CATABASIS PHARMACEUTICALS INC
Form 10-K
March 16, 2017

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# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION

**Washington, DC 20549**

# FORM 10-K

**(Mark One)**

ý **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

**For the fiscal year ended December 31, 2016**

**or**

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

**For the transition period from to**
**Commission File Number: 001-37467**

# Catabasis Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

| **Delaware** | **26-3687168** |
|---|---|
| (State or other jurisdiction of incorporation or organization) | (IRS Employer Identification No.) |
| **One Kendall Square Bldg. 1400E, Suite B14202 Cambridge, Massachusetts** | **02139** |
| (Address of principal executive offices) | (Zip Code) |

Registrant's telephone number, including area code **(617) 349-1971**

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

| **Title of each class** | **Name of each exchange on which registered** |
|---|---|
| **Common Stock, $0.001 par value per share** | **NASDAQ Global Market** |

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

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

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

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of 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. ý

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

| Large accelerated filer o | Accelerated filer o | Non-accelerated filer ý (Do not check if a smaller reporting company) | Smaller reporting company o |
|---|---|---|---|

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

Aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, based on the last sale price for such stock on June 30, 2016: $22,128,335.

As of March 8, 2017, there were 18,898,547 shares of the registrant's Common Stock, par value $0.001 per share, outstanding.

**DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the registrant's definitive proxy statement relating to its 2017 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. The registrant intends to file such proxy statement with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this Annual Report on Form 10-K relates.

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**SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA**

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management and expected market growth are forward-looking statements. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "should," "target," "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

These forward-looking statements include, among other things, statements about:

- our plans to identify, develop and commercialize novel therapeutics based on our SMART linker drug discovery platform;
- our plans to continue to evaluate data from Part C of our MoveDMD® clinical trial of edasalonexent for the treatment of Duchenne muscular dystrophy;
- ongoing and planned clinical trials for edasalonexent and other product candidates, whether conducted by us or by any future collaborators, including the timing of initiation of these trials and of the anticipated results;
- our plans to enter into collaborations for the development and commercialization of product candidates;
- the potential benefits of any future collaboration;
- our ability to receive research and development funding and achieve anticipated milestones under our collaborations;
- the timing of and our ability to obtain and maintain regulatory approvals for our product candidates;
- the rate and degree of market acceptance and clinical utility of any products for which we receive marketing approval;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property position and strategy;
- our ability to identify additional products or product candidates with significant commercial potential;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- developments relating to our competitors and our industry; and
- the impact of government laws and regulations.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the "Risk Factors" section, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, collaborations, joint ventures or investments that we may make or enter into.

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You should read this Annual Report on Form 10-K with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

**REFERENCES TO CATABASIS**

Except as otherwise indicated herein or as the context otherwise requires, references in this Annual Report on Form 10-K to "Catabasis," "the company," "we," "us," and "our" refer to Catabasis Pharmaceuticals, Inc. and its consolidated subsidiary.

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**PART I**

**Item 1. Business**

**Overview**

We are a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of novel therapeutics based on our proprietary Safely Metabolized And Rationally Targeted, or SMART, linker drug discovery platform. Our SMART linker drug discovery platform enables us to engineer product candidates that can simultaneously modulate multiple targets in a disease. Our proprietary product candidates impact pathways that are central to diseases where efficacy may be optimized by a multiple target approach. We have applied our SMART linker drug discovery platform to build an internal pipeline of product candidates for rare diseases, our primary focus, and plan to pursue partnerships to develop additional product candidates.

Our lead product candidate is edasalonexent, formerly known as CAT-1004, an oral small molecule. Based on its mechanism of action, the inhibition of NF-κB, or nuclear factor kappa-light-chain-enhancer of activated B cells, we believe edasalonexent has the potential to be a disease-modifying therapy for all patients affected by Duchenne muscular dystrophy, or DMD, regardless of the underlying dystrophin mutation. DMD is an ultimately fatal genetic disorder involving progressive muscle degeneration. The United States Food and Drug Administration, or FDA, has granted orphan drug, fast track and rare pediatric disease designations to edasalonexent for the treatment of DMD. The European Commission, or EC, has granted orphan medicinal product designation to edasalonexent for the treatment of DMD.

We are currently conducting the MoveDMD® Phase 1/2 trial of edasalonexent in ambulatory boys with DMD between ages four and seven. The MoveDMD trial is a three-part clinical trial investigating the safety and efficacy of edasalonexent in DMD. We previously reported positive safety, tolerability, pharmacokinetics and biomarker results from Part A of the MoveDMD trial. We reported top-line Part B results in January 2017, indicating that the primary efficacy endpoint of average change from baseline to week 12 in the magnetic resonance imaging, or MRI, T2 composite measure of lower leg muscles for the pooled edasalonexent treatment groups compared to placebo was not met. There were, however, consistent numerical improvements versus placebo across all functional exploratory endpoint measures for the higher dose, as well as numerical improvement versus placebo across multiple functional exploratory endpoint measures for the lower dose, while the lower dose had mixed results versus the higher dose. Changes in these functional measures were not statistically significant in Part B of the MoveDMD trial, which was not powered for functional measures. We believe that the potential treatment-associated effects from these exploratory endpoints warrant further evaluation in Part C of the MoveDMD trial, which is the ongoing open-label extension portion of the trial. We intend to transition all patients participating in Part C of the trial to the 100 mg/kg/day dose, the higher of the two dosing levels administered in Part B, and extending Part C by an additional 24 weeks, subject to institutional review board approval. We intend to report the results from Part C in 2017. We anticipate providing an interim update on Part C of the MoveDMD trial in the second quarter of 2017. In addition to our work in DMD, we are evaluating other diseases where the inhibition of NF-κB may be beneficial for further therapeutic applications of edasalonexent. There are a number of other rare diseases where NF-κB is believed to play an important role, such as Becker muscular dystrophy, which is one of nine types of muscular dystrophy and is characterized by slowly progressive muscle weakness of the legs and pelvis, and IgA nephropathy, a kidney disease that is believed to result from activation of mucosal immunity leading to the synthesis of aberrantly glycosylated polymeric immunoglobulin A1, or IgA1, which enters the circulation and lodges in a patient's kidneys interfering with their proper function.

In addition to edasalonexent, we are developing a pipeline of product candidates using our SMART linker drug discovery platform as potential treatments for rare diseases including cystic

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fibrosis, or CF, amyotrophic lateral sclerosis, or ALS, and Friedreich's ataxia, or FA. Our pipeline includes CAT-5571 and CAT-4001, for which we are currently conducting preclinical activities. We are developing CAT-5571 initially as a potential oral treatment for CF, with potential beneficial effects on both trafficking and function of cystic fibrosis transmembrane conductance regulator, or CFTR, and the clearance of *Pseudomonas aeruginosa*. In CF, a malfunctioning CFTR ion channel impairs chloride secretion, with deleterious effects on multiple organs, and particularly devastating effects on pulmonary, intestinal and pancreatic function. Patients affected with CF are also predisposed to respiratory failure caused by persistent lung infections, notably bacteria and most commonly *Pseudomonas aeruginosa*, that are difficult to treat with standard antibiotics. CAT-5571 is a small molecule that activates autophagy, a process that maintains cellular homeostasis and host defense mechanisms, which are known to be impaired in CF. In addition, we are developing CAT-4001 as a potential treatment for neurodegenerative diseases such as FA and ALS, irrespective of mutation status. FA is a rare genetic disease that causes nervous system damage and compromises motor coordination. ALS, sometimes called Lou Gehrig's disease or classical motor neuron disease, is a rapidly progressive, fatal neurological disease that attacks the nerve cells responsible for controlling voluntary muscles. CAT-4001 is a small molecule that activates Nuclear factor (erythroid-derived 2)-like 2, or Nrf2, and inhibits NF-κB, two pathways that have been implicated in FA and ALS.

We have previously applied our SMART linker drug discovery platform to engineer our CAT-2000 series product candidates to inhibit the Sterol Regulatory Element Binding Protein, or SREBP, pathway. Inhibitors of SREBP have been proposed for the treatment of nonalcoholic steatohepatitis, or NASH, based on the role of SREBP in lipid metabolism and known human polymorphisms associated with NASH disease progression. NASH is characterized by the build-up of fat in the liver and chronic inflammation, which can trigger progression to fibrosis and ultimately cirrhosis and sometimes hepatocellular carcinoma. We have advanced two CAT-2000 molecules, CAT-2003 and CAT-2054, into clinical development and intend to pursue a partnership for further development of the CAT-2000 series in NASH, which, in addition to CAT-2003 and CAT-2054, includes other discovery-stage molecules with intermediate rates of hydrolysis.

As of December 31, 2016, we owned five issued U.S. patents with composition of matter and method of use claims directed to edasalonexent, four issued U.S. patents with composition of matter and method of use claims directed to the CAT-2000 series, two issued U.S. patents with composition of matter claims generically covering CAT-5571 and two issued U.S. patents with composition of matter and method of use claims directed to CAT-4001. These patents are expected to expire between 2029 and 2031, without taking into account potential patent term extensions. In addition, our patent portfolio includes over 50 issued foreign patents, over 10 pending U.S. patent applications and over 35 pending foreign patent applications.

**Our Scientific Approach**

Our SMART linker drug discovery platform enables us to engineer product candidates that can simultaneously modulate multiple biological targets in a disease. Our proprietary product candidates impact pathways that are central to diseases where efficacy may be optimized by a multiple target approach.

Multi-target therapies have in many cases been developed to provide treatment options where single-target therapies have been ineffective. These multi-target therapies have traditionally followed one of two approaches: either use of a single drug that binds to multiple biological targets or co-administration of two or more drugs that interact with different targets. While each of these approaches has well-established benefits in a variety of indications, each is also characterized by significant limitations. For example, use of a single broadly targeted drug can lead to off-target toxicities, side-effects and tolerability issues, and co-administration of two or more drugs can be confounded by differences in the pharmacokinetics and tissue distribution of the drugs, thereby

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reducing the likelihood of each agent being simultaneously active in the same cell. Our SMART linker drug discovery platform is designed to address these issues.

Our aim is to leverage the growing body of knowledge associated with disease pathways, and to rationally design orally bioavailable product candidates that simultaneously interact with multiple biological targets in a disease. While other technologies exist to conjugate or combine two bioactives, we believe that our SMART linker drug discovery platform provides substantial improvements over previous approaches to bioactive conjugation.

**SMART Linker Drug Discovery Platform**

We have leveraged our SMART linker drug discovery platform to engineer molecules that can simultaneously modulate multiple biological targets in a disease. Our drug discovery platform includes a broad array of linkers that we use to engineer molecular series. The linkers used in our drug discovery platform are small chemicals designed to join two separate bioactives into a single conjugate molecule, and some linkers are also bioactives. In systemic circulation, our SMART linker conjugates are typically stable and inactive, potentially reducing off-target toxicities and side-effects. Certain of our conjugates are designed to be cleaved by specific enzymes exclusively within cells in order to release the two bioactives inside the cells. By releasing the bioactive components of the conjugate molecule inside cells, the SMART linker allows the bioactives to reach their targets more efficiently and have greater efficacy than if the bioactives were dosed independently or in combination.

To create a conjugate using our SMART linker drug discovery platform, we begin by analyzing pathways that are disrupted in a disease. We then select two bioactive molecules known for their clinical safety and demonstrated effect along one or more of these biological pathways. We then design a SMART linker that will conjugate the two selected bioactives, allow the conjugate molecule to be carried to biological tissues and, following entry into cells, be cleaved by enzymes resident in the cells to release the bioactives.

We have SMART linker conjugates that are designed to be stable with oral dosing, as well as stable in both the lumen of the intestine and in systemic circulation, which we have now observed in clinical trials for two product candidate series. We can design the SMART linker to chemically link the two bioactive molecules through their pharmacophores, the regions of the bioactive molecules that are responsible for carrying out their biological activity, resulting in inactivation of the bioactives while conjugated. Once the conjugate enters a cell, the SMART linker may be cleaved by specific enzymes which reside only within cells, releasing the two bioactives to interact with their biological targets. Simultaneous delivery of the bioactives through the SMART linker conjugate into the cell results in the two bioactives having the same pharmacokinetics and tissue distribution. As a result, our SMART linker conjugates can simultaneously modulate two biological targets in diseases of interest within the same cell. In addition, release of the bioactives inside cells can potentially reduce or eliminate off-target, extracellular activity of the bioactives, which may improve safety and tolerability.

We have observed in multiple preclinical studies that our SMART linker conjugates achieved greater efficacy than administration of the two bioactives either independently or in combination. In clinical trials, SMART linker conjugates have demonstrated significant improvements in activity on disease pathways and tolerability relative to equivalent doses of the two bioactives delivered in combination. We also have observed statistically significant pharmacological effects with SMART linker conjugates at dose levels significantly lower than the prescribed doses of the two component bioactives, as further described below under " Our Product Candidates Edasalonexent Edasalonexent Clinical Development Completed Clinical Trials". We are developing a pipeline of preclinical assets using our SMART linker drug discovery platform to potentially treat rare diseases including CF, ALS, FA, and others.

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We believe that our SMART linker drug discovery platform has the potential to:

- enhance activity on diseases through modulation of multiple biological targets;
- improve efficacy by matching the pharmacokinetics and tissue distribution of the component bioactives; and
- improve safety and tolerability by releasing the component bioactives within cells.

**Our Product Candidates**

The following chart summarizes key information regarding our product candidates. We hold rights to all of our product candidates throughout the world.

***Edasalonexent***

Edasalonexent is a SMART linker conjugate of salicylic acid and the omega-3 fatty acid docosahexaenoic acid, or DHA, a naturally occurring unsaturated fatty acid with anti-inflammatory properties. We designed edasalonexent to inhibit NF-κB, a protein that is activated in DMD and that drives inflammation, fibrosis and muscle degeneration, and suppresses muscle regeneration. We reported results from Part A of the MoveDMD trial in January 2016 and reported top-line safety and efficacy results for Part B of the trial in January 2017. Results from both Part A and Part B of the MoveDMD trial are described further below under " Edasalonexent Clinical Development". In July 2016, we initiated an open-label extension, Part C of the MoveDMD trial, which is expected to provide safety and efficacy data on edasalonexent when administered for up to 48 weeks. The FDA has granted edasalonexent orphan drug, fast track and rare pediatric disease designations for the treatment of DMD. The EC has granted orphan medicinal product designation to edasalonexent for the treatment of DMD.

In September 2016, we announced a pre-clinical joint research collaboration with Sarepta Therapeutics, Inc., or Sarepta, a commercial stage developer of RNA targeted therapeutics, established to explore a combination drug treatment approach for DMD. In the Catabasis and Sarepta

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collaboration, increased dystrophin protein expression was seen with an exon-skip modality in combination with edasalonexent in the designated mouse model of DMD.

*Overview of DMD*

DMD is a rare pediatric disorder involving progressive muscle degeneration that eventually leads to death. DMD is caused by various mutations in the dystrophin gene that result in a lack of functional dystrophin in muscle fibers, which renders muscle fibers more susceptible to mechanical stress. Dystrophin is a protein that resides in the membrane of muscle cells and is critical to the structural and membrane stability of muscle fibers in skeletal, including diaphragm, and cardiac muscle. When muscles contract or stretch during normal use, the absence of normally functioning dystrophin results in activation of the NF-κB pathway, triggering inflammation in the muscles, resulting in muscle damage and reducing the ability of muscles to regenerate. As muscle damage progresses, connective and adipose tissues replace muscle fibers, resulting in inexorable muscle weakness.

DMD occurs almost exclusively in males, occurring in approximately 1 in 3,500 live male births. Based on this incidence rate, we estimate that DMD affects a total of approximately 15,000 patients in the United States and approximately 19,000 patients in the European Union.

Children with DMD typically begin to show symptoms of disease between ages two and five, when they develop a waddling gait, frequently fall and have difficulty rising from the floor. Progressive weakness then develops in the voluntary muscles in the arms, legs and trunk. This muscle weakness is accompanied by fixations, or contractures, of joints, such as knees, hips and elbows. By age eight, most patients have difficulty ascending stairs. Patients typically lose walking ability between the ages of ten and fourteen and, by about twelve years of age, most people with DMD are unable to walk and need to use a power wheelchair on a regular basis. Patients' cardiac and respiratory muscles are also adversely affected, typically requiring use of ventilators in their late teens. Progressive weakening of cardiac and respiratory muscles of DMD patients eventually results in death, generally in their mid-twenties.

*The Role of NF-κB in Duchenne Muscular Dystrophy*

NF-κB plays an important role in regulating skeletal muscle health and appears to be especially important in regulating skeletal muscle mass in chronic diseases such as DMD. Activated NF-κB promotes the degradation of specific muscle proteins and leads to the induction of pro-inflammatory mediators such as cytokines, including tumor necrosis factor alpha, or TNF-α, interleukin 6, or IL-6, and interleukin-1 beta, or IL-1β; chemokines; cell adhesion molecules; and tissue degrading enzymes, such as matrix metallopeptidase 9, or MMP-9. In addition, activated NF-κB suppresses muscle stem cell differentiation that is required for muscle regeneration by preventing satellite stem cells from differentiating into myoblasts, progenitor cells that differentiate, to give rise to muscle cells. Activation of NF-κB is observed in muscle tissues of patients with DMD prior to the onset of other clinical manifestations, and activated NF-κB is persistently elevated in the immune cells and degenerating muscle fibers of patients with DMD. Moreover, evidence exists that mechanical stress activates NF-κB in muscles and increases levels of activated NF-κB by a factor of three to four times and drives NF-κB mediated inflammation. Muscles with increased mechanical stress and inflammation, such as quadriceps and hamstrings, show the greatest progression of disease.

*Unaddressed Market Opportunity*

There are currently only two therapies approved in the United States for the treatment of DMD: Sarepta's drug Exondys 51, also known as eteplirsen, an exon skipping therapy targeting the skipping of exon 51, that was granted accelerated approval by the FDA, and Marathon Pharmaceuticals' EMFLAZA , also known as deflazacort, a corticosteroid, which is indicated for the treatment of DMD

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in patients five years of age and older. Corticosteroid therapy, including treatment with prednisone, is often prescribed to treat the inflammation underlying DMD and to delay loss of ambulation. Corticosteroids have demonstrated efficacy in DMD patients, which is believed to be driven by reductions in activated NF-κB. However, corticosteroids primarily act through another pathway called the glucocorticoid receptor-mediated pathway, and also can cause significant complications including growth suppression, excessive weight gain, behavioral changes, reduction in bone strength and compromise of the immune system. Over time, corticosteroids induce chronic myopathy in many diseases through induction of muscle protein breakdown, which ultimately leads to muscle damage. DMD patients treated with corticosteroids typically show an initial improvement in measures of muscle function but then resume a progressive decline. Approximately half of DMD patients treated with steroids lose the ability to walk by age thirteen and the vast majority are in wheelchairs by age sixteen. DMD patients typically live until their mid-twenties, despite the availability of corticosteroids.

Additionally, there are several treatments for DMD that are approved or under review in the European Union or are expected to be under review by regulatory agencies in the near future. Santhera Pharmaceuticals, or Santhera, has filed a marketing authorization application with the European Medicines Agency, or EMA, for Raxone®, also known as idebenone, for the treatment of DMD in patients with respiratory function decline and not taking concomitant glucocorticoids. Sarepta's Exondys 51 is under review by the EMA, and PTC Therapeutics' ataluren is conditionally approved in the European Union and several other countries for treatment of nonsense mutation DMD under the trade name Translarna . PTC Therapeutics also re-filed a new drug application, or NDA, with the FDA in March 2017. Exondys 51 and ataluren target mechanisms to increase levels of dystrophin in muscles. Each of these agents addresses a specific type of genetic mutation in order to produce a partially functional dystrophin protein. The therapeutic goal of these product candidates is to reduce disease severity and extend survival in those DMD patients who are candidates for therapy with these agents. Based on the prevalence of the specific mutations that Exondys 51 and ataluren are designed to address, they would be expected to be effective in an aggregate of approximately 26% of DMD patients. We believe that DMD patients, including those treated with these dystrophin therapies, will continue to require treatments to reduce muscle inflammation and degeneration and enhance muscle regeneration.

Edasalonexent for the Treatment of Duchenne Muscular Dystrophy

Based on the mechanism of action by which edasalonexent suppresses NF-κB and the results that we have seen in preclinical models of DMD, we believe that edasalonexent has the potential to combine reduction of inflammation and muscle degeneration with positive effects on muscle regeneration, all of which may allow patients to retain muscle function longer. In addition, we believe that edasalonexent has the potential to be an effective therapy in all DMD patients, regardless of the underlying mutation, and to provide significant benefit to patients, both as monotherapy and when used in combination with other therapies, including dystrophin-targeted therapies and agents targeting utrophin. We intend to commercialize edasalonexent in North America ourselves and commercialize edasalonexent outside of North America either ourselves or with a collaborator.

*Edasalonexent Clinical Development*

*MoveDMD Phase 1/2 Trial of Edasalonexent in Patients with DMD*

Our MoveDMD Phase 1/2 trial enrolled ambulatory boys between ages four and seven with a genetically confirmed diagnosis of DMD who were steroid naive or had not used steroids for at least six months prior to the trial. Boys enrolled in the trial are not limited to any specific dystrophin mutations. The MoveDMD trial is designed to be conducted in three sequential parts, Part A and Part B, both of which have been completed, and Part C, an open-label extension initiated in July 2016, which is on-going.

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In Part A of the MoveDMD trial, which was conducted at three sites in the United States, we assessed the safety, tolerability and pharmacokinetics of edasalonexent in 17 patients, following seven days of dosing, across three dosing levels: 33 mg/kg/day, taken in a single daily dose, 67 mg/kg/day, taken in two daily doses, and 100 mg/kg/day, taken in three daily doses. We also compared edasalonexent exposure levels to exposure levels achieved in previous edasalonexent clinical trials in adults where inhibition of NF-κB was observed. In January 2016, we reported that all three doses of edasalonexent tested were generally well tolerated with no safety signals observed. The majority of adverse events were mild, and the most common adverse events were gastrointestinal, primarily diarrhea. There were no serious adverse events and no drug discontinuations. For the 67 mg/kg/day and 100 mg/kg/day dosing levels, pharmacokinetic results demonstrated edasalonexent plasma exposure levels consistent with those previously observed in adults at which inhibition of NF-κB was observed, and edasalonexent significantly reduced the expression of a set of genes that are controlled by NF-κB. We subsequently reported results with positive NF-κB biomarker data that supported NF-κB target engagement via statistically significant reduction in NF-κB controlled gene expression for the 67 mg/kg/day and 100 mg/kg/day dosing levels. These two dosing levels were advanced to Part B of the trial.

Thirty-one boys enrolled in Part B of the MoveDMD trial and all completed Part B of the trial. Both dose levels of edasalonexent evaluated were well tolerated with no safety signals observed. The majority of adverse events were mild in nature and the most common treatment-related adverse events were gastrointestinal, primarily mild diarrhea and vomiting. There were no treatment-related serious adverse events, no drug discontinuations and no dose reductions. Edasalonexent plasma exposure in Part B of the MoveDMD trial was consistent with that observed in Part A.

In Part B of the MoveDMD trial, we assessed the effects of edasalonexent using MRI T2 as an early biomarker at 12 weeks in a randomized, double-blind, placebo-controlled trial. Part B of the MoveDMD trial was conducted at five sites in the United States, and we believe that it was the first Phase 2 trial in DMD to use MRI as a primary endpoint. MRI is a non-invasive imaging technique that allows investigators to view muscle structure and composition and measure disease status in children with DMD. Changes in MRI measures, particularly fat fraction, have been correlated in natural history studies with longer-term changes in clinically meaningful measures of functional activity. We used MRI T2 as the primary endpoint to serve as an early biomarker for demonstrating a benefit on muscle composition that potentially would allow us to see an effect of edasalonexent at 12 weeks of treatment, as has been seen by others with corticosteroids. We announced in January 2017 that the primary efficacy endpoint of average change from baseline to week 12 in the MRI T2 composite measure of lower leg muscles for the pooled edasalonexent treatment groups compared to placebo was not met (0.37 milliseconds for the pooled edasalonexent treatment groups versus 0.47 milliseconds for placebo; a smaller increase in MRI T2 is believed to correlate with less muscle inflammation). Although we did not see a similar treatment effect as corticosteroids on the MRI T2 composite measure at 12 weeks, we observed potential treatment-associated functional effects at both dose levels of edasalonexent on the exploratory endpoints described below, as well as continued to observe acceptable safety, tolerability and plasma exposure data in Part B of the MoveDMD trial. Therefore, as planned, we are measuring the effects of edasalonexent on patients with DMD in the MoveDMD trial in Part C to see if signals strengthen in the longer-term data from the ongoing open-label extension.

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Exploratory endpoints also included the following functional tests in Parts B and C of the MoveDMD trial: timed function tests best suited for the age group of the trial subjects, including the 10-meter walk/run, 4-stair climb and time-to-stand tests; the North Star Ambulatory Assessment; assessments of muscle strength; and the Pediatrics Outcomes Data Collection Instrument, a parent-proxy measure of functional ability. The trial is not powered to detect statistically significant changes in any of the exploratory endpoints during Part B or Part C, and no significant changes were detected in these measures for those dosed with edasalonexent versus placebo at 12 weeks. Top-line results from Part B demonstrated that the edasalonexent 100 mg/kg/day treatment group, whose patients took 33mg/kg capsules three times a day, consistently showed numerical improvement versus placebo across all measures of the functional test exploratory endpoints, although the changes were not statistically significant. Similarly, the 67 mg/kg/day treatment group, whose patients took 33mg/kg capsules twice a day, consistently showed numerical improvement versus placebo across multiple measures of the functional test exploratory endpoints, although the changes were not statistically significant and were mixed compared to the 100 mg/kg/day treatment group. Compared to the placebo group, patients in the edasalonexent 100 mg/kg/day group had characteristics of more advanced disease at baseline. This was indicated by the age at onset, age at diagnosis and the baseline values for time to complete the 4-stair climb and time-to-stand. In addition, baseline assessments were performed at the beginning of Part A and Part B of the MoveDMD trial to compare changes in functional measures in this control period to those observed in Part B and Part C. There were twelve boys who participated in Part A and received active treatment in Part B, and the rate of decline in functional measures for these boys generally showed numerical improvement over the active treatment period compared to the control period. We believe that the top-line results from the functional exploratory endpoints and additional functional assessments warrant further evaluation as planned in Part C of the MoveDMD trial. We intend to transition all patients participating in Part C of the trial to the 100 mg/kg/day dose and extending Part C by an additional 24 weeks, subject to institutional review board approval, so that we have the opportunity to assess the higher dose in all of the boys in Part C and so that the boys that started the open-label extension since July last year are able to continue to receive edasalonexent treatment. We intend to report the results from Part C in 2017. We anticipate providing an interim update on Part C of the MoveDMD trial in the second quarter of 2017.

Following additional assessment of the effects in patients of edasalonexent in Part C of the MoveDMD trial, we will determine next steps for the edasalonexent program in DMD.

*Completed Clinical Trials*

To date, we have studied edasalonexent in three completed Phase 1 clinical trials, in addition to Part A of the MoveDMD trial, which is described above. The design for each of these other clinical trials are discussed below.

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***Edasalonexent Completed Phase 1 Clinical Trials***

| Trial | Description | Duration Of Dosing | Total | Subjects Treated with edasalonexent |
|---|---|---|---|---|
| CAT-1004-101 | Randomized, double-blind, placebo-controlled, single ascending dose clinical trial to evaluate safety, tolerability and pharmacokinetics of edasalonexent in healthy subjects | 1 day | 52 | 39 |
| CAT-1004-102 | Randomized, double-blind, placebo-controlled multiple ascending dose clinical trial to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of edasalonexent in adults with Type 2 diabetes | 14 days | 44 | 32 |
| CAT-1004-103 | Single-blind biomarker trial in healthy adults to compare activity of edasalonexent, a combination of salicylate and DHA, or placebo on activated NF-κB | 1 day | 9 | 8 |

*Phase 1 Single Ascending Dose Trial (CAT-1004-101):* We conducted a randomized, double-blind, placebo-controlled, single ascending dose Phase 1 clinical trial in 52 healthy volunteers at a single site in the United States to assess the safety, tolerability and pharmacokinetics of edasalonexent in both fasted and fed states. The participants were randomized to receive edasalonexent or placebo. Edasalonexent was administered orally in soft gelatin capsules at doses ranging from 300 mg to 6000 mg.

Single doses of edasalonexent, administered to subjects in both fed and fasted conditions, appeared to be well tolerated. Subjects in the fasted state reported few adverse events, with the most commonly reported adverse events being headache, diarrhea and dizziness. Of the 44 subjects in the fasted state, five reported headache, three reported diarrhea and two reported dizziness. The majority of the adverse events in the fasted state were mild in severity. Of the 35 subjects in the fed state, six reported diarrhea, six reported headache and four reported abdominal pain. The most common adverse events in the fed state were diarrhea, headache and abdominal pain, and all of the adverse events in the fed state were mild in severity. Subjects in the fed state receiving single doses of edasalonexent of 4000 mg or more reported gastrointestinal adverse events more frequently than subjects receiving lower doses. No treatment-related severe adverse events were reported. There were no observed trends in laboratory, vital signs or electrocardiogram results following edasalonexent administration in either the fasted or fed state.

Edasalonexent was rapidly absorbed in plasma, with mean maximum and overall plasma exposure generally increasing with edasalonexent dose levels. Neither component bioactive, salicylate or DHA, was detected in plasma at levels above background, consistent with intracellular cleavage of edasalonexent and intracellular delivery of the component bioactives. Administration of a high-fat meal increased edasalonexent mean maximum and overall exposure by approximately three- to eight-fold.

*Phase 1 Multiple Ascending Dose Trial (CAT-1004-102):* We conducted a randomized, double-blind, placebo-controlled, multiple ascending dose Phase 1 clinical trial in 44 subjects at a single center in the United States to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of edasalonexent. These subjects had Type 2 diabetes and mild background inflammation, which enabled us to assess the activity of edasalonexent on activated NF-κB. Subjects were randomized to receive

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edasalonexent or placebo. edasalonexent was administered orally in soft gelatin capsules at total daily doses ranging from 300 mg to 4000 mg.

Edasalonexent administered for two weeks appeared to be well tolerated. The adverse events reported in more than one subject were each reported by two subjects. These adverse events were diarrhea (both instances reported by subjects receiving 4000 mg daily doses of edasalonexent), gastroenteritis (one instance reported by a subject in the placebo group and the other by a subject receiving 1000 mg daily doses of edasalonexent) and upper respiratory tract infection (both instances reported by subjects receiving 4000 mg daily doses of edasalonexent). The majority of the adverse events were mild in severity. No treatment-related severe adverse events were reported.

Edasalonexent was rapidly absorbed in plasma, with mean maximum and overall plasma exposure generally increasing with escalating single or multiple doses of edasalonexent. Neither component bioactive, salicylate or DHA, was detected in plasma at levels above background, again consistent with intracellular cleavage of edasalonexent and intracellular delivery of the component bioactives.

In the Phase 1 multiple ascending dose trial, we observed by two methods that edasalonexent inhibited activated NF-κB. For the first method, we stimulated NF-κB activity *ex vivo* in whole blood from subjects treated with edasalonexent or placebo, and then observed NF-κB activity in monocytes, or immune cells, that we isolated from the whole blood. NF-κB activity was reduced in a majority of subjects following two weeks of edasalonexent treatment but not following treatment with placebo. For the second method, we performed gene expression analyses on whole blood taken from subjects prior to treatment and after two weeks of treatment with edasalonexent or placebo. Edasalonexent significantly reduced the expression of a set of genes that are controlled by NF-κB. In contrast, treatment with placebo for two weeks did not significantly reduce expression of NF-κB regulated genes.

*Phase 1 NF-κB Biomarker Trial (CAT-1004-103):* We conducted a single-blind, crossover Phase 1 clinical trial with edasalonexent in nine healthy adult volunteers at a single center in the United States to compare activity of a single dose of 2000 mg of edasalonexent on activated NF-κB to a combination of salicylate and DHA or placebo. No adverse events were reported in this clinical trial. The salicylate and DHA were dosed at approximately equivalent amounts to those contained in the edasalonexent conjugate. We assessed NF-κB activity in peripheral blood mononuclear cells, or PBMCs, isolated from subjects before dosing and two hours after dosing. PBMCs are circulating immune cells that can mount an NF-κB response and migrate into tissue such as muscle and drive inflammation. Prior to the determination of NF-κB activity, we stimulated whole blood with lipopolysaccharide, or LPS, to activate the NF-κB pathway. Treatment of subjects with edasalonexent significantly reduced the level of activated NF-κB, as measured by nuclear p65, a surrogate marker for activated NF-κB. In contrast, no change in the level of activated NF-κB was observed upon treatment with the combination of salicylate and DHA, or upon treatment with placebo. In this trial, edasalonexent, which is a SMART linker conjugate of salicylate and DHA, exhibited greater activity on the NF-κB pathway than the combination of its component bioactives.

*Edasalonexent Preclinical Development*

In preclinical studies, we have observed that edasalonexent inhibited NF-κB activity *in vitro* and *in vivo*, and produced disease-modifying effects in two established animal models of DMD, the *mdx* mouse model and the Golden Retriever muscular dystrophy, or GRMD, dog model.

*In Vivo Studies in Animal Models of DMD*

We have created several SMART linker conjugates that inhibit activated NF-κB. Two of these conjugates, edasalonexent and CAT-1041, exhibit very similar effects on NF-κB activity in cell based assays, in animal studies and on functional activity in animal models. CAT-1041 is a closely related analog of edasalonexent in which the DHA component of the salicylate-DHA conjugate has been

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replaced with the omega-3 fatty acid eicosapentaenoic acid, or EPA. In some preclinical studies, we used CAT-1041 as a surrogate for edasalonexent. Both edasalonexent and CAT-1041 produced disease-modifying efficacy in established animal models of DMD. We decided to advance edasalonexent into clinical trials rather than CAT-1041 based on scientific literature suggesting that DHA has superior anti-inflammatory activity compared to EPA.

*mdx Mouse Model.* We examined the potential therapeutic effects of edasalonexent using the *mdx* mouse model of DMD. We observed that four weeks of treatment with edasalonexent or prednisolone, a steroid, reduced muscle inflammation and the number of degenerating muscle fibers in *mdx* mice. However, only edasalonexent-treated animals showed preservation of muscle mass and an increase in the number of regenerating fibers, suggesting that chronic treatment with edasalonexent can protect muscle from the damage expected to occur over time in *mdx* mice.

In a long-term *mdx* mouse study, we observed that, compared to the control group of *mdx* mice, six months of treatment with CAT-1041 significantly improved muscle endurance as measured by mean weekly and total running distance determined based upon cumulative revolutions on a running wheel. Improvements in muscle endurance following CAT-1041 treatment versus control were also observed in post-mortem assessments of twitch force, tetanic force and specific force generation, each of which is an established measurement of muscle endurance, in excised diaphragm muscle.

We also observed in this same study that *mdx* mice treated with CAT-1041 showed significantly increased mass of two major leg muscles, the gastrocnemius and quadriceps. These increases were independent of changes in total body weight. CAT-1041 treated mice also had a statistically significant reduction in cardiac mass and fibrosis, suggesting that chronic treatment with CAT-1041 may have reduced the dilated cardiomyopathy typically observed in *mdx* mice.

In this study, we also observed that edasalonexent and CAT-1041 exhibited similar activity on muscle contractions of the extensor digitorum longus muscle in *mdx* mice with significant preservation of muscle function compared to control. Finally, in this study we observed a reduction in diaphragm and quadricep muscle fibrosis in *mdx* mice treated with CAT-1041 in comparison to control.

*Golden Retriever Dog Model.* We also evaluated the effects of edasalonexent in the GRMD dog model. A single oral dose of edasalonexent inhibited basal, or unstimulated, NF-κB activity by 48% in GRMD dogs. Edasalonexent also inhibited LPS-stimulated NF-κB activity by 75% and LPS-stimulated plasma levels of TNFα protein, a key marker of inflammatory response, by 77%. Together, these data suggest that a single oral dose of edasalonexent achieves sufficient exposure levels to inhibit activated NF-κB in a dog model of DMD.

*In Vitro Studies*

In an *in vitro* study in a mouse macrophage cell line, we observed that edasalonexent inhibited LPS-stimulated NF-κB activity to a greater extent than either of its components, salicylate and DHA, alone or in combination. We also observed that edasalonexent inhibited LPS-stimulated NF-κB activity in human PBMCs, which are a potential target tissue for edasalonexent. In studies performed with a mouse macrophage cell line, edasalonexent reduced the LPS-stimulated expression of a set of genes that encode pro-inflammatory mediators and whose expression is controlled by NF-κB.

*Edasalonexent Orphan Drug, Fast Track and Rare Pediatric Disease Designations*

The FDA has granted edasalonexent orphan drug, fast track and rare pediatric disease designations for the treatment of DMD. A product may be designated by the FDA as an "orphan drug" if it is intended to treat a rare disease or condition affecting fewer than 200,000 individuals in the United States. If a product with orphan status receives the first FDA approval for the disease or condition for which it has such designation, the FDA will not approve another sponsor's marketing

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application for the same product for the same use or indication before the expiration of seven years, except in certain limited circumstances. The FDA fast track process is designed to expedite the development and review of drugs to treat serious or life-threatening conditions and demonstrate the potential to address unmet medical needs. Companies that receive fast track designation are allowed to submit NDAs on a rolling basis, expediting the FDA review process, and benefiting from more frequent communication with the FDA to discuss all aspects of clinical development. In addition, drugs that receive fast track designation are eligible for accelerated approval and priority review if certain criteria are met. The FDA's rare pediatric disease designation gives us the potential to receive a priority review voucher if edasalonexent is approved. However, the rare pediatric disease program is set to expire in September 2020.

The EC has granted orphan medicinal product designation to edasalonexent for the treatment of DMD. Similar to the FDA orphan drug designation, the EC may designate a product as an orphan medicinal product if it is intended for the treatment of a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons. In Europe, marketing authorization for an orphan medicinal product generally leads to up to a ten-year period of market exclusivity if the product candidate is granted marketing authorization in the European Union.

***CAT-5571***

CAT-5571 is a SMART linker conjugate that contains cysteamine, a naturally occurring molecule that is a degradation product of the amino acid cysteine, and DHA. We are developing CAT-5571 initially as a potential oral treatment for CF with potential effects on both the CFTR and on the clearance of *Pseudomonas aeruginosa*. CAT-5571 is a small molecule that activates autophagy, a process that maintains cellular homeostasis and host defense mechanisms, which are known to be impaired in CF.

We have shown in preclinical studies that CAT-5571 synergistically activates autophagy in cultured primary human bronchial epithelial cells isolated from patients with CF. In addition, we have shown in *ex vivo* preclinical studies that CAT-5571, in combination with lumacaftor/ivacaftor, a combination drug that consists of lumacaftor, which increases CFTR proteins that are trafficked to the cell surface, and ivacaftor, which increases the activity of the CFTR protein at the surface of epithelial cell, enhances cell-surface trafficking and function of CFTR with the F508del mutation, which is the most frequent CFTR mutation and is present in 86% of patients included in the Cystic Fibrosis Foundation United States Patient Registry. We have also shown that CAT-5571 enhances the clearance of *Pseudomonas aeruginosa* infection in preclinical models of CF, irrespective of CFTR mutation status. We are conducting additional preclinical activities with CAT-5571.

In 2017, we plan to continue preclinical evaluation of CAT-5571 in animal models of CF, and to conduct investigational new drug, or IND, application-enabling activities for CAT-5571. If we are successful in these activities, we intend to advance CAT-5571 into a Phase 1 clinical trial in 2018.

*Cystic Fibrosis*

Cystic fibrosis is a rare, chronic, genetic, life-shortening orphan disease that affects over 70,000 patients worldwide, predominantly in the Caucasian population. In CF, a malfunctioning CFTR ion channel impairs chloride secretion, with deleterious effects on multiple organs, and particularly devastating effects on pulmonary, intestinal and pancreatic function. Patients affected with CF are also predisposed to respiratory failure caused by persistent lung infections, notably bacteria and most commonly *Pseudomonas aeruginosa,* that are difficult to treat with standard antibiotics. CF patients have frequent pulmonary exacerbations due to their inability to clear the persistent lung infections. Advancement in research and treatments have extended the life expectancy for those living with CF, however, there is currently no cure.

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***CAT-4001***

CAT-4001 is a SMART linker conjugate that we designed to combine the potentially beneficial activities of monomethyl fumarate and DHA on the Nrf2 and NF-κB pathways. CAT-4001 is a small molecule designed to activate the Nrf2 pathway and inhibit the NF-κB pathway. We are developing CAT-4001 initially for the treatment of severe, rare neurodegenerative diseases, such as FA and ALS, two diseases of the central nervous system in which the Nrf2 and NF-κB pathways have been implicated, irrespective of mutation status. Nrf2 is a gene transcription factor, a protein that works inside of cells to control the expression of genes, that control the body's response to cellular stress and oxidative damage. We are conducting preclinical activities with CAT-4001.

We have shown that CAT-4001 modulates the Nrf2 and NF-κB pathways in both cellular assays and animal models. In these studies, we have also observed that the activity produced by CAT-4001 was greater than that produced by the individual bioactives, monomethyl fumarate and DHA, either alone or in combination at approximately equivalent amounts to those contained in the CAT-4001 conjugate. Oxidative stress and neuroinflammation are believed to play a central role in a number of neurodegenerative diseases, including FA and ALS. In addition, monomethyl fumarate is the circulating form of the active ingredient of Biogen's Tecfidera (dimethyl fumarate), an FDA-approved treatment for multiple sclerosis, another neurodegenerative disease. We believe that this known therapeutic effectiveness of monomethyl fumarate offers further support for the potential for CAT-4001 to be developed for the treatment of neurodegenerative diseases.

Based on its mechanism of action, we believe that CAT-4001 has the potential to be a disease modifying agent in certain neurodegenerative diseases. In 2017, we plan to continue preclinical evaluation of CAT-4001 in animal models of FA as well as ALS.

*Friedreich's Ataxia*

Friedreich's ataxia is a rare genetic disease that causes nervous system damage and compromises motor coordination. FA is caused by a defect in the frataxin gene, which regulates iron levels in the mitochondria. In the majority of cases, the genetic defect in FA causes a reduction in the production of the frataxin protein and iron levels in mitochondria become poorly regulated. In FA, iron overload in mitochondria affects metabolism, causing oxidative stress and ultimately damaging mitochondrial DNA. Progressive degeneration of central and peripheral nervous systems in FA patients causes impaired gait and coordination, muscle loss and fatigue. Disease progression varies, but generally, the patient is confined to a wheelchair within 10 to 20 years after the appearance of the first symptoms. Patients may become completely incapacitated in later stages of the disease.

FA occurs in both males and females and is estimated to affect 1 in 50,000 individuals. Based on this prevalence rate, we believe there are up to 6,000 patients with FA in the US and up to 15,000 FA patients in the European Union.

The Friedreich's Ataxia Research Alliance announced in January 2016 that we were the recipient of the Kyle Bryant Translational Research Award. The Kyle Bryant Translational Research Award specifically focuses on pre-clinical and clinical investigations that target treatments for FA.

*Amyotrophic Lateral Sclerosis*

ALS, sometimes called Lou Gehrig's disease or classical motor neuron disease, is a rapidly progressive, fatal neurological disease that attacks the nerve cells responsible for controlling voluntary muscles. Eventually, muscle weakness and atrophy occur. People with ALS lose the ability to stand and walk, and use their hands and arms. In later stages of the disease, individuals have difficulty breathing as the muscles of the respiratory system weaken. Although ventilation support can enable breathing and

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prolong survival, it does not affect the progression of ALS. Most people with ALS die from respiratory failure, usually within three to five years of diagnosis.

According to the ALS Association, approximately 5,600 people in the United States are diagnosed with ALS each year. The incidence of ALS is two per 100,000 people, and it is estimated that as many as 30,000 Americans may have the disease at any given time. ALS occurs throughout the world and affects all racial, ethnic and socioeconomic groups.

***CAT-2000 Series***

Our CAT-2000 compounds are SMART linker conjugates of nicotinic acid and EPA. The linkers for our CAT-2000 series compounds are cleaved through intracellular enzymatic hydrolysis, to release the component bioactives to inhibit SREBP. By using different linkers, we have produced product candidates within the CAT-2000 series that possess different hydrolysis rates, resulting in distinct pharmacokinetics, biodistribution and pharmacology. We have been able to demonstrate enzymatic hydrolysis and inhibition of SREBP in *in vitro* studies with CAT-2000 molecules. In addition, *in vivo*, CAT-2000 molecules have demonstrated efficacy in multiple preclinical models of hyperlipidemias and NASH. We believe that our portfolio of CAT-2000 molecules, which includes the clinical-stage molecules CAT-2003 and CAT-2054 and other discovery-stage molecules with intermediate rates of hydrolysis, provides an opportunity to develop a therapy for NASH. We intend to pursue a partnership for further development of the CAT-2000 series in NASH.

**Sales and Marketing**

Given our stage of development, we have not yet established a commercial organization or distribution capabilities, nor have we entered into any collaboration or co-promotion arrangements. If we are able to progress our edasalonexent program, we intend to commercialize edasalonexent in North America ourselves and commercialize edasalonexent outside of North America either ourselves or with a collaborator. In addition, we intend to expand the drug development applications of our SMART linker drug discovery platform through selective collaborations with leading biotechnology and pharmaceutical companies.

**Manufacturing and Supply**

Each of our SMART linker conjugate product candidates is a small molecule compound manufactured from component raw materials. The omega-3 fatty acid materials that we use as bioactives are purified from natural sources by established pharmaceutical fine chemicals manufacturers. The other bioactive and linker raw materials that we use are also readily available from established pharmaceutical intermediate manufacturers. The components are conjugated to form the SMART linker product candidate using well understood, conventional chemistries.

We currently have no manufacturing facilities and limited personnel with manufacturing experience. We rely on contract manufacturers to produce both drug substance and drug product required for our clinical trials. We plan to continue to rely upon contract manufacturers and, potentially, collaborators to manufacture commercial quantities of our products, if approved.

**Competition**

The development and commercialization of new drugs is highly competitive. If we successfully develop and commercialize any of our product candidates, we and any future collaborators will face competition from pharmaceutical and biotechnology companies worldwide. Many of the entities developing and marketing potentially competing products have significantly greater financial resources and expertise than we do in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing. Our commercial opportunity will be reduced or eliminated if our competitors develop and commercialize products that are more effective, have fewer side effects, are more convenient or are less expensive than any products that we may develop.

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The key competitive factors affecting the success of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price and the availability of coverage and reimbursement from government and other third-party payors.

***Edasalonexent for Duchenne Muscular Dystrophy***

There are currently only two therapies approved in the United States for the treatment of DMD. Sarepta's drug Exondys 51, also known as eteplirsen, was approved by the FDA for the treatment of DMD under the accelerated approval pathway in September 2016 for patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. In addition, in February 2017, Marathon Pharmaceuticals, LLC announced that the FDA granted approval of EMFLAZA , also known as deflazacort, a corticosteroid, for the treatment of DMD in patients five years and older. Outside of the United States, PTC Therapeutics' drug ataluren, also known as Translarna , has been conditionally approved within the European Union Member States, Iceland, Liechtenstein, Norway, Israel and South Korea for the treatment of nonsense mutation DMD. Although not previously approved for the treatment of DMD, corticosteroid therapy, including prednisone, is considered standard of care and is often prescribed to treat the inflammation underlying DMD and to delay loss of ambulation.

A number of companies are developing therapies to treat DMD in patients with specific mutations in the dystrophin gene. In addition to eteplirsen, Sarepta has two additional exon-skipping therapies for DMD in Phase 3 clinical development. These agents, SRP-4053 and SRP-4045, target skipping of exons 53 and 45, respectively. Daiichi-Sankyo is developing an exon-skipping product candidate for DMD patients with out-of-frame deletion mutations amenable to exon 45 skipping, and announced in February 2016 that it began its first Phase 1/2 clinical trial for its product candidate, DS-5141b, in Japan. NS Pharma has a compound, NS-065/NCNP-01, in Phase 2 clinical development in the United States and Japan for patients with mutations amenable to exon 53 skipping. Based on the prevalence of the specific mutations that these product candidates being developed by Sarepta, Daiichi-Sankyo and NS-Pharma are designed to address, they would be expected to have the potential to be effective in an aggregate of approximately 16% of DMD patients. In addition to these clinical stage programs, BioMarin has announced its intent to continue to explore the development of next generation oligonucleotides for the treatment of DMD, and Wave Life Sciences is developing an exon 51 skipping candidate, WVE-210201, for which it has announced plans to enter the clinic in the second half of 2017.

In addition to exon-skipping therapies, other companies have alternative therapeutic approaches to the treatment of DMD in late stage clinical development. Santhera announced in September 2016 that it enrolled its first patient in its Phase 3 trial (SIDEROS) that will assess the efficacy of its drug Raxone®, also known as idebenone, in slowing the rate of respiratory function decline in DMD patients receiving concomitant glucocorticoids. Santhera has stated that successful completion of the SIDEROS trial will provide the necessary data to support an NDA filing with FDA for Raxone. Santhera has filed a marketing authorization application with the EMA for Raxone for the treatment of DMD in patients with respiratory function decline and not taking concomitant glucocorticoids. PTC Therapeutics' ataluren provides another alternative therapeutic approach to treating DMD, already approved outside of the United States as mentioned above. Ataluren is designed to enable the formation of a functioning dystrophin protein in patients with DMD caused by a nonsense mutation. In February 2016, PTC Therapeutics received a Refuse to File letter for ataluren from the FDA and appealed this decision, and this appeal was subsequently denied by the FDA in October 2016. PTC Therapeutics filed a new ataluren NDA for nonsense mutation DMD over protest with the FDA in March 2017. A number of companies also have products candidates in clinical development for DMD, including Akashi Therapeutics, Bristol-Myers Squibb, Capricor Therapeutics, Cardero Therapeutics, Italfarmaco SpA, Pfizer, Phrixus Pharmaceuticals, Reveragen, Summit Plc and Taiho Pharmaceuticals. If successfully

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developed, some of these alternative therapeutic appr