Aldeyra Therapeutics, Inc.
Form 10-K
March 08, 2019

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 transition period from to

Commission File Number 001-36332

ALDEYRA THERAPEUTICS, INC.

(Exact name of Registrant as specified in its charter)

Delaware	20-1968197
(State or other jurisdiction of incorporation)	(IRS Employer Identification No.)

131 Hartwell Avenue, Suite 320

Lexington, MA 02421

(Address of principal executive offices)

(781) 761-4904

(Registrant's telephone number, including area code)

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

Common Stock, $0.001 par value per share	The Nasdaq Stock Market, LLC
(Title of each class)	(Name of each exchange on which registered)

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

None

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

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

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File 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 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer a smaller reporting company or an emerging growth company. See the definitions of the "large accelerated filer," "accelerated filer," "non-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 Act). Yes No

As of June 29, 2018, the last business day of the registrant's last completed second quarter, the aggregate market value of the registrant's Common Stock held by non-affiliates of the registrant was approximately $148,308,896, based on the closing price of the registrant's Common Stock, as reported by The Nasdaq Capital Market. Shares of Common Stock held by each executive officer, director and stockholders known by the registrant to be affiliated with such individuals based on public filings and other information known to the registrant have been excluded since such persons may be deemed affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of March 8, 2019 there were 27,395,425 shares of the registrant's Common Stock issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Specified portions of the registrant's proxy statement with respect to the registrant's 2019 Annual Meeting of Stockholders, which is to be filed pursuant to Regulation 14A within 120 days after the end of the registrant's fiscal year ended December 31, 2018, are incorporated by reference into Part III of this Annual Report on Form 10-K.

Aldeyra Therapeutics, Inc.

Annual Report on Form 10-K

For the Fiscal Year Ended December 31, 2018

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

Various statements in this report are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements involve substantial risks and uncertainties. All statements, other than statements of historical facts, included in this report regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management are forward-looking statements. These statements are subject to risks and uncertainties and are based on information currently available to our management. Words such as, but not limited to, “anticipate,” “believe,” “estimate,” “expect,” “intend “may,” “plan,” “contemplates,” “predict,” “project,” “target,” “likely,” “potential,” “continue,” “ongoing,” “design,” “might,” “would,” “should,” “could,” or the negative of these terms and similar expressions or words, identify forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. The events and circumstances reflected in our forward-looking statements may not occur and actual results could differ materially from those projected in our forward-looking statements. Meaningful factors which could cause actual results to differ include, but are not limited to:

- the timing of enrollment, commencement, and completion of our clinical trials;
- the timing and success of preclinical studies and clinical trials conducted by us and our development partners;
- delay in or failure to obtain regulatory approval of our product candidates;
- the ability to maintain regulatory approval of our product candidates, and the labeling for any approved products;
- the risk that prior results, such as signals of safety, activity or durability of effect, observed from preclinical or clinical trials, will not be replicated or will not continue in ongoing or future studies or trials involving our product candidates;
- the scope, progress, expansion, and costs of developing and commercializing our product candidates;
- uncertainty as to our ability to commercialize (alone or with others) our product candidates following regulatory approval, if any;
- the size and growth of the potential markets and pricing for our product candidates and the ability to serve those markets;
- our expectations regarding our expenses and revenue, the sufficiency or use of our cash resources and needs for additional financing;
- the rate and degree of market acceptance of any of our product candidates;
- our expectations regarding competition;
- our anticipated growth strategies;
- our ability to attract or retain key personnel;
- our limited sales and marketing infrastructure;
- our ability to establish and maintain development partnerships;
- our ability to successfully integrate acquisitions into our business;
- our expectations regarding federal, state and foreign regulatory requirements;
- regulatory developments in the United States and foreign countries;
- our ability to obtain and maintain intellectual property protection for our product candidates; and
- the anticipated trends and challenges in our business and the market in which we operate.

All written and verbal forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section. We caution investors not to rely too heavily on the forward-looking statements we make or that are made on our behalf. We undertake no obligation, and specifically decline any obligation, to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise. You are advised, however, to consult any further disclosures we make on related subjects in any annual, quarterly or current reports that we may file with the Securities and Exchange Commission.

We encourage you to read the discussion and analysis of our financial condition and our financial statements contained in this annual report on Form 10-K. We also encourage you to read Item 1A of Part 1 of this annual report on Form 10-K, entitled “Risk Factors,” which contains a more complete discussion of the risks and uncertainties associated with our business. In addition to the risks described above and in Item 1A of this report, other unknown or unpredictable factors also could affect our results. Therefore, the information in this report should be read together with other reports and documents that we file with the SEC from time to time, including Forms 10-Q, 8-K and 10-K, which may supplement, modify, supersede or update those risk factors. There can be no assurance that the actual results or developments anticipated by us will be realized or, even if substantially realized, that they will have the expected consequences to, or effects on, us. Therefore, no assurance can be given that the outcomes stated in such forward-looking statements and estimates will be achieved.

As used in this annual report on Form 10-K, the terms “Aldeyra,” “Registrant,” “the Company,” “we,” “us,” and “our” mean Aldeyra Therapeutics, Inc. unless the context indicates otherwise.

INDUSTRY AND MARKET DATA

We obtained the industry, market and certain other data used throughout this annual report on Form 10-K from our own internal estimates and research, as well as from industry and general publications, surveys and studies conducted by third parties. Internal estimates are derived from publicly-available information released by industry analysts and third-party sources, our internal research, and our industry experience, and are based on assumptions made by us based on such data and our knowledge of our industry and market, which we believe to be reasonable. In addition, while we believe the industry, market, and other data included in this annual report on Form 10-K are reliable and based on reasonable assumptions, such data involves risks and uncertainties and are subject to change based on various factors, including those discussed in "Risk Factors." These and other factors could cause results to differ materially from those expressed in the estimates made by the independent parties and by us.

ITEM 1. BUSINESS

Overview

We are a biotechnology company devoted to developing and commercializing next-generation medicines to improve the lives of patients with immune-mediated diseases. Our lead product candidate, reproxalap, is a first-in-class treatment in late-stage development for dry eye disease, allergic conjunctivitis, noninfectious anterior uveitis, and Sjögren-Larsson Syndrome. We have additional product candidates in development for proliferative vitreoretinopathy and other retinal diseases, post-transplant lymphoproliferative disease, autoimmune disease, metabolic disease, and cancer. We currently intend to commercialize our products directly or through collaborations. None of our product candidates have been approved for sale in the United States or elsewhere.

Immune-mediated diseases are conditions that result from an imbalance of inhibitory and stimulatory factors that regulate the immune system. Immunological dysregulation can lead to a broad array of conditions that include autoimmune disease, allergy, immunoproliferative disease, and cancer. Many ocular, cardiovascular, metabolic, neurological, and musculoskeletal diseases, affecting tens of millions of patients in the United States and hundreds of millions of patients worldwide, are at least partially immune-mediated. An estimated 7% of western society suffers from some form of immune-mediated disease, and incidence has been increasing. Given the complexity of immune dysregulation, which involves many mediators and signaling pathways, rarely is any single therapeutic approach effective, and today most immune-mediated diseases are generally considered to be inadequately treated. As such, we believe immune-mediated diseases represent considerable unmet medical need, and that demand for novel immune-modulating therapies is high. Consistent with large patient populations and high therapeutic demand, the current market for the treatment of immune-mediated diseases is considerable, representing an excess of $40 billion worldwide.

Our product development pipeline is focused on immune-mediated ocular diseases and select systemic diseases, and encompasses three distinct biological mechanisms of actions: Reactive Aldehyde Species (RASP) inhibition, Dihydrofolate Reductase (DHFR) inhibition, and Heat Shock Protein 90 (Hsp90) inhibition. The immunological activity of our product candidates generally leads to diminished levels of pathological inflammation via down-regulation of immune cell activation or proliferation.

Our lead product candidate reproxalap is a RASP inhibitor that has been shown to diminish ocular inflammation, and has demonstrated statistically significant and clinically relevant improvements across an aggregate of five Phase 2 clinical trials in dry eye disease, allergic conjunctivitis, and noninfectious anterior uveitis. In a sixth Phase 2 clinical trial, reproxalap demonstrated statistically significant and clinically relevant improvements in ichthyosis (a severe skin disorder) caused by Sjögren-Larsson Syndrome, a rare RASP-mediated disease with no approved therapy. A growing body of clinical evidence supports the potential and relevance of RASP inhibition as a new and differentiated mechanism of action. We have discovered and are developing two additional RASP inhibitors, ADX-103 and ADX-629, for the treatment of retinal disease and autoimmune disease, respectively. Additionally, in February 2018, we announced a partnership with Janssen, a Johnson & Johnson company, to develop RASP inhibitors for systemic

inflammatory diseases. In the future, we may enter into additional partnerships that facilitate the development and commercialization of our product candidates.

As we continue to execute on our strategy of expanding our product candidate pipeline, we intend to license or acquire new immune-modulating approaches with novel therapeutic potential. In January 2019, we acquired Helio Vision, Inc. and thereby obtained rights to ADX-2191, an intravitreal DHFR inhibitor (methotrexate) for the prevention of proliferative vitreoretinopathy, a serious sight-threatening retinal disease with no approved treatment. In addition, in December 2016, we in-licensed the clinical-stage product candidate ADX-1612 (investigated in oncology under the name ganetespib) and ADX-1615 (an oral pro-drug of ADX-1612), both of which inhibit Hsp90, a mechanistically differentiated approach for the potential treatment of a number of inflammatory diseases.

As a result of the advancement of our product candidate pipeline, we expect to announce the results of a number of significant clinical trials in 2019:

- The ALLEVIATE Phase 3 clinical trial of topical ocular reproxalap in allergic conjunctivitis;
- The SOLACE Phase 3 clinical trial of topical ocular reproxalap in noninfectious anterior uveitis; and
- Part 1 of the RESET Phase 3 clinical trial of topical dermatological reproxalap in Sjögren-Larsson Syndrome.

In addition, we expect to initiate a variety of important clinical programs in 2019:

- The RENEW Phase 3 clinical trial of topical ocular reproxalap in dry eye disease;
- A Phase 3 clinical trial of ADX-2191 in proliferative vitreoretinopathy;
- A Phase 2 clinical trial of ADX-1612 in post-transplant lymphoproliferative disorder;
- A Phase 2 clinical trial of ADX-1612 in mesothelioma; and
- A Phase 1 clinical trial of ADX-629 in autoimmune disease.

By the end of 2019, we expect that our active clinical programs will include six unique product candidates, representing three distinct mechanisms of action across ten different potential indications. All of our development plans and timelines are subject to adjustment depending on recruitment rate, regulatory review, preclinical and clinical results, funding, and other factors that could delay the initiation, completion, or reporting of clinical trials. Our pipeline is illustrated below.

Product Candidate Development Pipeline

We have no products approved for sale. We will not receive any revenue from any product candidates that we develop until we obtain regulatory approval and commercialize such products or until we potentially enter into agreements with third parties for the development and commercialization of product candidates. If our development efforts for any of our product candidates result in regulatory approval or we enter into collaboration agreements with third parties, we may generate revenue from product sales or from such third parties. We have primarily funded our operations through the sale of our convertible preferred stock, common stock, convertible promissory notes, warrants, and borrowings under debt facilities.

We will need to raise additional capital in the form of debt or equity or through partnerships to fund additional development of our product candidates, and we may in-license, acquire, or invest in complementary businesses or products. In addition, contingent on capital resources, we may augment, diminish, or otherwise modify the clinical development plan described herein.

Since our incorporation, we have devoted substantially all of our resources to the preclinical and clinical development of our product candidates. Our ability to generate revenues, if any, largely depends upon our ability, alone or with others, to complete development of and obtain regulatory approvals for our product candidates, and to successfully manufacture, market, and sell our product candidates. The results of our operations will vary significantly from year-to-year and quarter-to-quarter, and depend on a number of factors, including risks related to our business and industry, risks relating to intellectual property and other legal matters, risks related to our common stock, and other risks that are detailed in the section of this annual report on Form 10-K entitled “Risk Factors.”

The Markets for Our Product Candidates

Dry Eye Disease and Allergic Conjunctivitis – Two Prevalent Diseases with Significant Comorbidity

The symptoms of dry eye disease (ocular pain, dryness, gritty sensation) and allergic conjunctivitis (ocular itching and tearing) are chronic and persistently disturbing, impacting quality of life and leading to loss of work and substantial economic burden. Dry eye disease and allergic conjunctivitis are two of the most common diseases treated by ophthalmologists, and physicians and patients regard therapy as inadequate in a substantial number of cases.

There are approximately 20 million dry eye disease patients in the United States, yet only two drugs are approved for dry eye disease treatment, cyclosporine (0.05% as Restasis® or 0.09% as Cequa®) and lifitegrast (5% as Xiidra®). The activity of both drugs has been observed to be minimal or lacking in the majority of patients, and weeks or months of treatment may be required to achieve even modest clinical benefit.

There are approximately 100 million patients in the United States with allergic conjunctivitis, and we estimate that up to 30 million of such allergic conjunctivitis patients do not respond adequately to, or are dissatisfied with, topical antihistamines, the current standard of care. A primary reason for dissatisfaction with antihistamines appears to be lack of durable activity, which may be due to the fact that histamine is only one of the biological mediators of the disease, and the fact that increased histamine levels persist for only 10 to 20 minutes following allergen exposure.

Many patients manifest symptoms of both dry eye disease and allergic conjunctivitis, and differential diagnosis can be challenging for physicians. Approximately half of dry eye patients complain of itching, which is generally considered the result of allergy, and approximately half of allergic conjunctivitis patients complain of dryness, which is generally considered the result of dry eye disease. There are currently no United States Food and Drug Administration (FDA)-approved products that are indicated to treat both dry eye disease and allergic conjunctivitis. Neither cyclosporine nor lifitegrast have been approved for use in patients with allergic conjunctivitis, and antihistamines are known to exacerbate ocular dryness. Thus, with the possible exception of topical corticosteroids (discussed below), we believe that no currently available drug for dry eye disease or allergic conjunctivitis is likely to be effective for the treatment of patients who experience symptoms of both diseases.

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By inhibiting RASP, which are elevated in a variety of inflammatory diseases, reproxalap represents a novel mechanism for diminishing ocular inflammation in dry eye disease and allergic conjunctivitis. In two Phase 2 clinical trials in dry eye disease and two Phase 2 clinical trials in allergic conjunctivitis, reproxalap demonstrated consistent statistically significant and clinically relevant activity. We believe that reproxalap may have a commercially differentiated product profile versus currently approved drugs for each indication, having shown the potential for early and broad activity in dry eye disease, and durable activity in allergic conjunctivitis. Additionally, reproxalap also has added potential of being the only product able to effectively treat dry eye disease and allergic conjunctivitis, uniquely addressing the needs of the large underserved population that suffers from both diseases.

Based on Phase 2 clinical trial results to date, discussed below, we believe reproxalap could offer superior efficacy relative to existing dry eye disease medications, particularly relative to early onset of action and breadth of activity. Thus, our current expectation is that reproxalap could be priced similarly to, or at a premium to, currently marketed drugs for dry eye disease, which are generally priced in the range of $500-550 per month. The potential size of the dry eye disease market is substantial. There are approximately 20 million diagnosed dry eye disease patients in the United States. Assuming approximately one-third of diagnosed patients are candidates for prescription medication (roughly 5.3 million patients), and assuming approximately six months of therapy per year, the potential total addressable market for reproxalap therapy in dry eye disease is greater than $17 billion in the United States.

Contingent on the results of current and planned clinical trials in DED and AC, in addition to regulatory authority approval, we intend to commercialize reproxalap ophthalmic solution directly or through marketing partnerships. Based in part on similar proprietary topical ocular product launches, we expect that approximately 200-225 sales representatives will be required in the United States to launch reproxalap for ocular inflammation associated with dry eye disease and allergic conjunctivitis.

Noninfectious Anterior Uveitis

There are approximately 260,000 patients in the United States with noninfectious anterior uveitis, a potentially blinding disease that is currently treated with topical ocular corticosteroids. Topical ocular corticosteroid therapy is generally effective but can result in serious ocular toxicity. We estimate that about half of uveitis patients have recurrent (approximately between two to three flares per year) or chronic (four or more flares per year) forms of noninfectious anterior uveitis, requiring multiple consecutive courses of treatment. The known risks of ocular corticosteroid use, including increased intraocular pressure leading to glaucoma, cataract formation, secondary ocular infections, and corneal and scleral thinning, are elevated in recurrent and chronic patients. Given the risks associated with extended corticosteroid use, there is considerable demand for novel therapies that do not cause ocular toxicity following repeated administration.

In a Phase 2 clinical trial in which patients were treated with either reproxalap, topical corticosteroids, or a combination of reproxalap and low-dose topical corticosteroids, reproxalap monotherapy was statistically non-inferior to either corticosteroid monotherapy or combination therapy, suggesting that reproxalap treatment was as effective as corticosteroid treatment. Unlike corticosteroids, in the Phase 2 clinical trial, reproxalap did not induce elevations in intraocular pressure. Thus, reproxalap represents a potentially safer therapeutic option for patients suffering from noninfectious anterior uveitis. Given the fact that noninfectious anterior uveitis is a rare but potentially blinding disease, and given the potential safety advantage of reproxalap versus corticosteroids, we believe that a one-month treatment course of reproxalap therapy could be priced up to $1,500. On average, recurrent and relapsing noninfectious anterior uveitis patient populations require two to five months of treatment per year.

Contingent upon the current Phase 3 clinical program results and regulatory authority approval, we intend to commercialize reproxalap ophthalmic solution for the treatment of NAU. Because the recurrent and chronic forms of NAU are severe and require particular medical expertise, we intend to focus on the roughly 200 uveitis and ocular inflammation sub-specialists in the United States. Thus, we expect that a small number of sales representatives and medical science liaisons will be required for commercialization.

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There are many ocular inflammatory diseases that are treated with topical ocular corticosteroids, including scleritis, post-operative inflammation, graft versus host disease, blepharitis, and cyclitis. In 2016, according to IMS data, total sales of topical ocular corticosteroids were approximately $800 million in the United States. Given the potential safety advantages over corticosteroids, reproxalap and similar product candidates have the potential to be first-line treatment options for corticosteroid-responsive ocular diseases in the United States, assuming FDA marketing approval.

Proliferative Vitreoretinopathy and Other Retinal Diseases

Proliferative vitreoretinopathy (PVR) is a rare inflammatory disorder of the retina that leads to severe retinal scarring and blindness, and is the leading cause of failure of retinal reattachment surgery. Over 50% of PVR cases result in severe uncorrectable vision loss (visual acuity of 20/320 or worse), and 76% of PVR patients suffer from at least moderate uncorrectable vision loss. PVR occurs after up to 10% of surgeries for retinal detachment and 50% or more of surgeries for open globe injury. Based on the prevalence of primary retinal detachment, in addition to retinal detachment that occurs as a result of trauma, we estimate that there are, in aggregate, more than 20,000 treatable cases of PVR in the United States, Europe, and Japan. By inhibiting cell growth and thereby diminishing scar formation, ADX-2191 has the potential to be the first FDA-approved drug for prevention of PVR. In April 2018, ADX-2191 received orphan drug designation from the FDA for the prevention of PVR.

In addition to PVR, the retina is susceptible to a variety of immune-mediated diseases, many of which are mediated by RASP. Inflammatory retinal disorders that involve RASP include both posterior and pan-uveitis, uveitis-associated macular edema, diabetic macular edema, and diabetic retinopathy. Separately, RASP and RASP-adducts accumulate in dry age-related macular degeneration, Stargardt’s Disease (juvenile dry age-related macular degeneration-like disease), and Sjögren-Larsson Syndrome-associated maculopathy. We believe that the number of patients affected by immune-mediated retinal disorders is considerable. In 2010, the National Eye Institute estimated that diabetic retinopathy and age-related macular degeneration represent approximately 10 million patients in the United States, and is expected to grow to almost 18 million by 2030. In 2017, the global ophthalmic drugs market was valued at $23 billion, and the market for retinal diseases accounted 39%, or approximately $9 billion, one of the largest ocular segments. Therefore, we believe the total market potential of RASP inhibitors for the treatment of retinal disease is substantial.

Sjögren-Larsson Syndrome

Sjögren-Larsson Syndrome (SLS) is a rare systemic disease and inborn error of metabolism caused by mutations in an enzyme that metabolizes fatty (long-chain carbon) RASP, resulting in severe skin, neurological, and retinal disorders. Genetic mutation analysis suggests that there are approximately 1,300 SLS patients in the United States, and a greater number of SLS patients in Europe.

The primary day-to-day complaint of SLS patients and their caregivers is ichthyosis, a severe skin disorder characterized by thick, scaly, dry, flaking, wrinkled, pigmented, pruritic (itchy), inflamed skin. SLS patients are persistently disturbed by pruritus, and often excoriate skin by scratching. The scales that accumulate on the surface of the skin are subject to bacterial overgrowth, which results in an unpleasant odor that is associated with some SLS patients. The ichthyosis in SLS is usually present at birth and stabilizes within the first two years of life, affecting most of the body except the face, palms, and soles. SLS patients are often unable to care for themselves, and require constant monitoring, intensive daily patient care that includes extended bathing routines over multiple hours, and frequent doctor visits. The time required to attend to SLS patients often prevents caregivers from working outside the home. In addition, considerable social stigma and emotional burden is common, especially given scale odor, the flaking skin, and the external misperception that SLS patients suffer from diffuse cutaneous infectious disease. There is currently no therapy approved for the treatment of SLS, though some patients and their caregivers apply non-specific topical creams, including keratinolytics (acids that soften skin), moisturizers, and retinoids. We believe that the effects of keratinolytic and moisturizing creams are minimal or non-existent in treating SLS ichthyosis, and, due to toxicity, retinoids are not suitable for chronic use.

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The ichthyosis in SLS is thought to be caused by RASP-mediated modification of lipids (fats) that are generated in the epidermis (the most superficial layer of skin) to form a moisture barrier that holds water in the skin. Moisture barrier compromise leads to water loss, which in turn leads to the epidermal dryness and thickening that are characteristic of ichthyosis. We believe that by lowering levels of RASP and thereby preventing lipid modification and the ensuing moisture barrier dysfunction, reproxalap, when applied topically to the skin, has the potential to ameliorate the dermatologic symptoms of SLS. In April 2017, reproxalap received orphan drug designation from the FDA for the treatment of congenital ichthyosis, including the ichthyosis characteristic of SLS.

We have completed a payer survey to assess potential pricing of topical dermatologic reproxalap for the treatment of ichthyosis associated with SLS. During the survey, payers were informed that topical dermatologic reproxalap is unlikely to affect the neurological and retinal aspects of SLS, and that daily lifelong topical therapy covering 90% of the body surface could be required for disease control. Assuming genetic diagnosis of SLS, payers generally noted that coverage was possible within a range of $200,000 to $400,000 per patient per year.

Immune-Mediated Systemic Diseases

Immune-mediated systemic diseases, such as autoimmune disease, are generally chronic conditions characterized by excessive and misdirected inflammatory responses. In aggregate, autoimmune diseases and related systemic inflammatory disorders represent tens of millions of patients in the United States, with aggregate drug sales expected to exceed $74 billion by 2022. In 2017, three of the top five highest-selling drugs, totaling more than $32 billion globally and $20 billion in United States sales, were prescribed for a variety of immune-mediated disorders, including Crohn’s disease, rheumatoid arthritis, psoriasis, ulcerative colitis, and ankylosing spondylitis. The potential market for immune-modulating therapies could continue to expand as a result of growing evidence that excessive inflammation may be critical to the development and progression of cardiovascular disease, diabetes, Alzheimer’s disease, and many other common conditions that are not typically defined as inflammatory or autoimmune diseases.

Given the complex pathophysiology of systemic immune-mediated disorders, many of which are caused by a variety of pro-inflammatory mediators, therapy often requires combinations of drugs with distinct mechanisms of action. As such, we believe novel product candidates for immune-mediated diseases are in high demand.

ADX-1612 (investigated in oncology under the name ganetespib) is a novel drug candidate that inhibits Heat Shock Protein 90 (Hsp90). Hsp90 is involved in the processing of a variety of proteins, and appears to be particularly important in cellular proliferation. Many immune-mediated diseases are at least in part the result of hyper-proliferation of immune cells, a phenomenon known as lymphoproliferation. Lymphoproliferative diseases include systemic lupus erythematosus (lupus), autoimmune lymphoproliferative syndrome, Waldenstrom’s macroglobulinemia, Wiskott-Aldrich syndrome, post-transplant lymphoproliferative disorder, and myelodysplastic syndromes. We are not aware of any other company that is developing an Hsp90 inhibitor for systemic immune-mediated disease. Similar to lymphoproliferative disease, cancer is also characterized by uncontrolled cellular replication, and ADX-1612, may represent a new therapeutic approach for the treatment of certain cancers in combination with other cancer drugs.

Additionally, our RASP inhibitor platform represents a potential novel therapeutic approach for a variety of common systemic immune-mediated conditions. Because RASP appear to be involved in the generation and potentiation of inflammation in general, we believe the potential therapeutic applicability of RASP inhibitors is broad. We are not aware of any other company actively developing RASP inhibitors, although we have partnered with Janssen, a Johnson & Johnson company, to develop novel RASP inhibiting agents for the treatment of systemic immune-mediated disease. In 2019, we expect to begin clinical testing of ADX-629, a novel drug candidate that inhibits RASP, in autoimmune disease.

The Competitive Landscape of Our Product Candidates

The pharmaceutical industry is characterized by intense competition and rapid innovation. Our potential competitors include large pharmaceutical and biotechnology companies, specialty pharmaceutical companies, academic institutions, government agencies, and research institutions. We believe that the key competitive factors that will affect the development and potential commercial success of our product candidates are efficacy, safety, tolerability, and the ability to reduce the dependence on, or the dose of, more toxic drug products.

Many of our potential competitors have substantially greater financial, technical, and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products, and the commercialization of those products. Accordingly, our competitors may be more successful than we may be in obtaining regulatory approval for products and achieving widespread market acceptance. Our competitors' products may be more effective, or more effectively marketed and sold, than any product that we may commercialize, and may render our product candidates obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our product candidates. We anticipate that we will face intense and increasing competition as new products enter the market and advanced technologies become available. In addition, the development of new treatment methods for the diseases we are targeting could render our products non-competitive or obsolete.

While our product candidates may manifest efficacy or safety advantages, many marketed therapies are generic or may be priced considerably lower than the pricing we anticipate for our product candidates. Pricing factors may discourage the initial or prolonged use of our product candidates. In addition, the recent growth of Pharmacy Benefit Managers has diminished the profitability of drug commercialization for smaller companies, and may hamper our ability to support our operations or compete effectively in the marketplace following regulatory approval, if any.

RASP Inhibitor Platform

A number of academic groups have published on the concept of reducing RASP levels, primarily by using compounds with amines (certain nitrogen-containing molecules) that react with RASP through a chemical process known as the Schiff base reaction. Various RASP-binding amines have been described, particularly carnosine (a naturally occurring dipeptide), which has other potential mechanisms of action unrelated to RASP. At least one group has published on the use of certain nitrogen-containing marketed products to temporarily, in a reversible manner, bind retinaldehyde (a RASP) as a potential therapy for retinal disease. Schiff base reactions have also been mentioned as possible explanations for a portion of the activity of aminoguanidine, pyridoxamine, and possibly other non-proprietary amine-containing compounds that have been tested in clinical trials for diabetic nephropathy. However, the Schiff base reaction is reversible, and generally the substrates (precursors) and products of the reaction exist in equilibrium such that, at any point in time, the RASP substrate may be bound or unbound. In this way, Schiff base reactions alone represent reversible and temporary RASP binding, and likely lead to the relocation of RASP rather than the elimination of RASP. We believe that reproxalap and chemically related product candidates that we have discovered are differentiated from the above approaches in that the chemical structures of our product candidates are novel, and the reaction with RASP has been observed to be essentially irreversible in vivo, which, we believe, may result in a more effective means of diminishing RASP.

Other Immune-Modulating Pharmacotherapies

A myriad of new treatments have been or are being developed to treat inflammatory diseases, and have been used, or in theory could be used, for the treatment of the diseases that our product candidates are intended to target. Immune-modulating products include cytokine inhibitors, immune cell receptor inhibitors, complement inhibitors, and Janus kinase inhibitors. Companies that currently market such therapies include Abbvie, Inc., Johnson & Johnson, UCB Inc. and UCB S.A., Amgen, Inc., Bristol-Myers Squibb Co., and Pfizer, Inc. Currently marketed products may manifest efficacy and safety advantages over our product candidates, and may be used to treat the diseases for which we are developing our product candidates. In addition, Hsp90 inhibitors other than ADX-1612 are in development for the treatment of cancer, and such compounds could theoretically be used for the treatment of immune-mediated diseases. Methotrexate, the active drug substance of ADX-2191, is generically available and has been used as a chemotherapeutic and immune modulating agent, and other formulations or application methods of methotrexate could be developed for the treatment of inflammatory retinal diseases.

Competitive Product Candidates by Indication

We believe the primary competitors by indication with respect to our current programs in late stage-clinical testing are as follows:

Competitive Pharmaceuticals by Indication

Indication	Competitive Products
Dry Eye Disease	Topical immunomodulators, such as cyclosporine (0.05% as Restasis® or 0.09% as Cequa®) and lifitegrast (5% as Xiidra®), topical corticosteroids and artificial tear solutions
Allergic Conjunctivitis	Topical antihistamines and corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and mast cell stabilizers
Noninfectious Anterior Uveitis	Topical corticosteroids
Sjögren-Larsson Syndrome	Off-label use of retinoids, keratinolytics, and moisturizers
Proliferative Vitreoretinopathy	None

We believe that there is significant unmet medical need for the diseases that we intend to target. If proven to be safe and effective, we believe that our product candidates could be used in place of, or in addition to, current therapies. Currently available therapies for the treatment of dry eye disease are generally considered by physicians and patients to be inadequate, may require weeks or months of treatment to achieve even moderate clinical benefit, and have not demonstrated clinical activity in allergic conjunctivitis, a common comorbidity. Topical antihistamines for the treatment of allergic conjunctivitis are not effective for all patients, in part due to lack of durable activity following exposure to allergen and, in addition, exacerbation of ocular dryness. Topical corticosteroids for noninfectious anterior uveitis and other ocular inflammatory diseases are associated with toxicity including glaucoma, cataracts, and ocular infection, and are not recommended for extended use. There is no approved therapy for Sjögren-Larsson Syndrome, and we believe that the current non-specific creams and medications for Sjögren-Larsson Syndrome are poorly effective, if effective at all. There is no approved therapy for proliferative vitreoretinopathy.

Many drugs are in development for allergic conjunctivitis and dry eye disease. Novartis/Alcon (ESBA105, LME636) and EyeGate Pharmaceuticals, Inc. (EGP-437) have conducted clinical trials in anterior uveitis. We believe that there are no drugs in development for both dry eye disease and allergic conjunctivitis, Sjögren-Larsson Syndrome, or proliferative vitreoretinopathy. For the diseases we intend to study, there may be other developmental therapies of which we are not aware.

Our ability to compete successfully will depend in part on our ability to utilize our drug development expertise to identify, develop, secure rights to, and obtain regulatory approvals for promising pharmaceutical products before others are able to develop competitive products. Our ability to compete successfully will also depend on our ability to attract and retain skilled and experienced personnel. Additionally, our ability to compete may be diminished by insurers and other third-party payors, which generally encourage the use of cheaper, non-innovative, or generic products.

Clinical Trial Results and Development Plans

Prior to applying for marketing approval, our product candidates must satisfy regulatory authority requirements for safety and efficacy, including pivotal Phase 3 clinical assessment. Our active clinical programs with reproxalap have

consistently demonstrated statistically and clinically significant efficacy, and have advanced to late-stage clinical testing. In addition, reproxalap has been observed to be well tolerated and reported adverse events were generally mild in our clinical trials to date. Our material clinical results have been disclosed elsewhere in detail, and we encourage review of all clinical trial disclosures. Our programs in allergic conjunctivitis, noninfectious anterior uveitis, and Sjögren-Larsson Syndrome have begun Phase 3 clinical testing, and our programs

in dry eye disease and proliferative vitreoretinopathy are expected to begin Phase 3 clinical testing in 2019. All of our development plans and timelines are subject to adjustment depending on recruitment rate, regulatory review, preclinical and clinical results, funding, and other factors that could delay the initiation, completion, or reporting of clinical trials.

Dry Eye Disease

In September 2017, we announced that the results of a randomized, parallel-group, double-masked Phase 2a clinical trial of reproxalap ophthalmic solution demonstrated statistically and clinically relevant improvement from baseline in multiple signs and symptoms associated with dry eye disease. In September 2018, we announced that the results of a randomized, vehicle-controlled, parallel-group, multi-center, double-masked Phase 2b clinical trial of 0.1% and 0.25% concentrations of reproxalap topical ophthalmic solution demonstrated statistically significant improvement over vehicle in ocular signs and symptoms associated with dry eye disease (see figure below). Relative to patients treated with vehicle, patients treated with the 0.25% concentration of reproxalap demonstrated statistically significant and clinically relevant reductions in the Four-Symptom Ocular Dryness Score and the Overall Ocular Discomfort Symptom Score. For drug-treated patients, improvement greater than that of vehicle was consistently observed across all symptoms, and activity versus vehicle was evident as early as two weeks, the first assessment following initiation of therapy. The early onset of symptomatic improvement is consistent with the Phase 2a clinical trial of topical ocular reproxalap in dry eye disease, and is supportive of a differentiated product profile relative to standard of care. Patients treated with the 0.25% concentration of reproxalap also demonstrated reductions in ocular fluorescein staining score that were statistically superior to those of patients treated with vehicle. Both 0.1% and 0.25% reproxalap concentrations demonstrated activity relative to vehicle, and a clear dose response was observed. Consistent with previous clinical trials, topical ocular reproxalap was well-tolerated, and reported adverse events were generally mild. Based on the success of the Phase 2 clinical trials we plan to initiate Part 1 of a two-part adaptive Phase 3 clinical trial in the first half of 2019. The clinical trial will evaluate the efficacy of reproxalap ophthalmic solution (0.25%) vs. vehicle in 400 patients with moderate-to-severe dry eye disease. Results from Part 1 will confirm dosing and size for Part 2 of the Phase 3 clinical trial. The co-primary endpoints of this trial will be ocular dryness, and fluorescein nasal region staining in pre-specified moderate to severe patient subsets analyzed over twelve weeks of therapy using Mixed effects Model Repeated Measures.

Phase 2b Dry Eye Disease Clinical Trial Results

Allergic Conjunctivitis

In February 2016, we announced that the results of a randomized, parallel-group, double-masked, vehicle-controlled Phase 2a clinical trial of reproxalap ophthalmic solution in patients with allergic conjunctivitis demonstrated statistically and clinically significant activity of reproxalap over vehicle in reducing ocular itching and tearing. In June 2017, we announced that the results of a randomized, parallel-group, double-masked, vehicle-controlled, multi-center Phase 2b clinical trial of 0.1% and 0.5% topical ocular reproxalap in patients with allergic conjunctivitis demonstrated statistically and clinically significant activity of reproxalap over vehicle in reducing ocular itching. In the Phase 2b clinical trial, which assessed ocular itching (scale 0 to 4) via a conjunctival allergen challenge model (allergen administered directly to the eye), the activity of reproxalap in subjects challenged with seasonal allergens was statistically significantly superior to activity in vehicle-treated subjects, as measured by area under the itch score curve from 10 to 60 minutes post-challenge. In addition, responder (two-point improvement from baseline itch score) probability in drug-treated patients was statistically superior to that of vehicle-treated patients for subjects challenged with seasonal allergens (see figure below). A clear dose response was observed. Reproxalap was generally well tolerated and there were no safety concerns observed during the trial.

Phase 2b Allergic Conjunctivitis Clinical Trial Results

In 2018, based on the success of the Phase 2 clinical trials, we initiated the Phase 3 ALLEVIATE clinical trial of topical ocular reproxalap for the treatment of allergic conjunctivitis. The trial has enrolled over 300 patients, randomized equally to receive a single dose of either 0.25% topical ocular reproxalap, 0.5% topical ocular reproxalap, or vehicle. The primary endpoint is ocular itch score area under the curve 10 to 60 minutes post-challenge. Two-point responder probability is the key secondary endpoint. We expect to report the results of the Phase 3 trial in early 2019. In addition, in preparation for a subsequent Phase 3 clinical trial in allergic conjunctivitis, we have initiated two clinical methods development studies to assess the feasibility of measuring ocular itching following environmental exposure to allergen.

Noninfectious Anterior Uveitis

In May 2016, we announced that the results of our randomized, parallel-group, investigator-masked, active-controlled Phase 2 clinical trial of 0.5% reproxalap ophthalmic solution in patients with noninfectious anterior uveitis demonstrated that reproxalap reduced inflammatory cell count in the anterior chamber of the eye to a degree similar to that of standard-of-care corticosteroid therapy (which may lead to cataracts and glaucoma in some patients), but without the intraocular pressure elevations that were observed in subjects treated with corticosteroids. Forty-five subjects were randomized equally to receive six weeks of treatment with one of the following: 0.5% topical ocular reproxalap four times daily; Pred Forte® (1% prednisolone acetate, a corticosteroid) four times daily (tapered); or 0.5% topical ocular reproxalap four times daily and Pred Forte® two times daily (tapered). The results of the trial demonstrated that the activity of reproxalap was statistically non-inferior to Pred Forte® in reducing anterior chamber inflammatory cell count (see figure below). At the week 4 visit, grade 0 cell count (zero cells) was

observed in 53% of reproxalap-treated patients versus 38% of corticosteroid-treated patients. Elevations of intraocular pressure observed in corticosteroid-treated patients were not observed in reproxalap-treated patients (see figure below). Topical ocular reproxalap was observed to be generally well tolerated and there were no serious adverse events.

Noninfectious Anterior Uveitis Phase 2 Clinical Trial Results for Anterior Chamber Cell Count Grade

Noninfectious Anterior Uveitis Phase 2 Clinical Trial Results for Intraocular Pressure (mmHg)

In 2017, based on the success of the Phase 2 clinical trial, we initiated the Phase 3 SOLACE clinical trial of 0.5% topical ocular reproxalap for the treatment of noninfectious anterior uveitis. The trial is expected to enroll approximately 100 patients, randomized equally to receive either topical ocular reproxalap 0.5% or vehicle for four weeks. The primary endpoint is time to zero inflammatory cells in the anterior chamber of the eye. We expect to report results of the Phase 3 clinical trial in the second half of 2019.

Sjögren-Larsson Syndrome

In August 2016, we announced that the results of a randomized, parallel-group, double-blind, vehicle-controlled clinical trial of a dermatologic formulation of 1% reproxalap for the treatment of the skin manifestations of Sjögren-Larsson Syndrome (SLS) demonstrated clinically relevant activity of reproxalap in diminishing the severity of ichthyosis, a serious dermatologic disease characteristic of SLS. Twelve SLS patients with moderate to severe ichthyosis were randomized equally to receive reproxalap 1% dermatologic formulation or vehicle formulation administered once daily on a 4 x 10 inch area of skin for two months. Ichthyosis was graded by a blinded central review of digital photographs, as well as by clinical exam, using the Ichthyosis Severity Score, which is comprised of assessments of global impression, scaling, erythema (redness), lichenification (thickness) and excoriation (abrasion). As assessed by central review, five of six subjects (83%) treated with reproxalap achieved a rating of “almost clear” or “mild” on global assessment. Six of six (100%) subjects treated with reproxalap improved over the course of therapy as assessed by central review, and the improvement was statistically significantly greater than that observed with vehicle-treated patients. For reproxalap-treated subjects, mean reductions in ichthyosis severity were greater after eight weeks of therapy than after four weeks of therapy, suggesting a disease modifying effect of reproxalap (see figure below). Topical dermal reproxalap was observed to be generally well tolerated, and there were no significant adverse events, serious adverse events, or discontinuations in the trial.

Sjögren-Larsson Syndrome Phase 2 Clinical Trial Results for Each Reproxalap-Treated Patient as Assessed by Clinical Exam

In 2018, based on the success of the Phase 2 clinical trial, we initiated the two-part Phase 3 RESET clinical trial of 1% topical dermatologic reproxalap for the treatment of ichthyosis associated with SLS. Part 1 of the trial is expected to enroll approximately nine patients, randomized 2:1 to receive either topical dermatologic reproxalap or vehicle, respectively, for six months. Body surface area coverage will escalate from 20% to 90% over the course of treatment. The primary endpoint will be ichthyosis scaling in drug-treated patients, as assessed by clinical exam using the Visual Index for Ichthyosis Severity, a scoring system similar to the Ichthyosis Severity Score. Part 2 of the RESET trial will be powered based on the results Part 1. The design of Part 2 is expected to be similar to that of Part 1, except that 90% of the body surface area will be treated for six months. We expect to report the results of Part 1 of the Phase 3 trial in the second half of 2019.

Proliferative Vitreoretinopathy

Standard of care treatment for proliferative vitreoretinopathy ("PVR") results in subsequent retinal detachment surgical rates that approximate 50%. In a single-arm, open-label, investigator-sponsored Phase 1b clinical trial performed at the Massachusetts Eye and Ear Infirmary, approximately 20% of patients with PVR treated with multiple injections of ADX-2191 required subsequent surgery for retinal detachment. Thus, relative to standard of care, ADX-2191 may reduce incidence of retinal detachment following the development of PVR, thereby increasing the probability of preservation of visual function.

We plan to begin a two-part, multi-center, non-masked, randomized, controlled, adaptive Phase 3 clinical trial of ADX-2191 in patients with PVR in the second half of 2019, following discussions with regulatory authorities. The trial is expected to compare patients treated with ADX-2191 to patients receiving standard of care. We expect to report results in 2020.

Mesothelioma and Other Cancers

In September 2018, we announced positive results from the MESO-2 investigator-sponsored Phase 1/2 clinical trial of ADX-1612 in patients with pleural malignant mesothelioma. ADX-1612, when combined with standard pemetrexed and platinum therapy, resulted in partial response rates that exceeded historical standard of care. Twenty-seven patients with pleural malignant mesothelioma were enrolled at a single site in the United Kingdom, and were divided into one of three cohorts receiving 100, 150, or 200 mg/m_2 of ADX-1612 on days 1 and 15 every 21 days. Of 23 evaluable patients, 22 patients (96%) manifested stable disease or clinical response, and one patient (4%) with non-epithelial histology progressed, as measured by via RECIST (Response Evaluation Criteria in Solid Tumors) criteria. The overall response rate was 61%, relative to historical standard of care response rates of 20% to 40%. The response rate in patients with epithelial histology was 76%. In seven patients, reduction of tumor burden was greater than 50%. One patient remained progression-free after 37 months. ADX-1612 was observed to be well-tolerated, and dose-limiting toxicity was observed in three patients, all of whom were enrolled in the highest dose group. Pending discussions with regulatory authorities, we plan to initiate a Phase 2 clinical trial of ADX-1612 in mesothelioma in 2019. In addition, a European-based investigator-sponsored trial (EUDARIO) of ADX-1612 in combination with either platinum therapy or a PARP (poly [ADP-ribose] polymerase) inhibitor has been initiated in ovarian cancer patients.

The Science Supporting Our Product Candidates

Reactive Aldehyde Species

In response to infection, injury, endogenous and exogenous chemical triggers, heat, and other stimuli, pro-inflammatory reactive aldehyde species (RASP) are generated through a variety of metabolic processes, including alcohol oxidation, enzymatic and non-enzymatic lipid oxidation, and sphingosine metabolism. RASP appear to effect inflammation signaling via covalent binding to thiol (sulfur-containing) and amine (nitrogen-containing) residues on proteins, including receptors and enzymes. RASP-protein adducts directly influence the function of proteins, leading to activation of intracellular inflammatory factors, including NF-kB, an important mediator in the inflammatory response. In addition, RASP adducts bind to Scavenger Receptor A, which also initiates pro-inflammatory signaling and leads to the formation of antibodies against the adducted protein, at least in part explaining the presence of host-directed antibodies in autoimmune diseases such as rheumatoid arthritis. Levels of RASP are generally observed to be elevated in ocular and systemic inflammatory disease, and thus represent therapeutic targets for immune-modulation.

Because of the inherent toxicity of RASP, most, if not all, living organisms contain enzymes, such as aldehyde reductases and aldehyde dehydrogenases, that convert RASP into non-toxic molecules. Genetic mutations in the RASP-metabolizing enzymes cause disease. In Sjögren-Larsson Syndrome, mutations in fatty aldehyde

dehydrogenase are responsible for skin, neurological, and retinal disease. In particular, ichthyosis, the severe skin disease associated with Sjögren-Larsson Syndrome, is thought to be due to RASP binding to epidermal fats that prevent moisture loss, leading to thick, scaly, dry, flaking, wrinkled, pigmented, pruritic (itchy), inflamed skin.

Aside from the stimulation of inflammation, there is no generally accepted biological role of high levels of RASP. Some physiologic molecules have RASP forms, including retinaldehyde (a form of Vitamin A) and pyridoxal and pyridoxal phosphate (forms of Vitamin B6), but the activity of physiological RASP is highly restricted by chaperone and other proteins that prevent reaction with other molecules, including our RASP inhibitors. Thus, pharmacotherapeutic RASP inhibition is expected not to adversely affect normal physiologic processes. Consistent with the lack of accessibility of physiologic RASP, our most advanced RASP inhibitor, reproxalap, which has been administered to over 450 patients across seven completed clinical trials, has been observed to be generally well tolerated and has not resulted in any serious adverse events.

The RASP Inhibitor Platform

We are currently developing reproxalap, a new chemical entity, and other novel RASP inhibitors for the treatment of immune-mediated disease. Reproxalap is a small molecule designed specifically to bind, and thereby allow for the degradation of, RASP. In in vitro and animal studies, reproxalap does not appear to affect most cellular components, including most receptors, enzymes, ion channels, or other proteins. Reproxalap has been shown to outcompete cellular constituents to covalently bind and trap RASP. Reproxalap-RASP adducts appear to be rapidly degraded in cellular environments, after which neither reproxalap nor RASP are detectable. Outside of biological systems, reproxalap-RASP adducts have shown to be remarkably non-reactive and stable, suggesting that reproxalap-RASP binding may be effectively irreversible. By forming covalent drug-RASP adducts that are then degraded, reproxalap and other RASP inhibitors have the potential to substantially lower RASP levels.

We believe we have been the first to demonstrate the beneficial effects of RASP inhibition in a variety of animal models relating to immune-mediated disease, suggesting that reproxalap and analogs may have potent anti-inflammatory effects that persist hours after administration at a variety of different doses relevant to clinical testing.

- In mouse models of ocular inflammation and post-surgical healing, topically applied reproxalap ophthalmic solution reduced ocular redness and inflammatory cytokines comparable to corticosteroid therapy and slowed the development of corneal haze (fibrosis). (Data presented at the Association for Research in Vision and Ophthalmology 2015 Annual Meeting)
- In mice injected with a pro-inflammatory agent known as endotoxin, intraperitoneally administered reproxalap statistically reduced a variety of inflammatory cytokines (protein inflammatory mediators), including IL-5, Il-1ß, IL-17, and TNF-a, while up-regulating the primary anti-inflammatory cytokine, IL-10. Additionally, in models of mouse contact dermatitis (induced by phorbol myristate acetate) and allergic contact dermatitis (induced by sensitivity to oxazolone), reproxalap statistically reduced inflammation as measured by edema (swelling). (Data presented at the American Academy of Asthma Allergy and Immunology 2015 Annual Meeting)
- In a model of radiation mucositis (oral inflammation) in hamsters, chronic subcutaneous administration of reproxalap reduced healing time and decreased fibrosis (scarring). (Data presented at the Multinational Association of Supportive Care in Cancer – International Society of Oral Oncology 2015 Annual Meeting)
- In two different mouse models of inflammatory pain, intraperitoneally administered reproxalap dose-dependently reduced nociceptive behavior, suggesting that reproxalap down-regulates pain signaling in inflammation. (Data presented at the 2016 International Conference on Pain Research and Management)
- In rat cardiomyocyte culture, reproxalap prevented fibrotic transformation, and inhibited NF-kB activation and IL-1ß release. (Data presented at the 2016 American Society for Cell Biology Annual Meeting)
- In a mouse model of lung inflammation, intraperitoneal administration of reproxalap reduced infiltration of inflammatory cells and levels of pro-inflammatory cytokines in the lung. (Data presented at the 2017 World Congress on Inflammation Annual Meeting)
- In a rat model of intraocular inflammation, a single intravitreal injection of ADX-103 reduced the development of retinal pathology. (Data presented at the Association for Research in Vision and Ophthalmology 2018 Annual Meeting)

- In a rat model of diabetic macular edema, intravitreal injection of ADX-103 reduced retinal inflammatory cell infiltration. (Data presented at the Association for Research in Vision and Ophthalmology 2018 Annual Meeting)

Thus, we believe that the immune-modulating mechanism of action of RASP inhibition is potentially multifactorial – lowering inflammation, reducing healing time, diminishing scarring, and mitigating inflammatory pain – and may ameliorate inflammatory disease and deter disease progression in different ways simultaneously.

In addition to the development of reproxalap, we intend to continue the discovery and development of other novel RASP inhibitors, and we intend to continue to develop intellectual property around such molecules. We have identified, synthesized, and tested numerous molecules that may be more potent than reproxalap in inhibiting RASP. We are currently screening novel product candidates to address diseases where topical and systemic administration may reduce RASP-mediated pathology. We have nominated two new RASP inhibitors, ADX-103 and ADX-629, for clinical development, which may begin in 2019, depending on additional preclinical data, regulatory discussions, funding, and other factors.

The Immune Modulating and Anti-Proliferative Activity of Hsp90 Inhibition

ADX-1612 is a novel, highly potent small molecule Hsp90 inhibitor that has completed numerous clinical trials in oncologic diseases. Hsp90 is a protein involved in the processing of other proteins that are critical for physiologic cellular function. Inhibition of Hsp90 leads to diminished cellular replication. We intend to develop ADX-1612 for the treatment of one or more systemic lymphoproliferative inflammatory diseases where excessive immune cell replication leads to inflammation, organomegaly, and other pathologies. ADX-1612 appears to be reasonably well tolerated at doses that may be sufficient to diminish immune cell replication.

Hsp90 is elevated in autoimmune disease, and is believed to lead to broad activation of the immune system. Preclinical results have shown the potential of ADX-1612 to diminish inflammatory cytokines, immune cell numbers, autoantibody formation, and lymphadenopathy (pathologic swelling of the lymph glands, in part due to immune cell hyper-proliferation). In addition, ADX-1612 appears to preserve organ function in animal models of autoimmune disease. The immune-modulating potential of ADX-1612 was observed clinically in a patient treated for Chronic Myelocytic Leukemia, in whom resolution of vasculitis (a systemic autoimmune disease) occurred during treatment.

ADX-1612, and an oral pro-drug of ADX-1612 (ADX-1615), in combination with DNA-damaging agents, may have utility in the treatment of certain cancers. Hsp90 is required for DNA repair, and Hsp90 inhibition in the setting of DNA damage could lead to cancer cell death. In ovarian cancer cell lines, preclinical studies have demonstrated the anti-proliferative synergy of ADX-1612 in combination with platinum-containing DNA damaging agents.

The Potential of ADX- 2191 to Prevent Proliferative Vitreoretinopathy

Proliferative vitreoretinopathy (PVR) is characterized by excessive replication and pro-inflammatory activity of retinal cells, at least a portion of which synthesize collagen, the principal component of scar tissue. Retinal scarring can lead to impairment of vision, including blindness. Methotrexate, the active component of ADX-2191 (intravitreal methotrexate), is a dihydrofolate reductase inhibitor, which has been used to treat cancer and autoimmune disease. The anti-proliferative and anti-inflammatory properties of dihydrofolate reductase inhibition are well described. In preclinical studies of primary cell cultures from PVR patients, dihydrofolate reductase inhibition reduced pathological cell proliferation and scar-like collagen deposition. Thus, the observed clinical activity of ADX-2191 in PVR is believed to be the result of down-regulation of aberrant retinal cell proliferation and activity, thereby leading to reduced retinal scarring.

Intellectual Property and Proprietary Rights

Overview

In the United States and abroad, we are building an intellectual property portfolio for reproxalap and other RASP inhibitors, Hsp90 inhibitors, and the therapeutic methods of use of dihydrofolate reductase inhibition. We currently seek, and intend to continue to seek, patent protection in the United States and internationally for our product candidates, methods of use, and processes for manufacture, and for other technologies, where appropriate. Our current policy is to actively seek to protect our proprietary position by, among other things, filing patent applications in the United States and abroad relating to proprietary technologies that are important to the development of our business. We also rely on, and will continue to rely on, trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop and maintain our proprietary position. We cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our technology.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for the technologies that we consider important to our business, our ability to defend our patents, and our ability to preserve the confidentiality of our trade secrets and operate our business without infringing the patents and proprietary rights of third parties.

Patent Portfolio

Our patent portfolio currently includes patents and patent applications covering the composition, formulation, and uses of reproxalap, ADX-103, ADX-629, ADX-1612, ADX-1615, and other novel compounds. As of December 31, 2018, we owned eleven United States patents and eight pending United States non-provisional patent applications, as well as numerous foreign counterparts to these patents and patent applications, relating to reproxalap, ADX-103, and ADX-629. Additionally, we have in-licensed certain patents and patent applications relating to ADX-1612 and ADX-1615, and retain an exclusive license to certain patents related to the use of ADX-2191 for the prevention of proliferative vitreoretinal disease.

We expect the issued reproxalap composition of matter patent in the United States, if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2028. It is possible that the term of the composition of matter patent in the United States may be extended up to five additional years under the provisions of the Hatch-Waxman Act. We expect the foreign reproxalap composition of matter patents, if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2026. We expect other patent applications in the portfolio, if issued, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2026 to 2034. Reproxalap composition of matter patents have been issued in Australia, Canada, China, Europe (validated in approximately 14 member countries), Hong Kong, India, Japan, Mexico, Russia and South Korea. Reproxalap composition of matter patent claims are pending in Brazil.

Licenses and Agreements

We are developing ADX-1612 pursuant to a License Agreement with Madrigal Pharmaceuticals, Inc. (Madrigal), entered into on December 26, 2016 (the Madrigal Agreement). Pursuant to the Madrigal Agreement, we obtained an exclusive, worldwide license from Madrigal under certain patents and patent applications, and other licenses to intellectual property, to develop and commercialize Hsp90 inhibitors, including ADX-1612 and ADX-1615 (Madrigal Agreement Products). We have agreed to use our commercially reasonable efforts to develop Madrigal Agreement Products.

In consideration for the rights licensed under the Madrigal Agreement, we paid Madrigal an upfront license fee of $250,000 and are obligated to make future regulatory and development and sales-dependent milestone payments to Madrigal of less than $340 million in the aggregate (over 80% of such amount being tied to our achievement of increasingly greater annual worldwide net sales milestones), as well as royalty payments to Madrigal at a rate which, as a percentage of net sales, is in the high single digits for products containing ADX-1612 and mid-single digits for any other Hsp90 inhibitor product. We are also obligated under the Madrigal Agreement to pay Madrigal a percentage of certain sublicense revenue that we receive in connection with entering into any sublicensing arrangements with any third parties, at a percentage rate which tiers downward from the mid-twenties to low-single digits based on the development stage of the product at the time of the sublicense.

The Madrigal Agreement will remain in effect until all payment obligations under the Madrigal Agreement expire. We may terminate the Madrigal Agreement in its entirety or on a Madrigal Agreement Product-by-Madrigal Agreement Product basis with timely notice to Madrigal. Either party may terminate the Madrigal Agreement for uncured material breach by the other party or upon certain insolvency or bankruptcy proceedings involving the other party, both with timely notice to the other party. In addition, Madrigal has the right to terminate the Madrigal Agreement if we, our affiliates, or sublicensees interfere with, challenge the validity or enforceability of, oppose the extension of, or grant of a supplementary protection certificate with respect to any of our licensed patents under the Madrigal Agreement. In the event of an early termination of the Madrigal Agreement, all rights licensed and developed by us under the Madrigal Agreement may revert back to Madrigal. Each party has agreed to indemnify the other party for certain third party claims arising under the Madrigal Agreement.

Other Intellectual Property Rights

Our marks ALDEYRA THERAPEUTICS and our logo are registered with the United States Patent and Trademark Office.

Confidential Information and Inventions Assignment Agreements

We currently require and will continue to require each of our employees and consultants to execute confidentiality agreements upon the commencement of such individual's employment, consulting or collaborative relationships with us. These agreements provide that all confidential information developed or made known during the course of the relationship with us be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions resulting from such individual's work performed for us, utilizing our property or relating to our business and conceived or completed by the individual during employment shall be our exclusive property to the extent permitted by applicable law. Our consulting agreements also provide for assignment to us of any intellectual property resulting from services performed by a consultant for us.

Manufacturing

We do not own or operate manufacturing facilities for the production of our product candidates, nor do we have plans to develop our own manufacturing operations in the foreseeable future. We currently depend on third-party contract manufacturers for all of our required raw materials, drug substance and finished drug product for our preclinical research and clinical trials. We have no immediate plans to purchase, erect, or otherwise create any manufacturing facilities to be owned by us for any of these purposes, and intend to continue to depend on third-party contract manufacturers for the foreseeable future. We do not have any current contractual relationships for the manufacture of commercial supplies of our product candidates. If our product candidates are approved by any regulatory agency, we intend to enter into agreements with third-party contract manufacturers for the commercial production at such time. We may utilize third-party consultants to manage our manufacturing contractors. We believe that the active pharmaceutical ingredient and other materials needed for the formulation of our product candidates are relatively easy to manufacture, and that multiple suppliers and formulators could be employed for this purpose. Further, we believe the raw materials needed for manufacture of our product candidates, as well as other components of our formulations, are generally readily available currently from multiple sources.

Employees

As of December 31, 2018, we had 19 full time employees and had engaged a number of consultants. We intend to increase our employee base in connection with the continuing clinical development of our product candidates. We expect that a number of consultants previously engaged in development of our product candidates will participate in ongoing clinical and manufacturing activities. None of our employees is represented by a labor union. We have not experienced any work stoppages, and we consider our relations with our employees to be good.

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Government Regulation

FDA Approval Process

In the United States, pharmaceutical products are subject to extensive regulation by the FDA. The Food Drug and Cosmetic Act (FDCA) and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of pharmaceutical products. Failure to comply with applicable FDA or other requirements may subject a company to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending applications, a clinical hold, warning letters, recall or seizure of products, partial or total suspension of production, withdrawal of the product from the market, injunctions, fines, civil penalties or criminal prosecution.

FDA approval is required before any new drug, such as a new chemical entity, or a new dosage form, new use or new route of administration of a previously approved product, can be marketed in the United States. The process required by the FDA before a new drug product may be marketed in the United States generally involves:

- completion of preclinical laboratory and animal testing and formulation studies in compliance with the FDA's good laboratory practice (GLP) regulation;
- submission to the FDA of an Investigational New Drug application (IND) for human clinical testing which must become effective before human clinical trials may begin in the United States;
- approval by an independent institutional review board (IRB) at each site where a clinical trial will be performed before the trial may be initiated at that site;
- performance of adequate and well-controlled human clinical trials in accordance with current good clinical practices (cGCP) to establish the safety and efficacy of the proposed product candidate for each intended use;
- submission to the FDA of a new drug application (NDA) which must be accepted for filing by the FDA;
- satisfactory completion of an FDA pre-approval inspection(s) of the facility or facilities at which the product is manufactured to assess compliance with the FDA's current Good Manufacturing Practices (cGMP) regulations;
- satisfactory completion of an FDA advisory committee review, if applicable;
- payment of user fees, if applicable; and
- FDA review and approval of the NDA.

The preclinical and clinical testing and approval process requires substantial time, effort and financial resources. Preclinical tests include laboratory evaluation of product chemistry, formulation, manufacturing and control procedures and stability, as well as animal studies to assess the toxicity and other safety characteristics of the product. The results of preclinical tests, together with manufacturing information, analytical data and a proposed clinical trial protocol and other information, are submitted as part of an IND to the FDA. Preclinical testing may continue even after the IND is submitted. The IND becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions and places the clinical trial on a partial or complete clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, our submission of an IND may not result in FDA authorization to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during product development. Even if the IND becomes effective and the trial proceeds without initial FDA objection, the FDA may stop the trial at a later time if it has concerns, such as if the potential for unacceptable safety risks arise.

Further, an independent IRB, covering each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and informed consent information for subjects before the trial commences at that site and it must monitor the study until completed. The FDA, the IRB, or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk or for failure to comply with the FDA's or IRB's requirements. Other conditions may also be imposed.

Clinical trials involve the administration of the investigational new product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Sponsors of clinical trials generally must register and report, at the NIH-maintained website ClinicalTrials.gov, key parameters of certain clinical trials. For purposes of an NDA submission and approval, human clinical trials are typically conducted in the following sequential phases, which may overlap or be combined:

- Phase 1: The investigational drug product is initially introduced into healthy human subjects or patients and tested for safety, dose tolerance, absorption, metabolism, distribution and excretion and, if possible, to gain an early indication of its effectiveness.
- Phase 2: The investigational drug product is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted indications and to determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more extensive clinical trials.
- Phase 3: These are commonly referred to as pivotal studies. When Phase 2 evaluations suggest that certain dosing regimens may be efficacious and may have an acceptable safety profile, trials may be undertaken in larger patient populations to further evaluate dosage and to obtain evidence of potential clinical efficacy and safety. These studies may include multiple, geographically-dispersed clinical trial sites. Data generated from these studies may be used to establish the overall risk-benefit profile of the investigational drug product and to provide adequate information for the labeling of the product, if approved.
- Phase 4: In some cases, the FDA may condition approval of an NDA for a product candidate on the sponsor's commitment to conduct additional clinical trials to further assess the product's safety and/or effectiveness after NDA approval. Such post-approval trials are typically referred to as Phase 4 studies.

The results of product development, preclinical studies and clinical trials are submitted to the FDA as part of an NDA. NDAs must also contain extensive information relating to the product's pharmacology, chemistry, manufacturing and controls and proposed labeling, among other things.

For some products, the FDA may require a risk evaluation and mitigation strategy (REMS) which could include measures imposed by the FDA such as prescribing restrictions, requirements for post-marketing studies and reporting or certain restrictions on distribution and use. Under federal law, the submission of most NDAs is additionally subject to a substantial application user fee, and the manufacturer and/or sponsor under an approved NDA are also subject to prescription drug program fees. The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the NDA must be resubmitted with the additional information and is subject to payment of additional user fees. The resubmitted application is also subject to review before the FDA accepts it for filing.

Once the submission has been accepted for filing, the FDA begins an in-depth substantive review. Under the Prescription Drug User Fee Act (PDUFA), the FDA agrees to specific performance goals for NDA review time through a two-tiered classification system, Standard Review and Priority Review. Standard Review NDAs have a goal of being completed within a ten-month timeframe after acceptance of filing. A Priority Review designation is given to products that offer major advances in treatment or provide a treatment where no adequate therapy exists. The goal for completing a Priority Review is six months after acceptance of filing.

It is likely that our product candidates will be granted a Standard Review. The review process may be extended by the FDA for three additional months to consider certain information or obtain clarification regarding information already provided in the submission. The FDA may refer applications for novel products or products which present difficult questions of safety or efficacy to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendation of an advisory committee, but it considers such recommendations carefully when making decisions. In addition, for combination products, the FDA's review may include the participation of both the FDA's Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the FDA's Center for Devices and Radiological Health. This has the potential to complicate or prolong review of the application.

Before approving an NDA, the FDA may inspect the facility or facilities where the drug substance or drug product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP. FDA may also inspect sponsor facilities to determine if nonclinical and clinical studies were conducted in compliance with applicable regulations and guidelines.

After the FDA evaluates the NDA and, in some cases, the related manufacturing facilities, it may issue an approval letter or a Complete Response Letter (CRL) to indicate that the review cycle for an application is complete and that the application is not ready for approval. CRLs generally outline the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when the deficiencies have been addressed to the FDA's satisfaction, the FDA may issue an approval letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications.

Once issued, the FDA may withdraw product approval if ongoing regulatory requirements are not met or if potential adverse safety findings are identified after the product reaches the market. In addition, the FDA may require post-approval testing, including Phase 4 studies, and surveillance programs to monitor the effect of approved products which have been commercialized, and the FDA has the power to prevent or limit further marketing of a product based on the results of these post-marketing programs.

Products may be promoted only for the approved labeled indications and in accordance with the provisions of the approved label, and, even if the FDA approves a product, it may limit the approved indications for use for the product or impose other conditions, including labeling or distribution restrictions or other risk-management mechanisms, such as a Black Box Warning, which highlights a specific warning. Further, if there are any modifications to the product, including changes in indications, labeling, or manufacturing processes or facilities, a company would be required to submit and obtain FDA approval of a new or supplemental NDA, which may require the company to develop additional data or conduct additional preclinical studies and clinical trials.

Post-Approval Requirements

Once an NDA is approved, a product will be subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to product/facility listing, recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and may require prior FDA approval before being implemented. FDA regulations may also require investigation and correction of any deviations from cGMP and may impose reporting and documentation requirements upon us and any third-party manufacturers. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

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Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated seriousness, severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

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

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. The FDA does not regulate the practice of medicine. Physicians may prescribe for off-label uses; manufacturers may only promote 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, both at the federal and state levels.

The Food and Drug Administration Amendments Act of 2007 gave the FDA the authority to require a Risk Evaluation and Mitigation Strategy, or REMS, from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks. In determining whether a REMS is necessary, FDA must consider the size of the population likely to use the drug, the seriousness of the disease or condition to be treated, the expected benefit of the drug, the duration of treatment, the seriousness of known or potential adverse events, and whether the drug is a new molecular entity. If the FDA determines a REMS is necessary, the drug sponsor must agree to the REMS plan at the time of approval. A REMS may be required to include various elements, such as a medication guide or patient package insert, a communication plan to educate health care providers of the drug's risks, limitations on who may prescribe or dispense the drug, or other measures that the FDA deems necessary to assure the safe use of the drug. In addition, the REMS must include a timetable to assess the strategy at 18 months, three years, and seven years after the strategy's approval. The FDA may also impose a REMS requirement on a drug already on the market if the FDA determines, based on new safety information, that a REMS is necessary to ensure that the drug's benefits outweigh its risks.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug intended to treat a rare disease or condition which is defined as one affecting fewer than 200,000 individuals in the United States or more than 200,000 individuals where there is no reasonable expectation that the product development cost will be recovered from product sales in the United States. Orphan drug designation must be requested before submitting an NDA and does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. Reproxalap has received orphan designation for the treatment of congenital ichthyosis, and ADX-2191 has received orphan designation for the prevention of proliferative vitreoretinopathy.

If an orphan drug-designated product subsequently receives the first FDA approval for the disease for which it was studied, the sponsor will be entitled to seven years of product marketing exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same indication, except in very limited and rare circumstances, for seven years. If a competitor obtains approval of the same drug, as defined by the FDA, or if our product candidate is determined to be contained within the competitor's product for the same indication or disease, the competitor's exclusivity could block the approval of our product candidate in the designated orphan indication for seven years, unless superior safety or efficacy of our drug is demonstrated.

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Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of FDA approval of the use of our drug candidates, some of our United States patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act. The Hatch-Waxman Act permits 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 an NDA, plus the time between the submission date of an NDA and the approval of that application. Only one patent applicable to an approved drug is eligible for the extension and the application for extension must be made prior to expiration of the patent. The United States 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 intend to apply for restorations of patent term for some of our currently owned or licensed patents to add patent life beyond their current expiration date, depending on the expected length of clinical trials and other factors involved in the submission of the relevant NDA.

Market exclusivity provisions under the FDCA also can delay the submission or the approval of certain applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application (ANDA) or a 505(b)(2) NDA submitted by another company for another version of such drug where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement. The FDCA also provides three years of marketing exclusivity for an NDA, 505(b)(2) NDA or supplement to an approved NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example, for new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the conditions associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the original active agent. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Manufacturing Requirements

We and our third-party manufacturers must comply with applicable FDA regulations relating to FDA's cGMP regulations and, if applicable, quality system regulation requirements for medical devices. The cGMP regulations include requirements relating to, among other things, organization of personnel, buildings and facilities, equipment, control of components and drug product containers and closures, production and process controls, packaging and labeling controls, holding and distribution, laboratory controls, records and reports, and returned or salvaged products. The manufacturing facilities for our products must meet cGMP requirements to the satisfaction of the FDA and may be subject to a pre-approval inspection before we can use them to manufacture our products. We and our third-party manufacturers are also subject to periodic unannounced inspections of facilities by the FDA and other authorities, including procedures and operations used in the testing and manufacture of our products to assess our compliance with applicable regulations. Failure to comply with statutory and regulatory requirements subjects a manufacturer to possible legal or regulatory action, including, among other things, warning letters, voluntary corrective action, the seizure of products, injunctions, consent decrees placing significant restrictions on or suspending manufacturing operations and civil and criminal penalties.

Other Regulatory Requirements

We are also subject to various laws and regulations regarding laboratory practices, the experimental use of animals, and the use and disposal of hazardous or potentially hazardous substances in connection with our research. In each of these areas, as above, the FDA has broad regulatory and enforcement powers, including, among other things, the ability to levy fines and civil penalties, suspend or delay issuance of approvals, seize or recall products, and withdraw approvals, any one or more of which could have an adverse effect on our ability to operate our business and generate revenues. Compliance with applicable environmental laws and regulations is expensive, and current or future environmental regulations may impair our research, development and production efforts, which could harm our business, operating results and financial condition. There are evolving legal requirements and other statutory and regulatory regimes that will continue to affect our business.

Research and Development Expenses

Substantially all of our research and development expenses incurred to date have been related to the development of reproxalap and our other product candidates. Our research and development expenses totaled $29.8 million for the year ended December 31, 2018 and $16.3 million for the year ended December 31, 2017.

We anticipate that we will incur additional research and development expenses in the future as we evaluate and possibly pursue the development of our product candidates for additional indications, or develop additional product candidates.

We recognize research and development expenses as they are incurred. Our research and development expenses consist primarily of:

- salaries and related expenses for personnel;
- fees paid to consultants and contract research organizations in conjunction with independently monitoring clinical trials and acquiring and evaluating data in conjunction with clinical trials, including all related fees such as investigator grants, patient screening, lab work and data compilation and statistical analysis;
- costs incurred with third parties related to the establishment of a commercially viable manufacturing process for our product candidates;
- costs related to production of clinical materials, including fees paid to contract manufacturers;
- costs related to upfront, milestone payments under in-licensing agreements as well as costs for unapproved inventory for which there is no future alternative use;
- costs related to compliance with FDA regulatory requirements;
- consulting fees paid to third-parties involved in research and development activities; and
- costs related to stock options or other stock-based compensation granted to personnel in development functions.

We expense both internal and external development costs as they are incurred.

We expect that a large percentage of our research and development expenses in the future will be incurred in support of our current and future non-clinical, preclinical and clinical development programs. These expenditures are subject to numerous uncertainties in terms of both their timing and total cost to completion. We expect to continue to develop stable formulations of our product candidates, test such formulations in preclinical studies for toxicology, safety and efficacy and to conduct clinical trials for each product candidate. We anticipate funding clinical trials for our product candidates ourselves, but we may engage collaboration partners at certain stages of clinical development. As we obtain results from clinical trials, we may elect to discontinue or delay clinical trials for certain product candidates or programs in order to focus our resources on more promising product candidates or programs. Completion of clinical trials by us or our future collaborators may take several years or more, the length of time generally varying with the type, complexity, novelty and intended use of a product candidate. The costs of clinical trials may vary significantly over the life of a project owing to but not limited to the following:

- the number of sites included in the trials;
- the length of time required to enroll eligible patients;

- the number of patients that participate in the trials;
- the number of doses that patients receive;
- the drop-out or discontinuation rates of patients;
- the duration of patient follow-up;
- the phase of development the product candidate is in; and
- the efficacy and safety profile of the product candidate.

Our expenses related to clinical trials are based on estimates of the services received and efforts expended pursuant to contracts with multiple research institutions and contract research organizations that conduct and manage clinical trials on our behalf. The financial terms of these agreements are subject to negotiation and vary from contract to contract and may result in uneven payment flows. Generally, these agreements set forth the scope of work to be performed at a fixed fee or unit price. Payments under the contracts depend on factors such as the successful enrollment of patients or the completion of clinical trial milestones. Expenses related to clinical trials generally are accrued based on contracted amounts applied to the level of patient enrollment and activity according to the protocol. If timelines or contracts are modified based upon changes in the clinical trial protocol or scope of work to be performed, we modify our estimates of accrued expenses accordingly on a prospective basis.

None of our product candidates have received FDA or foreign regulatory marketing approval. In order to grant marketing approval, a health authority such as the FDA or foreign regulatory agencies must conclude that clinical and preclinical data establish the safety and efficacy of our product candidates with an appropriate benefit to risk profile relevant to a particular indication, and that the product can be manufactured under cGMP in a reproducible manner to deliver the product's intended performance in terms of its stability, quality, purity and potency. Until our submission is reviewed by a health authority, there is no way to predict the outcome of their review. Even if the clinical studies meet their predetermined primary endpoints, and a registration dossier is accepted for filing, a health authority could still determine that an appropriate benefit to risk relationship does not exist for the indication that we are seeking.

We cannot forecast with any degree of certainty which of our product candidates will be subject to future collaborations or how such arrangements would affect our development plan or capital requirements.

As a result of the uncertainties discussed above, we are unable to determine the duration and completion costs of our development projects or when and to what extent we will receive cash inflows from the commercialization and sale of an approved product candidate.

Corporate Information

We were incorporated in the state of Delaware on August 13, 2004 as Neuron Systems, Inc. On December 20, 2012, we changed our name to Aldexa Therapeutics, Inc. and on March 17, 2014, we changed our name to Aldeyra Therapeutics, Inc. Our principal executive offices are located at 131 Hartwell Avenue, Suite 320, Lexington, Massachusetts 02421. Our telephone number is (781) 761-4904. Our website address is www.aldeyra.com. Information contained on our website is not incorporated by reference into this annual report on Form 10-K, and you should not consider information contained on our website to be part of this annual report on Form 10-K or in deciding whether to purchase shares of our common stock. Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, are available free of charge on the Investors portion of our website at http://ir.aldeyra.com/ as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC.

ITEM 1A. RISK FACTORS

Our business is subject to numerous risks. You should carefully consider the risks described below together with the other information set forth in this annual report on Form 10-K, which could materially affect our business, financial condition, and future results. The risks described below are not the only risks facing our company. Risks and uncertainties not currently known to us or that we currently deem to be immaterial also may materially adversely affect our business, prospects, financial condition, and operating results.

Risks Related to our Business and the Development and Commercialization of our Product Candidates

We have incurred significant operating losses since inception and we expect to incur significant losses for the foreseeable future. We may never become profitable or, if achieved, be able to sustain profitability.

We have incurred significant operating losses since we were founded in 2004 and expect to incur significant losses for the next several years as we continue our clinical trial and development programs for reproxalap and our other product candidates. Net loss for the years ended December 31, 2018 and 2017 was approximately $38.9 million and $22.3 million, respectively. As of December 31, 2018, we had total stockholders' equity of $86.6 million and an accumulated deficit of $138.5 million. Losses have resulted principally from costs incurred in our clinical trials, research and development programs and from our general and administrative expenses. In the future, we intend to continue to conduct research and development, clinical testing, regulatory compliance activities, and, if reproxalap or any of our other product candidates is approved, sales and marketing activities that, together with anticipated general and administrative expenses, will likely result in our incurring further significant losses for the next several years.

We currently generate no revenue from sales, and we may never be able to commercialize reproxalap or our other product candidates. We do not currently have the required approvals to market any of our product candidates and we may never receive them. We may not be profitable even if we or any of our future development partners succeed in commercializing any of our product candidates. Because of the numerous risks and uncertainties associated with developing and commercializing our product candidates, we are unable to predict the extent of any future losses or when we will become profitable, if at all.

Our business is dependent in large part on the success of a single product candidate, reproxalap. We cannot be certain that we will be able to obtain regulatory approval for, or successfully commercialize, reproxalap.

Our product candidates, including reproxalap, are in the early stage of development and will require additional preclinical studies, substantial clinical development and testing, and regulatory approval prior to commercialization. We have not yet completed development of any product candidate. We have only one product candidate that has been the focus of significant clinical development: reproxalap, a novel small molecule chemical entity that is believed to trap and allow for the degradation of RASP, toxic chemical species suspected to cause and exacerbate numerous diseases in humans and animals. We are in part dependent on successful continued development and ultimate regulatory approval of reproxalap for our future business success. We have invested, and will continue to invest, a significant portion of our time and financial resources in the development of reproxalap. We will need to raise sufficient funds for, and successfully enroll and complete, our current and planned clinical trials of reproxalap and our other product candidates. The future regulatory and commercial success of our product candidates is subject to a number of risks, including the following:

- we may not have sufficient financial and other resources to complete necessary clinical trials;
- we may not be able to provide evidence of safety and efficacy;
- we may not be able to timely or adequately finalize the design or formulation of any product candidate or demonstrate that a formulation of our product candidate will be stable for commercially reasonable time periods;
- the safety and efficacy results of our later phase or larger clinical trials may not confirm the results of our earlier trials;

- there may be variability in patients, adjustments to clinical trial procedures and inclusion of additional clinical trial sites;
- the results of our clinical trials may not meet the endpoints, or level of statistical or clinical significance required by the FDA, or comparable foreign regulatory bodies, for marketing approval;
- the initial parts of adaptive clinical trials are not designed to be pivotal or definitive, as such we may need to revise the design or endpoints to achieve success in later parts of the trial or potentially abandon the trial;
- the FDA, or comparable foreign regulatory bodies, may implement new standards, or change the interpretation of existing standards or requirements for the regulatory approval, in general or with respect to the indications our product candidates are being developed to treat; the FDA, or comparable foreign bodies, may require clinical data in addition to the clinical trial programs we expect or may require changes to the designs and endpoints of the subsequent clinical trials;
- patients in our clinical trials may demonstrate greater response rates or improvements from vehicle or in the non-treatment arm then was expected when designing and powering our clinical trials;
- patients in clinical trials for our product candidates may suffer adverse effects or die for reasons that may or may not be related to our product candidates;
- if approved for certain diseases, our product candidates will compete with well-established and other products or therapeutic options already approved for marketing by the FDA, or comparable foreign regulatory bodies;
- the effects of legislative or regulatory reform of the health care system in the United States or other jurisdictions in which we may do business; and
- we may not be able to obtain, maintain, or enforce our patents and other intellectual property rights.

Of the large number of drugs in development in the pharmaceutical industry, only a small percentage result in the submission of a NDA to the FDA, and even fewer are approved for commercialization. Furthermore, even if we do receive regulatory approval to market reproxalap and our other product candidates, any such approval may be subject to limitations on the indicated uses for which we may market the product. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, we cannot assure that reproxalap and our other product candidates will be successfully developed or commercialized. If we or any of our future development partners are unable to develop, or obtain regulatory approval for or, if approved, successfully commercialize, reproxalap and our other product candidates, we may not be able to generate sufficient revenue to continue our business.

Because the Company has no experience in commercializing pharmaceutical products, there is a limited amount of information about us upon which to evaluate our product candidates and business prospects.

We have not yet demonstrated an ability to successfully overcome many of the pre-commercial and commercial risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical area. For example, to execute our business plan we will need to successfully:

- execute our product candidate development activities, including successfully designing and completing our clinical trial programs and product design and formulation of future product candidates, in a cost- effective manner;
- obtain required regulatory approvals for our product candidates;
- manage our spending as costs and expenses increase due to the performance and completion of clinical trials, attempting to obtain regulatory approvals, manufacturing and commercialization;
- secure substantial additional funding;
- develop and maintain successful strategic relationships;

- build and maintain a strong intellectual property portfolio;
- build and maintain appropriate clinical, regulatory, quality, manufacturing, compliance, sales, distribution, and marketing capabilities on our own or through third parties;
- price our product candidates, if approved, at expected levels and obtain and maintain sufficient insurance and reimbursement from insurers and other programs; and
- gain broad market acceptance for our product candidates.

If we are unsuccessful in accomplishing these objectives, we may not be able to develop product candidates, raise capital, expand our business, or continue our operations.

The results of preclinical studies and earlier clinical trials are not always predictive of future results. Any product candidate we or any of our future development partners advance into clinical trials, including reproxalap, may not have favorable results in later clinical trials, if any, or receive regulatory approval.

Drug development has inherent risk. We or any of our future development partners will be required to demonstrate through adequate and well-controlled clinical trials that our product candidates are safe and effective, with a favorable benefit-risk profile, for use in their target indications before we can seek regulatory approvals for their commercial sale. Drug development is a long, expensive and uncertain process, and delay or failure can occur at any stage of development, including after commencement of any of our clinical trials. In addition, as product candidates proceed through development, the trial designs may often be different and may need to evolve and change from phase to phase or within the same phase or same trial, in the case of an adaptive trial design, the vehicles or controls may be modified from trial to trial and the product formulations or manufacturing process may differ due to the need to test product candidate samples that can be manufactured on a commercial scale. Success in earlier clinical trials or clinical trials focused on a different indication does not mean that later clinical trials will be successful because product candidates in later-stage clinical trials may fail to demonstrate sufficient safety or efficacy despite having progressed through other phases of clinical testing. Companies frequently suffer significant setbacks in advanced clinical trials, even after earlier clinical trials have shown promising results. Moreover, only a small percentage of drugs under development result in the submission of an NDA to the FDA and even fewer are approved for commercialization.

Because we are developing novel product candidates for the treatment of diseases in a manner which there is little clinical drug development experience and, in some cases, are designing adaptive trials or using new endpoints or methodologies, the regulatory pathways for approval are not well defined, and, as a result, there is greater risk that our clinical trials will not result in our desired outcomes or require additional trials.

Our clinical focus is on the development of new products for inflammation and an inborn error of metabolism. Our Phase 3 vehicle-controlled clinical program in noninfectious anterior uveitis and our Phase 3 clinical program in SLS represent the first such clinical trials performed. Our Phase 3 clinical trial in SLS is an adaptive trial, where Part 1 is not designed to be pivotal or definitive. Rather, Part 1 is expected to provide data to allow us to design Part 2 of the trial, which could require design changes, including but not limited to, different end points. Further, we have proposed to the FDA a novel assessment methodology for our Phase 3 clinical program in allergic conjunctivitis, which may require changes to the design of subsequent Phase 3 clinical trials. As we prepare for a subsequent Phase 3 clinical trial in allergic conjunctivitis, we have initiated two clinical methods development studies to assess the feasibility of measuring ocular itching following environmental exposure to allergen. If neither clinical methods study yields favorable results, subsequent Phase 3 testing may not be feasible or cost-effective, and it may be difficult or impossible for us to complete clinical testing of reproxalap for the treatment of allergic conjunctivitis. As such, the likelihood of success in our late-stage clinical programs cannot necessarily be predicted.

We could also face challenges in designing clinical trials and obtaining regulatory approval of our product candidates due to the lack of historical clinical trial experience for novel classes of therapeutics. Thus, it is difficult to determine whether regulatory agencies will be receptive to the approval of our product candidates and to predict the time and costs associated with obtaining regulatory approvals. The clinical trial requirements of the FDA and other regulatory agencies and the criteria these regulators use to determine the safety and efficacy of a product candidate vary

substantially according to the type, complexity, novelty, and intended use and market of the potential

products. The regulatory approval process for novel product candidates such as ours can be more expensive, take longer and require more trial data than for other, better known or more extensively studied classes of product candidates. Any inability to design clinical trials with protocols and endpoints acceptable to applicable regulatory authorities, and to obtain regulatory approvals for our product candidates, would have an adverse impact on our business, prospects, financial condition, and results of operations.

Because our product candidates are, to our knowledge, new chemical entities, it is difficult to predict the time and cost of development and our ability to successfully complete clinical development of these product candidates and obtain the necessary regulatory approvals for commercialization.

Our product candidates are, to our knowledge, new chemical entities, and unexpected problems related to new technologies may arise that can cause us to delay, suspend or terminate our development efforts. As a result, short and long-term safety, as well as prospects for efficacy, are not fully understood and are difficult to predict. Regulatory approvals of new product candidates can be more expensive and take longer than approvals for well-characterized or more extensively studied pharmaceutical product candidates. Following discussions with the FDA and experts in the field, we may determine that it is not cost effective for us to develop one or more of our product in certain indications and we may decide to cease development in that area or seek a strategic partner.

Our dermatologic topical formulation of reproxalap is unlikely to affect other clinical manifestations of Sjögren-Larsson Syndrome, which may decrease the likelihood of regulatory and commercial acceptance.

While the primary day-to-day complaint of SLS patients and their caregivers are symptoms associated with severe skin disease, SLS patients also manifest varying degrees of delay in mental development, spasticity, seizures, and retinal disease. In August 2016, we announced that the results of our randomized, parallel-group, double-masked, vehicle-controlled clinical trial of a dermatologic formulation of reproxalap for the treatment of the skin manifestations of SLS demonstrated clinically relevant activity of reproxalap in diminishing the severity of ichthyosis, a serious dermatologic disease characteristic of SLS. Given the expected low systemic exposure of reproxalap when administered topically to the skin, it is not possible to anticipate the effect of reproxalap on the non-dermatologic conditions of SLS. Lack of effect in neurologic and ocular manifestations of SLS may negatively impact the potential market for reproxalap in SLS, and may also negatively impact reimbursement, pricing, and commercial acceptance of reproxalap, if approved.

Reproxalap and our other product candidates are subject to extensive regulation, compliance with which is costly and time consuming, and such regulation may cause unanticipated delays, or prevent the receipt of the required approvals to commercialize our product candidates.

The clinical development, manufacturing, labeling, storage, record-keeping, advertising, promotion, import, export, marketing, and distribution of our product candidates are subject to extensive regulation by the FDA in the United States and by comparable authorities in foreign markets. In the United States, we are not permitted to market our product candidates until we receive regulatory approval from the FDA. The process of obtaining regulatory approval is expensive, often takes many years, and can vary substantially based upon the type, complexity, and novelty of the products involved, as well as the target indications, and patient population. Approval policies or regulations may change and the FDA has substantial discretion in the drug approval process, including the ability to delay, limit, or deny approval of a product candidate for many reasons. Despite the time and expense invested in clinical development of product candidates, regulatory approval and subsequent commercial success is uncertain and never guaranteed.

Reproxalap and our other product candidates and the activities associated with development and potential commercialization, including testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to extensive regulation by the FDA and other regulatory agencies in the United States and by comparable authorities in other jurisdictions.

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Our ongoing research and development activities and planned clinical development for our product candidates may be delayed, modified or ceased for a variety of reasons, including:

- determining that a product candidate is ineffective or potentially causes harmful side effects during preclinical studies or clinical trials;
- difficulty establishing predictive preclinical models for demonstration of safety and efficacy of a product candidate in one or more potential therapeutic areas for clinical development;
- patients in our clinical trials may demonstrate greater response rates or improvements from vehicle or in the non-treatment arm than was expected when designing and powering our clinical trials;
- difficulties in manufacturing a product candidate, including the inability to manufacture a product candidate in a sufficient quantity, suitable form, or in a cost-effective manner, or under processes acceptable to the FDA for marketing approval;
- the proprietary rights of third parties, which may preclude us from developing or commercializing a product candidate;
- determining that a product candidate may be uneconomical for us to develop or commercialize, or may fail to achieve market acceptance or adequate pricing or reimbursement;
- our inability to secure strategic partners which may be necessary for advancement of a product candidate into clinical development or commercialization; or
- our prioritization of other product candidates for advancement.

The FDA or comparable foreign regulatory authorities can delay, limit, or deny approval of a product candidate for many reasons, including but not limited to:

- such authorities may disagree with the design or implementation of our or any of our future development partners' clinical trials, including the endpoints of our clinical trials; such authorities may require clinical data in addition to clinical trial programs we expect, or may require changes to the designs and endpoints of subsequent clinical trials;
- we or any of our future development partners may be unable to demonstrate to the satisfaction of the FDA or other regulatory authorities that a product candidate is safe and effective for any indication;
- such authorities may not accept clinical data from trials if conducted at clinical facilities or in countries where the standard of care is potentially different from the United States;
- the results of clinical trials may not demonstrate the safety or efficacy required by such authorities for approval;
- we or any of our future development partners may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- such authorities may disagree with our interpretation of data from preclinical studies or clinical trials or the design of such trials;
- changes in the leadership or operation of such authorities, which may result in, among other things, the implementation of new standards, or changes to the interpretation or enforcement of existing regulatory standards and requirements;
- such authorities may find deficiencies in the manufacturing processes or facilities of third-party manufacturers with which we or any of our future development partners contract for clinical and commercial supplies; or
- the approval policies, standards or regulations of such authorities may significantly change in a manner rendering our or any of our future development partners' clinical data insufficient for approval.

With respect to foreign markets, approval procedures vary among countries and, in addition to the aforementioned risks, can involve additional product testing, administrative review periods and agreements with pricing authorities. In addition, events raising questions about the safety of certain marketed pharmaceuticals may result in increased cautiousness by the FDA and comparable foreign regulatory authorities in reviewing new drugs based on safety, efficacy or other regulatory considerations and may result in significant delays in obtaining regulatory approvals. Any delay in obtaining, or inability to obtain, applicable regulatory approvals would prevent us or any of our future development partners from commercializing our product candidates. Moreover, we cannot predict healthcare reform initiatives, including potential reductions in federal funding or insurance coverage, that may be adopted in the future and whether or not any such reforms would have an adverse effect on our business and our ability to obtain regulatory approval for our current or future product candidates. There are evolving legal requirements and other statutory and regulatory regimes that will continue to affect our business.

Any termination or suspension of, or delays in the commencement or completion of, our clinical trials could result in increased costs to us, delay or limit our ability to generate revenue and adversely affect our commercial prospects.

Delays in the commencement or completion of our planned clinical trials for reproxalap or other product candidates could significantly affect our product development costs and timeline. We do not know whether future trials will begin on time or be completed on schedule, if at all. The commencement and completion of clinical trials can be delayed for a number of reasons, including delays related to:

- the FDA, or an institutional review board, or IRB, failing to grant permission to proceed or placing a clinical trial on hold;
- subjects failing to enroll or remain in our clinical trials at the rate we expect;
- subjects choosing an alternative treatment for the indication for which we are developing reproxalap or other product candidates, or participating in competing clinical trials;
- lack of adequate funding to continue the clinical trial;
- subjects experiencing severe, serious or unexpected drug-related adverse effects, whether drug-related or otherwise;
- a facility manufacturing reproxalap, any of our other product candidates or any of their components being ordered by the FDA or other government or regulatory authorities, to temporarily or permanently shut down due to violations of current Good Manufacturing Practices, or cGMP, or other applicable requirements, or infections or cross-contaminations of product candidates in the manufacturing process;
- any changes to our manufacturing process that may be necessary or desired;
- inability to timely manufacture sufficient quantities of the applicable product candidate for a clinical trial or expiration of materials intended for use in a clinical trial;
- third-party clinical investigators losing the licenses or permits necessary to perform our clinical trials, not performing our clinical trials on our anticipated schedule or consistent with the clinical trial protocol, current Good Clinical Practice or regulatory requirements, or other third parties not performing data collection or analysis in a timely or accurate manner;
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