unable to successfully develop or commercialize AKB-9778.

We are not permitted to market AKB-9778 in the United States until we receive approval of an NDA from the FDA, or in any foreign countries until we receive the requisite approval from such countries. As a condition to submitting an NDA to the FDA for AKB-9778 regarding its ability to treat patients with DR, we must complete our ongoing clinical trials, Phase 3 trials, and any additional nonclinical studies or clinical trials required by the FDA. To date, we have only completed a Phase 2 clinical trial for AKB-9778 and five other early stage trials. AKB-9778 may not be successful in clinical trials or receive regulatory approval. Further, AKB-9778 may not receive regulatory approval even if it is successful in clinical trials. Obtaining approval of an NDA is a complex, lengthy, expensive and uncertain process that typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, the policies or regulations, or the type and amount of clinical data necessary to gain approval, may change during the course of a product candidate's clinical development and may vary among jurisdictions. Our development activities could be harmed or delayed by a partial shutdown of the U.S. government, including the FDA. We have not obtained regulatory approval for any product candidate and it is possible that AKB-9778 will never obtain regulatory approval. The FDA may delay, limit or deny approval of AKB-9778 for many reasons, including, among others:

- we may not be able to demonstrate that AKB-9778 is safe and effective in treating patients with DR to the satisfaction of the FDA;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA for marketing approval;
- the FDA may disagree with the number, design, size, conduct or implementation of our clinical trials;
- the FDA may not approve the formulation, labeling or specifications of AKB-9778;
- the FDA may require that we conduct additional clinical trials;
- the contract research organizations, or CROs, or the clinical investigators that we retain to conduct our clinical trials may take actions outside of our control that materially adversely impact our clinical trials;
- we, our CROs or clinical investigators may fail to perform in accordance with the FDA's good clinical practice, or GCP, requirements;
- the FDA may disagree with our interpretation of data from our preclinical studies and clinical trials;

- the FDA may find deficiencies with the manufacturing processes or facilities of third-party manufacturers with which we contract; or
- the policies or regulations of the FDA may significantly change in a manner that renders our clinical data insufficient for approval or may require that we amend or submit new clinical protocols.

In addition, similar reasons may cause the EMA or other regulatory authorities to delay, limit or deny approval of AKB-9778 outside the United States.

Any of these factors, many of which are beyond our control, could jeopardize our ability to obtain regulatory approval for and successfully market AKB-9778. Because our business is substantially dependent upon AKB-9778, any such setback in our pursuit of regulatory approval would have a material adverse effect on our business and prospects.

Alternatively, even if we obtain regulatory approval, that approval may be for indications or patient populations that are not as broad as we intend or desire or may require labeling that includes significant use or distribution restrictions or safety warnings. We may also be required to perform additional, unanticipated clinical trials to obtain approval or be subject to additional post marketing testing requirements to maintain regulatory approval. In addition, regulatory authorities may withdraw their approval of a product or the FDA may require a risk evaluation and mitigation strategy, or REMS, for a product, which could impose restrictions on its distribution. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

We have not obtained agreement with the FDA, EMA or other regulatory authorities on the design of our Phase 3 development program.

We have not obtained agreement with the FDA on the design of our Phase 3 development program for AKB-9778 or any other product candidate. We plan to hold an end of Phase 2 meeting with the FDA upon successful completion of our Phase 2 clinical program for AKB-9778. If the FDA determines that the Phase 2 trial results do not support moving into a pivotal program, we would be required to conduct additional Phase 2 studies. Alternatively, the FDA could disagree with our proposed design of our Phase 3 development program and could suggest a larger number of subjects or a longer course of treatment than our current expectations. If the FDA takes such positions, the costs of our AKB-9778 development program could increase materially and the potential market introduction of AKB-9778 could be delayed or we could risk not obtaining FDA approval even if the Phase 3 trials meet their primary endpoints. The FDA also may require that we conduct additional clinical, nonclinical or manufacturing validation studies and submit that data before it will consider an NDA application.

While we intend to follow the regulatory pathway that ranibizumab and aflibercept undertook when they were approved for DR in the presence of DME, we have not yet sought guidance for the regulatory path for AKB-9778 with the EMA or other regulatory authorities. We cannot predict what additional requirements may be imposed by these regulatory authorities or how such requirements might delay or increase costs for our planned Phase 3 development program. For example, ranibizumab and aflibercept are anti-vascular endothelial growth factor, or anti-VEGF, therapies, which block vascular endothelial growth factor, used in the treatment of DR, DME, age-related macular degeneration and retinal vein occlusion, while AKB-9778 is a small molecule activator of the Tie-2 pathway, and such differences may result in a different regulatory pathway for AKB-9778, including one that may be longer, more complex or expensive than that of ranibizumab or aflibercept. Because our business is almost entirely dependent upon the successful development, regulatory approval, and commercialization of AKB-9778, any such delay or increase in costs would have an adverse effect on our business.

We may find it difficult to enroll patients in our clinical trials, which could delay or prevent clinical trials of our product candidates.

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on the speed at which we can recruit patients to participate in testing our product candidates. Our competitors may have ongoing clinical trials for product candidates that could be competitive with our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. For example, while we have completed patient dosing in our TIME-2b clinical trial, there is no guarantee that we can successfully enroll patients in a timely manner for future trials. As a result, the timeline for recruiting patients, conducting trials and obtaining regulatory approval of potential products may be delayed. These delays could result in increased costs, delays in advancing our development of AKB-9778 or termination of the clinical trials altogether.

We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics to achieve diversity in a trial, to complete our clinical trials in a timely manner. Patient enrollment is affected by factors including:

- severity of the disease under investigation;
- design of the trial protocol;
- size and nature of the patient population;
- eligibility criteria for the trial in question;
- perceived risks and benefits of the product candidate under study;
- proximity and availability of clinical trial sites for prospective patients;
- availability of competing therapies and clinical trials and clinicians' and patients' perceptions as to the potential advantages of AKB-9778 or any other product candidate in relation to available therapies or other products under development;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians; and
- ability to monitor patients adequately during and after treatment.

We may not be able to initiate or continue clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by regulatory agencies. If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit or terminate ongoing or planned clinical trials, any of which would have an adverse effect on our business.

We may not be able to comply with requirements of foreign jurisdictions in conducting trials outside of the United States. In addition, we may not be able to obtain regulatory approval in foreign jurisdictions.

If AKB-9778 is successful in Phase 2 development, we currently expect to conduct our Phase 3 program for AKB-9778 that may include trial sites outside of the United States, including Japan and the European Union, and seek regulatory approval for AKB-9778 for the treatment of patients with DR in major markets in addition to the United States, including the European Union. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country, should we attempt to do so, is subject to numerous risks unique to conducting business in international markets, including:

- difficulty in establishing or managing relationships with qualified CROs and physicians;
- different local standards for the conduct of clinical trials;
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatments; and
- the acceptability of data obtained from trials conducted in the United States to the EMA and other regulatory authorities.

If we fail to successfully meet requirements for the conduct of clinical trials outside of the United States, we may be delayed in obtaining, or be unable to obtain, regulatory approval for AKB-9778 in countries outside of the United States.

Regulatory authorities outside the United States will require compliance with numerous and varying regulatory requirements. The approval procedures vary among jurisdictions and may involve requirements for additional testing, and the time required to obtain approval may differ from that required to obtain FDA approval. In addition, in many countries outside the United States, a product must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our products is also subject to approval. Approval by the FDA 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. However, the failure to obtain approval in one jurisdiction may negatively impact our ability to obtain approval in another jurisdiction. The foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. We may not obtain foreign regulatory approvals on a timely basis, if at all. We may not be able to file for regulatory approvals and may not receive necessary approvals to commercialize our products in any market.

Clinical drug development is a lengthy and expensive process with an uncertain outcome, and positive results from Phase 1 and Phase 2 clinical trials of AKB-9778 are not necessarily predictive of the results of our ongoing and any future clinical trials of AKB-9778. If we cannot replicate the positive results from our Phase 1 and Phase 2 clinical trials of AKB-9778 in our ongoing and subsequent clinical trials, we may be unable to successfully develop, obtain regulatory approval for and commercialize AKB-9778.

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. Success in preclinical studies may not be predictive of similar results in humans during clinical trials, and successful results from early or small clinical trials may not be replicated in later and larger clinical trials. For example, our early encouraging preclinical and clinical results for AKB-9778 do not ensure that the results of our ongoing clinical trials, including TIME-2b, or any future clinical trials will demonstrate similar results. Our planned Phase 3 development program will enroll a larger number of subjects and will treat subjects for longer periods than our prior trials, which will result in a greater likelihood that adverse events may be observed. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in early stage development, and we may face similar setbacks. If the results of our ongoing or future clinical trials for AKB-9778 are inconclusive with respect to efficacy, if we do not meet our clinical endpoints with statistical significance, or if there are safety concerns or adverse events, we may be prevented from or delayed in obtaining marketing approval for AKB-9778.

We may experience delays in the planned clinical development program for AKB-9778, including in our Phase 2 clinical trial, and we do not know whether planned clinical trials will begin on time, need to be redesigned, enroll patients on time or be completed on schedule, if at all.

Clinical trials can be delayed or aborted for a variety of reasons, including delay or failure to:

- obtain regulatory approval to commence a clinical trial;
- reach agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtain institutional review board, or IRB, approval at each site;
- recruit, enroll and retain patients through the completion of clinical trials;
- maintain clinical sites in compliance with trial protocols and regulatory requirements through the completion of clinical trials;
- address any patient safety concerns that arise during the course of the trial;
- initiate or add a sufficient number of clinical trial sites; or
- manufacture sufficient quantities of our product candidate for use in clinical trials.

We could encounter delays if a clinical trial is suspended or terminated by us, by the relevant IRBs at the sites at which such trials are being conducted, by the Data Safety Monitoring Board, or DSMB, for such trial or by the FDA or other regulatory authorities. 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 or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, changes in laws or regulations, or lack of adequate funding to continue the clinical trial. Any delays in completing our clinical trials will increase our costs, slow down our product candidate development and approval process and jeopardize our ability to commence product sales and generate revenues. Any of these occurrences may harm our business, financial condition and prospects significantly.

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

Any regulatory approvals that we receive for our product candidates may be subject to limitations on the approved indicated uses for which the product may be marketed or to 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 products. In addition, if the FDA approves any of our product candidates, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the product will be subject to extensive and ongoing regulatory requirements. These requirements

include submissions of safety and other post-marketing information and reports, establishment registration, as well as continued compliance with current Good Manufacturing Practice, or cGMP, requirements and GCP requirements for any clinical trials that we conduct post-approval.

Post-approval discovery of previously unknown problems with an approved product, including adverse events of unanticipated severity or frequency or relating to manufacturing operations or processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of the product, withdrawal of the product from the market, or product recalls;
- fines, untitled or warning letters or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications submitted by us, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products;
- a REMS program; and
- injunctions or the imposition of civil or criminal penalties.

The FDA's policies may change and additional government regulations may be enacted. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or are not able to maintain regulatory compliance, we may lose any marketing approval that may have been obtained and we may not achieve or sustain profitability, which would adversely affect our business.

Risks Related to Our Reliance on Third Parties

We rely on third parties to conduct preclinical studies and clinical trials for our product candidates, and if they do not properly and successfully perform their obligations to us, we may not be able to obtain regulatory approvals for our product candidates.

We rely on third party CROs and other third parties to assist in managing, monitoring and otherwise carrying out our ongoing trial of AKB-9778. We expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators to conduct our clinical trials in the future, including our Phase 3 development program for AKB-9778. We compete with many other companies for the resources of these third parties. The third parties on whom we rely may terminate their engagements with us at any time, and having to enter into alternative arrangements would delay development and commercialization of our product candidates.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, the FDA and foreign regulatory authorities require compliance with regulations and standards, including GCP requirements, for designing, conducting, monitoring, recording, analyzing and reporting the results of clinical trials to ensure that the data and results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Although we rely on third parties to conduct our clinical trials, we are responsible for ensuring that each of these clinical trials is conducted in accordance with its general investigational plan and protocol under legal and regulatory requirements. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our investigators or CROs fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, EMA or other regulatory authorities may require us to perform additional clinical trials before approving 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. In addition, our clinical trials must be conducted with product produced under applicable cGMP regulations. Failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process.

If these third parties do not successfully carry out their duties under their agreements, if the quality or accuracy of the data they obtain is compromised due to their failure to adhere to clinical trial protocols or to regulatory requirements, or if they otherwise fail to comply with clinical trial protocols or meet expected deadlines, the clinical trials of our product candidates may not meet regulatory requirements. If clinical trials do not meet regulatory requirements or if these third parties need to be replaced, preclinical development activities or clinical trials may be extended, delayed, suspended or terminated. If any of these events occur, we may not be able to obtain regulatory approval of our product candidates on a timely basis or at all.

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue.

We intend to rely on third parties to conduct some or all aspects of our product manufacturing, and these third parties may not perform satisfactorily.

We do not have any manufacturing facilities and do not expect to independently conduct our product candidate manufacturing for research and preclinical and clinical testing. We currently rely, and expect to rely, on third parties to manufacture and supply drug products for our AKB-9778 clinical trials, and we expect to continue to rely on third parties for the manufacture of clinical and, if necessary, commercial quantities of our product candidates. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

Any of these third parties may terminate their engagement with us at any time. We currently have arrangements in place for the manufacturing of drug substance and drug product for our planned Phase 3 development program. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur significant delays and added costs in identifying, qualifying and contracting with any such replacement, as well as producing the drug product. The FDA or comparable foreign regulatory authorities may find deficiencies with the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies. Manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP requirements relating to quality control, quality assurance and corresponding maintenance of records and documents. In addition, we have to enter into technical transfer agreements and share our know-how with the third-party manufacturers, which can be time-consuming and may result in delays. These delays could result in a suspension of our clinical trials or, if AKB-9778 is approved and marketed, a failure to satisfy patient demand.

Reliance on third party manufacturers entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- reduced control as a result of using third party manufacturers for all aspects of manufacturing activities, including regulatory compliance and quality assurance;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- disruptions to the operations of our manufacturers or suppliers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier or a catastrophic event affecting our manufacturers or suppliers.

Any of these events could lead to clinical study delays or failure to obtain regulatory approval or affect our ability to successfully commercialize future products. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of production.

The facilities used by our contract manufacturers to manufacture our product candidates must be evaluated by the FDA pursuant to inspections that will be conducted after we submit our NDA to the FDA. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturers for compliance with cGMP requirements for manufacture of both drug substance and finished drug product. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA, we will not be able to secure and/or maintain regulatory approval for our product candidates. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA, EMA or other regulatory authorities find deficiencies with or do not approve these facilities for the manufacture of our product candidates, or if they find deficiencies or withdraw any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved.

Moreover, our failure, or the failure of our third party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our drug products or product candidates.

In addition, our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. Certain of these manufacturing facilities may be contractually prohibited from manufacturing our product due to non-compete agreements with our competitors. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Our current and anticipated future dependence upon others for the manufacture of our product candidates or products may adversely affect our future profit margins and our ability to commercialize any products that receive marketing approval on a timely and competitive basis.

If we are unable to manufacture our product candidates in sufficient quantities, at sufficient yields, we may experience delays in product development, clinical trials, regulatory approval and commercial distribution.

Completion of our clinical trials and commercialization of our product candidates require access to, or development of, facilities to manufacture our product candidates at sufficient yields and at commercial scale. We have limited experience manufacturing, or managing third parties in manufacturing, any of our product candidates in the volumes that will be necessary to support large-scale clinical trials or commercial sales. Efforts to establish these capabilities may not meet initial expectations as to scheduling, scale-up, reproducibility, yield, purity, cost, potency or quality.

Our reliance on contract manufacturers may adversely affect our operations or result in unforeseen delays or other problems beyond our control. Because of contractual restraints and the limited number of third-party manufacturers with the expertise and facilities to manufacture our bulk drug product on a commercial scale, replacement of a manufacturer may be expensive and time-consuming and may cause interruptions in the production of our drug product. A third-party manufacturer may also encounter difficulties in production. These problems may include:

- difficulties with production costs, scale-up and yields;
- availability of raw materials and supplies;
- quality control and assurance;
- shortages of qualified personnel;
- compliance with strictly enforced federal, state and foreign regulations that vary in each country where a product might be sold; and
- lack of capital funding.

Any delay or interruption in our supply of product candidates could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We may not be successful in establishing and maintaining strategic collaborations, which could adversely affect our ability to develop and commercialize our product candidates, negatively impacting our operating results.

If approved, we plan to commercialize AKB-9778 ourselves in the United States and intend to seek one or more strategic collaborators to commercialize AKB-9778 in additional markets. With respect to ARP-1536, we are evaluating its development options. We face competition in seeking appropriate collaborators for our product candidates, and the negotiation process is time-consuming and complex. In order for us to successfully collaborate with a third party on our product candidates, potential collaborators must view these product candidates as economically valuable. Even if we are successful in our efforts to establish strategic collaborations, the terms that we agree upon may not be favorable to us, and we may not be able to maintain such strategic collaborations if, for example, development or approval of a product is delayed or sales of an approved product are disappointing. Any delay in entering into strategic collaboration agreements related to our product candidates could delay the development and commercialization of our product candidates and reduce their competitiveness even if they reach the market.

In addition, our strategic collaborators may terminate any agreements they enter into with us, and we may not be able to adequately protect our rights under these agreements. Furthermore, our strategic collaborators will likely negotiate for certain rights to control decisions regarding the development and commercialization of our product candidates, if approved, and may not conduct those activities in the same manner as we do.

On June 24, 2018, we entered into a license agreement with Gossamer pursuant to which we granted to Gossamer an exclusive, sublicensable license to develop and commercialize AKB-4924 and other structurally related products worldwide. We received an upfront payment of $20.0 million in connection with this license and are eligible to receive additional development and milestone payments contingent upon the achievement of specified milestones. We are also eligible to receive tiered royalties on sales of licensed products and additional payments upon the occurrence of specified events involving the licensed products. However, there can be no assurance that we will satisfy the conditions to receive any such payments from Gossamer in a timely manner or at all. While Gossamer is obligated to use its commercially reasonable efforts to develop and commercialize the licensed products, there can be no assurance that such products would be successfully developed and commercialized. In addition, the license agreement contains an exclusivity provision pursuant to which we are prohibited from developing, manufacturing or commercializing certain HIF stabilizing compounds as described in the agreement. While the license agreement expires on a licensed product-by-licensed product and country-by-country basis on the later of fifteen years from the date or first commercial sale or when there is no longer a valid patent claim covering such licensed product in such country, either party may terminate the license agreement for an uncured material breach by the other party or upon the bankruptcy or insolvency of the other party. In addition, Gossamer may terminate the license agreement in the event it determines that there is a potential safety or efficacy issue with the licensed products. Therefore, there can be no assurance that the license agreement will continue for its full duration or that we will realize the intended benefits of the license agreement.

If we fail to establish and maintain strategic collaborations related to our product candidates for the indications and in the geographies in which we do not intend develop and commercialize ourselves, we will bear all of the risk and costs related to the development and commercialization of any such product candidate, and we may need to seek additional financing, hire additional employees and otherwise develop expertise. This could negatively affect the development of any product candidate for which we do not locate a suitable strategic partner.

Risks Related to Our Intellectual Property

If our efforts to protect our proprietary technologies are not adequate, we may not be able to compete effectively in our market.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our technologies. We will only be able to protect our product candidates, proprietary technologies and their uses from unauthorized use by third parties to the extent that valid and enforceable patents or trade secrets cover them. Any disclosure to or misappropriation by third parties of our confidential proprietary information could enable competitors to quickly duplicate or surpass our technological achievements, thus eroding our competitive position in our market.

The patenting process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. In addition, we may not pursue or obtain patent protection in all relevant markets. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Our pending and future patent applications may not result in issued patents that protect our technology or products, in whole or in part. In addition, our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from using our technology or from developing competing products and technologies.

Composition-of-matter patents on the active pharmaceutical ingredient are generally considered to be the strongest form of intellectual property protection for pharmaceutical products, as such patents provide protection without regard to any method of use. Method-of-use patents protect the use of a product for the specified method.

This type of patent does not prevent a competitor from making and marketing a product that is identical to our products for an indication that is outside the scope of the patented method. Likewise, a competitor may make and market a product similar to our products but that are not covered by the scope of our patents. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products “off-label.” Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent or prosecute. In addition, our patents will eventually expire, and the active pharmaceutical ingredients in our current product candidates will become commercially available in generic drug products. Thus, no patent protection may be available with regard to formulation or method of use.

The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own or license may fail to result in issued patents in the United States or in other foreign countries. Even if the patents do successfully issue, third parties may challenge the validity, enforceability, inventorship, or scope thereof, which may result in such patents being narrowed, invalidated or held unenforceable. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims. If the breadth or strength of protection provided by the patent applications we hold with respect to our product candidates is threatened, it could dissuade companies from collaborating with us to develop, and threaten our ability to commercialize, our product candidates. Moreover, the inventors of our patents or patent applications or our scientific consultants may become involved with competitors, develop products or processes which design around our patents, or become hostile to us or the patents or patent applications on which they are named as inventors. Likewise, our collaborators may become hostile to us or develop products or processes that are adjacent to or compete with us, including products and processes outside the scope of our patents. For example, a hostile collaborator may use technology similar to ours to pursue treatment of an indication that we plan to pursue, and may obtain approval for a product before we do. A hostile collaborator may file patent applications based on information learned from us. Such patent applications may become prior art that will be detrimental to future patent applications by us on similar technology.

Further, if we encounter delays in our clinical trials, the period of time during which we could market our product candidates under patent protection would be reduced. Since patent applications in the United States and most other countries are confidential for a period of time after filing, we cannot be certain that we were the first to file any patent application related to our product candidates. Furthermore, for applications in which all claims are entitled to a priority date before March 16, 2013, an interference proceeding can be provoked by a third-party or instituted by the United States Patent and Trademark Office, or the USPTO, to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. For applications containing a claim not entitled to priority before March 16, 2013, there is greater level of uncertainty in the patent law with the passage of the America Invents Act (2011), which brings into effect significant changes to the U.S. patent laws and which introduces new procedures for challenging pending patent applications and issued patents. A primary change under this reform is creating a "first to file" system in the United States. We, or our collaborators, might not have been the first to file patent applications on certain inventions. Likewise, our collaborators may file patent applications on certain inventions without our knowledge, prior to our filing patent applications on those inventions. This will require us to be cognizant of the time from invention to filing of a patent application.

In addition to the protection afforded by patents, we seek to rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our drug discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. Although we require all of our employees to assign their inventions to us, and require all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot be certain that our trade secrets and other confidential proprietary information will not be disclosed, willfully or unintentionally, or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Trade secrets are difficult to protect, and we have limited control over the protection of trade secrets used by our licensors, collaborators, and suppliers. Furthermore, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent unauthorized material disclosure of our intellectual property to third parties, we will not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, operating results and financial condition.

We currently have a non-exclusive license to one U.S. patent, which we have licensed to Gossamer as part of the June 24, 2018 license agreement. We rely on the licensor to maintain this patent and otherwise protect the intellectual property covered by this non-exclusive license. We have limited control over these activities or over any other intellectual property that may be related to our in-licensed intellectual property. For example, we cannot be certain that activities by the licensor have been or will be conducted in compliance with applicable laws and regulations. We may have no control or input over whether, and in what manner, our licensor may enforce or defend the patent against a third-party. The licensor may enforce or defend the patent less vigorously than if we had enforced or defended the patent ourselves. Further, the licensor may not necessarily seek enforcement in scenarios in

which we would feel that enforcement was in our best interests. For example, the licensor may not enforce the patent against a competitor of ours who is not a direct competitor of the licensor. If our in-licensed intellectual property is found to be invalid or unenforceable, then the licensor may not be able to enforce the patent against a competitor of ours. Our non-exclusive license does not prevent a third party from seeking and obtaining a non-exclusive license to the same patent that we license. If we fail to meet our obligations under the non-exclusive license agreement, then the licensor may terminate the license agreement. If the license agreement is terminated, the former licensor may seek to enforce the intellectual property against us. We may choose to terminate the license agreement, and doing so would allow a third party to seek and obtain an exclusive license to the patent. If a third party obtains an exclusive license to intellectual property formerly licensed to us, then the third party may seek to enforce the intellectual property against us. The occurrence of any of the foregoing may negatively impair our collaboration with Gossamer and prevent us from realizing the intended benefits of this collaboration.

Our patents covering one or more of our products or product candidates could be found invalid or unenforceable if challenged.

Any of our intellectual property rights could be challenged or invalidated despite measures we take to obtain patent and other intellectual property protection with respect to our product candidates and proprietary technology. For example, if we were to initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that our patent is invalid and/or unenforceable. In patent litigation in the U.S. and in some other jurisdictions, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld material information from the USPTO or the applicable foreign counterpart, or made a misleading statement, during prosecution. A litigant or the USPTO itself could challenge our patents on this basis even if we believe that we have conducted our patent prosecution in accordance with the duty of candor and in good faith. The outcome following such a challenge is unpredictable.

With respect to challenges to the validity of our patents, for example, there might be invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on a product candidate. Even if a defendant does not prevail on a legal assertion of invalidity and/or unenforceability, our patent claims may be construed in a manner that would limit our ability to enforce such claims against the defendant and others. The cost of defending such a challenge, particularly in a foreign jurisdiction, and any resulting loss of patent protection could have a material adverse impact on one or more of our product candidates and our business. Enforcing our intellectual property rights against third parties may also cause such third parties to file other counterclaims against us, which could be costly to defend, particularly in a foreign jurisdiction, and could require us to pay substantial damages, cease the sale of certain products or enter into a license agreement and pay royalties (which may not be possible on commercially reasonable terms or at all). Any efforts to enforce our intellectual property rights are also likely to be costly and may divert the efforts of our scientific and management personnel, even if we are successful in stopping infringement of our patents.

There is also the risk that, even if the validity of these patents is upheld, the court will refuse to stop the third party on the ground that such third party's activities do not infringe our patents. In addition, the U.S. Supreme Court has recently changed some legal principles that affect patent applications, granted patents and assessment of the eligibility or validity of these patents. As a consequence, issued patents may be found to contain invalid claims according to the newly revised eligibility and validity standards. Some of our patents may be subject to challenge and subsequent invalidation or significant narrowing of claim scope in proceedings before the USPTO, or during litigation, under the revised criteria which could also make it more difficult to obtain patents.

We may not be able to detect infringement against our patents, as the case may be, which may be especially difficult for formulation patents. Even if we detect infringement by a third party of our patents, we may choose not to pursue litigation against or settlement with the third party. If we later sue such third party for patent infringement, the third party may have certain legal defenses available to it, which otherwise would not be available except for the delay between when the infringement was first detected and when the suit was brought. Such legal defenses may make it impossible for us to enforce our patents against such third party.

If another party questions the patentability of any of our claims in our U.S. patents, the third party can request that the USPTO review the patent claims such as in an *inter partes* review, *ex parte* re-exam or post-grant review

proceedings. These proceedings are expensive and may result in a loss of scope of some claims or a loss of the entire patent. In addition to potential USPTO review proceedings, we may become a party to patent opposition proceedings in the European Patent Office, or EPO, or similar proceedings in other foreign patent offices, where our foreign patents are challenged. The costs of these opposition or similar proceedings could be substantial, and may result in a loss of scope of some claims or a loss of the entire patent. An unfavorable result at the USPTO, EPO or other patent office may result in the loss of our right to exclude others from practicing one or more of our inventions in the relevant country or jurisdiction, which could have a material adverse effect on our business.

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 research and develop and to manufacture our product candidates, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with our advisors, employees, third-party contractors 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, including our trade secrets. 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 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 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. Moreover, enforcing a claim that a third party illegally obtained and is using any of our trade secrets is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing to protect trade secrets. If we choose to go to court to stop a third party from using any of our trade secrets, we may incur substantial costs. These lawsuits may consume our time and other resources even if we are successful. These lawsuits also may impact our ability to pursue agreements with third parties in the future.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors and consultants to publish data potentially relating to our trade secrets, although our agreements may contain certain limited publication rights. For example, any academic institution that we may collaborate with in the future will usually expect to be granted rights to publish data arising out of such collaboration, provided that we are notified in advance and given the opportunity to delay publication for a limited time period in order for us to secure patent protection of intellectual property rights arising from the collaboration, in addition to the opportunity to remove confidential or trade secret information from any such publication. In the future we may also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development or similar agreements. A collaborator at such academic institution may use the information learned from the collaboration to compete with us, either in an academic or commercial setting. The collaborator may use the results obtained through the academic collaboration for the benefit of another commercial entity. The collaborator may use technology for the benefit of a third party even if we were entitled to a license or the right to negotiate for a license to the technology from the academic institution. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of our agreements with third parties, independent development or publication of information by any of our third-party collaborators. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

Moreover, our reliance on third parties may be exploited by a third party with knowledge of our company, including knowledge of company strategies, intellectual property, research programs, trade secrets, and scientific discovery including, for example, drug targets, pharmaceutically active ingredients, dosing regimens and mechanisms of action. A third party may start a competing company or may join a competing company. If a third party with whom we have an agreement does become a competitor, this may lead to questions of intellectual property ownership, ownership of physical assets, inventorship and breach of contracts in place with the third party. If we seek to resolve this issue by a law suit, then we expect counter claims that may jeopardize the validity and enforceability of our patents. The third parties with whom we collaborate also may have business or legal conflicts of interest. These conflicts of interest can lead to litigation or impact the ability of the third party to fulfill their obligations to us.

Third-party claims of intellectual property infringement may be costly and time consuming, and may delay or harm our drug discovery and development efforts.

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. The pharmaceutical and biotechnology industries are characterized by extensive litigation over patent and other intellectual property rights. We may become a party to, or threatened with, future adversarial litigation or other proceedings regarding intellectual property rights with respect to our drug candidates. As the pharmaceutical and biotechnology industries expand and more patents are issued, the risk increases that our drug candidates may give rise to claims of infringement of the patent rights of others.

While our product candidates are in preclinical studies and clinical trials, we believe that the use of our product candidates in these preclinical studies and clinical trials in the United States falls within the scope of the exemptions provided by 35 U.S.C. Section 271(e), which provides that it shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention solely for uses reasonably related to the development and submission of information to the FDA. As our product candidates progress toward commercialization, the possibility of a patent infringement claim against us increases. We attempt to ensure that our product candidates and the methods we employ to manufacture them, as well as the methods for their use we intend to promote, do not infringe other parties' patents and other proprietary rights. There can be no assurance they do not, however, and competitors or other parties may assert that we infringe their proprietary rights in any event.

Third parties may hold or obtain patents or other intellectual property rights and allege in the future that the use of our product candidates infringes these patents or intellectual property rights, or that we are employing their proprietary technology without authorization. Under U.S. law, a party may be able to patent a discovery of a new way to use a previously known compound, even if such compound itself is patented, provided the newly discovered use is novel and nonobvious. Such a method-of-use patent, however, if valid, only protects the use of a claimed compound for the specified methods claimed in the patent. This type of patent does not prevent persons from using the compound for any previously known use of the compound. Further, this type of patent does not prevent persons from making and marketing the compound for an indication that is outside the scope of the patented method.

There may be patents of third parties of which we are currently unaware with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our drug candidates. Also, because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may infringe. Notwithstanding the above, third parties may in the future claim that our product candidates and other technologies infringe upon these patents and may file suit against us.

Parties making claims against us may seek and obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize AKB-9778 or other product candidates. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process or any final product itself, then the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire or they are finally determined to be held invalid or unenforceable. Similarly, if any third-party patent were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or our intended methods of use, then the holders of any such patent may be able to block or impair our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires or is finally determined to be held invalid or unenforceable. We may also elect to enter into a license in order to settle litigation or in order to resolve disputes prior to litigation. Furthermore, even in the absence of litigation, we may need to acquire or obtain licenses from third parties to advance our research or allow commercialization of our product candidates, and there can be no assurance that we will be able to do so on commercially reasonable terms or at all.

Additionally, we may in the future from time to time collaborate with academic institutions to accelerate our preclinical research or development under written agreements with these institutions. In certain cases, these institutions may provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to others, potentially blocking our ability to pursue our program. The institution also may only offer a nonexclusive license, providing an opportunity for competitors to license intellectual property important

to us. If we are unable to successfully obtain rights to required third-party intellectual property or to maintain the existing intellectual property rights we have, we may have to abandon development of such program and our business and financial condition could suffer. The academic institutions, or our collaborators at those institutions, also may violate the terms of our agreements with them. For example, a collaborator could use proprietary knowledge based on the collaboration to compete with us. These violations may result in litigation, which can be costly and may impact our ability to use resources for product development or other necessary functions.

The licensing and acquisition of third-party intellectual property rights is a competitive practice, and companies that may be more established, or have greater resources than we do, may also be pursuing strategies to license or acquire third-party intellectual property rights that we may consider necessary or attractive in order to commercialize our product candidates. More established companies may have a competitive advantage over us due to their larger size and cash resources or greater clinical development and commercialization capabilities. There can be no assurance that we will be able to successfully complete such negotiations and ultimately acquire the rights to the intellectual property surrounding the additional product candidates that we may seek to acquire.

Further, defense of infringement claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties or redesign our products, which may be impossible or require substantial time and monetary expenditure.

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

Competitors may infringe or otherwise violate our patents, trademarks, copyrights or other intellectual property. To counter infringement or other violations, we may be required to file claims, which can be expensive and time consuming. Any such claims could provoke these parties to assert counterclaims against us, including claims alleging that we infringe their patents or other intellectual property rights. In addition, in a patent infringement proceeding, a court may decide that one or more of the patents we assert is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to prevent the other party from using the technology at issue on the grounds that our patents do not cover the technology. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In such a case, we could ultimately be forced to cease use of such marks. In any intellectual property litigation, even if we are successful, any award of monetary damages or other remedy we receive may not be commercially valuable. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

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

Periodic maintenance fees on any issued patent are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign governmental patent agencies also require compliance with a number of procedural, documentary, fee payment (such as annuities) and other similar provisions during the patent application process. While an inadvertent 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. In such an event, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We have received confidential and proprietary information from collaborators, prospective licensees and other third parties. In addition, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of these third parties or our employees' former

employers. We may also be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. We may be subject to ownership disputes in the future arising, for example, from conflicting obligations of consultants or others who are involved in developing our drug candidates. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against these claims, litigation could result in substantial cost and be a distraction to our management and employees.

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

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some countries do not protect intellectual property rights to the same extent as laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other countries. Competitors may use our technologies in countries where we have not obtained patent protection to develop their own products and further, may infringe our patents in territories where we have patent protection, but enforcement is not as strong as in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in certain countries. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property, particularly those relating to pharmaceutical and biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign countries could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Risks Related to Commercialization

Our future commercial success depends upon attaining significant market acceptance of our product candidates, if approved, among physicians, patients, third-party payors and others in the medical community.

Even if we obtain marketing approval for AKB-9778 or any other product candidates that we may develop or acquire in the future, these product candidates may not gain market acceptance among physicians, third-party payors, patients and others in the medical community. In addition, market acceptance of any approved products depends on a number of other factors, including:

- the efficacy and safety of the product, as demonstrated in clinical trials;
- the clinical indications for which the product is approved and the label approved by regulatory authorities for use with the product, including any warnings that may be required on the label;
- acceptance by physicians and patients of the product as a safe and effective treatment and the willingness of the target patient population to try new therapies and of physicians to prescribe new therapies;
- the cost, safety and efficacy of treatment in relation to alternative treatments;
- the availability of adequate coverage and reimbursement by third party payors and government authorities;
- relative convenience and ease of administration;
- the prevalence and severity of adverse side effects;
- the effectiveness of our sales and marketing efforts; and
- the restrictions on the use of our products together with other medications, if any.

For example, the current established treatments for DME are anti-VEGF medications, including bevacizumab and ranibizumab, and the current established treatments for DR in the absence of DME include laser photocoagulation.

We believe that that prescribers may be resistant to prescribing AKB-9778 with or instead of anti-VEGF medications, or instead of laser photocoagulation, which is currently the standard of care for DME and DR, respectively.

Market acceptance is critical to our ability to generate significant revenue. In addition, any product candidate, if approved and commercialized, may be accepted in only limited capacities or not at all. If any approved products are not accepted by the market at all or to the extent that we expect, we may not be able to generate significant revenue and our business would suffer.

If we are unable to establish sales, marketing and distribution capabilities or to enter into agreements with third parties to market and sell our product candidates, we may not be successful in commercializing our product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any product for which we obtain marketing approval, we will need to establish a sales and marketing organization or make arrangements with third parties to perform these services.

There are risks involved with establishing our own sales, marketing and distribution capabilities. For example, recruiting and training a sales force are expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our products on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;
- state and federal transparency reporting requirements that require us to register our sales representatives and report any gifts, payments for speaking engagements, travel costs, donations, or other support offered to physicians or teaching hospitals which may create additional burden on sales and marketing personnel;
- our inability to effectively manage a geographically dispersed sales and marketing team;
- 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; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we are unable to establish our own sales, marketing and distribution capabilities and have to enter into arrangements with third parties to perform these services, our profitability, if any, is likely to be materially diminished in relation to if we were to market, sell and distribute any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell, market and distribute our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

Coverage and reimbursement may be limited or unavailable in certain market segments for any approved products, which could make it difficult for us to sell our products profitably.

Market acceptance and sales of any approved products will depend significantly on the availability of adequate coverage and reimbursement from third-party payors and may be affected by existing and future healthcare reform measures. Government authorities and third-party payors decide which drugs they will pay for and establish formularies and reimbursement levels. Coverage and reimbursement by a third-party payor may depend upon a number of 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 approval for a product from a government or other third-party payor is a time consuming and costly process that could require us to provide supporting scientific, clinical and cost-effectiveness data for the use of our products to the payor. Additionally, we may be required to enter into contracts with third-party payors to obtain favorable formulary status. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. We cannot be sure that coverage or adequate reimbursement will be available for any of our product candidates. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates, but also have their own methods and approval process apart from Medicate determinations. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. Even if we obtain coverage for our product candidates, third-party payors may not establish adequate reimbursement amounts, which may reduce the demand for, or the price of, our products. If reimbursement is not available or is available only to limited levels, we may not be able to commercialize certain of our products. In addition, in the United States, third-party payors are increasingly attempting to contain healthcare costs by limiting both coverage and the level of reimbursement of new drugs. As a result, significant uncertainty exists as to whether and how much third-party payors will reimburse patients for their use of newly approved drugs, which in turn will put pressure on the pricing of drugs.

Price controls may be imposed, which may adversely affect our future profitability.

In some countries, particularly member states of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after receipt of marketing approval for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. 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 distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product candidates to other available products in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be adversely affected.

The impact of recent healthcare reform and other changes in the healthcare industry and in healthcare spending is currently unknown and may adversely affect our business model.

Our revenue prospects could be affected by changes in healthcare spending and policy in the United States and abroad. We operate in a highly regulated industry and new laws, regulations or judicial decisions, or new interpretations of existing laws, regulations or decisions related to healthcare availability, the method of delivery or payment for healthcare products and services could negatively impact our business, operations and financial condition.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, also called the MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician-administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. As a result of this legislation and the expansion of federal coverage of products, we expect that there will be additional pressure to reduce costs. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policies and payment limitations in setting their own reimbursement rates, and any reduction in reimbursement that results from the MMA may cause a similar reduction in payments from private payors. Similar regulations or reimbursement policies may be enacted in international markets which could similarly impact our business.

In addition, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively ACA, was enacted in 2010 with a goal of reducing the cost of healthcare and substantially changing the way healthcare is financed by both government and private insurers. The ACA, among other things, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug

Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of certain branded prescription drugs and biologic products, and creates a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D. In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. On August 2, 2011, the Budget Control Act of 2011 created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect on April 1, 2013 and will remain in effect through 2027 unless additional Congressional action is taken.

It is likely that federal and state legislatures within the United States and foreign governments will continue to consider changes to existing healthcare legislation. Some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. 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 such Executive Order directed 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 burden on states or a cost, fee, tax, penalty or regulatory burden on 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. The loss of the cost share reduction payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. Further, on June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

Other legislative changes have been proposed and adopted since the ACA was enacted, including aggregate reductions to Medicare payments to providers of 2% per fiscal year through 2027. 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 and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. While Congress has not passed comprehensive repeal legislation, it has enacted laws that modify certain provisions of the ACA, including eliminating a tax-based shared responsibility payment imposed 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. 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, 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.

Further, the Trump administration's budget proposal for fiscal year 2019 contained further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. Additionally, the Trump administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. In response to the Blueprint, on November 30, 2018, CMS announced a proposed rule that would amend the Medicare Advantage and Medicare Part D prescription drug benefit regulations to reduce out of pocket costs for plan enrollees and allow Medicare plans to negotiate lower rates for certain drugs. Among other things, the proposed rule changes would allow Medicare Advantage plans to use pre-authorization (PA) and step therapy (ST) for six protected classes of drugs, with certain exceptions, permit plans to implement PA and ST in Medicare Part B drugs, changes the definition of "negotiated prices" in the regulations and adds a definition of "price concession" to the regulation. It is unclear whether these proposed changes will be accepted, and if so, what effect such changes will have on our business and our ability to receive adequate reimbursement for our future products.

We cannot predict the reform initiatives that may be adopted in the future or whether initiatives that have been adopted will be repealed or modified. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare may adversely affect:

- the demand for any products for which we may obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to obtain coverage and reimbursement approval for a product;
- our ability to generate revenues and achieve or maintain profitability; and
- the level of taxes that we are required to pay.

We expect that changes and challenges to the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies, and additional downward pressure on the price that we receive for any future approved product.

We face substantial competition, which may result in others discovering, developing or commercializing products before, or more successfully, than we do.

The development and commercialization of new products is highly competitive. Our future success depends on our ability to demonstrate and maintain a competitive advantage with respect to the development and commercialization of our product candidates. Our objective is to develop and commercialize new products with superior efficacy, convenience, tolerability and safety. In many cases, the products that we commercialize will compete with existing, market-leading products.

If AKB-9778 is approved and launched commercially, competing drugs may include current anti-VEGF drugs administered by repeated injection into the eye, including Lucentis, Eylea and Avastin in the treatment of DME and DR, current therapies including laser photocoagulation in the treatment of DR. We may face competition from potential DME and DR treatments currently in development, e.g. brolucizumab (Novartis) or RG7716 (Roche/Genentech).

Many of our potential competitors have significantly greater financial, manufacturing, marketing, drug development, technical and human resources than we do. Large pharmaceutical companies, in particular, have extensive experience in clinical testing, obtaining regulatory approvals, recruiting patients and in manufacturing pharmaceutical products. Large and established companies such as Roche and Regeneron, among others, compete in the market for products to treat DR and DME. In particular, these companies have greater experience and expertise in securing government contracts and grants to support their research and development efforts, conducting testing and clinical trials, obtaining regulatory approvals to market products, manufacturing such products on a broad scale and marketing approved products. These companies also have significantly greater research and marketing capabilities than we do and may also have products that have been approved or are in late stages of development, and have collaborative arrangements in our target markets with leading companies and research institutions. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel compounds or to in-license novel compounds that could make the product that we develop obsolete. As a result of

all of these factors, our competitors may succeed in obtaining patent protection and/or FDA approval or discovering, developing and commercializing products before, or more effectively than, we do. In addition, any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and safety in order to overcome price competition and to be commercially successful. If we are not able to compete effectively against potential competitors, our business will not grow and our financial condition and operations will suffer.

Our product candidates may cause undesirable side effects or have other properties that delay or prevent their regulatory approval or limit their commercial potential.

Undesirable side effects caused by our product candidates or even competing products in development that utilize a common mechanism of action could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in the denial of regulatory approval by the FDA or other regulatory authorities and potential products liability claims. AKB-9778 is currently in Phase 2 clinical development. Serious adverse events deemed to be caused by our product candidates could have a material adverse effect on the development of our product candidates and our business as a whole. The most common drug-related adverse events to date in the clinical trial evaluating the safety and tolerability of AKB-9778 in DME have been dizziness and asymptomatic decreases in blood pressure. Our understanding of the relationship between AKB-9778 and these events, as well as our understanding of adverse events in future clinical trials of other product candidates, may change as we gather more information, and additional unexpected adverse events may be observed.

If we or others identify undesirable side effects caused by our product candidates either before or after receipt of marketing approval, a number of potentially significant negative consequences could result, including:

- our clinical trials may be put on hold;
- patient recruitment could be slowed, or enrolled patients may not want to complete a clinical trial;
- we may be unable to obtain regulatory approval for our product candidates or regulatory authorities may withdraw approvals of product candidates;
- regulatory authorities may require additional warnings on the label;
- a medication guide outlining the risks of such side effects for distribution to patients may be required;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of our products and could substantially increase commercialization costs.

Risks Related to Our Business and Industry

If we fail to attract and keep senior management and key scientific personnel, we may be unable to successfully develop our product candidates, conduct our clinical trials and commercialize our products.

We are highly dependent on members of our senior management, including Stephen Hoffman, our Chief Executive Officer, Michael Rogers, our Chief Financial Officer, Joseph Gardner, our President and Founder and former Chief Executive Officer, Kevin G. Peters, our Chief Scientific Officer and Stephen Pakola, our Chief Medical Officer. The loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize products. We may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the intense competition among numerous biopharmaceutical companies for similar personnel.

We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other

entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

Our employees, independent contractors, principal investigators, contract research organizations, consultants and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading.

We are exposed to the risk that our employees, independent contractors, principal investigators, CROs, consultants and vendors may engage in fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or unauthorized activities that violate: (1) FDA regulations, including those laws that require the reporting of true, complete and accurate information to the FDA, (2) manufacturing standards, (3) federal and state healthcare fraud and abuse laws and regulations, or (4) laws that require the reporting of true and accurate financial information and data. Specifically, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. 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 be in compliance with such laws or regulations. If any such actions are instituted against us, and if 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 may encounter difficulties in managing our growth and expanding our operations successfully.

As we seek to advance our product candidates through clinical trials and commercialization, we will need to expand our development, regulatory, manufacturing, marketing and sales capabilities or contract with third parties to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various strategic collaborators, suppliers and other third parties. Future growth will impose significant added responsibilities on members of management. Our future financial performance and our ability to commercialize AKB-9778, if approved, and any other product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to manage our development efforts and clinical trials effectively and hire, train and integrate additional management, administrative and, if necessary, sales and marketing personnel. We may not be able to accomplish these tasks, and our failure to accomplish any of them could prevent us from successfully growing our company.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk if we commercialize any products. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for any product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals, or labeling, marketing or promotional restrictions;

- loss of revenue;
- the inability to commercialize any product candidates that we may develop; and
- a decline in our stock price.

Failure to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop. We currently carry product liability insurance covering our clinical trials in the amount of $10 million in the aggregate. Although we maintain product liability insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. 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 for failure to comply with such laws and regulations.

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.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Our business and operations would suffer if we sustain cyber-attacks or other privacy or data security incidents that result in security breaches.

Our information technology may be subject to cyber-attacks, security breaches or computer hacking. Experienced computer programmers and hackers may be able to penetrate our security controls and misappropriate or compromise sensitive personal, proprietary or confidential information, create system disruptions or cause shutdowns. They also may be able to develop and deploy malicious software programs that attack our systems or otherwise exploit any security vulnerabilities. Our systems and the data stored on those systems may also be vulnerable to security incidents or security attacks, acts of vandalism or theft, misplaced or lost data, human errors, or other similar events that could negatively affect our systems and our data, as well as the data of our business partners. Further, third parties that provide services to us, could also be a source of security risk in the event of a failure of their own security systems and infrastructure.

The costs to eliminate or address the foregoing security threats and vulnerabilities before or after a cyber-incident could be significant. Our remediation efforts may not be successful and could result in interruptions, delays or cessation of service, and loss of existing or potential suppliers, manufacturers or other third parties. In addition, breaches of our security measures and the unauthorized dissemination of sensitive personal, proprietary or confidential information about us, our business partners, participants in our clinical trials or other third parties could expose us to significant potential liability and reputational harm. In addition, the loss of clinical trial data from completed or ongoing or planned clinical trials as a result of a data security incident or other systems failure could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. As threats related to cyber-attacks develop and grow, we may also find it necessary to make additional

investments to protect our data and infrastructure, which may impact our profitability. We could also be negatively impacted by existing and proposed laws and regulations, as well as government policies and practices related to cybersecurity, data privacy, data localization and data protection such as GDPR.

We face risks arising from the results of the public referendum held in United Kingdom and its membership in the European Union.

The ongoing developments following from the United Kingdom's public referendum vote to exit from the European Union could cause disruptions to and create uncertainty surrounding our business, including affecting our relationships with existing and potential suppliers, manufacturers and other third parties. Negotiations have commenced to determine the terms of the United Kingdom's future relationship with the European Union, including the terms of trade between the United Kingdom and the European Union. The effects of Brexit will depend upon any agreements the United Kingdom makes to retain access to European Union markets either during a transitional period or more permanently. The measures could potentially have corporate structural consequences, adversely change tax benefits or liabilities in these or other jurisdictions and could disrupt some of the markets and jurisdictions in which we operate. In addition, Brexit could lead to legal uncertainty and potentially divergent national laws and regulations as the United Kingdom determines which European Union laws to replace or replicate. In addition, the announcement of Brexit has caused significant volatility in global stock markets and currency exchange rate fluctuations, including the strengthening of the USD against some foreign currencies, and the Brexit negotiations may continue to cause significant volatility. The progress and outcomes of Brexit negotiations also may create global economic uncertainty. Any of these effects of Brexit, among others, could materially adversely affect the business, business opportunities, and financial condition of our company.

Risks Related to Ownership of Our Common Stock

We are eligible to be treated as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, and we cannot be certain if the reduced disclosure requirements applicable to emerging growth companies will make our common stock less attractive to investors.

We are an "emerging growth company", as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;
- not being required to comply with the auditor attestation requirements regarding the assessment of our internal control over financial reporting;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

We have taken advantage of these reduced reporting burdens. In particular, we have provided only two years of audited consolidated financial statements and have not included all of the executive compensation related information that would be required if we were not an emerging growth company. Investors may find our common stock less attractive if we continue to 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 these accounting standards until they would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption 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 could be an emerging growth company for up to five years, although circumstances could cause us to lose that status earlier, including if the market value of our common stock held by non-affiliates exceeds $700 million as of any June 30 before that time or if we have total annual gross revenue of $1.07 billion (as may be inflation-adjusted by the SEC from time to time) or more during any fiscal year before that time, in which cases we would no longer be an emerging growth company as of the following December 31 or, if we issue more than $1.07 billion in non-convertible debt during any three-year period before that time, we would cease to be an emerging growth company

immediately. Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company" if the market value of our common stock held by non-affiliates is below $250 million as of June 30 in any given year (or $700 million if we had less than $100 million in revenues), which would allow us to take advantage of many of the same exemptions from disclosure requirements, including exemption from the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements.

FINRA sales practice requirements may limit a stockholder's ability to buy and sell our stock.

The Financial Industry Regulatory Authority, or FINRA, has adopted rules requiring that, in recommending an investment to a customer, a broker-dealer must have reasonable grounds for believing that the investment is suitable for that customer. Prior to recommending speculative or low-priced securities to their non-institutional customers, broker-dealers must make reasonable efforts to obtain information about the customer's financial status, tax status, investment objectives and other information. Under interpretations of these rules, FINRA has indicated its belief that there is a high probability that speculative or low-priced securities will not be suitable for at least some customers. If these FINRA requirements are applicable to us or our securities, they may make it more difficult for broker-dealers to recommend that at least some of their customers buy our common stock, which may limit the ability of our stockholders to buy and sell our common stock and could have an adverse effect on the market for and price of our common stock.

The market price of our common stock may be highly volatile, and may be influenced by numerous factors, some of which are beyond our control.

If a market for our common stock develops, its market price could fluctuate substantially due to a variety of factors, including market perception of our ability to meet our growth projections and expectations, quarterly operating results of other companies in the same industry, trading volume in our common stock, changes in general conditions in the economy and the financial markets or other developments affecting our business and the business of others in our industry. In addition, the stock market itself is subject to extreme price and volume fluctuations. This volatility has had a significant effect on the market price of securities issued by many companies for reasons related and unrelated to their operating performance and could have the same effect on our common stock. The market price of shares of our common stock could be subject to wide fluctuations in response to many risk factors listed in this section, and others beyond our control, including:

- results of clinical trials of our product candidates;
- the timing of the release of results of our clinical trials;
- results of clinical trials of our competitors' products;
- safety issues with respect to our products or our competitors' products;
- regulatory actions with respect to our products or our competitors' products;
- actual or anticipated fluctuations in our financial condition and operating results;
- publication of research reports by securities analysts about us or our competitors or our industry;
- our failure or the failure of our competitors to meet analysts' projections or guidance that we or our competitors may give to the market;
- additions and departures of key personnel;
- strategic decisions by us or our competitors, such as acquisitions, divestitures, spin-offs, joint ventures, strategic investments or changes in business strategy;
- the passage of legislation or other regulatory developments affecting us or our industry;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- sales of our common stock by us, our insiders or our other stockholders;
- speculation in the press or investment community;
- announcement or expectation of additional financing efforts;
- changes in accounting principles;
- terrorist acts, acts of war or periods of widespread civil unrest;
- natural disasters and other calamities;
- changes in market conditions for biopharmaceutical stocks; and
- changes in general market and economic conditions.

In addition, the stock market has recently experienced significant volatility, particularly with respect to pharmaceutical, biotechnology and other life sciences company stocks. The volatility of pharmaceutical,

biotechnology and other life sciences company stocks often does not relate to the operating performance of the companies represented by the stock. As we operate in a single industry, we are especially vulnerable to these factors to the extent that they affect our industry or our products, or to a lesser extent our markets. In the past, securities class action litigation has often been initiated against companies following periods of volatility in their stock price. This type of litigation could result in substantial costs and divert our management's attention and resources and could also require us to make substantial payments to satisfy judgments or to settle litigation.

Our principal stockholders and management own a significant percentage of our stock and will be able to exercise significant influence over matters subject to stockholder approval.

As of December 31, 2018, our executive officers, directors and principal stockholders, together with their respective affiliates, owned approximately 44.7% of our common stock, including shares subject to outstanding options that are exercisable within 60 days after such date. Accordingly, these stockholders will be able to exert a significant degree of influence over our management and affairs and over matters requiring stockholder approval, including the election of our board of directors and approval of significant corporate transactions. This concentration of ownership could have the effect of entrenching our management and/or the board of directors, delaying or preventing a change in our control or otherwise discouraging a potential acquirer from attempting to obtain control of us, which in turn could have a material and adverse effect on the fair market value of our common stock.

Because we became a reporting company under the Exchange Act by means other than a traditional underwritten initial public offering, we may not be able to attract the attention of research analysts at major brokerage firms.

Because we did not become a reporting company by conducting an underwritten initial public offering of our common stock, and because we only recently became listed on a national securities exchange, we may obtain research coverage from fewer analysts than we would have obtained. In addition, investment banks may be less likely to agree to underwrite secondary offerings on our behalf or recommend the purchase of our common stock than if we became a public reporting company by means of an underwritten initial public offering, because they may be less familiar with our company as a result of more limited coverage by analysts and the media, and because we became public at an early stage in our development. The failure to receive research coverage or support in the market for our shares could have an adverse effect on our ability to develop a liquid market for our common stock.

The resale of shares covered by a registration statement could adversely affect the market price of our common stock in the public market, should one develop, which result would in turn negatively affect our ability to raise additional equity capital.

The sale, or availability for sale, of our common stock in the public market may adversely affect the prevailing market price of our common stock and may impair our ability to raise additional capital by selling equity or equity-linked securities. We filed and caused to become effective a registration statement with the SEC registering the resale of 27,367,117 shares of our common stock issued in connection with the reverse merger and the concurrent private placement offering in March 2017 and an additional registration statement covering 2,973,682 shares purchased by certain stockholders in June 2018 and subsequent open market purchases. This registration statement permits the resale of these shares at any time. The resale of a substantial number of shares of our common stock in the public market could adversely affect the market price for our common stock and make it more difficult for you to sell shares of our common stock at times and prices that you feel are appropriate. Furthermore, we expect that, because there will be a large number of shares registered pursuant to a registration statement, selling stockholders will continue to offer shares covered by such registration statement for a significant period of time, the precise duration of which cannot be predicted. Accordingly, the adverse market and price pressures resulting from an offering pursuant to a registration statement may continue for an extended period of time and continued negative pressure on the market price of our common stock could have a material adverse effect on our ability to raise additional equity capital.

Issuance of stock to fund our operations may dilute your investment and reduce your equity interest.

We may need to raise capital in the future to fund the development of our drug candidates or for other purposes. Any equity financing may have significant dilutive effect to stockholders and a material decrease in our stockholders' equity interest in us. Equity financing, if obtained, could result in substantial dilution to our existing stockholders. At its sole discretion, our board of directors may issue additional securities without seeking stockholder approval, and we do not know when we will need additional capital or, if we do, whether it will be available to us.

We have broad discretion in the use of our cash and may not use them effectively.

We currently intend to use our cash and cash equivalents for continuing clinical development of AKB-9778 in patients with diabetic retinopathy, including the continuation of our ongoing trials and the preparation for and initiation of the Phase 3 trials and for working capital and other general corporate purposes. Although we currently intend to use our cash and cash equivalents in such a manner, we will have broad discretion in the application of such cash and cash equivalents. Our failure to apply these funds effectively could affect our ability to continue to develop and commercialize our product candidates. Pending their use, we may invest our cash and cash equivalents in a manner that does not produce income or loses value.

As a result of recently becoming a public company, we are incurring increased costs and our management devotes substantial time to public company compliance programs.

As a public company, we incur significant legal, insurance, accounting and other expenses that we did not incur as a private company. In addition, our administrative staff is required to perform additional tasks. We are investing resources to comply with evolving laws, regulations and standards, and this investment will result in increased general and administrative expenses and may divert management's time and attention from product development activities. If our efforts to comply with new laws, regulations and standards differ from the activities intended by regulatory or governing bodies due to ambiguities related to practice, regulatory authorities may initiate legal proceedings against us and our business may be harmed. In connection with the reverse merger, pursuant to which we acquired Aerpio, we increased our directors' and officers' insurance coverage, which increased our insurance cost. In the future, it will be more expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced coverage or incur substantially higher costs to obtain coverage. These factors could also make it more difficult for us to attract and retain qualified members of our board of directors, particularly to serve on our audit committee and compensation committee, and qualified executive officers.

In addition, in order to comply with the requirements of being a public company, we may need to undertake various actions, including implementing new internal controls and procedures and hiring new accounting or internal audit staff. The Sarbanes-Oxley Act requires that we maintain effective disclosure controls and procedures and internal control over financial reporting. We are continuing to develop and refine our disclosure controls and other procedures that are designed to ensure that information required to be disclosed by us in the reports that we file with the SEC is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that information required to be disclosed in reports under the Securities Exchange Act of 1934 as amended, or the Exchange Act, is accumulated and communicated to our principal executive and financial officers. Any failure to develop or maintain effective controls could adversely affect the results of periodic management evaluations. In the event we are not able to demonstrate compliance with the Sarbanes-Oxley Act, our internal control over financial reporting is perceived as inadequate, or we are unable to produce timely or accurate financial statements, investors may lose confidence in our operating results and the price of our ordinary shares could decline. In addition, if we are unable to continue to meet these requirements, we may not be able to maintain our listing on a national securities exchange.

Our management team and board of directors will need to devote significant efforts to maintaining adequate and effective disclosure controls and procedures and internal control over financial reporting in order to comply with applicable regulations, which may include hiring additional legal, financial reporting and other finance and accounting staff and engaging consultants to assist in designing and implementing such procedures. Additionally, any of our efforts to improve our internal controls and design, implement and maintain an adequate system of disclosure controls may not be successful and will require that we expend significant cash and other resources. In addition, our management will be required to certify financial and other information in our quarterly and annual reports and provide an annual management report on the effectiveness of our internal control over financial reporting commencing with our second annual report. This assessment will need to include the disclosure of any material weaknesses in our internal control over financial reporting identified by our management or our independent registered public accounting firm. To achieve compliance with 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 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 consolidated financial statements.

Our independent registered public accounting firm will not be required to formally attest to the effectiveness of our internal control over financial reporting following this annual report until the first annual report required to be filed with the SEC following the date we are no longer an "emerging growth company" as defined in the JOBS Act. We cannot assure you that there will not be material weaknesses or significant deficiencies in our internal controls in the future.

Provisions in our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our amended and restated certificate of incorporation and amended and restated by-laws may have the effect of discouraging, delaying or preventing a change in control of us or changes in our management. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- authorize "blank check" preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors pursuant to a resolution adopted by a majority of the directors then in office;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- prohibit the consummation of a liquidation event unless approved by a supermajority (66 2/3% and majority of the minority, if applicable) vote of the holders of our voting stock;
- prohibit the consummation of an affiliate transaction with a majority stockholder that holds more than 50% of the voting power of our capital stock unless approved by a supermajority (66 2/3%) vote of directors then in office;
- provide that the number of directors on our board of directors may only be changed with a supermajority (66 2/3%) of directors then in office, even though less than a quorum;
- provide that our directors may be removed only for cause and by a supermajority (66 2/3%) vote of the holders of our voting stock;
- provide that vacancies on our board of directors may be filled only by a supermajority (66 2/3%) of directors then in office, even though less than a quorum;
- require a supermajority (66 2/3% and majority of the minority, if applicable) vote of the holders of our voting stock or the supermajority (66 2/3%) vote of the members of our board of directors then in office to amend our amended and restated by-laws; and
- require a supermajority (66 2/3% and majority of the minority, if applicable) vote of the holders of our voting stock and a supermajority (66 2/3%) vote of the holders of each class of our voting stock entitled to vote thereon to amend certain provisions of our amended and restated certificate of incorporation.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the

person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

Any provision of our amended and restated certificate of incorporation, our amended and restated by-laws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Our ability to use net operating losses to offset future taxable income may be subject to certain limitations.

In general, under Section 382 of the Internal Revenue Code of 1986, as amended, or the Code, a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change net operating losses, or NOLs, to offset future taxable income. Our existing NOLs may be subject to substantial limitations arising from previous ownership changes under Section 382 of the Code. Future analysis will still be required on any historical NOLs as no studies have been performed to evaluate a change in ownership. In addition, future changes in our stock ownership, many of which are outside of our control, could result in an ownership change under Section 382 of the Code. Our NOLs may also be impaired under state law. Accordingly, we may not be able to utilize a material portion of our NOLs. Furthermore, our ability to utilize our NOLs is conditioned upon our attaining profitability and generating U.S. federal taxable income. As described above under "—Risks related to our financial position and need for additional capital," we have incurred significant net losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future; thus, we do not know whether or when we will generate the U.S. federal taxable income necessary to utilize our NOLs. A full valuation allowance has been provided for the entire amount of our NOLs.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

You should not rely on an investment in our common stock to provide dividend income. We do not anticipate that we will pay any cash dividends to holders of our common stock in the foreseeable future. Instead, we plan to retain any earnings to maintain and expand our operations. In addition, any future debt financing arrangement may contain terms prohibiting or limiting the amount of dividends that may be declared or paid on our common stock. Accordingly, investors must rely on sales of their common stock after price appreciation, which may never occur, as the only way to realize any return on their investment. As a result, investors seeking cash dividends should not purchase our common stock.

On December 22, 2017, The Tax Cuts and Jobs Act (the "2017 Tax Act") was enacted and could have a material impact on our current and future income tax provision and disclosures.

Our effective tax rates could be affected by numerous factors, such as intercompany transactions, entry into new businesses and geographies, changes to our existing businesses and operations, acquisitions and investments and how they are financed, potential changes in our stock price, changes in our deferred tax assets and liabilities and their valuation, and changes in the relevant tax, accounting, and other laws, regulations, administrative practices, principles, and interpretations. Finally, U.S. State governments may enact tax laws in response to the 2017 Tax Act that could result in further changes to taxation and materially affect our financial position and results of operations.

The 2017 Tax Act significantly changes how the U.S. taxes corporations. The 2017 Tax Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense, limitation of the deduction for net operating losses and elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such tax losses may be carried forward indefinitely), and modifying or repealing many business deductions and credits. The 2017 Tax Act requires complex computations to be performed that were not previously required in U.S. tax law, significant judgments to be made in interpretation of the provisions of 2017 Tax Act and significant estimates in calculations, and the preparation and analysis of information not previously relevant or regularly produced. The U.S. Treasury Department, the IRS, and other standard-setting bodies could interpret or issue guidance on how provisions of the 2017 Tax Act will be applied or otherwise administered that is different from our interpretation. We have completed our determination of the accounting implications of the 2017 Tax Act during 2018 upon filing our Federal Income Tax Return, and there were no material adjustments to the Company's provisional estimate with the 2018 provision for income taxes.

An active trading market for our common stock may not develop or be sustainable. If an active trading market does not develop, investors may not be able to resell their shares at or above the purchase price and our ability to raise capital in the future may be impaired.

Our common stock was recently listed on The Nasdaq Capital Market on June 26, 2018. The initial listing price for our common stock was determined through negotiations with the underwriters. This price may not reflect the price at which investors in the market will be willing to buy and sell our shares. Although our common stock is listed on The Nasdaq Capital Market, an active trading market for our shares may never develop or, if developed, be maintained. If an active market for our common stock does not develop or is not maintained, it may be difficult for you to sell shares you purchase without depressing the market price for the shares or at all. An inactive trading market may also impair our ability to raise capital to continue to fund operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Our corporate headquarters are located in Cincinnati, Ohio. We currently lease three properties:

- Cincinnati, Ohio: 7,580 square feet of office space in Cincinnati under a lease that expires on July 31, 2021;
- Lexington, Massachusetts: 4,000 square feet of office space in Lexington under a lease that expires on December 31, 2021; and
- Dexter Michigan: 687 square feet of office space in Dexter under a lease that expires on October 31, 2019.

We believe that our existing facilities are adequate to meet our current needs, and that suitable additional alternative spaces will be available in the future on commercially reasonable terms for our future growth.

Item 3. Legal Proceedings.

As of the date of this Annual Report on Form 10-K, we are not currently involved in any material legal proceedings. However, from time to time, we could be subject to various legal proceedings and claims that arise in the ordinary course of our business activities. Regardless of the outcome, legal proceedings can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

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 began trading on the OTC Markets – OTCQB Tier on August 8, 2017 and subsequently uplisted to the Nasdaq Capital Market on June 26, 2018 under the symbol "ARPO." The following table sets forth, for the periods indicated, the high and low intraday sales prices of our common stock as reported by the Nasdaq Capital Market and OTC Markets – OTCQB Tier.

	Common Stock	
	High	Low
2018		
First Quarter	$ 5.25	$ 4.00
Second Quarter	$ 5.00	$ 3.29
Third Quarter	$ 4.35	$ 3.00
Fourth Quarter	$ 3.17	$ 1.56

	High	Low
2017		
Third Quarter	$ 6.75	$ 5.90
Fourth Quarter	$ 6.60	$ 4.00

Stockholders

As of March 1, 2019, there were 222 stockholders of record of our common stock.

Dividends

We have never declared nor paid any cash dividends to stockholders. We do not intend to pay cash dividends on our common stock for the foreseeable future, and currently intend to retain any future earnings to fund our operations and the development and growth of our business. The declaration of any future cash dividends, if any, would be at the discretion of our Board of Directors (subject to limitations imposed under applicable Delaware law) and would depend on our earnings, if any, our capital requirements and financial position, our general economic conditions and other pertinent conditions.

Issuer Purchases of Equity Securities

There were no repurchases of shares of common stock made during the year ended December 31, 2018.

Item 6. Selected Financial Data.

Not applicable.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations.

The following discussion and analysis of the financial condition and results of operations should be read together with our consolidated financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K for the year ending December 31, 2018. Some of the information contained in this discussion and analysis, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve significant 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. Please also refer to the section under the heading "Note Regarding Forward-Looking Statements."

Operating Overview

Aerpio Pharmaceuticals, Inc., (the "Company" or "Aerpio") is a biopharmaceutical company focused on advancing first-in-class treatments for ocular disease. Our lead product candidate, AKB-9778, a small molecule activator of the Tie2 pathway, is being developed for the treatment of non-proliferative diabetic retinopathy, or NPDR, a disease characterized by progressive compromise of blood vessels in the back of the eye. The Tie2 receptor is expressed almost exclusively in endothelial cells (cells that line the inside of blood vessels) and its activity is essential for maintaining vascular stability and preventing blood vessel compromise associated with diabetes. We have completed a Phase 2a trial of AKB-9778 in 144 patients with diabetic eye disease. Based on the results from this trial, we believe AKB-9778 has the potential to slow down or possibly reverse the damage to blood vessels caused by diabetes. In contrast to marketed treatments for NPDR that are administered by a physician via intraocular injection, we intend to deliver AKB-9778 systemically by self-administered subcutaneous injection, similar to insulin. We believe this delivery method provides an opportunity to treat diabetic eye disease at an earlier stage and reduces the likelihood of developing vision-threatening complications.

In June 2017, we initiated a 48-week, double-masked, Phase 2b clinical trial, which we refer to as TIME-2b, in patients with NPDR who have not developed more serious complications such as diabetic macular edema, or DME, or proliferative diabetic retinopathy, or PDR. The TIME-2b study is a double-masked, placebo-controlled multi-center trial that is currently on-going and has enrolled 167 patients randomized evenly to receive either AKB-9778 15 mg subcutaneously once daily, AKB-9778 15 mg subcutaneously twice daily or placebo for a 48-week treatment period. The primary endpoint of the TIME-2b study is the percentage of patients who improve by at least 2 steps in Diabetic Retinopathy Severity Score, or DRSS, in the study eye. We expect to report top line results of the Phase 2b clinical trial data in March 2019.

Compromise of Tie2 function is also implicated in other vascular complications of diabetes. We believe systemic treatment with AKB-9778 may address some of the most debilitating of these complications, including diabetic nephropathy. If we are successful in developing and commercializing AKB-9778 for NPDR, we may conduct clinical trials to evaluate AKB-9778's potential to reduce or delay the need for kidney dialysis. In post-hoc analysis of Aerpio's TIME-2b clinical trial, there was a 21% reduction (geometric mean) in urine albumin-to-creatinine ration (UACR) from baseline in the AKB-9778 treatment arms, but an overall increase in UACR in the placebo arm. The study provides clinical evidence of the potential beneficial effects of Tie2 activation in diabetic kidney disease.

In addition to diabetic vascular disease, existing preclinical and clinical evidence suggest the potential of AKB-9778 for reducing intraocular pressure in primary open angle glaucoma, or POAG, and ocular hypertension. We plan to initiate a Phase 1b clinical trial in the second quarter of 2019 to evaluate AKB-9778, administered via topical eye drops, and, if we observe positive results, we expect to initiate a Phase 2 program for this indication.

In June 2018, we licensed AKB-4924, a selective stabilizer of hypoxia-inducible factor-1 alpha, or HIF-1 alpha to Gossamer Bio, Inc., (Gossamer) ("Gossamer License") AKB-4924, renamed GB004, is being developed for the treatment of inflammatory bowel disease. HIF-1 alpha is involved in mucosal wound healing and the reduction of inflammation in the gastrointestinal tract. We have completed a single ascending dose clinical trial in healthy volunteers for GB004 and initiated a multiple ascending dose, or MAD study in the second quarter of 2018. Gossamer is currently conducting a multiple ascending dose study and is responsible for all remaining development and commercial activities for GB004.

ARP-1536, our humanized monoclonal antibody directed at the same target as AKB-9778, is in preclinical development. We are evaluating development options for ARP-1536, including subcutaneous injection for the treatment of diabetic vascular complications and intravitreal injection for the treatment of advanced diabetic eye disease such as DME or PDR.

Our operations to date have been limited to organizing and staffing our operations, business planning, raising capital, acquiring and developing our technology, identifying potential product candidates and undertaking preclinical and clinical studies. For the year ended December 31, 2018, we generated $20.2 million in revenue

related to the Gossamer License agreement and transition services provided to Gossamer. However, there can be no assurance of future revenues either from future payments related to the Gossamer License, transition services or from our product candidates. Our product candidates are subject to long development cycles, and there is no assurance we will be able to successfully develop, obtain regulatory approval for or market our product candidates. As of December 31, 2018, we had an accumulated deficit of $119.0 million and anticipate incurring additional losses for the next several years.

Our primary source of liquidity to date has been through public and private sales of our common stock, redeemable convertible preferred stock, convertible debt and the proceeds from the Gossamer License. We will need to raise additional funds to further advance our clinical research programs, commence additional clinical trials and commercialize our products, if approved. While we will continue to pursue financing alternatives, which may include equity financing, business development arrangements, licensing arrangements and business combination transactions, financing may not be available to us in the necessary time frame, in the amounts that we need, on terms that are acceptable to us or at all. If we are unable to raise the necessary funds when needed or reduce spending on currently planned activities, we may not be able to continue the development of our product candidates or we could be required to delay, scale back, or eliminate some or all of our development programs and other operations and will materially harm our business and consolidated financial position. We expect to continue to incur significant expenses and operating losses for the foreseeable future as a result of our ongoing activities.

We are subject to a number of risks similar to other life science companies in the current stage of our life cycle, including, but not limited to, the need to obtain adequate additional funding, possible failure of preclinical testing or clinical trials, competitors developing new technological innovations and protection of proprietary technology. If we do not successfully mitigate any of these risks, we will be unable to generate revenue or achieve profitability.

The Company's inability to obtain required funding in the near future could have a material adverse effect on its operations and strategic development plan for future growth. If the Company cannot successfully raise additional capital and implement its strategic development plan, its liquidity, financial condition and business prospects will be materially and adversely affected, and the Company may have to cease operations. Based on the Company's current cash and cash equivalents of $62.6 million at December 31, 2018 and financial condition as of this Annual Report on Form 10-K, we believe our existing cash and cash equivalent will be sufficient to fund currently planned operations at least into the second quarter of 2020.

Other Recent Developments

Listing on the Nasdaq Capital Market

Shares of our common stock were up-listed from OTC Markets – OTCQB Tier to Nasdaq Capital Markets and began trading on June 26, 2018.

Basis of Presentation

The following discussion highlights Aerpio's results of operations and the principal factors that have affected our financial condition as well as our liquidity and capital resources for the periods described and provides information management believes is relevant for an assessment and understanding of the consolidated balance sheets and the consolidated statements of operations and comprehensive loss presented herein. The following discussion and analysis are based on the Company's consolidated financial statements contained in this Annual Report on Form 10-K, which we have prepared in accordance with U.S. generally accepted accounting principles. You should read the discussion and analysis together with such consolidated financial statements and the related notes thereto.

Components of Consolidated Statements of Operations and Comprehensive Loss

License Revenue, and Other

License revenue, and other consists of the upfront payment received upon execution of the Gossamer License agreement during the second quarter of 2018 and certain transition services provided to Gossamer as part of the Gossamer License.

For the foreseeable future, we expect substantially all of our revenue will be generated from the Gossamer License and any other collaborations into which we may enter.

Research and Development Expenses

Research and development expenses consist primarily of

- personnel-related expenses, including salaries, benefits, travel and stock-based compensation expense of our research and development personnel;
- expenses incurred under agreements with Contract Research Organizations, or CRO's and investigative sites that conduct our clinical studies;
- the cost of acquiring, developing and manufacturing clinical study materials; and
- costs associated with preclinical, clinical and regulatory activities.

Research and development costs are expensed as incurred. Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and clinical sites.

As we continue to invest in basic research and clinical development of our product candidates, we expect research and development expenses to increase in absolute dollars.

General and Administrative Expenses

General and administrative expenses consist primarily of compensation and related costs for finance, human resources and other administrative personnel, including stock-based compensation expense, employee benefits and travel. In addition, general and administrative expenses include third-party consulting, legal, patent, audit, accounting services and facilities costs. We expect general and administrative expenses will continue to increase in conjunction with the growth of our business.

Grant Income

Grant income is recognized as earned based on contract work performed.

Interest Income (Expense), net

Interest income consists primarily of interest received on cash and cash equivalents. Interest expense consists primarily of interest and amortization of debt issuance costs related to our secured convertible promissory notes. The secured convertible notes converted into shares of our common stock in connection with the financing activities which took place during 2017.

Results of Consolidated Operations

The following tables set forth our results of operations:

	Years Ended December 31,	
	2018	**2017**
License revenue, and other	**$ 20,157,430**	$ —
Operating expenses		
Research and development	**17,852,756**	12,147,132
General and administrative	**13,485,918**	9,241,411
Total operating expenses	**31,338,674**	21,388,543
Loss from operations	**(11,181,244)**	(21,388,543)
Grant income	**6,394**	93,719
Interest income (expense), net	**778,215**	(105,782)
Total other income (expense)	**784,609**	(12,063)
Net and comprehensive loss	**$ (10,396,635)**	$ (21,400,606)

Comparison of Years Ended December 31, 2018 and 2017

License Revenue, and Other

License revenue, and other consists of the $20.0 million upfront payment received upon execution of the Gossamer License during the second quarter of 2018 and certain transition services provided to Gossamer as part of the Gossamer License.

Operating Expenses

The following table sets forth our operating expenses:

	Years Ended December 31,	
	2018	2017
Operating expenses:		
Research and development	$ 17,852,756	$ 12,147,132
General and administrative	13,485,918	9,241,411
Total operating expenses	$ 31,338,674	$ 21,388,543

Research and Development

Research and development expenses for the year ended December 31, 2018, increased $5.7 million, or 47.0%, compared to the year ended December 31, 2017. This increase is primarily attributed to twelve-months of ongoing research activity related to AKB-9778, specifically, the TIME-2b clinical trial initiated in the second quarter of 2017 which makes up the majority of the spend in 2018.

General and Administrative

General and administrative expenses for the year ended December 31, 2018, increased $4.2 million, or 45.9%, compared to the year ended December 31, 2017. This increase was primarily attributable to an increase in stock-based compensation of $2.8 million related to stock-based awards granted in 2017 and during 2018, and personnel-related expenses of $1.4 million for salaries and related benefits for new employees, offset by a reduction of $1.0 million in legal and other expenses.

Other Income (Expense), net

The following table sets forth our other income (expense), net:

	Years Ended December 31,	
	2018	2017
Grant income	$ 6,394	$ 93,719
Interest income (expense), net	778,215	(105,782)
Total other income (expense)	$ 784,609	$ (12,063)

Grant Income

Grant income is recognized as earned based on contract work performed. Grant income amounts can vary greatly from period to period depending on the funding and work performed. Grant income decreased in year ended December 31, 2018 compared to year ended December 31, 2017 primarily due to the expiration of various grants during 2018.

Interest Income (Expense), net

Interest income for the year ended December 31, 2018, reflects interest earned on short term money market instruments (cash equivalents). Interest expense for the year ended December 31, 2017 was primarily related to the senior secured convertible notes issued in fiscal 2016, totaling an aggregate principal amount of $12.5 million, and one note financing in the first quarter of fiscal 2017, totaling an aggregate principal amount of $0.3 million (collectively "the Notes"), offset in part by interest earned on invested cash balances related to net proceeds of issuance of common stock of $37.2 million. The Notes accrued interest at the rate of eight percent (8%) annum, compounded annually. The principal and accrued interest on the secured convertible notes were converted into common stock on March 15, 2017, in connection with the financing activities which took place during 2017.

Liquidity and Capital Resources

Since inception, we have incurred significant net losses and negative cash flows from operations. For the years ended December 31, 2018 and 2017, we had net losses of $10.4 million and $21.4 million, respectively. At December 31, 2018 and 2017, we had an accumulated deficit of $119.0 million and $108.6 million, respectively.

In February 2018, we filed a shelf registration statement on Form S-3 with the Securities and Exchange Commission (SEC) which was declared effective by the SEC on April 11, 2018 (the "Form S-3"). The shelf registration statement allows us to sell from time-to-time up to $150.0 million of common stock, preferred stock, debt securities, warrants, or units comprised of any combination of these securities, for our own account in one or more offerings. The shelf registration statement is intended to provide us flexibility to conduct registered sales of our securities, subject to market conditions and our future capital needs. The terms of any offering under the shelf registration statement will be established at the time of such offering and will be described in a prospectus supplement filed with the SEC prior to the completion of any such offering.

Additionally, on February 21, 2018, and pursuant to the Form S-3, we entered into a Controlled Equity Offering Sales Agreement (the "Sales Agreement") with Cantor Fitzgerald & Co. ("Cantor"), pursuant to which we may issue and sell, from time to time, shares of our common stock having an aggregate offering price of up to $75.0 million through Cantor as our sales agent. Cantor may sell our common stock by any method permitted by law deemed to be an "at the market offering" as defined in Rule 415(a)(4) of the Securities Act, including sales made directly on or through the Nasdaq Capital Market or any other existing trade market for our common stock, in negotiated transactions at market prices prevailing at the time of sale or at prices related to prevailing market prices, or any other method permitted by law. The shares of our common stock to be sold under the Sales Agreement will be sold and issued pursuant to the Form S-3 and the related prospectus and one or more prospectus supplements. We will pay Cantor 3.0% of the aggregate gross proceeds from each sale of shares of common stock under the Sales Agreement. As of December 31, 2018, no shares of common stock had been sold under this Sales Agreement.

On June 28, 2018, we closed an underwritten public offering, pursuant to the S-3 filed in February 2018, for the sale of 11,688,000 shares of our common stock and subsequently, on July 2, 2018, we closed on the sale of an additional 1,720,200 shares of our common stock, pursuant to the underwriters' partial exercise of their option to purchase additional shares of common stock (collectively, the "2018 Offering"). In the aggregate, we received net proceeds of approximately $48.1 million from the 2018 Offering after deducting underwriting discounts and commissions and offering expenses. In June 2018, we received $20.0 million of cash in connection with the Gossamer License.

At December 31, 2018, we had cash and cash equivalents of $62.6 million. To date, we have financed our operations principally through public and private sales of our common stock, redeemable convertible preferred stock, convertible debt and proceeds from the Gossamer License. Based on our current plans, we expect that our existing cash and cash equivalents, will enable us to conduct our planned operations at least into the second quarter of 2020.

The following table summarizes our cash flows:

	Year Ended December 31,	
	2018	**2017**
Net cash used in operating activities	**$ (5,808,046)**	$ (18,883,535)
Net cash (used in) provided by investing activities	**(37,912)**	41,104
Net cash provided by financing activities	**48,195,859**	37,496,846
Net increase in cash and cash equivalents	**$ 42,349,901**	$ 18,654,415

Operating Activities

We have historically experienced negative cash flows as we developed AKB-9778, ARP-1536 and AKB-4924. Our net cash used in operating activities primarily resulted from our net loss adjusted for non-cash expenses and changes in working capital components. Our cash flows from operating activities will continue to be affected by increased spending to advance and support our remaining product candidates and other operating and general administrative activities.

For the year ended December 31, 2018, operating activities used $5.8 million in cash primarily as a result of a net loss of $10.4 million offset by $1.1 million in working capital and $3.5 million in non-cash expenses related to stock-based compensation and depreciation expense. Net cash used in operating activities for the year ended December 31, 2018 includes $20.0 million of revenue earned from the Gossamer License. We do not expect revenue will reoccur until milestones outlined in the Gossamer License are achieved.

For the year ended December 31, 2017, operating activities used $18.9 million in cash primarily as a result of a net loss of $21.4 million offset by $1.5 million in working capital and $1.0 million of non-cash expenses, consisting of

stock-based compensation expense, non-cash interest expense, amortization of debt issuance costs and depreciation expense.

Investing Activities

Net cash used in investing activities for the year ended December 31, 2018 was related to capital expenditures to support operations. Cash provided by investing activities for the year ended December 31, 2017 was due to the sale of short-term investments, partially offset by capital expenditures to support our operations.

Financing Activities

For the year ended December 31, 2018, we received $48.1 million net proceeds from the 2018 Offering and $0.08 million from the exercise of stock options.

For the year ended December 31, 2017, we received net proceeds of $37.2 million from the sale of common stock in our March 2017 private placement offering, $0.04 million from the exercise of stock options and $0.3 million from an extension to the Aerpio senior secured convertible notes. The outstanding principal and accrued interest under the secured convertible notes were converted into shares of Aerpio common stock immediately prior to the effective time of the Merger and exchanged for shares of our common stock pursuant to the Merger.

Contractual Obligations and Commitments

In July 2018, the Company renewed its lease for 7,580 square feet of office space in Cincinnati, Ohio which includes one month of free rent, escalating rent payments and expires in July 2021. Beginning in December 2018, the Company entered a lease for 4,000 square feet of office space in Lexington, Massachusetts which expires in December 2021. The Company also leases 687 square feet of space in Dexter, Michigan which expires in October 2019. Total rent expense for all operating leases was $0.2 million for both the years ended December 31, 2018 and 2017

The Company contracts with various organizations to conduct research and development activities, including clinical trial organizations to manage clinical trial activities. The scope of the services under these research and development contracts can be modified and the contracts cancelled by the Company upon written notice. In the event of a cancellation, the Company would be liable for the cost and expenses incurred to date as well as any close out costs of the service arrangement.

Off-Balance Sheet Arrangements

As of December 31, 2018 and 2017, we did not have any off-balance sheet arrangements as defined by applicable SEC regulations.

US Tax Reform

On December 22, 2017, The Tax Cuts and Jobs Act (the "2017 Tax Act") was enacted, which is generally effective January 1, 2018. The Act includes a number of provisions, including lowering the U.S. corporate federal income tax rate from a maximum of 35% to 21% and changing or limiting certain tax deductions. In addition, the 2017 Tax Act alters the landscape of taxation and provides immediate deductions for certain new investments, among other provisions.

The Company expects its effective income tax rate to remain at 0% for the foreseeable future as a result of the full recognition of a valuation allowance. Such estimates are based on management's current assumptions with respect to, among other things, the Company's earnings, state income tax levels and tax deductions. The Company completed its determination of the accounting implications of the 2017 Tax Act during 2018, and there was no material impact to the Company's provision for income taxes during 2018.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of financial position and results of consolidated operations are based on consolidated financial statements prepared in accordance with U.S. generally accepted accounting principles. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets, liabilities, expenses and related disclosures. On an ongoing basis, we evaluate our estimates and judgments, including those related to prepaid and accrued research and development expenses, revenue recognition and stock-based compensation. We base our estimates on historical experience, known trends and events, and various other factors that are believed to be reasonable under the circumstances, the results of which

form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

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 to be most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Revenue Recognition

At the inception of an arrangement, the Company evaluates if a counterparty to a contract is a customer, if the arrangement is within the scope of revenue from contracts with customers guidance and the term of the contract. The Company recognizes revenue when its customer obtains control of promised goods or services in a contract for an amount that reflects the consideration the Company expects to receive in exchange for those goods or services. For contracts with customers, the Company applies the following five-step model in order to determine this amount: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations, including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) the Company satisfies each performance obligation. The Company only applies the five-step model to contracts when it is probable that the entity will collect the consideration it is entitled to in exchange for the goods or services it transfers to the customer. As part of the accounting for contracts with customers, the Company must develop assumptions that require judgment to determine the standalone selling price of each performance obligation identified in the contract. The Company then allocates the total transaction price to each performance obligation based on the estimated standalone selling prices of each performance obligation. The Company recognizes the amount of the transaction price as revenue that is allocated to the respective performance obligation when the performance obligation is satisfied or as it is satisfied.

The Company enters into collaboration arrangements, under which it licenses certain rights to its intellectual property to third parties. The terms of these agreements may include payment to the Company of one or more of the following: nonrefundable upfront license fees; development, sale and commercial milestone payments and royalties on net sales of licensed products. Each of these types of payments are classified as license revenue except for revenue from royalties on net sales of licensed products, which are classified as royalty revenue.

For each collaboration agreement that results in revenues, the Company identifies all material promised goods and services, which may include a license to intellectual property, research and development activities and/or transition activities. Promised goods or services are considered to be separate performance obligations if they are distinct. In order to determine the transaction price to be allocated to each performance obligation, in addition to any upfront payment, the Company estimates the amount of variable consideration at the outset of the contract either utilizing the expected value or most likely amount method, depending on the facts and circumstances relative to the contract. The Company constrains (reduces) the estimates of variable consideration such that it is probable that a significant reversal of previously recognized revenue will not occur throughout the life of the contract. When determining if variable consideration should be constrained, management considers whether there are factors outside the Company's control that could result in a significant reversal of revenue. In making these assessments, the Company considers the likelihood and magnitude of a potential reversal of revenue. These estimates are re-assessed each reporting period as required.

Once the estimated transaction price is established, amounts are allocated to the performance obligations that have been identified. The transaction price is generally allocated to each separate performance obligation on a relative standalone selling price basis. The Company must develop assumptions that require judgment to determine the standalone selling price (SSP) in order to account for these agreements. To determine the standalone selling price the Company's assumptions may include (i) assumptions regarding the probability of obtaining marketing approval for the drug candidate; (ii) estimates regarding the timing of and the expected costs to develop and commercialize the drug candidate; (iii) estimates of future cash flows from potential product sales with respect to the drug candidate; and (iv) appropriate discount and tax rates. Standalone selling prices used to perform the initial allocation are not updated after contract inception. The Company does not include a financing component to its estimated transaction price at contract inception unless it estimates that certain performance obligations will not be satisfied within one year.

Upfront License Fees: If a license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenues from nonrefundable, upfront license fees based on the relative value prescribed to the license compared to the total value of the arrangement. The revenue is recognized when the license is transferred to the collaborator and the collaborator is able to use and benefit from the license. For licenses that are not distinct from other obligations identified in the arrangement, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time. If the combined performance obligation is satisfied over time, the Company applies an appropriate method of measuring progress for purposes of recognizing revenue from nonrefundable, upfront license fees. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Development Milestone Payments: Depending on facts and circumstances, the Company may conclude it is appropriate to include the milestone in the estimated transaction price using the most likely amount method or it is appropriate to fully constrain the milestone. A milestone payment is included in the transaction price in the reporting period the Company concludes that it is probable that recording revenue in the period will not result in a significant reversal in amounts recognized in future periods. The Company may record revenues from certain milestones in a reporting period before the milestone is achieved if the Company concludes that achievement of the milestone is probable and that recognition of revenue related to the milestone will not result in a significant reversal in amounts recognized in future periods. The Company records a corresponding contract asset when this conclusion is reached. Milestone payments that have not been included in the transaction price to date are fully constrained. These milestones remain fully constrained until the Company concludes that achievement of the milestone is probable and recognition of revenue related to the milestone will not result in a significant reversal in amounts recognized in future periods. The Company re-evaluates the probability of achievement of such development milestones and any related constraint each reporting period. The Company adjusts its estimate of the overall transaction price, including the amount of collaborative revenue that it has recorded, if necessary.

Sales-based Milestone and Royalty Payments: The Company's collaborators may be required to pay the Company sales-based milestone payments or royalties on future sales of commercial products. The Company recognizes revenues related to sales-based milestone and royalty payments upon the later to occur of (i) achievement of the collaborator's underlying sales or (ii) satisfaction of any performance obligation(s) related to these sales, in each case assuming the license to the Company's intellectual property is deemed to be the predominant item to which the sales-based milestones and/or royalties relate.

Prepaid and Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our prepaid and accrued research and development expenses. This process involves reviewing open contracts and purchase orders, 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 service 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. We make estimates of our prepaid and accrued research and development expenses as of each consolidated balance sheet date in our consolidated financial statements based on facts and circumstances known to us at the time. We confirm the accuracy of estimates with the service providers and make adjustments if necessary. Examples of estimated prepaid and accrued research and development expenses include expenses for:

- CROs in connection with clinical studies;
- Investigative sites in connection with clinical studies;
- Vendors in connection with preclinical development activities; and
- Vendors related to product manufacturing, development and distribution of clinical materials.

We base our expenses related to clinical studies on our estimates of the services received and efforts expended pursuant to contracts with multiple CROs that conduct and manage clinical studies on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. The scope of services under these contracts can be modified and some of the agreements may be cancelled by either party upon written notice. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of subjects and the completion of clinical study milestones. 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 prepaid accordingly.

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

Stock-Based Compensation

We issue stock-based awards generally in the form of stock options and restricted stock. We account for our stock-based compensation awards in accordance with FASB ASC Topic 718, *Compensation—Stock Compensation*, or ASC 718. ASC 718 requires all stock-based payments to employees, including grants of employee stock options and restricted stock and modifications to existing stock awards to be recognized in the consolidated statements of operations and comprehensive loss based on their fair values. Described below is the methodology we have utilized in measuring stock-based compensation expense.

We estimate the fair value of our options to purchase shares of common stock to employees using the Black-Scholes option pricing model, which requires the input of highly subjective assumptions, including (a) the expected stock price volatility, (b) the calculation of 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 trading of our common stock and a lack of company-specific historical and implied volatility data, we have based our estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. The historical volatility is calculated based on a period of time commensurate with the expected term assumption. The computation of expected volatility is based on the historical volatility of a representative group of companies with similar characteristics to our company, including stage of product development and life science industry focus. We are a development stage company in an early stage of product development with no revenues and the representative group of companies has certain similar characteristics. We believe the group selected has sufficient similar economic and industry characteristics and includes companies that are most representative of our company. 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 and non-employees as we do 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 we do not expect substantially different exercise or post-vesting termination behavior among our employee population. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected life 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, similar to our peer group. The grant date fair value of restricted stock award grants is based on the estimated value of our common stock at the date of grant.

Our stock-based awards are subject to service-based vesting conditions. Compensation expense related to awards to employees with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award. Awards to non-employees are adjusted through share-based compensation expense as the award vests to reflect the current fair value of such awards and are expensed using an accelerated attribution model.

For the years ended December 31, 2018 and 2017, stock-based compensation expense was $3.4 million and $0.6 million, respectively. As of December 31, 2018, we had $3.9 million of total unrecognized stock-based compensation costs for stock options, which we expect to recognize over a weighted-average period of 2.55 years.

JOBS Act Accounting Election

We are an "emerging growth company" within the meaning of the JOBS Act. Section 107 of the JOBS Act provides that an emerging growth company can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act of 1933 for complying with new or revised accounting standards. Thus, an emerging growth company can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this extended transition period and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other public companies that are not emerging growth companies.

Recent Accounting Pronouncements

See Note 2 to the consolidated financial statements for a discussion of recent accounting pronouncements.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

Interest Rate Risk

The Company's cash and cash equivalents at December 31, 2018 consist of all cash on hand, deposits and funds invested in short-term investments with original maturities of three months or less at the time of purchase and earn interest income. Therefore, there was minimal or no interest rate risk.

Item 8. Consolidated Financial Statements and Supplementary Data.

Beginning on page 73 are the consolidated financial statements with applicable notes and the related Report of Independent Registered Public Accounting Firm.

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Aerpio Pharmaceuticals, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Aerpio Pharmaceuticals, Inc. (the Company) as of December 31, 2018 and 2017, and the related consolidated statements of operations and comprehensive loss, redeemable convertible preferred stock and stockholders' equity (deficit) and cash flows for each of the two 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 two 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 2011

Cincinnati, Ohio

March 7, 2019

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

AERPIO PHARMACEUTICALS, INC.

Consolidated Balance Sheets

	Year Ended December 31, 2018	2017
Assets		
Current assets:		
Cash and cash equivalents	**$ 62,614,010**	$ 20,264,109
Prepaid research and development contracts	**754,392**	313,140
Other current assets	**615,681**	322,221
Total current assets	**63,984,083**	20,899,470
Furniture and equipment, net	**98,449**	107,223
Deposits	**40,960**	20,960
Total assets	**$ 64,123,492**	$ 21,027,653
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable and accrued expenses	**$ 5,456,917**	$ 3,592,164
Total current liabilities	**5,456,917**	3,592,164
Commitments and contingencies (Note 11)		
Stockholders' equity:		
Common stock, $0.0001 par value per share; 300,000,000 shares authorized and 40,588,004 and 27,070,038 shares issued and outstanding at December 31, 2018 and 2017, respectively.	**4,059**	2,707
Additional paid-in capital	**177,621,807**	125,995,438
Accumulated deficit	**(118,959,291)**	(108,562,656)
Total stockholders' equity	**58,666,575**	17,435,489
Total liabilities and stockholders' equity	**$ 64,123,492**	$ 21,027,653

The accompanying notes are an integral part of these consolidated financial statements.

AERPIO PHARMACEUTICALS, INC.

Consolidated Statements of Operations and Comprehensive Loss

	Year Ended December 31,	
	2018	**2017**
License revenue, and other	**$ 20,157,430**	$ —
Operating expenses		
Research and development	**17,852,756**	12,147,132
General and administrative	**13,485,918**	9,241,411
Total operating expenses	**31,338,674**	21,388,543
Loss from operations	**(11,181,244)**	(21,388,543)
Grant income	**6,394**	93,719
Interest income (expense), net	**778,215**	(105,782)
Total other income (expense)	**784,609**	(12,063)
Net and comprehensive loss	**$ (10,396,635)**	$ (21,400,606)
Reconciliation of net loss attributable to common stockholders:		
Net and comprehensive loss	**$ (10,396,635)**	$ (21,400,606)
Adjustment of redeemable convertible preferred stock to redemption value	**—**	(943,297)
Net loss attributable to common stockholders	**$ (10,396,635)**	$ (22,343,903)
Net loss per share attributable to common stockholders, basic and diluted	**$ (0.31)**	$ (1.03)
Weighted average number of common shares used in computing net loss per share attributable to common stockholders, basic and diluted	**33,930,846**	21,673,349

The accompanying notes are an integral part of these consolidated financial statements.

AERPIO PHARMACEUTICALS, INC.

Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)

	Redeemable Convertible Preferred Stock		Stockholders' Equity (Deficit)				
			Common Stock		Additional Paid-In	Accumulated	
	Shares	Total	Shares	Par Value	Capital	Deficit	Total
Balance at December 31, 2016	14,015,016	$ 73,757,890	1,240,925	$ 124	—	$ (86,218,753)	$ (86,218,629)
Adjustment of redeemable convertible preferred stock to redemption value	—	943,297	—	—	—	(943,297)	(943,297)
Conversion of redeemable convertible preferred stock	(14,015,016)	(74,701,187)	14,015,016	1,402	74,699,785	—	74,701,187
Conversion of convertible notes and accrued interest			2,744,059	274	13,447,660	—	13,447,934
Share exchange in connection with Merger	—	—	1,000,000	100	(100)	—	—
Issuance of common stock, net of issuance costs of $3,084,385	—	—	8,049,555	805	37,162,585	—	37,163,390
Issuance of common stock upon exercise of stock options	—	—	25,729	3	36,098	—	36,101
Forfeiture of restricted stock	—	—	(5,246)	(1)	1	—	—
Share-based compensation expense	—	—	—	—	649,409	—	649,409
Net and comprehensive loss	—	—	—	—	—	(21,400,606)	(21,400,606)
Balance at December 31, 2017	—	$ -	27,070,038	2,707	$ 125,995,438	$ (108,562,656)	$ 17,435,489
Issuance of restricted stock	—		**60,000**	**6**	**(6)**	—	—
Issuance of common stock upon exercise of stock options	—	—	**52,099**	**5**	**76,827**	—	**76,832**
Issuance of common stock, net of issuance costs of $3,502,543	—	—	**13,408,200**	**1,341**	**48,117,686**	—	**48,119,027**
Forfeiture of restricted stock	—	—	**(2,333)**	—	—	—	—
Share-based compensation expense	—	—	—	—	**3,431,862**	—	**3,431,862**
Net and comprehensive loss	—	—	—	—	—	**(10,396,635)**	**(10,396,635)**
Balance at December 31, 2018	—	**$** —	**40,588,004**	**$ 4,059**	**$ 177,621,807**	**$ (118,959,291)**	**$ 58,666,575**

The accompanying notes are an integral part of these consolidated financial statements.

AERPIO PHARMACEUTICALS, INC.

Consolidated Statements of Cash Flows

	Year Ended December 31, 2018	2017
Operating activities:		
Net and comprehensive loss	**$ (10,396,635)**	$ (21,400,606)
Adjustments to reconcile net and comprehensive loss to net cash used in operating activities:		
Depreciation	**46,686**	51,268
Stock-based compensation	**3,431,862**	649,409
Amortization of debt issuance costs	**—**	75,561
Interest expense related to convertible note conversion	**—**	204,929
Changes in operating assets and liabilities:		
Prepaid research and development contracts	**(441,252)**	40,294
Other current assets	**(293,460)**	(109,026)
Deposits	**(20,000)**	—
Accounts payable and accrued expenses	**1,864,753**	1,604,636
Net cash used in operating activities	**(5,808,046)**	(18,883,535)
Investing activities:		
Purchase of furniture and equipment	**(37,912)**	(8,896)
Proceeds from maturities of short-term investments	**—**	50,000
Net cash (used in) provided by investing activities	**(37,912)**	41,104
Financing activities:		
Proceeds from exercise of stock options	**76,832**	36,100
Proceeds from issuances of convertible notes	**—**	297,354
Proceeds from sale of common stock	**51,621,570**	40,247,777
Cash paid in connection with the sale of common stock	**(3,502,543)**	(3,084,385)
Net cash provided by financing activities	**48,195,859**	37,496,846
Net increase in cash and cash equivalents	**42,349,901**	18,654,415
Cash and cash equivalents at beginning of year	**20,264,109**	1,609,694
Cash and cash equivalents, at end of year	**$ 62,614,010**	$ 20,264,109
Non-cash financing activities		
Conversion of redeemable convertible preferred stock into common stock	**—**	$ 74,701,187
Conversion of convertible notes and accrued interest into common stock	**—**	13,447,934
Accretion of redeemable convertible preferred stock to redemption value	**—**	943,297

The accompanying notes are an integral part of these consolidated financial statements.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Nature of Organization and Operations

Aerpio Pharmaceuticals, Inc. (the "Company") incorporated as Zeta Acquisition Corp. II ("Zeta") in the State of Delaware on November 16, 2007. Prior to the Merger, (as defined below), Zeta was a "shell company" (as defined in Rule 12b-2 of the Securities Exchange Act of 1934, as amended).

On March 3, 2017, the Company's Board of Directors, and on March 10, 2017, the Company's pre-Merger (as defined below) stockholders, approved an amended and restated certificate of incorporation, which, among other things, increased authorized capital stock from 100,000,000 shares of common stock, par value $0.0001 per share, and 10,000,000 shares of preferred stock, par value $0.0001 per share, to 300,000,000 shares of common stock, par value $0.0001 per share, and 10,000,000 shares of preferred stock, par value $0.0001 per share.

On March 15, 2017, Zeta changed its name to Aerpio Pharmaceuticals, Inc. and its wholly-owned subsidiary, Aerpio Acquisition Corp., a corporation formed in the State of Delaware on March 3, 2017, merged with and into Aerpio Therapeutics, Inc., ("Aerpio"), (the "Merger"), a corporation incorporated on November 17, 2011 in the State of Delaware. Pursuant to the Merger, Aerpio remained as the surviving corporation and became the Company's wholly-owned subsidiary.

At the effective time of the Merger, the shares of the Aerpio's (i) common stock issued and outstanding immediately prior to the closing of the Merger (including restricted common stock, whether vested or unvested, issued under the Aerpio's 2011 Equity Incentive Plan), and (ii) redeemable convertible preferred stock issued and outstanding immediately prior to the closing of the Merger, were converted into shares of the Company's common stock. In addition, immediately prior to the Merger, the outstanding amounts under certain senior secured convertible notes issued by Aerpio to its pre-Merger noteholders were converted into shares of Aerpio's preferred stock, which were then converted to shares of Aerpio's common stock and subsequently were converted into shares of the Company's common stock, together with the other shares of Aerpio's common stock described above. In addition, pursuant to the Merger Agreement options to purchase shares of Aerpio's common stock issued and outstanding immediately prior to the closing of the Merger were assumed and converted into options to purchase shares of the Company's common stock. All the outstanding capital stock of Aerpio was converted into shares of the Company's common stock on a 2.3336572:1 basis.

As a result of the Merger, the Company acquired the business of Aerpio and has continued the existing business operations of Aerpio as a public reporting company under the name Aerpio Pharmaceuticals, Inc. Immediately after the Merger, on March 15, 2017, Aerpio converted into a Delaware limited liability company (the "Conversion").

Immediately following the Conversion, the pre-Merger stockholders of Zeta surrendered for cancellation 4,000,000 of the 5,000,000 shares of the outstanding common stock of Zeta, (the "Share Cancellation"). Following the Share Cancellation, on March 15, 2017, the Company closed a private placement offering (the "2017 Offering") of 8,049,555 shares of the Company's common stock, at a purchase price of $5.00 per share, for net proceeds of $37.2 million and the issuance of warrants with a term of three years, to purchase 317,562 shares of the Company's common stock at an exercise price of $5.00 per share.

The Merger was treated as a recapitalization and reverse acquisition for financial reporting purposes. The Company is the legal acquirer of Aerpio in the transaction. However, Aerpio is considered the acquiring company for accounting purposes since (i) former Aerpio stockholders owned in excess of 50% of the combined enterprise on a fully diluted basis immediately following the Merger and 2017 Offering, and (ii) all members of the Company's executive management and Board of Directors were from Aerpio. In accordance with "reverse merger" or "reverse acquisition" accounting treatment, the consolidated financial statements for the years ended December 31, 2018 and 2017 include the accounts of the Company and its wholly owned subsidiary, Aerpio Therapeutics, LLC.

On June 28, 2018, the Company closed an underwritten public offering for the sale of 11,688,000 shares of its common stock, and subsequently on July 2, 2018, the Company closed on the sale of an additional 1,720,200 shares of its common stock, pursuant to the underwriters' partial exercise of their option to purchase additional shares of common stock (the "2018 Offering"). In the aggregate, the Company received net proceeds of $48.1 million from the 2018 Offering after a deduction of $3.5 million related to underwriting discounts and commissions and offering expenses paid in conjunction with the 2018 Offering.

The Company is a biopharmaceutical company focused on advancing first-in-class treatments for ocular disease. The Company's lead product candidate, AKB-9778, a small molecule activator of the Tie2 pathway, is being developed for the treatment of non-proliferative diabetic retinopathy ("NPDR"). Tie2 signaling is essential for regulating blood vessel development and the stability of mature vessels. The Company has completed a Phase 2a

clinical trial in diabetic macular edema ("DME"), a swelling of the retina that is a common cause of vision loss in patients with DR and during the second quarter of 2017, initiated a double-blind Phase 2b clinical trial in patients with DR who have not developed more serious complications such as DME or proliferative diabetic retinopathy.

In addition, the Company has a pipeline program, ARP-1536, a humanized monoclonal antibody drug candidate for ocular disease. Humanized antibodies are antibodies from non-human species whose protein sequences have been modified to increase their similarity to antibodies produced naturally in humans. The Company is currently in preclinical development for ARP-1536.

The Company's operations to date have been limited to organizing and staffing the Company, business planning, raising capital, acquiring and developing its technology, identifying potential product candidates and undertaking preclinical and clinical studies. The Company's revenue has been primarily limited to license revenue from Gossamer Bio. Inc., ("Gossamer") pursuant to a license agreement ("Gossamer License"). Future revenue is dependent on the terms of the Gossamer License. The Company's product candidates are subject to long development cycles and there is no assurance the Company will be able to successfully develop, obtain regulatory approval for, or market its product candidates.

The Company is subject to a number of risks similar to other life science companies in the current stage of its life cycle including, but not limited to, the need to obtain adequate additional funding, possible failure of preclinical testing or clinical trials, the need to obtain marketing approval for its product candidates, competitors developing new technological innovations, the need to successfully commercialize and gain market acceptance of any of the Company's products that are approved, and protection of proprietary technology. If the Company does not successfully commercialize any of its products or mitigate any of these other risks, it will be unable to generate revenue or achieve profitability.

The Company incurred losses from operations and had a negative cash flows from operating activities for the years ended December 31, 2018 and 2017 (and since inception). The Company's current operating plan indicates that it will continue to incur losses from operations and generate negative cash flows from operating activities given ongoing expenditures related to the completion of its ongoing clinical trials and the Company's lack of product revenue generating activities. However, the Company believes it has the ability to control its current operating plan and that existing cash and cash equivalents of approximately $62.6 million at December 31, 2018 will be sufficient to allow the Company to fund its current operating plan into at least the second quarter of 2020, and as a result, through at least twelve months from the filing of the Company's 2018 Annual Report on Form 10-K.

There can be no assurance, however, that the current operating plan will be achieved in the time frame anticipated by the Company, or that its cash resources will fund the Company's operating plan for the period anticipated by the Company or that additional funding will be available on terms acceptable to the Company, or at all. The Company will need to raise additional funds in order to further advance its clinical research programs, commence additional clinical trials, and operate its business and meet its obligations as they come due. The Company is pursuing financing alternatives, which include permanent equity financing, business development arrangements, and licensing arrangements. However, financing may not be available to the Company in the necessary time frame, in amounts that the Company requires, on terms that are acceptable to the Company, or at all. If the Company raises additional funds through collaboration, licensing or other similar arrangements, it may be necessary to relinquish valuable rights to its potential products or proprietary technologies or grant licenses on terms that are not favorable to the Company. If the Company is unable to raise the necessary funds when needed or reduce spending on currently planned activities, it may not be able to continue the development of its product candidates or the Company could be required to delay, scale back, or eliminate some or all of its development programs and other operations and will materially harm its business, financial position and results of operations.

2. Summary of Significant Accounting Policies

Basis of Presentation

The consolidated financial statements have been prepared in conformity with U.S. generally accepted accounting principles (U.S. GAAP). Any reference in these notes to applicable guidance is meant to refer to the authoritative U.S. GAAP as found in the Accounting Standards Codification (ASC) and Accounting Standards Update (ASU) of the Financial Accounting Standards Board (FASB).

The Company's consolidated financial statements are prepared in accordance with U.S. GAAP and stated in U.S. dollars.

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, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business in one operating segment, which is the business of developing and commercializing proprietary therapeutics. All the assets and operations of the Company are located in the U.S.

Use of Estimates

The preparation of consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenue and expenses during the reporting period. Actual results may differ from those estimates. Management considers many factors in selecting appropriate financial accounting policies and controls, and in developing the estimates and assumptions that are used in the preparation of these consolidated financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, including: expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes, and management must select an amount that falls within that range of reasonable estimates. Estimates are used in the following areas, among others: prepaid and accrued research and development expense, stock-based compensation expense, revenue recognition and income taxes.

Cash and Cash Equivalents

Cash and cash equivalents consist of all cash on hand, certificates of deposits, and funds invested in available for sale securities with original maturities of three months or less at the time of purchase. At December 31, 2018 and 2017, the Company's cash equivalents are primarily in money market funds. The Company has maintained balances with its banks in excess of federally insured limits.

Revenue Recognition

At the inception of an arrangement, the Company evaluates if a counterparty to a contract is a customer, if the arrangement is within the scope of revenue from contracts with customers guidance and the term of the contract. The Company recognizes revenue when its customer obtains control of promised goods or services in a contract for an amount that reflects the consideration the Company expects to receive in exchange for those goods or services. For contracts with customers, the Company applies the following five-step model in order to determine this amount: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations, including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) the Company satisfies each performance obligation. The Company only applies the five-step model to contracts when it is probable that the entity will collect the consideration it is entitled to in exchange for the goods or services it transfers to the customer. As part of the accounting for contracts with customers, the Company must develop assumptions that require judgment to determine the standalone selling price of each performance obligation identified in the contract. The Company then allocates the total transaction price to each performance obligation based on the estimated standalone selling prices of each performance obligation. The Company recognizes the amount of the transaction price as revenue that is allocated to the respective performance obligation when the performance obligation is satisfied or as it is satisfied.

The Company enters into collaboration arrangements, under which it licenses certain rights to its intellectual property to third parties. The terms of these agreements may include payment to the Company of one or more of the following: nonrefundable upfront license fees; development, sale and commercial milestone payments and royalties on net sales of licensed products. Each of these types of payments are classified as license revenue except for revenue from royalties on net sales of licensed products, which are classified as royalty revenue.

For each collaboration agreement that results in revenues, the Company identifies all material promised goods and services, which may include a license to intellectual property, research and development activities and/or transition activities. Promised goods or services are considered to be separate performance obligations if they are distinct. In

order to determine the transaction price to be allocated to each performance obligation, in addition to any upfront payment, the Company estimates the amount of variable consideration at the outset of the contract either utilizing the expected value or most likely amount method, depending on the facts and circumstances relative to the contract. The Company constrains (reduces) the estimates of variable consideration such that it is probable that a significant reversal of previously recognized revenue will not occur throughout the life of the contract. When determining if variable consideration should be constrained, management considers whether there are factors outside the Company's control that could result in a significant reversal of revenue. In making these assessments, the Company considers the likelihood and magnitude of a potential reversal of revenue. These estimates are re-assessed each reporting period as required.

Once the estimated transaction price is established, amounts are allocated to the performance obligations that have been identified. The transaction price is generally allocated to each separate performance obligation on a relative standalone selling price basis. The Company must develop assumptions that require judgment to determine the standalone selling price (SSP) in order to account for these agreements. To determine the standalone selling price the Company's assumptions may include (i) assumptions regarding the probability of obtaining marketing approval for the drug candidate; (ii) estimates regarding the timing of and the expected costs to develop and commercialize the drug candidate; (iii) estimates of future cash flows from potential product sales with respect to the drug candidate; and (iv) appropriate discount and tax rates. Standalone selling prices used to perform the initial allocation are not updated after contract inception. The Company does not include a financing component to its estimated transaction price at contract inception unless it estimates that certain performance obligations will not be satisfied within one year.

Upfront License Fees

If a license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenues from nonrefundable, upfront license fees based on the relative value prescribed to the license compared to the total value of the arrangement. The revenue is recognized when the license is transferred to the collaborator and the collaborator is able to use and benefit from the license. For licenses that are not distinct from other obligations identified in the arrangement, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time. If the combined performance obligation is satisfied over time, the Company applies an appropriate method of measuring progress for purposes of recognizing revenue from nonrefundable, upfront license fees. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Development Milestone Payments

Depending on facts and circumstances, the Company may conclude it is appropriate to include the milestone in the estimated transaction price using the most likely amount method or it is appropriate to fully constrain the milestone. A milestone payment is included in the transaction price in the reporting period the Company concludes that it is probable that recording revenue in the period will not result in a significant reversal in amounts recognized in future periods. The Company may record revenues from certain milestones in a reporting period before the milestone is achieved if the Company concludes that achievement of the milestone is probable and that recognition of revenue related to the milestone will not result in a significant reversal in amounts recognized in future periods. The Company records a corresponding contract asset when this conclusion is reached. Milestone payments that have not been included in the transaction price to date are fully constrained. These milestones remain fully constrained until the Company concludes that achievement of the milestone is probable and recognition of revenue related to the milestone will not result in a significant reversal in amounts recognized in future periods. The Company re-evaluates the probability of achievement of such development milestones and any related constraint each reporting period. The Company adjusts its estimate of the overall transaction price, including the amount of collaborative revenue that it has recorded, if necessary.

Sales-based Milestone and Royalty Payments

The Company's collaborators may be required to pay the Company sales-based milestone payments or royalties on future sales of commercial products. The Company recognizes revenues related to sales-based milestone and royalty payments upon the later to occur of (i) achievement of the collaborator's underlying sales or (ii) satisfaction of any performance obligation(s) related to these sales, in each case assuming the license to the Company's

intellectual property is deemed to be the predominant item to which the sales-based milestones and/or royalties relate.

Grant Income

Grant income is recognized as earned based on contract work performed.

Research and Development

Research and development costs are expensed as incurred. Research and development expense consists of (i) employee-related expenses, including salaries, benefits, travel and stock-based compensation expense; (ii) external research and development expenses incurred under arrangements with third parties, such as contract research organizations and consultants; (iii) the cost of acquiring, developing and manufacturing clinical study materials; and (iv) costs associated with preclinical activities and regulatory operations.

The Company enters into consulting, research, and other agreements with commercial firms, researchers, universities and others for the provision of goods and services. Under such agreements, the Company may pay for services on a monthly, quarterly, project or other basis. Such arrangements are generally cancellable upon reasonable notice and payment of costs incurred. Costs are considered incurred based on an evaluation of the progress to completion of specific tasks under each contract using information and data provided to the Company by its clinical sites and vendors. These costs consist of direct and indirect costs associated with specific projects, as well as fees paid to various entities that perform certain research on behalf of the Company.

Patents

Costs incurred in connection with the application for and issuances of patents are expensed as incurred.

Income Taxes

Income taxes are recorded in accordance with ASC Topic 740, *Income Taxes,* or ASC 740, which provides for deferred taxes using an asset and liability approach. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the consolidated financial statements or tax returns. Deferred tax assets and liabilities are determined based on the difference between the consolidated financial statement and tax bases of assets and liabilities and for loss and credit carryforwards using enacted tax rates anticipated to be in effect for the year in which the differences are expected to reverse. Valuation allowances are provided, if, based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position, as well as consideration of the available facts and circumstances. As of December 31, 2018 and 2017, the Company does not have any uncertain tax positions. The Company recognizes interest and penalties related to uncertain tax positions, if any exist, in income tax expense.

Net Loss per Share Attributable to Common Stockholders

The Company's basic net loss per share attributable to common stockholders is calculated by dividing the net loss attributable to common stockholders by the weighted average number of shares of common stock outstanding for the period. The diluted net loss per share attributable to common stockholders is computed by adjusting the weighted average shares outstanding for the dilutive effect of common stock equivalents outstanding for the period, determined using the treasury stock method.

Stock-Based Compensation

The Company accounts for its stock-based compensation awards in accordance with ASC Topic 718, *Compensation – Stock Compensation,* or ASC 718. ASC 718 requires all stock-based payments to employees, including grants of employee stock options and restricted stock, to be recognized in the consolidated statements of operations and comprehensive loss based on their fair values. All the Company's stock-based awards are subject only to service-based vesting conditions. The Company estimates the fair value of its stock-based awards using the Black-Scholes option pricing model, which requires the input of assumptions, including (a) the expected stock price

volatility, (b) the calculation of expected term of the award, (c) the risk-free interest rate and (d) expected dividends. The fair value of restricted stock awards is determined based on the Company's estimated common stock value.

Due to the historical lack of a public market for the trading of the Company's common stock and a lack of company-specific historical and implied volatility data, the Company has based its estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. The computation of expected volatility is based on the historical volatility of a representative group of companies with similar characteristics to the Company, including stage of product development and life science industry focus. The Company believes the group selected has sufficient similar economic and industry characteristics and includes companies that are most representative of the Company.

The Company uses the simplified method as prescribed by the SEC Staff Accounting Bulletin No. 107, *Share-Based Payment*, to calculate the expected term, as it does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term for options granted to employees, and utilizes the contractual term for options granted to non-employees. 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. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected life of the stock options.

Compensation expense related to awards to employees is calculated on a straight-line basis by recognizing the grant date fair value over the associated service period of the award, which is generally the vesting term.

Fair Value of Financial Instruments

The Company's financial instruments consist of cash and cash equivalents, accounts payable and accrued expenses. The Company values cash equivalents using quoted market prices. The fair value of accounts payable and accrued expenses approximates its carrying value because of its short-term nature.

The Company is required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. ASC Topic 820, *Fair Value Measurements and Disclosures* (ASC 820), establishes a hierarchy of inputs used in measuring fair value that maximizes the use of observable inputs and minimizes the use of unobservable inputs by requiring that the observable inputs be used when available.

Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the asset or liability and are developed based on the best information available in the circumstances. The fair value hierarchy applies only to the valuation inputs used in determining the reported fair value of the investments and is not a measure of the investment credit quality. The three levels of the fair value hierarchy are described below:

- Level 1 – Valuations based on unadjusted quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date
- Level 2 – Valuations based on quoted prices for similar assets or liabilities in markets that are not active or for which all significant inputs are observable, either directly or indirectly
- Level 3 – Valuations that require inputs that reflect the Company's own assumptions that are both significant to the fair value measurement and unobservable

To the extent that a 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. There were no transfers within the fair value hierarchy in the years ended December 31, 2018 and 2017. The assets of the Company measured at fair value on a recurring basis as of December 31, 2018 and 2017 are summarized below:

	Fair Value Measurements Using			
	Level 1	Level 2	Level 3	Total
December 31, 2018				
Assets:				
Cash and cash equivalents	**$ 62,614,010**	**$ —**	**$ —**	**$ 62,614,010**
Total assets	**$ 62,614,010**	**$ —**	**$ —**	**$ 62,614,010**
December 31, 2017				
Assets:				
Cash and cash equivalents	$ 20,264,109	$ —	$ —	$ 20,264,109
Total assets	$ 20,264,109	$ —	$ —	$ 20,264,109

Concentrations of Credit Risk and Off-Balance Sheet Risk

Cash and cash equivalents are the only financial instruments that potentially subject the Company to concentrations of credit risk. At December 31, 2018 and 2017, the Company maintains its cash and cash equivalents with high-quality, accredited financial institutions and, accordingly, such funds are subject to minimal credit risk. The Company has no significant off-balance sheet concentrations of credit risk, such as foreign currency exchange contracts, option contracts, or other hedging arrangements.

Comprehensive Loss

Comprehensive 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, if any. Comprehensive loss equaled net loss for all periods presented.

Furniture and Equipment

Furniture and equipment is stated at cost, less accumulated depreciation. Furniture and equipment is depreciated using the straight-line method over the estimated useful lives of the assets, generally three to seven years. Such costs are periodically reviewed for recoverability when impairment indicators are present. Such indicators include, among other factors: operating losses, unused capacity, market value declines and technological obsolescence. Recorded values of asset groups of furniture and equipment that are not expected to be recovered through undiscounted future net cash flows are written down to current fair value, which generally is determined from estimated discounted future net cash flows (assets held for use) or net realizable value (assets held for sale).

Recent 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 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 May 2014, the FASB issued amended guidance for revenue recognition, ASU 2014-09, *"Revenue from Contracts with Customers (Topic 606)."* This ASU outlines a single comprehensive model for entities to use in accounting for revenue arising from contracts with customers. The core principle of the guidance is that an entity should recognize revenue for the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods and services. Additionally, the ASU requires improved disclosure to help users of financial statements better understand the nature, amount, timing and uncertainty of revenue that is recognized. The Company adopted the new guidance on January 1, 2018, as discussed in Footnote 15.

In February 2016, the FASB issued ASU 2016-02, *"Leases."* This ASU will require lessees to recognize almost all leases on the balance sheet as a right-of-use asset and a lease liability. For statement of operations purposes, the FASB retained a dual model, requiring leases to be classified as finance leases or operating leases. In July 2018, the FASB issued ASU No. 2018-11, *Leases (Topic 842): Targeted Improvements*, to provide an additional transition method options available to registrants. In accordance with Topic 842, a registrant can elect not to present comparative financial information under Topic 842 if it recognizes a cumulative-effect adjustment to retained earnings upon adoption. The Company intends to make this transition election. Additionally, the Company will elect the package of practical expedients permitted under the transition guidance within the new standard, which among other things, allows the Company to carryforward the historical lease classification. The amendments in Topic 842 are effective for the Company for fiscal years beginning with 2019, including interim periods within that year, with early adoption permitted. The Company has performed an assessment of the impact of the adoption of the amendments within Topic 842 on the Company's consolidated balance sheet for the Company's leases, which primarily consist of facility leases. Based on the Company's assessment, the estimated impact of the adoption of Topic 842 will result in the recognition of approximately $550,000 to $600,000 of right-of-use assets and lease liabilities as of January 1, 2019 on the consolidated balance sheet. The right-of-use assets and lease liabilities are based on the present value of future minimum lease payments defined within the corresponding facility lease agreements. The impact from the adoption of Topic 842 to the Company's accumulated deficit as of January 1, 2019 or post adoption impact to our consolidated statement of operations and comprehensive loss is not expected to be material.

In March 2016, the FASB issued ASU 2016-09, *"Improvements to Employee Share-Based Payment Accounting."* This ASU is intended to simplify accounting for share-based payments and requires that excess tax benefits for share-based payments be recorded as a reduction of income tax expense and reflected within operating cash flows rather than being recorded within equity and reflected within financing cash flows. The ASU also provides an option for companies to recognize forfeitures as they occur rather than estimating the number of awards expected to be forfeited. The Company adopted this ASU on January 1, 2017 and has applied the new guidance related to excess tax benefits on a prospective basis. The Company also elected to account for forfeitures of share-based payments as they occur. The adoption of this ASU was not material to the consolidated financial statements.

In August 2016, the FASB issued ASU 2016-15, "*Statement of Cash Flows (Topic 230)."* The objective of this ASU is to provide additional guidance and reduce diversity in practice when classifying certain transactions within the statement of cash flows. The Company adopted this ASUs as of January 1, 2018. The adoption of this ASUs did not have a material impact on the Company's consolidated financial statements.

In November 2016, the FASB issued ASU 2016-18, *"Statement of Cash Flows (Topic 230): Restricted Cash."* This ASU requires that the 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. These ASUs are effective for financial statements issued for fiscal years beginning after December 15, 2017, including interim periods within those fiscal years. The Company adopted these ASUs as of January 1, 2018. The adoption of these ASUs did not have a material impact on the Company's consolidated financial statements.

In May 2017, the FASB issued ASU 2017-09, "*Stock Compensation - Scope of Modification Accounting."* This ASU provides clarification around which changes to the terms or conditions of a share-based payment award require the application of modification accounting under ASC 718. The Company adopted this ASU as of January 1, 2018. The adoption of this ASU did not have a material impact on the Company's consolidated financial statements.

In June 2018, the FASB issued ASU 2018-07, *"Improvements to Nonemployee Share-Based Payment Accounting."* This ASU improves financial reporting for share-based payments issued to nonemployees under ASC 718 by expanding the scope of the employee share-based payments guidance to include share-based payments issued to nonemployees. The amendments in this ASU are effective for public companies for fiscal years beginning after December 31, 2018, including interim periods within that fiscal year. The adoption of this ASU is not anticipated to have a material impact on the Company's consolidated financial statements.

3. Accounts Payable and Accrued Expenses

Accounts payable and accrued expenses consist of the following as of:

	December 31, 2018	2017
Accounts payable	**$ 595,680**	$ 1,276,537
Professional fees	**487,923**	277,217
Accrued bonus	**1,877,455**	833,650
Accrued vacation	**90,663**	69,549
Accrued project costs	**2,232,014**	1,069,852
Other	**173,182**	65,359
Total accounts payable and accrued expenses	**$ 5,456,917**	$ 3,592,164

4. Furniture and Equipment

Furniture and equipment consist of the following as of:

	December 31, 2018	2017
Furniture	**$ 156,928**	$ 156,928
Computers	**75,716**	109,204
Equipment	**141,067**	141,067
Leasehold improvements	**35,869**	35,869
Total furniture and equipment	**409,580**	443,068
Accumulated depreciation	**(311,131)**	(335,845)
Furniture and equipment, net	**$ 98,449**	$ 107,223

5. Common Stock

As of December 31, 2018 and 2017, the Company had 300,000,000 shares of authorized common stock with par value of $0.0001 per share.

The common stock has the following characteristics:

Voting

The holders of common stock are entitled to one vote for each share of common stock held at all meetings of stockholders and written actions in lieu of meetings.

Dividends

The holders of common stock are entitled to receive dividends, if and when declared by the Board of Directors. Since the Company's inception, no dividends have been declared or paid to the holders of common stock.

Liquidation

In the event of any voluntary or involuntary liquidation, dissolution, or winding-up of the Company, the holders of common stock are entitled to share ratably in the Company's assets.

Warrants to Purchase Common Stock

At December 31, 2018 and 2017, the Company had warrants outstanding for the purchase of 317,562 shares of the Company's common stock at an exercise price of $5.00 per share. The warrants have a three-year term and expire on March 15, 2020. The Warrants were issued in connection with the 2017 Offering. At the expiration date of the warrants, if the fair value of the Company's common stock exceeds the exercise price, the warrant will be automatically exercised and the exercise price will be fulfilled through the net share settlement provisions. The number of shares and the exercise price shall be adjusted for standard ant-dilution events such as stock splits, combinations, reorganizations, or issue shares as part of a common stock dividend. Upon a change of control, the warrant holder will have the right to receive securities, cash or other properties it would have been entitled to receive

had the warrant been exercised. The warrants are equity classified instruments and do not contain contingent exercise provisions, or other features, that would preclude the Company from concluding that the warrants are indexed solely to the Company's common stock.

6. Preferred Stock

As of December 31, 2018 and 2017, the Company had 10,000,000 shares of preferred stock, par value $0.0001 per share, in authorized capital. No preferred stock was issued and outstanding at December 31, 2018 and 2017. In connection with the Merger (Note 1), all the Aerpio redeemable convertible preferred stock issued and outstanding prior to the Merger was converted into shares of the Company's common stock.

7. Stock-Based Compensation

In March 2017, the Company's Board of Directors adopted, and the stockholders approved, the 2017 Stock Option and Incentive Plan (the "2017 Plan"), that became effective in April 2017. The 2017 Plan provides for the issuance of incentive awards up to 4,600,000 shares of common stock to officers, employees, consultants and directors, less the number of shares subject to issued and outstanding awards under the Aerpio Therapeutics, Inc. 2011 Equity Incentive Plan (the "2011 Plan") that were assumed in the Merger. The 2017 Plan also provides that the number of shares reserved for issuance thereunder will be increased annually on the first day of each year beginning in 2018 by four percent (4%) of the shares of our common stock outstanding on the last day of the immediately preceding year or such smaller increase as determined by our Board of Directors. In April 2018, the Company's Board of Directors approved a 4% increase adding 1,082,802 shares to the 2017 Plan.

Stock Options

The options granted generally vest over 48 months. Under the 2017 Plan, options vest in installments of 25% at the one-year anniversary and thereafter in 36 equal monthly installments beginning on the 1st of the month after the one-year anniversary date, subject to the employee's continuous service with the Company. The options generally expire ten years after the date of grant. The fair value of the options at the date of grant is recognized as an expense over the requisite service period.

During the years ended December 31, 2018 and 2017, 1,615,200 and 1,014,018 option awards were granted, respectively. In 2017, two inducement grants for 733,570 shares related to hiring the CEO and CFO and three option awards for 280,448 shares were issued under the 2017 Equity Plan. All option awards granted during 2018 were under the 2017 Equity Plan. At December 31, 2018 and 2017, 2,959,562 and 3,391,960 shares were reserved for issuance under the 2017 Plan, respectively.

The following table summarizes the stock option activity during the years ended December 31, 2018 and 2017:

	Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in Years)	Aggregate Intrinsic Value
Outstanding, January 1, 2017	927,592	$ 1.70	7.48	$ 1,030,217
Granted	1,014,018	5.50		
Exercised	(25,729)	1.40		
Expired/cancelled	(2,901)	2.11		
Outstanding, December 31, 2017	1,912,980	$ 3.72	8.24	$ 2,738,704
Expected to vest, December 31, 2017	1,161,495	$ 5.02	9.65	$ 441,553
Options exercisable, December 31, 2017	751,485	$ 1.69	6.07	$ 2,297,151
Outstanding, January 1, 2018	1,912,980	$ 3.72	8.24	$ 2,738,704
Granted	1,615,200	3.64		
Exercised	(52,099)	1.47		
Expired/cancelled	(124,949)	3.23		
Outstanding, December 31, 2018	3,351,132	$ 3.73	8.24	$ 142,788
Expected to vest, December 31, 2018	2,197,619	$ 4.17	9.19	$ —
Options exercisable, December 31, 2018	1,153,513	$ 2.90	6.37	$ 142,788

Aggregate intrinsic value represents the estimated fair value of the Company's common stock at the end of the period in excess of the weighted average exercise price multiplied by the number of options outstanding or exercisable. The aggregate intrinsic value of the options at December 31, 2018 and 2017 was $142,788 and $2,738,704, respectively.

Stock options exercised during 2018 and 2017 had an intrinsic value of $139,108 and $92,544, respectively.

For the years ended December 31, 2018 and 2017, the Company recognized compensation expense for stock options of $2,982,173 and $327,649, respectively. As of December 31, 2018, there was $3,865,709 of unrecognized compensation cost related to stock options, which is expected to be recognized over a weighted average period of 2.55 years.

The Company uses the Black-Scholes option pricing model to determine the estimated fair value for stock-based awards. For the years ended December 31, 2018 and 2017, there were 1,615,200 and 1,014,018 options granted out of the 2017 Plan, respectively, except for two option awards for 733,570 shares that were inducement grants related to hiring the CEO and CFO in December 2017. Option pricing models require the input of various assumptions, including the option's expected life, expected dividend yield, price volatility and risk-free interest rate of the underlying stock. As there has not been significant public market activity of the Company's Common Stock, the Company has determined the volatility assumption for options granted based on data from a peer group of companies that issued options with substantially similar terms. The expected volatility of options granted has been determined using the average of the historical volatility measures of this peer group of companies for a period equal to the expected life of the option. The risk-free interest rate is based on the rate applicable to U.S. Treasury zero-coupon issues, with remaining maturities commensurate with the expected term of the options granted in effect on the date of grant. The Company has not paid, and does not anticipate paying, cash dividends on shares of Common Stock; therefore, the expected dividend yield is assumed to be zero in the option valuation model. Accordingly, the weighted-average fair value of the options granted during the years ended December 31, 2018 and 2017, was $2.22 and $3.39, respectively. The calculation was based on the following assumptions.

	Year Ended December 31,	
	2018	2017
Expected term (years)	**6.07**	5.94
Risk-free interest rate	**2.85%**	2.19%
Expected volatility	**65.99%**	67.57%
Expected dividend yield	—	—

Restricted Stock

Shares of restricted stock generally had similar vesting terms as stock options. A summary of the Company's restricted stock activity and related information for the years ended December 31, 2018 and 2017 is as follows:

	Shares	Weighted Average Grant Date Fair Value
Nonvested, January 1, 2017	241,096	$ 1.91
Granted	—	—
Vested	(144,274)	1.91
Forfeited	(5,246)	2.20
Nonvested, December 31, 2017	91,576	$ 2.12
Nonvested, January 1, 2018	91,576	$ 2.12
Granted	60,000	4.75
Vested	(149,243)	3.18
Forfeited	(2,333)	2.25
Nonvested, December 31, 2018	—	$ —

For the years ended December 31, 2018 and 2017, the Company recognized compensation expense for restricted stock of $449,689 and $321,760, respectively. As of December 31, 2018, all restricted stock had vested.

Compensation Expense Summary

The Company recognized the following compensation cost related to employee and non-employee stock-based compensation activity for the periods presented below.

	Year Ended December 31, 2018	2017
Research and development	**$ 392,470**	$ 393,347
General and administrative	**3,039,392**	256,062
Total	**$ 3,431,862**	$ 649,409

The increase in compensation expense during the year ended December 31, 2018, is primarily due to vesting under the contractual terms of the option grants awarded during 2017 and 2018.

8. Income Taxes

The Tax Cuts and Jobs Act ("2017 Tax Act") was signed into law on December 22, 2017. The 2017 Tax Act significantly revised the U.S. corporate tax by, among other things, lowering the statutory corporate tax rate from 35% to 21% in 2018. The Company completed its determination of the accounting implications of the 2017 Tax Act during 2018, and there was no material impact to the Company's provision for income taxes during 2018.

The Company did not record a current or deferred income tax expense or benefit for the years ended December 31, 2018 and 2017, due to the Company's net losses and increases in its deferred tax asset valuation allowance. A reconciliation of the statutory federal income tax with the provision for income taxes are as follows:

	Year Ended December 31,	
	2018	**2017**
Federal tax at statutory rate	**(21.00%)**	(34.00%)
State and local tax at statutory rates, net of federal income tax	**(4.15)**	(0.83)
Research and development credits	**(6.37)**	(1.72)
Other	**4.27**	1.42
Change in valuation allowance	**27.25**	(17.64)
Remeasurement of U.S. net deferred tax assets from 35% to 21%	**—**	52.77
Effective tax rate	**0.00%**	0.00%

The Company's income tax provision was computed based on the federal statutory rate and the average state statutory rates, net of the related federal benefit.

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amounts of the assets and liabilities for financial reporting purposes and the amounts used for income and for tax carryforwards, recorded at the enacted federal statutory income tax rate. Significant components of the Company's deferred tax assets and liabilities are as follows:

	December 31,	
	2018	**2017**
Deferred tax assets:		
Net operating loss carryforwards	**$ 19,946,123**	$ 18,819,077
Accrued expenses	**595,209**	204,599
Stock-based compensation	**603,408**	96,578
Research and development credits	**3,852,714**	3,038,863
Other	**13,276**	13,953
Total deferred tax assets	**25,010,730**	22,173,070
Deferred tax liabilities:		
Furniture and equipment	**8,390**	3,606
Total deferred tax liabilities	**8,390**	3,606
Net deferred tax assets before valuation allowance	**25,002,340**	22,169,464
Less valuation allowance	**(25,002,340)**	(22,169,464)
Net deferred tax asset	**$ —**	$ —

When realization of the deferred tax asset is more likely than not to occur, the benefit related to the deductible temporary differences attributable to operation is recognized as a reduction of income tax expense. Valuation allowances are provided against deferred tax assets when, based on all available evidence, it is considered more likely than not that some portion or all of the recorded deferred tax assets will not be realized in future periods. The Company cannot be certain that future taxable income will be sufficient to realize its deferred tax assets, and accordingly, a full valuation allowance has been provided on its net deferred tax assets. The valuation allowance increased $2,832,876 in 2018 as a result of an increase in the net operating loss (NOL) and an increase of research and development credits carryforwards and decreased $3,774,722 in 2017 primarily as a result of the changes in the 2017 Tax Act offset by an increase with allowance on the NOL carryforward. The Company continues to monitor the need for a valuation allowance based on the profitability of its future operations.

At December 31, 2018, the Company has $84,173,000 of federal NOL carryforwards with expirations between 2032 and 2038. The Company has $5,668,095 of federal NOL carryforwards with no expiration as a result of the

2017 Tax Act. Additionally, the Company has $66,253,204 of state and local NOL carryforwards with expiration between 2019and 2039. Finally, at December 31, 2018, the Company has $3,852,714 of federal research and development credit carryforwards that expire at various dates through 2039.

Under the provisions of the Internal Revenue Code, NOL and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities until fully utilized. NOL and tax credit carryforwards may be subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant stockholders by more than 50% over a three-year period, as defined in Sections 382 and 383 of the Internal Revenue Code and similar state provisions. The amount of the annual limitation is determined based on the value of the Company immediately before the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has not completed a study to assess whether a change of control has occurred or whether there have been multiple changes of control since the date of the Company's formation due to the significant complexity and cost associated with such study and that there could be additional changes in control in the future. As a result, the Company is unable to estimate the effect of these limitations, if any, on the Company's ability to utilize NOL and tax credit carryforwards in the future. A full valuation allowance has been provided against the Company's NOL and tax credit carryforwards and, if an adjustment is required, this adjustment would be offset by an adjustment to the deferred tax asset established for the NOL and tax credit carryforwards and the valuation allowance.

The Company has not yet conducted a study to document whether its research activities may qualify for the research and development tax credit. Such a 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 credit 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.

As of December 31, 2018 and 2017, the Company had no accrued uncertain tax positions or associated interest or penalties and no amounts have been recognized in the Company's consolidated statements of operations and comprehensive loss.

The Company files income tax returns in the U.S. federal jurisdiction and various state jurisdictions. All years remain open and are subject to examination by federal and state taxing authorities.

9. Net Loss per Share Attributable to Common Stockholders

The following table sets forth the computation of the Company's basic and diluted net loss per share attributable to common stockholders for the periods presented:

	Year Ended December 31,	
	2018	**2017**
Net and comprehensive loss	**$ (10,396,635)**	$ (21,400,606)
Adjustment of redeemable convertible preferred stock to redemption value	**—**	(943,297)
Net loss attributable to common stockholders	**$ (10,396,635)**	$ (22,343,903)
Net loss per share attributable to common stockholders, basic and diluted	**$ (0.31)**	$ (1.03)
Weighted average common shares used in computing net loss per share attributable to common stockholders, basic and diluted	**33,930,846**	21,673,349

The following weighted average common stock equivalents were excluded from the calculation of diluted net loss per share attributable to common stockholders for the periods presented because including them would have had an anti-dilutive effect:

	Year Ended December 31,	
	2018	**2017**
Options to purchase common stock	**3,351,132**	1,912,980
Warrants to purchase common stock	**317,562**	317,562

10. Quarterly Results (unaudited)

The following is a summary of our unaudited quarterly results for the years ended December 31, 2018 and 2017.

	Quarter Ended			
	March 31, 2018	June 30, 2018	September 30, 2018	December 31, 2018
	(unaudited)			
License revenue, and other	$ —	$ 1,333,333	$ 18,821,953	$ 2,144
Total operating expenses	7,476,648	7,369,788	7,623,916	8,868,322
(Loss) income from operations	(7,476,648)	(6,036,455)	11,198,037	(8,866,178)
Other income	51,116	46,464	339,441	347,588
Net and comprehensive (loss) income attributable to common stockholders	$ (7,425,532)	$ (5,989,991)	$ 11,537,478	$ (8,518,590)
Net (loss) income per share attributable to common stockholders, basic and diluted	$ (0.27)	$ (0.22)	$ 0.28	$ (0.21)
Weighted average number of common shares used in computing net (loss) income per share:				
Basic	27,045,509	27,340,914	40,527,722	40,587,928
Diluted	27,045,509	27,340,914	40,961,620	40,587,928

	Quarter Ended			
	March 31, 2017	June 30, 2017	September 30, 2017	December 31, 2017
	(unaudited)			
Total operating expenses	$ 4,759,585	$ 5,583,862	$ 4,756,238	$ 6,288,858
Loss from operations	(4,759,585)	(5,583,862)	(4,756,238)	(6,288,858)
Other (expense) income, net	(236,118)	63,555	106,671	53,829
Net loss and comprehensive loss	$ (4,995,703)	$ (5,520,307)	$ (4,649,567)	$ (6,235,029)
Reconciliation to net loss attributable to common stockholders:				
Net loss and comprehensive loss	$ (4,995,703)	$ (5,520,307)	$ (4,649,567)	$ (6,235,029)
Adjustment of redeemable convertible preferred stock to redemption value	(943,297)	—	—	—
Net loss attributable to common stockholders	$ (5,939,000)	$ (5,520,307)	$ (4,649,567)	$ (6,235,029)
Net loss per share attributable to common stockholders, basic and diluted	$ (1.06)	$ (0.21)	$ (0.17)	$ (0.23)
Weighted average number of common shares used in computing net loss per share attributable to common stockholders, basic and diluted	5,605,151	26,895,164	26,926,673	26,965,293

The sum of the quarterly net loss per share attributable to common stockholders may not equal the annual amounts reported because per share amounts are computed independently for each quarter and for full year based on respective weighted-average common shares outstanding and other dilutive potential common stockholders.

The diluted EPS calculation for the three months ended September 30, 2018 includes the dilutive common share impact of 426,860 options to purchase common stock and 7,038 unvested restricted stock. Furthermore, the diluted EPS calculation for the three months ended September 30, 2018 excludes 2.4 million options to purchase common stock that was outstanding but unvested and the effect of weighted average common stock share equivalents of 0.1 million for options to purchase common stock and 0.3 million for warrants to purchase common stock as their effect is anti-dilutive. Holders of non-vested stock-based compensation awards do not have voting rights. Diluted and Basic weighted average number of common shares were the exact same in every other period presented within the table above.

11. Commitments and Contingencies

The Company is a party to three property leases with the following terms: (i) in March 2018, the Company signed a fourth lease amendment covering 7,580 square feet of space in Cincinnati, Ohio which contains one month of free

rent and escalating rent payments and extends the lease through July 2021; (ii) beginning in December 2018, the Company entered into a three-year lease covering 4,000 square feet of space in Lexington, Massachusetts; and (iii) in November 2017, the Company renewed a lease covering 687 square feet of space in Dexter, Michigan that expires in October 2019. Rent expense is recorded on the straight-line basis over the initial term with the difference between rent expense and rent payments recorded as deferred rent. Total rent expense for all operating leases was $183,222 and $208,478 for the years ended December 31, 2018 and 2017, respectively. As of December 31, 2018 and 2017, the Company had total deferred rent of $9,340 and $42,660, respectively, for the Cincinnati, Ohio space. Deferred rent is included in accrued expenses in the accompanying consolidated balance sheets. As of December 31, 2018, non-cancellable future minimum lease payments related to operating leases are as follows:

	2019	2020	2021 and Thereafter
Operating leases	$ 257,050	$ 239,781	$ 191,686

The Company contracts with various organizations to conduct research and development activities, including clinical trial organizations to manage clinical trial activities. The scope of the services under these research and development contracts can be modified and the contracts cancelled by the Company upon written notice. In the event of a cancellation, the Company would only be liable for the cost and expenses incurred to date.

12. Employee Retirement Plan

The Company maintains a 401(k) plan (the "401k Plan") in 2015 for the benefit of its employees. All employees who have attained the age of 21 are eligible to participate in the 401k Plan as of the first Entry Date, as defined by the 401k Plan document, following the employment date. Each employee can contribute a percentage of compensation up to a maximum of the statutory limits per year. Company contributions are discretionary. No contributions were made during 2018 or 2017.

13. Employee Bonus Plan

The Company maintains a bonus plan for certain employees based on the achievement of certain goals and milestones. At December 31, 2018 and 2017, the Company accrued $1,877,455 and $833,650, respectively, for bonuses.

14. Employee Stock Purchase Plan

In March 2017, the Board of Directors adopted and the stockholders approved the Employee Stock Purchase Plan that became effective in April 2017. On June 20, 2018, the Company's shareholders approved the Amended and Restated 2017 Employee Stock Purchase Plan (as amended, the "ESPP") at the Annual Meeting of Shareholders. Pursuant to the terms of the ESPP, the Company will reserve for issuance 300,000 shares of the Company's common stock in the aggregate. Additionally, on January 1, 2019 and each January 1 thereafter through January 1, 2028, the number of shares of the Company's common stock reserved and available for issuance under the ESPP will be cumulatively increased by the least of: (i) one percent (1%) of the number of shares of the Company's common stock issued and outstanding on the immediately preceding December 31; (ii) 350,000 shares; or (iii) such lesser number of shares of the Company's common stock as determined by the Board of Directors, in each case subject to adjustment in accordance with the terms of the ESPP. No shares under the ESPP are outstanding at December 31, 2018 and 2017 for the purchases made under the ESPP.

15. License Agreement

On June 24, 2018, the Company entered into a License Agreement (the "Gossamer License") with a wholly-owned subsidiary of Gossamer Bio, Inc., GB004, Inc. (collectively "Gossamer"), under which the Company granted Gossamer an exclusive, sublicensable license to develop and commercialize AKB-4924 and other structurally related products worldwide, with initial development expected in the indications of induction and maintenance in ulcerative colitis and Crohn's Disease (collectively "initial indications"). Prior to the execution of the Gossamer License, AKB-4924 was a pipeline program for the Company that recently completed a Phase 1a clinical trial in healthy volunteers.

Gossamer is responsible for the development and commercialization of the licensed products, and a joint development committee has been formed to oversee the development and manufacturing activities related to the licensed products. Under the terms of the Gossamer License, Gossamer is obligated to use its commercially reasonable efforts to develop and commercialize licensed products in the United States, two major European countries and Japan for at least one of the initial indications. The Gossamer License includes an exclusivity provision that prohibits the Company from developing, manufacturing or commercializing, and prohibits Gossamer from clinically developing or commercializing certain HIF stabilizing compounds other than as permitted in the Gossamer License. Pursuant to the terms of the Gossamer License, Gossamer made an upfront payment to the Company of $20.0 million on June 28, 2018. The $20.0 million of license revenue is recorded within the consolidated statement of operations and comprehensive loss for the year ended December 31, 2018.

The Company is also eligible to receive development, commercial and sales milestone payments, with such payments contingent on the achievement of specified milestones with respect to the first licensed product for each of the first two initial indications. The Company is also eligible to receive tiered royalties on sales of licensed products at percentages ranging from a high-single-digit to mid-teens, subject to certain customary reductions. In addition, under certain circumstances, in lieu of receiving the foregoing milestone payments and royalties, the Company may elect to receive a specified percentage of payments received by Gossamer and its stockholders (with some exclusions) in connection with Gossamer's grant of a sublicense or other rights to the licensed products or if Gossamer undergoes a change of control and the value of the transaction exceeds a certain value (provided that Gossamer can prevent the Company from exercising this option if the parent company of Gossamer is the entity undergoing the change of control). Conversely, the Company could be required to accept such a specified percentage of those payments if Gossamer agrees to pay the Company a certain minimum upon Gossamer and its stockholders being paid. Such amount may be reduced if the subject transaction includes pharmaceutical candidates or products or other named asset categories in addition to the licensed products.

The Gossamer License expires on a licensed-product-by-licensed-product and country-by-country basis on the later of fifteen years from the date of first commercial sale or when there is no longer a valid patent claim covering such licensed product in such country. Either party may terminate the Gossamer License for an uncured material breach by the other party or upon the bankruptcy or insolvency of the other party. Gossamer may terminate the Gossamer License in the event Gossamer determines there is a potential safety or efficacy issue with the licensed products. The Company may terminate the Gossamer License if Gossamer institutes certain actions related to the licensed patents. Under certain termination circumstances, the Company would have worldwide rights to the terminated program.

As of December 31, 2018, all development milestones, sales-based milestones and royalty payments within the Gossamer License are constrained to the point where no transaction price has been allocated to the future milestones or royalty payments.

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.

The Company maintains disclosure controls and procedures that are designed to provide reasonable assurance that information required to be disclosed in the Company's reports under the Exchange Act, is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to management, including the Company's Chief Executive Officer (CEO) and Chief Financial Officer (CFO), as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives. Management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

In connection with the preparation of this Annual Report on Form 10-K, an evaluation is performed under the supervision and with the participation of the Company's management, including the CEO and CFO, of the effectiveness of the design and operation of the Company's disclosure controls and procedures (as defined in Rule 13a-15(e) under the Exchange Act) as of December 31, 2018. Based on that evaluation, the CEO and CFO conclude whether the Company's disclosure controls and procedures are effective as of December 31, 2018, at the reasonable assurance level.

In connection with this Annual Report on Form 10-K for the year ended December 31, 2018, an evaluation was performed of the effectiveness of the design and operation of the Company's disclosure controls and procedures as of December 31, 2018. Based on that evaluation, the CEO and CFO have concluded based upon the evaluation described above that, as of December 31, 2018, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Report on Internal Control over Financial Reporting

Management is responsible for establishing and maintaining adequate internal control over financial reporting for us. Internal control over financial reporting (as defined in Rule 13a-15(f) of the Exchange Act) is a process to provide reasonable assurance regarding the reliability of our financial reporting for external purposes in accordance with U.S. generally accepted accounting principles. Internal control over financial reporting includes maintaining records that in reasonable detail accurately and fairly reflect our transactions; providing reasonable assurance that transactions are recorded as necessary for preparation of our consolidated financial statements; providing reasonable assurance that receipts and expenditures of company assets are made in accordance with management authorization; and providing reasonable assurance that unauthorized acquisition, use or disposition of company assets that could have a material effect on our consolidated financial statements would be prevented or detected on a timely basis. Because of its inherent limitations, internal control over financial reporting is not intended to provide absolute assurance that a misstatement of our consolidated financial statements would be prevented or detected.

Management conducted an evaluation of the effectiveness, as of December 31, 2018, of our internal control over financial reporting based on the framework in *Internal Control—Integrated Framework* issued by the Committee of Sponsoring Organizations of the Treadway Commission in 2013. Based on this evaluation, management concluded that our internal control over financial reporting was effective as of December 31, 2018.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act during the three months ended December 31, 2018 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

/s/ Stephen Hoffman, M.D., Ph.D.
Stephen Hoffman
Chief Executive Officer

/s/ Michael Rogers
Michael Rogers
Chief Financial Officer

March 7, 2019

Item 9B. Other Information.

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this Item 10 is omitted from this Annual Report on Form 10-K and is incorporated herein by reference from our definitive proxy statement relating to our 2019 Annual Meeting of Stockholders (the "Definitive Proxy Statement").

Item 11. Executive Compensation.

The information required by this Item 11 will be contained in the Definitive Proxy Statement and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

The information required by this Item 12 will be contained in the Definitive Proxy Statement and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

The information required by this Item 13 will be contained in the Definitive Proxy Statement and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services.

The information required by this Item 14 will be contained in the Definitive Proxy Statement and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statements.

(a)(1) Financial Statements.

The consolidated financial statements required by this item are submitted in a separate section beginning on page 73 of this report.

(a)(2) Exhibits.

Exhibit Index

Exhibit Number	Description
3.1	Amended and Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.2 to the Registrant's Form 8-K filed with the Securities and Exchange Commission on March 17, 2017, File No. 000-53057)
3.2	Amended and Restated By-laws of the Registrant, as currently in effect (incorporated by reference to Exhibit 3.3 to the Registrant's Form 8-K filed with the Securities and Exchange Commission on March 17, 2017, File No. 000-53057)
4.1	Specimen Stock Certificate evidencing shares of common stock (incorporated by reference to Exhibit 4.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-217320) filed April 14, 2017)
4.2	Form of Warrant Agreements (incorporated by reference to Exhibit 4.1 to the Registrant's Form 8-K filed with the Securities and Exchange Commission March 17, 2017, File No. 000-53057)
10.1#	2011 Equity Incentive Plan and forms of award agreements thereunder, assumed in the Merger (incorporated herein by reference to Exhibit 10.1 to the Company's 8-K filed with the Securities and Exchange Commission on March 17, 2017, File No. 000-53057)
10.2#	2017 Stock Option and Incentive Plan and forms of award agreements thereunder (incorporated herein by reference to Exhibit 10.2 to the Company's 8-K filed with the Securities and Exchange Commission on March 17, 2017, File No. 000-53057)
10.3#	Amended and Restated 2017 Employee Stock Purchase Plan (incorporated herein by reference to Exhibit 10.1 to the Company's 8-K filed with the Securities and Exchange Commission on December 18, 2017, File No. 000-53057)
10.4#	Form of Indemnification Agreement (incorporated herein by reference to Exhibit 10.4 to the Company's 8-K filed with the Securities and Exchange Commission on March 17, 2017, File No. 000-53057)
10.5	Registration Rights Agreement, dated March 15, 2017, by and among the Company and the persons listed on Exhibit A attached thereto (incorporated herein by reference to Exhibit 10.5 to the Company's 8-K filed with the Securities and Exchange Commission on March 17, 2017, File No. 000-53057)
10.6	Subscription Agreement, dated March 15, 2017, by and between the Company and the investors party thereto (incorporated herein by reference to Exhibit 10.6 to the Company's 8-K filed with the Securities and Exchange Commission on March 17, 2017, File No. 000-53057)
10.7	Office Lease at 10300 Alliance Road, Cincinnati, OH dated as of September 29, 2009, by and between Akebia Therapeutics, Inc. and Duke Realty Ohio, as amended by the First Lease Amendment dated as of April 23, 2010 by and between Akebia Therapeutics, Inc. and Duke Realty Ohio, as amended by the Second Lease Amendment and Assignment and Assumption of Lease dated as of April 25, 2012 by and between DP Landings Building II, LLC, Akebia Therapeutics, Inc., and Aerpio, as amended by the Third Amendment to Office Lease dated as of February 27, 2015 by and between RT Landings Building II, LLC and Aerpio (incorporated herein by reference to Exhibit 10.7 to the Company's 8-K filed with the Securities and Exchange Commission on March 17, 2017, File No. 000-53057)
10.8	Fourth Amendment to Office Lease and Assignment and Assumption of Lease dated as of March 29, 2018 by and between Blue Ash Landings Acquisition, LLC and Aerpio (incorporated herein by reference to Exhibit 10.1 to the Company's 8-K filed with the Securities and Exchange Commission on April 2, 2018, File No. 000-53057))
10.9	License Agreement dated June 24, 2018, by and between Aerpio and Gossamer Bio, Inc. (incorporated herein by reference to Exhibit 10.1 to the Company's Form 8-K filed with the Securities and Exchange Commission on June 25, 2018 (File No. 000-53057))
10.10#	Employment Agreement, dated March 15, 2017, between the Company and Joseph H. Gardner (incorporated herein by reference to Exhibit 10.8 to the Company's Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 14, 2017, File No. 333-217320)

10.11#	Employment Agreement, dated as of March 15, 2017, between the Company and Kevin G. Peters (incorporated herein by reference to Exhibit 10.9 to the Company's Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 14, 2017, File No. 333-217320)
10.12#	Employment Agreement, dated as of March 15, 2017, between the Company and Stephen Pakola (incorporated herein by reference to Exhibit 10.10 to the Company's Registration Statement on Form S-1 filed with the Securities and Exchange Commission on April 14, 2017, File No. 333-217320)
10.13	Employment Agreement, entered into on October 8, 2017, by and between the Company and Stephen Hoffman (incorporated herein by reference to Exhibit 10.1 to the Company's 8-K filed with the Securities and Exchange Commission on October 10, 2017, File No. 000-53057)
10.14	First Amendment to Employment Agreement, dated October 8, 2017, by and between the Company and Joseph Gardner (incorporated herein by reference to Exhibit 10.1 to the Company's 8-K filed with the Securities and Exchange Commission on October 10, 2017, File No. 000-53057)
10.15	Employment Agreement, effective as of November 15, 2017, by and between the Company and Michael Rogers (incorporated herein by reference to Exhibit 10.1 to the Company's 8-K filed with the Securities and Exchange Commission on November 14, 2017, File No. 000-53057)
10.16	Registration Rights Agreement by and among the Company and certain former stockholders of Aerpio (incorporated herein by reference to Exhibit 10.9 to the Company's 8-K filed with the Securities and Exchange Commission on March 17, 2017, File No. 000-53057).
10.17	Senior Cash Incentive Bonus Plan of the Company (incorporated herein by reference to Exhibit 10.15 to the Company's Annual Report on Form 10-K filed with Securities and Exchange Commission on March 15, 2018, File No. 000-53057).
10.18#	Form of Inducement Stock Option Award (incorporated herein by reference to Exhibit 99.1 to the Company's Form S-8 filed with the Securities and Exchange Commission on December 28, 2018 (File No. 333-229089)
21.1	Subsidiaries of the Registrant (incorporated herein by reference to Exhibit 21.1 to the Company's 8-K filed with the Securities and Exchange Commission on March 17, 2017, File No. 000-53057).
23.1*	Consent of Ernst & Young LLP
31.1*	Certification of Principal Executive Officer 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.
31.2*	Certification of Principal Financial Officer 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.
32.1*	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2*	Certification of 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.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

* Filed herewith.

\# Indicates a management contract or any compensatory plan, contract or arrangement.

Item 16. Form of 10-K Summary

We may voluntarily include a summary of information required by Form 10-K under this Item 16. We have elected not to include such summary information.

SIGNATURES

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

AERPIO PHARMACEUTICALS, INC.

Date: March 7, 2019

By: */s/ Stephen Hoffman, M.D., Ph.D.*
Stephen Hoffman, M.D., Ph.D.
Chief Executive Officer and Principal Executive Officer

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

Name	Title	Date
/s/ Stephen Hoffman, M.D., Ph.D. **Stephen Hoffman, M.D., Ph.D.**	Director, Chief Executive Officer and Principal Executive Officer	March 7, 2019
/s/ Michael Rogers **Michael Rogers**	Chief Financial Officer and Principal Financial and Accounting Officer	March 7, 2019
/s/ Joseph Gardner, Ph.D **Joseph Gardner**	Director, President and Founder	March 7, 2019
/s/ Muneer A. Satter **Muneer A. Satter**	Director	March 7, 2019
/s/ Chau Khuong **Chau Khuong**	Director	March 7, 2019
/s/ Steven Prelack **Steven Prelack**	Director	March 7, 2019
/s/ Cheryl Cohen **Cheryl Cohen**	Director	March 7, 2019
/s/ Caley Castelein, M.D. **Caley Castelein**	Director	March 7, 2019
/s/ Anupam Dalal, M.D. **Anupam Dalal**	Director	March 7, 2019
/s/ Pravin Dugel, M.D. **Pravin Dugel**	Director	March 7, 2019

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 No. 333-220057) of Aerpio Pharmaceuticals, Inc., pertaining to the Aerpio Therapeutics, Inc. 2011 Equity Incentive Plan, Aerpio Pharmaceuticals, Inc. 2017 Stock Option and Incentive Plan, and Aerpio Pharmaceuticals, Inc. 2017 Employee Stock Purchase Plan,
2) Registration Statement (Form S-3 No. 333-223113) of Aerpio Pharmaceuticals, Inc., for the registration of common stock, preferred stock, debt securities, warrants, and/or units,
3) Registration Statement (Form S-8 No. 333-224189) of Aerpio Pharmaceuticals, Inc., pertaining to the 2017 Stock Option and Grant Plan,
4) Registration Statement (Form S-3 No. 333-217320) of Aerpio Pharmaceuticals, Inc., for the registration of common stock,
5) Registration Statement (Form S-3 No. 333-229087) of Aerpio Pharmaceuticals Inc., for the registration of common stock,
6) Registration Statement (Form S-8 No. 333-229089) of Aerpio Pharmaceuticals, Inc., pertaining to the Inducement Stock Option Agreements, and

of our report dated March 7, 2019, with respect to the consolidated financial statements of Aerpio Pharmaceuticals, Inc., included in this Annual Report (Form 10-K) of Aerpio Pharmaceuticals, Inc. for the year ended December 31, 2018.

/s/ Ernst & Young LLP

Cincinnati, Ohio
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, Stephen Hoffman, certify that:

1. I have reviewed this annual report on Form 10-K of Aerpio 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)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

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

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (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.

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

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

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

Date: March 7, 2019

By: */s/ Stephen Hoffman, M.D., Ph.D.*

Stephen Hoffman, M.D., Ph.D.
Chief Executive Officer
(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, Michael Rogers, certify that:

1. I have reviewed this annual report on Form 10-K of Aerpio 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)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

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

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (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.

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

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

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

Date: March 7, 2019

By: */s/ Michael Rogers*

Michael Rogers
Chief Financial Officer
(Principal Financial Officer and Principal 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 of Aerpio Pharmaceuticals, Inc. (the "Company") on Form 10-K for the period ending December 31, 2018 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and result of operations of the Company.

Date: March 7, 2019

By: *<u>/s/ Stephen Hoffman, M.D., Ph.D.</u>*

Stephen Hoffman, M.D., Ph.D.
Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

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 of Aerpio Pharmaceuticals, Inc. (the "Company") on Form 10-K for the period ending December 31, 2018 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and result of operations of the Company.

Date: March 7, 2019

By: **

Michael Rogers
Chief Financial Officer
(Principal Financial Officer and Principal Accounting Officer)