CATABASIS PHARMACEUTICALS INC
Form 10-K
March 15, 2016

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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, 2015

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

EXPLANATORY NOTE: Under the Jumpstart Our Business Startups Act, the registrant qualifies as an "emerging growth company." We therefore incorporate the scaled disclosures required of an emerging growth company in this Annual Report on Form 10-K.

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, 2015: $69,104,534.

As of March 7, 2016, there were 15,336,333 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 2016 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 initiate Part B of our MoveDMD[SM] clinical trial of CAT-1004 for the treatment of Duchenne muscular dystrophy in the first half of 2016;
- ongoing and planned clinical trials for CAT-1004, CAT-2054 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.

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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. Our primary focus is on treatments for rare diseases. We are also developing other product candidates for the treatment of serious lipid disorders. We have applied our SMART linker drug discovery platform to build an internal pipeline of product candidates for rare diseases and plan to pursue partnerships to develop additional product candidates.

CAT-1004 is an oral small molecule that we believe 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. CAT-1004 is a SMART linker conjugate of salicylate, a non-steroidal anti-inflammatory drug, and the omega-3 fatty acid docosahexaenoic acid, or DHA, a naturally occurring unsaturated fatty acid with anti-inflammatory properties. We designed CAT-1004 to inhibit NF-κB, or nuclear factor kappa-light-chain-enhancer of activated B cells, a protein that is activated in DMD and drives inflammation, fibrosis and muscle degeneration, and suppresses muscle regeneration. In animal models of DMD, CAT-1004 inhibited NF-κB activity, reduced muscle degeneration and improved muscle regeneration and function. Beneficial effects were observed in skeletal, diaphragm and cardiac muscle. In Phase 1 clinical trials in adults, CAT-1004 inhibited NF-κB and was well tolerated with no observed safety concerns. The United States Food and Drug Administration, or FDA, has granted orphan drug, fast track and rare pediatric disease designations to CAT-1004 for the treatment of DMD. The European Commission, or EC, also has granted orphan medicinal product designation to CAT-1004 for the treatment of DMD.

We are currently conducting the MoveDMD Phase 1/2 trial of CAT-1004 in boys with DMD between ages four and seven. We reported positive top-line results from Part A of the MoveDMD trial in January 2016. Top-line results indicated that all three doses of CAT-1004 studied were generally well tolerated with no safety signals observed. Top-line pharmacokinetic results demonstrated CAT-1004 average plasma exposure levels consistent with those previously observed in adults at which inhibition of NF-κB was observed. Subject to regulatory approval of our proposed protocol, we expect to initiate Part B of the MoveDMD trial in the first half of 2016 and to report top-line Part B data in late 2016, contingent on patient enrollment. If the results from our MoveDMD clinical trial and discussions with regulatory authorities regarding a pivotal trial are positive, we intend to initiate a six-month Phase 3 pivotal clinical trial of CAT-1004 in 2017. If the results from the Phase 3 clinical trial are positive, we intend to seek marketing approval for CAT-1004. We hold rights to CAT-1004 throughout the world.

Our CAT-2000 series is our other clinical-stage program. We applied our SMART linker drug discovery platform to engineer the CAT-2000 series product candidates to inhibit the Sterol Regulatory Element Binding Protein, or SREBP, pathway. We used different SMART linkers to produce two CAT-2000 series product candidates, CAT-2054 and CAT-2003. These product candidates possess different pharmacokinetic and biodistribution characteristics. CAT-2003, our first generation product candidate, is an orally administered molecule that inhibits the SREBP pathway predominately in the intestine. CAT-2054, our second generation product candidate, is an orally administered molecule that inhibits the SREBP pathway predominately in the liver. We are developing CAT-2054 for serious lipid disorders such as hypercholesterolemia.

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Hypercholesterolemia is a disease that increases the risk of cardiovascular events. By modulating the SREBP pathway, CAT-2054 may inhibit production of important cholesterol metabolism proteins, such as proprotein convertase subtilisin kexin 9, or PCSK9; 3-hydroxy-3-methyl-glutaryl-CoA reductase, or HMG-CoA reductase; adenosine triphosphate citrate lyase, or ATP citrate lyase; and Niemann-Pick C1-like 1, or NPC1L1. In a clinical trial of CAT-2003, we observed statistically significant reductions in triglycerides and low-density lipoprotein cholesterol, or LDL-C, suggesting an impact of SREBP modulation on cholesterol metabolism. Because the liver is the primary regulator of cholesterol metabolism, we specifically designed the SMART linker in CAT-2054 to deliver more of the intact conjugate to the liver than CAT-2003. We believe that CAT-2054, if approved, has the potential to be the first therapy to simultaneously modulate cholesterol synthesis, clearance and absorption. By inhibiting SREBP, a master regulator of lipid metabolism in the body, CAT-2054 has the potential to significantly reduce LDL-C; it may also have beneficial effects on other metabolic parameters such as triglycerides, glucose and liver fat. This profile may differentiate CAT-2054 from currently approved therapies for hypercholesterolemia and others in development. We are developing CAT-2054 to be used in addition to statins in patients who cannot achieve their LDL-C goals with statins alone. In August 2015, we announced positive top-line Phase 1 clinical trial data for CAT-2054. Based on these data, we initiated a Phase 2a trial in patients with hypercholesterolemia in December 2015, which is ongoing. We anticipate that we will report top-line data from the Phase 2a trial in the third quarter of 2016. Additionally, we are currently conducting studies and have generated positive data in preclinical models that support the therapeutic potential of the CAT-2000 series in Nonalcoholic Steatohepatitis, or NASH. We hold rights to CAT-2054 throughout the world, and we intend to seek a partner for the program prior to initiating Phase 3 clinical trials.

CAT-4001 is a SMART linker conjugate of monomethyl fumarate and DHA. CAT-4001 is a small molecule that activates Nrf2 and inhibits NF-κB that we are developing as a potential treatment for neurodegenerative diseases such as Friedreich's ataxia and amyotrophic lateral sclerosis, or ALS. Nrf2, or Nuclear factor (erythroid-derived 2)-like 2, is a gene transcription factor, a protein that works inside of cells to control the expression of genes, that controls the body's response to cellular stress and oxidative damage. We believe that CAT-4001 modulates the disease pathway by enhancing the movement of Nrf2 to the nucleus of the cells and inhibits NF-κB by reducing the movement of activated NF-κB to the nucleus of the cells. The Nrf2 and NF-κB pathways have been implicated in Friedreich's ataxia and ALS. We plan to conduct investigational new drug application, or IND, enabling studies in 2016 for CAT-4001. We hold rights to CAT-4001 throughout the world.

As of December 31, 2015, we owned four issued U.S. patents relating to composition of matter and method of use claims directed to CAT-1004, two issued U.S. patents relating to composition of matter and method of use claims directed to the CAT-2000 series, and one issued U.S. patent relating to composition of matter and method of use claims direct 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 20 issued foreign patents, over 25 pending U.S. patent applications and over 100 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

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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 reducing the likelihood of each agent being simultaneously active in the same cell.

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. In systemic circulation, our SMART linker conjugates are 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 to 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. 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. 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 efficacy with SMART linker conjugates at dose levels significantly lower than the prescribed doses of the two component bioactives. We are developing a pipeline of preclinical assets using our SMART linker drug discovery platform to potentially treat rare diseases including ALS, Friedreich's ataxia, cystic fibrosis 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.

CAT-1004

We believe that CAT-1004 has the potential to be the first disease-modifying oral therapy for the treatment of DMD that both inhibits muscle degeneration and promotes muscle regeneration, regardless of the underlying mutation. CAT-1004 is an orally administered SMART linker conjugate of salicylate and DHA, which we designed to enhance the activity of salicylate and DHA to inhibit the NF-κB pathway at multiple points. The CAT-1004 conjugate is inactive outside the cell, and, once inside the cell, CAT-1004 is cleaved releasing DHA and salicylate simultaneously inside the same cell. Emerging data suggest that NF-κB drives the loss of skeletal muscle mass in multiple diseases, including muscular dystrophies, atrophy and inflammatory myopathies. Scientific data also suggests that NF-κB is involved in the progression of a number of other rare diseases, and we are currently evaluating certain of these diseases as potential indications for CAT-1004. In December 2014, we submitted an IND to the FDA for CAT-1004 for DMD.

We are currently conducting the MoveDMD trial, a Phase 1/2 clinical trial of CAT-1004 for the treatment of DMD, in two parts. Part A of the MoveDMD trial enrolled ambulatory boys between ages four and seven with a genetically confirmed diagnosis of DMD across a range of

dystrophin mutations.

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The enrolled boys were steroid naive or had not used steroids for at least six months prior to the trial. Part A of the MoveDMD trial was conducted at three sites in the United States and assessed the safety, tolerability and pharmacokinetics of CAT-1004 in patients at three dosing levels following seven days of dosing. We reported top-line results in January 2016 indicating that all three doses of CAT-1004 studied 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. Top-line pharmacokinetic results demonstrated CAT-1004 average plasma exposure levels consistent with those previously observed in adults at which inhibition of NF-κB was observed. Part B of the MoveDMD trial will be a randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of CAT-1004 in DMD over a 12-week period. Subject to regulatory approval of our proposed protocol, we expect to initiate Part B of the MoveDMD trial in the first half of 2016, and to report top-line Part B data in late 2016, contingent on patient enrollment. If the results from our MoveDMD clinical trial and discussions with regulatory authorities regarding a pivotal trial are positive, we intend to initiate a six-month Phase 3 pivotal clinical trial of CAT-1004 in 2017. If the results from the Phase 3 clinical trial are positive, we intend to seek marketing approval for CAT-1004.

The FDA has granted CAT-1004 orphan drug, fast track and rare pediatric disease designations for the treatment of DMD. The EC has granted orphan medicinal product designation to CAT-1004 for the treatment 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, diaphragm and heart 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 results in fixations, or contractures, of joints, such as knees, hips and elbows. By age eight, most patients have difficulty ascending stairs. By their early teens, patients typically lose walking ability and are confined to wheelchairs. 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,

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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. This more rapid deterioration of muscles bearing greater mechanical stress, and thus more activated NF-κB mediated inflammation, in boys with DMD can be observed through magnetic resonance imaging, or MRI.

Unaddressed Market Opportunity

There are no therapies approved for the treatment of DMD in the United States. Corticosteroid therapy 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, 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 eleven and almost all are in wheelchairs by age sixteen. DMD patients typically live until their mid-twenties, despite the availability of corticosteroids.

Several companies are exploring new therapies for the treatment of DMD. Three of the most advanced product candidates, Sarepta Therapeutics' eteplirsen, PTC Therapeutics' ataluren, and BioMarin Pharmaceutical's drisapersen, target mechanisms to increase levels of dystrophin in muscles. Each of these product candidates compensates for a specific 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 with the specific mutation. Based on the prevalence of the specific mutations that these product candidates 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.

CAT-1004 for the Treatment of Duchenne Muscular Dystrophy

Based on the mechanism of action by which CAT-1004 suppresses NF-κB, we believe that CAT-1004 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 CAT-1004 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 CAT-1004 in North America ourselves and commercialize CAT-1004 outside of North America either ourselves or with a collaborator.

In Phase 1 clinical trials in adults and in Part A of our MoveDMD clinical trial in boys affected by DMD, CAT-1004 was observed to be well tolerated with no safety signals. We expect to initiate Part B

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of the MoveDMD trial in the first half of 2016, subject to regulatory approval of our proposed protocol.

CAT-1004 Clinical Development

Phase 1/2 Trial of CAT-1004 in Patients with DMD

Our CAT-1004 MoveDMD Phase 1/2 trial was designed to enroll ambulatory boys between ages four and seven with a genetically confirmed diagnosis of DMD who are 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 was designed to be conducted in two sequential parts, Part A, which is completed, and Part B, which we expect to initiate in the first half of 2016, subject to regulatory approval of our proposed protocol.

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 CAT-1004 in 17 patients across three dosing levels following seven days of dosing. We also compared CAT-1004 exposure levels to exposure levels achieved in previous CAT-1004 clinical trials where inhibition of NF-κB was observed. In January 2016, we reported that all three doses of CAT-1004 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. Pharmacokinetic results demonstrated CAT-1004 average plasma exposure levels consistent with those previously observed in adults at which inhibition of NF-κB was observed.

Part B of the MoveDMD trial is expected to be a randomized, double-blind, placebo-controlled trial. In Part B, we plan to treat patients with one of two dosing levels of CAT-1004 or placebo for 12 weeks. After 12 weeks of dosing, patients receiving placebo are expected to be crossed over to one of two doses of CAT-1004 for an additional 12 weeks. We have designed the MoveDMD trial with the assistance of ImagingDMD, a group of investigators at clinical sites in the United States with clinical leadership and expertise in the use of MRI as an assessment tool for DMD. We expect that the MoveDMD trial will be conducted at ImagingDMD's clinical sites in the United States.

We anticipate that the primary efficacy endpoint in Part B of the MoveDMD trial will be change in muscle inflammation as measured by MRI of leg muscles. MRI is a non-invasive imaging technique that allows investigators to view muscle structure and composition and measure disease status in children with DMD. MRI is sensitive to the changes in muscle structure and composition induced by disease processes such as inflammation, water accumulation, muscle damage and fat infiltration that occur in DMD. MRI studies in DMD have recently shown that inflammatory changes occur before development of fibrosis and infiltration of fat into muscle. Inflammatory changes are most evident in muscles that ultimately show the greatest replacement by non-contractile tissues. Changes in the inflammatory MRI signal may be seen in less than 12 weeks, while changes in fat infiltration measures may take longer. Changes in these MRI measures have been correlated with longer-term changes in clinically meaningful measures of functional activity. Changes in MRI can show the effects of an investigational therapy on disease progression in DMD in an objective and quantifiable manner.

Both inflammation and fat infiltration are correlated with functional ability in boys with DMD. Additionally, third party studies have shown that in young DMD patients that are still ambulatory, decreases in muscle inflammation over 12 weeks of glucocorticoid therapy can be clearly identified through MRI imaging. Similarly, glucocorticoids have been observed to improve muscle strength and performance in timed functional tests after short periods of treatment. In early ambulatory DMD boys, functional abilities such as the 10 meter walk/run are relatively stable and more homogeneous than in older boys in whom functional ability is declining. We plan to include as exploratory endpoints timed function tests best suited for the age group of the trial subjects, specifically the 10 meter walk/run, time to stand and four-stair climb tests. In addition, assessments of muscle strength and a parent-proxy measure of functional ability will be included.

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Subject to regulatory approval of our proposed protocol, we expect to initiate Part B of the MoveDMD trial in the first half of 2016, and to report top-line Part B data in late 2016, contingent on patient enrollment. If the results from our MoveDMD clinical trial and discussions with regulatory authorities regarding a pivotal trial are positive, we intend to initiate a six-month Phase 3 pivotal clinical trial of CAT-1004 in 2017. If the results from the Phase 3 clinical trial are positive, we intend to seek marketing approval for CAT-1004.

Parent Project Muscular Dystrophy and the Muscular Dystrophy Association are collaborating with us on the MoveDMD trial, including providing funding to support participant travel.

Completed Clinical Trials

To date, we have studied CAT-1004 in three completed Phase 1 clinical trials. The design and results for these clinical trials are discussed below.

CAT-1004 Completed Phase 1 Clinical Trials

Trial	Description	Duration	Subjects Total	Subjects Treated with CAT-1004
CAT-1004-101	Randomized, double-blind, placebo-controlled, single ascending dose clinical trial to evaluate safety, tolerability and pharmacokinetics of CAT-1004 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 CAT-1004 in adults with Type 2 diabetes	14 days	44	32
CAT-1004-103	Single-blind biomarker trial in healthy adults to compare activity of CAT-1004, 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 CAT-1004 in both fasted and fed states. The participants were randomized to receive CAT-1004 or placebo. CAT-1004 was administered orally in soft gelatin capsules at doses ranging from 300 mg to 6000 mg.

Single doses of CAT-1004, 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 CAT-1004 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,

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vital signs or electrocardiogram results following CAT-1004 administration in either the fasted or fed state.

CAT-1004 was rapidly absorbed in plasma, with mean maximum and overall plasma exposure generally increasing with CAT-1004 dose levels. Neither component bioactive, salicylate or DHA, was detected in plasma at levels above background, consistent with intracellular cleavage of CAT-1004 and intracellular delivery of the component bioactives. Administration of a high-fat meal increased CAT-1004 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 CAT-1004. These subjects had Type 2 diabetes and mild background inflammation, which enabled us to assess the activity of CAT-1004 on activated NF-κB. Subjects were randomized to receive CAT-1004 or placebo. CAT-1004 was administered orally in soft gelatin capsules at total daily doses ranging from 300 mg to 4000 mg.

CAT-1004 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 CAT-1004), gastroenteritis (one instance reported by a subject in the placebo group and the other by a subject receiving 1000 mg daily doses of CAT-1004) and upper respiratory tract infection (both instances reported by subjects receiving 4000 mg daily doses of CAT-1004). The majority of the adverse events were mild in severity. No treatment-related severe adverse events were reported.

CAT-1004 was rapidly absorbed in plasma, with mean maximum and overall plasma exposure generally increasing with escalating single or multiple doses of CAT-1004. Neither component bioactive, salicylate or DHA, was detected in plasma at levels above background, again consistent with intracellular cleavage of CAT-1004 and intracellular delivery of the component bioactives.

In the Phase 1 multiple ascending dose trial, we observed by two methods that CAT-1004 inhibited activated NF-κB. For the first method, we stimulated NF-κB activity *ex vivo* in whole blood from subjects treated with CAT-1004 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 CAT-1004 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 CAT-1004 or placebo. CAT-1004 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 CAT-1004 in nine healthy adult volunteers at a single center in the United States to compare activity of a single dose of 2000 mg of CAT-1004 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 CAT-1004 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. As shown in the graph below, treatment of subjects with CAT-1004 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, CAT-1004, which is a

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SMART linker conjugate of salicylate and DHA, exhibited greater activity on the NF-κB pathway than the combination of its component bioactives.

Effect of CAT-1004 on Activated NF-κB

These results were statistically significant, with a p-value of less than 0.005. P-value is a conventional statistical method for measuring the statistical significance of clinical results. A p-value of 0.05 or less represents statistical significance, meaning that there is a 1-in-20 or less statistical probability that the observed results occurred by chance.

CAT-1004 Preclinical Development

In preclinical studies, we have observed that CAT-1004 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, CAT-1004 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 CAT-1004 in which the DHA component of the salicylate-DHA conjugate has been replaced with the omega-3 fatty acid eicosapentaenoic acid, or EPA. In some preclinical studies, we used CAT-1041 as a surrogate for CAT-1004. Both CAT-1004 and CAT-1041 produced disease-modifying efficacy in established animal models of DMD. We decided to advance CAT-1004 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 CAT-1004 using the *mdx* mouse model of DMD. We observed that four weeks of treatment with CAT-1004 or prednisolone, a steroid, reduced muscle inflammation and the number of degenerating muscle fibers in *mdx* mice. However, only CAT-1004-treated animals showed preservation of muscle mass and an increase in the number of regenerating fibers, suggesting that chronic treatment with CAT-1004 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.

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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 heart mass, 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 CAT-1004 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 CAT-1004 in the GRMD dog model. A single oral dose of CAT-1004 inhibited basal, or unstimulated, NF-κB activity by 48% in GRMD dogs. CAT-1004 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 CAT-1004 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 CAT-1004 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 CAT-1004 inhibited LPS-stimulated NF-κB activity in human PBMCs, which are a potential target tissue for CAT-1004. In studies performed with a mouse macrophage cell line, CAT-1004 reduced the LPS-stimulated expression of a set of genes that encode pro-inflammatory mediators and whose expression is controlled by NF-κB.

CAT-1004 Orphan Drug, Fast Track and Rare Pediatric Disease Designations

The FDA has granted CAT-1004 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 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 New Drug Applications, or 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 CAT-1004 is approved. However, the rare pediatric disease program is set to expire in September 2016 under a provision that sunsets the law after the FDA approves the third pediatric review voucher, which occurred in March 2015. There is pending legislation that would extend the program through December 2018.

The EC has granted orphan medicinal product designation to CAT-1004 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

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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-2000 Series

Our other clinical-stage program is our CAT-2000 series. We applied our SMART linker drug discovery platform to engineer these product candidates as SMART linker conjugates of EPA and nicotinic acid in order to inhibit the SREBP pathway. Because we used different SMART linkers for CAT-2054 and CAT-2003, they possess different characteristics such as rates of cleavage, pharmacokinetics and biodistribution. CAT-2003, our first generation product candidate in the CAT-2000 series, is an orally administered molecule that inhibits the SREBP pathway predominately in the intestine. CAT-2054, our second generation product candidate in the CAT-2000 series, is an orally administered molecule designed to inhibit the SREBP pathway predominately in the liver. We are developing CAT-2054 for the treatment of serious lipid disorders, such as hypercholesterolemia. We are currently conducting preclinical studies in collaboration with academic institutions and have also observed positive data in preclinical models that support the therapeutic potential of the CAT-2000 series in NASH.

Overview of the SREBP Pathway

SREBP is a master regulator of lipid and energy metabolism and regulates the levels of LDL-C, triglycerides and fatty acids in the body. SREBP controls lipid levels by controlling the expression of genes such as PCSK9, HMG-CoA reductase, ATP citrate lyase and NPC1L1. Dysregulation of SREBP activity has been implicated in a number of human metabolic diseases, including hyperlipidemias, such as hypercholesterolemia and hypertriglyceridemia, and chronic liver diseases, including NASH. Modulators of SREBP activity could have therapeutic benefit in treating these SREBP-mediated diseases.

We designed the CAT-2000 molecules to inhibit the maturation of SREBP and reduce the expression of key proteins involved in LDL-C, triglyceride and glucose metabolism. SREBP regulates cholesterol levels by controlling expression of PCSK9, a protein that controls the clearance of LDL-C from circulation through the reduction of the amount of the LDL receptor on the surface of the liver; HMG-CoA reductase, an enzyme that plays a central role in the synthesis of LDL-C in the liver; ATP citrate lyase, an enzyme in the LDL-C synthetic pathway; and NPC1L1, which is the critical mediator of cholesterol absorption in the gastrointestinal tract epithelial cells as well as in liver cells. These four proteins are important in regulating cholesterol levels because they control cholesterol clearance, synthesis and absorption.

SREBP regulates triglyceride levels by controlling the expression of apolipoprotein C3, or ApoC3; angiopoietin-like protein 3, or Angptl3; and angiopoietin-like protein 4, or Angptl4, which inhibit the activity of lipoprotein lipase, or LPL, an enzyme responsible for the breakdown of triglycerides in the blood. SREBP regulates fatty acid levels by controlling the expression of fatty acid synthase, or FASN, and acetyl-CoA carboxylase 2, or ACC-2, enzymes that play a central role in the synthesis of fatty acids and the regulation of fatty acid oxidation. We believe that inhibiting SREBP activity will lead to an inhibition of fatty acid synthesis and an increase in fatty acid oxidation, and will increase LPL enzyme activity to accelerate clearance of triglycerides.

SREBP activity has also been implicated in a number of other metabolic processes that may provide further therapeutic applications for our CAT-2000 series of compounds. We believe that inhibition of SREBP in the liver has the potential to enhance insulin signaling and increase glucose metabolism, and thereby improve insulin resistance without increasing liver fat content, which may be useful in the treatment of type 2 diabetes. We also believe that inhibition of SREBP has the potential

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to inhibit fatty acid synthesis and activate fatty acid oxidation to reduce liver triglyceride content, which may be useful in the treatment of fatty liver diseases. In addition, SREBP is believed to regulate Palatin-like phospholipase domain-containing protein 3, or PNPLA3, which is an enzyme found in cells that may play a role in cellular energy storage and metabolism, as well as a specific mutation of PNPLA3 that is associated with liver fat accumulation and increased risk of chronic liver diseases. Accordingly, we believe that the CAT-2000 series may potentially be effective in the treatment of liver diseases associated with this specific mutation of PNPLA3, such as NASH, and their progression to hepatocellular carcinoma.

CAT-2054

We are developing CAT-2054 for the treatment of patients with hypercholesterolemia, or elevated LDL-C, for whom existing treatments are insufficient. As described above, by modulating the SREBP pathway, CAT-2054 may inhibit production of important cholesterol metabolism proteins, such as PCSK9, HMG-CoA reductase, ATP citrate lyase and NPC1L1. In a clinical trial of our first generation SREBP modulator, CAT-2003, we observed statistically significant reductions in triglycerides and LDL-C, which we believe demonstrate the impact of SREBP modulation on cholesterol metabolism. Because the liver is the primary regulator of cholesterol metabolism, we specifically designed the SMART linker in CAT-2054 to deliver more of the intact conjugate to the liver than CAT-2003. We believe that CAT-2054 has the potential for beneficial effects on levels of LDL-C, triglycerides, glucose and liver fat. This profile may differentiate CAT-2054 from currently approved therapies for hypercholesterolemia and others in development. We are developing CAT-2054 to be used in addition to statins in patients who cannot reach their LDL-C goals with statins alone.

We submitted an IND to the FDA for CAT-2054 in November 2014. In August 2015, we announced positive top-line data for CAT-2054 from a Phase 1 clinical trial. In this double-blind, randomized clinical trial, CAT-2054 was well tolerated with no serious adverse events observed in either single or multiple ascending dose arms. In the multiple ascending dose arm of the trial, decreases in median LDL-C levels of up to 20% were observed in healthy volunteers after 14 days of dosing and seven days of follow-up. CAT-2054 was also found to be well tolerated in combination with atorvastatin, the statin drug most commonly used in the treatment of hypercholesterolemia, and there was no evidence for impact of CAT-2054 on the pharmacokinetics of atorvastatin. Based on these data, we initiated a Phase 2a trial in patients with hypercholesterolemia in December 2015, which is ongoing. We anticipate that we will report top-line data from this trial in the third quarter of 2016. We are currently conducting studies, and have also observed positive data in preclinical models, that support the therapeutic potential of the CAT-2000 series in NASH. We hold rights to CAT-2054 throughout the world, and we intend to seek a partner for the program prior to initiating Phase 3 clinical trials.

Hypercholesterolemia Market Overview

Hypercholesterolemia is a major risk factor for cardiovascular disease, or CVD, a leading cause of mortality and morbidity in the United States. Hypercholesterolemia is a complex disease involving redundant biological pathways that are tightly regulated and have built-in feedback mechanisms. Current treatment guidelines recognize lowering of LDL-C as a primary target for reducing the risk of CVD.

Several of the lipid-lowering therapies currently available or in development target proteins in the SREBP pathway:

Statins. Statins are typically prescribed as first-line therapy for reducing LDL-C based on their efficacy, established safety and proven benefit in reducing cardiovascular event risk. Statins inhibit HMG-CoA reductase. Crestor®, or rosuvastatin, the largest remaining branded

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prescription statin, generated worldwide sales of $5.0 billion for the 12-month period ended December 2015.

Cholesterol Absorption Inhibitors. Ezetimibe is a cholesterol absorption inhibitor that targets NPC1L1, reducing LDL-C by inhibiting cholesterol absorption in the small intestine. It may be used alone, marketed as Zetia® or Ezetrol®, for example in statin-intolerant patients, or together with statins, such as in ezetimibe/simvastatin, marketed as Vytorin® and Inegy®, when statins alone do not adequately control cholesterol. Zetia and the combination product Vytorin together generated worldwide sales of $3.8 billion for the 12-month period ended December 2015.

Monoclonal antibodies against PCSK9. Alirocumab, or Praluent , marketed by Sanofi and Regeneron and evolocumab, or Repatha , marketed by Amgen were approved by the FDA and European Medicines Agency, or EMA, in 2015 for the treatment of hypercholesterolemia in the United States and European Union. These drugs are injectable products that target PCSK9, increasing the clearance of LDL-C. Industry analysts project that these agents will achieve combined global sales of $4.4 billion in 2020, based on the ability of these agents to lower LDL-C by more than 50%. Other PCSK9 inhibitors in clinical development include Pfizer's bococizumab, and Alnylam/The Medicine Company's investigational RNAi therapeutic, ALN-PCSsc.

Inhibitors of ATP citrate lyase. In addition to the marketed therapies, Esperion Therapeutics is developing an agent that targets the synthesis of LDL-C through inhibition of ATP citrate lyase. ATP citrate lyase inhibitors target cholesterol synthesis in the liver but at an earlier step of the pathway than statins.

Despite the availability of these classes of drugs that lower LDL-C, many patients are unable to achieve their LDL-C goals using currently marketed therapies. A 2011 report of the Centers for Disease Control and Prevention estimated that, of the 34 million adults in the United States receiving treatment for high LDL-C, 11 million had uncontrolled LDL-C. The limitations of the efficacy of some existing therapies, including statins, may be partly the result of feedback mechanisms in the SREBP pathway, which ensure that cellular cholesterol levels are maintained at levels required for normal cellular function. For example, doubling the dose of a statin is accompanied by only an incremental 6% lowering of lipids. This non-linear decrease in LDL-C as the statin dose increases is due to feedback mechanisms that are triggered when HMG-CoA reductase is inhibited to a greater extent. As the statin dose is increased, intracellular levels of cholesterol decrease, ultimately resulting in activation of the SREBP pathway. Activated SREBP induces the expression of PCSK9 which promotes the degradation of the LDL receptor, resulting in reduced clearance of LDL-C from circulation. The feedback mechanism ensures that the cell is never completely depleted of cholesterol because cholesterol is required for cellular viability. Thus, high-dose statins trigger a feedback mechanism that counteracts their beneficial effects on lipids.

Several biotechnology and pharmaceutical companies have pursued compounds to inhibit SREBP. However, we believe that Medivation, Inc., which is testing MDV-4463 in a Phase 1 clinical trial, is the only other company with a SREBP inhibitor in clinical development. The goal of these programs has been to identify small molecule drugs that can block the activity of SREBP and produce beneficial effects on lipids. Directly reducing active SREBP may have a significant benefit on LDL-C levels in circulation. SREBP modulators may work synergistically with inhibitors of proteins that are downstream of SREBP such as PCSK9, HMG-CoA reductase and ATP citrate lyase. In addition, SREBP modulators may substantially reduce feedback mechanisms that are activated by other classes of LDL-C lowering drugs such as statins and ezetimibe.

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CAT-2054 for the Treatment of Hypercholesterolemia

CAT-2054 is designed to inhibit SREBP in the liver and to reduce LDL-C levels in patients with hypercholesterolemia. We have observed in *in vitro* studies that, once cleaved in human liver cells, CAT-2054 inhibited the activity of SREBP by blocking its maturation, a conversion from an inactive to an active form. As a result, the amount of mature SREBP protein in the nucleus of the cells is reduced. This inhibition reduces the expression of downstream target genes in the SREBP pathway, including HMG-CoA reductase, PCSK9, ATP citrate lyase, and NPC1L1. Based on this mechanism, we believe CAT-2054 may be effective in reducing elevated LDL-C and positively affect other metabolic parameters. If approved, CAT-2054 has the potential to be prescribed in patients whose hypercholesterolemia is inadequately controlled by statins alone or who are intolerant to statins. CAT-2054 has the potential to be used before injectable PCSK9 monoclonal antibodies.

We intend to seek a partner for the CAT-2054 program prior to initiating Phase 3 clinical trials.

CAT-2054 Clinical Development

Phase 1 Clinical Trial Results (CAT-2054-101)

We conducted a randomized, double-blind, placebo-controlled Phase 1 trial in 118 healthy volunteers at a single center in the United States to assess the safety, tolerability and pharmacokinetics of single and multiple doses of CAT-2054 in both fasting and fed states. The trial also included multiple doses of CAT-2054 with atorvastatin to assess safety and pharmacokinetics of both compounds in combination in preparation for Phase 2 clinical trials. In August 2015, we reported positive top-line data from this trial. CAT-2054 was well tolerated with no serious adverse events observed in either the single or multiple ascending dose arms of the trial. In the multiple ascending dose arm of the trial, decreases in median LDL-C levels of up to 20% were observed in healthy volunteers after 14 days of dosing and seven days of follow-up. Importantly, CAT-2054 was also found to be well tolerated in combination with atorvastatin, the statin drug most commonly used in the treatment of hypercholesterolemia, and there was no evidence for impact of CAT-2054 on the pharmacokinetics of atorvastatin.

In the single ascending dose portion of the Phase 1 clinical trial, 40 healthy volunteers were randomized to receive CAT-2054 in capsules at doses ranging from 50 mg to 1000 mg or placebo. When single doses of CAT-2054 were administered under fed and fasted conditions, CAT-2054 was well tolerated and no serious adverse events were reported. No safety signals were observed in laboratory, vital sign or electrocardiogram results following CAT-2054 administration. The observed adverse events occurring under fed and fasted conditions at doses up to 500 mg were similar for CAT-2054 and placebo. The most common adverse events observed in fed and fasting conditions were nausea and diarrhea and all reported adverse events were mild. Of the 40 subjects, 10 subjects received placebo, two of whom reported diarrhea and one of whom reported nausea. Thirty subjects received CAT-2054, of whom six reported nausea, five reported diarrhea and three reported abdominal pain. Nicotinic acid is known to interact with a specific extracellular receptor, GPR109A, and causes flushing and immediate decreases in free fatty acids, followed by a rebound. We assessed flushing using a subjective questionnaire, and administration of CAT-2054 was not associated with flushing. Because decreases in free fatty acid levels are generally associated with nicotinic acid, we also measured free fatty acid levels after administration of CAT-2054, and observed no differences in free fatty acid levels relative to placebo. This is consistent with intracellular cleavage of CAT-2054 and intracellular delivery of the component bioactives.

In the data from the single ascending dose portion of the Phase 1 clinical trial, we observed that the plasma exposure of CAT-2054 increased with dose, which was measured using a common statistical method known as area under the curve. The plasma exposure of CAT-2054 was greater than the plasma

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exposure observed for the first generation CAT-2000 product candidate, CAT-2003, in the CAT-2003-101 Phase 1 clinical trial, and consistent with our expectations for the design of the molecule.

In the multiple ascending dose portion of the Phase 1 trial, 70 healthy volunteers received CAT-2054 in soft gelatin capsules or placebo at total daily doses ranging from 100 to 750 mg given orally once or twice per day for 14 days. CAT-2054 was also given concurrently with atorvastatin in one cohort. Similar to the single ascending dose portion of the trial, the multiple ascending dose portion of the trial was designed to assess safety, tolerability and pharmacokinetics. CAT-2054 was well tolerated with no serious adverse events reported. No safety signals were observed in laboratory, vital signs or electrocardiogram results following CAT-2054 administration, and all subjects completed dosing. At the highest doses, the most common adverse events were gastrointestinal, all of which were mild. CAT-2054 was also well tolerated with no safety signals in subjects receiving atorvastatin. There was no evidence of clinically significant changes in atorvastatin pharmacokinetics when co-administered with CAT-2054.

We also measured lipid biomarkers in the healthy volunteers enrolled in the Phase 1 trial. In preliminary data from the multiple ascending dose portion of the Phase 1 trial, decreases in LDL-C were observed at the end of the 14-day dosing period at doses of 500 and 750 mg. Decreases in LDL-C of up to 20%, which were statistically significant compared to baseline for all dose levels, were observed after 14 days of dosing and seven days of follow-up. We did not observe statistically significant changes in PCSK9 in this Phase 1 trial in healthy adults. Based on the results of this trial, we believe that the magnitude of LDL-C reduction with CAT-2054 may increase with continued dosing beyond 14 days. Based on our preclinical studies, we believe that patients with elevated PCSK9 levels reflective of activated SREBP, such as those on statins, may experience greater LDL-C reductions with CAT-2054. We also studied a coated capsule formulation of CAT-2054 in eight of the healthy volunteers in this trial. However, we do not plan further development of the coated capsule formulation; the results discussed above refer only to the uncoated formulation.

Phase 2a Clinical Trial

We initiated a randomized, double-blind, placebo-controlled Phase 2a trial of CAT-2054 in patients with hypercholesterolemia at multiple sites in the United States in December 2015. The CAT-2054 Phase 2a trial is a four-week randomized, double-blind, placebo-controlled trial. We plan to enroll approximately 150 patients who, after a run-in period of at least four weeks of receiving 40 mg of atorvastatin per day, will receive either one of four doses of CAT-2054 or placebo, in each case in addition to continuation of the atorvastatin regimen. The four CAT-2054 cohorts will receive the following doses of CAT-2054: 250 mg once daily, 250 mg twice daily, 400 mg once daily and 400 mg twice daily. Patients will be treated for four weeks, with 25 to 30 patients in each arm. The primary efficacy endpoint for this trial will be percent reduction in LDL-C. We also plan to assess the safety and tolerability of CAT-2054, as well as the activity of CAT-2054 on other metabolic parameters such as triglycerides and glucose and glycosylated hemoglobin, or HbA1c, which is a measure of glucose levels over time. We anticipate that we will report top-line data from this trial in the third quarter of 2016.

Preclinical Data for CAT-2054

Based on a comprehensive program of preclinical testing of CAT-2054, including several *in vitro* analyses and *in vivo* studies in animal models, we believe that CAT-2054 may be effective in reducing elevated LDL-C and have positive effects on other metabolic parameters. Key findings from our preclinical program included the following:

- CAT-2054 reduced LDL-C by week six in rhesus monkeys that were maintained on a high fat, high cholesterol diet. We observed no effect on food consumption or body weight. We dosed the animals with CAT-2054 at 500 mg by capsule once daily for six weeks. At the end of the treatment period, we observed a statistically significant reduction of 31% in LDL-C levels

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relative to baseline. The effect of CAT-2054 on plasma LDL-C levels was most pronounced in the monkeys with the highest baseline LDL-C levels. Additionally, we observed that LDL-C levels returned to near baseline after a washout period following the end of dosing with CAT-2054.

CAT-2054 significantly reduced fasting plasma LDL-C in cynomolgus macaque monkeys that had developed age-related spontaneous dyslipidemia, which were maintained on a normal diet. In this study, we dosed the animals with CAT-2054 at 100 mg/kg by oral gavage, once daily for four weeks. We observed no effect on body weight. The mean reduction in fasting LDL-C after 14 days of treatment with CAT-2054 was 21%. The effect of CAT-2054 on plasma LDL-C levels was most pronounced in the monkeys with the highest baseline LDL-C levels. CAT-2054 treatment essentially returned LDL-C to normal levels in these monkeys without significantly decreasing LDL-C below the normal threshold.

In *in vitro* studies, we observed that treatment of a human liver cell line with CAT-2054 reduced the amount of mature SREBP protein and that this reduction was greater than what we observed with approximately equivalent amounts of EPA and nicotinic acid administered either alone or in combination.

In an *in vitro* study, we observed that treatment of a human liver cell line with CAT-2054 reduced the secretion of PCSK9 protein. The reduction in PCSK9 protein secretion was dependent on dose of CAT-2054 with higher doses resulting in greater reductions. We also observed the bioactive components of CAT-2054, EPA and nicotinic acid, did not have a significant effect on PCSK9 secretion when administered to cells either individually or in combination at similar concentrations.

In an *in vitro* study, we observed that CAT-2054 induced an increase in LDL receptor protein levels on the surface of a human liver cell line. The increase in LDL receptor protein was dependent on the dose of CAT-2054, with higher doses resulting in greater increases.

In *in vitro* studies, we have observed that treatment of a human liver cell line with the statin atorvastatin caused an approximately two-fold increase in the amount of mature SREBP. CAT-2054 inhibited the activation of SREBP2, a form of SREBP that controls the expression of genes involved in LDL-C synthesis and clearance in the liver, in the presence of atorvastatin. As expected, due to feedback mechanisms in the SREBP pathway, treatment with atorvastatin alone increased the activation of SREBP2. These data suggest that CAT-2054 may inhibit SREBP2 maturation and subsequent SREBP2-mediated gene transcription in the presence of a statin.

In *in vitro* studies, we have observed that treatment of a human liver cell line with the statin atorvastatin caused an increase in the amount of secreted PCSK9. CAT-2054 abrogated the statin-induced increase in PCSK9 secretion.

In an *in vitro* study, we observed that after a 24-hour incubation, treatment of a human liver cell line with CAT-2054 inhibited the expression of multiple SREBP2 target genes, including PCSK9 and four genes involved in cholesterol synthesis: HMG-CoA reductase, ATP citrate lyase, Mevalonate decarboxylase and Squalene epoxidase.

CAT-2003

CAT-2003 is our first generation product candidate in the CAT-2000 series. We engineered CAT-2003 as an orally administered SMART linker conjugate of EPA and nicotinic acid to modulate the SREBP pathway. We designed CAT-2003 to target triglyceride levels in the blood and studied it for the treatment of multifactorial chylomicronemia, or MFC, and refractory severe hypertriglyceridemia, or rSHTG, diseases of severe triglyceride elevations with niche patient populations. We submitted an IND to the FDA for CAT-2003 in September 2012. We have completed three Phase 2a trials in patient

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populations with elevated triglyceride levels or hypertriglyceridemia in which we observed positive effects of CAT-2003 on triglycerides, LDL-C and glucose. We also observed gastrointestinal side effects. These side effects were reduced, but not eliminated, through the use of a coated soft gelatin capsule formulation with modified release characteristics.

While we have chosen to prioritize the development of CAT-2054 over CAT-2003, we believe that the clinical trial data for CAT-2003 support the utility of our SMART linker technology and the potential to treat lipid and metabolic disorders by modulating the SREBP pathway. We are conducting exploratory evaluation of CAT-2003 in other serious diseases that involve alterations in the SREBP pathway, such as NASH and hepatocellular carcinoma, either to support our development efforts for CAT-2054 or to develop CAT-2003 as a product candidate.

Effect of CAT-2003 in Hyperlipidemias

We have completed three Phase 2a clinical trials of CAT-2003 in patients with elevated triglycerides and two Phase 1 clinical trials in healthy volunteers. In the Phase 2a clinical trials, CAT-2003 reduced elevated triglycerides, including in patients treated with other triglyceride and lipid lowering therapies. CAT-2003 also demonstrated in Phase 2a clinical trials beneficial effects on other lipid and cardio-metabolic parameters, such as LDL-C and blood glucose levels. In our clinical trials, CAT-2003 showed no observed trends in laboratory values, vital signs, electrocardiogram or physical examination at up to 12 weeks of patient dosing. Mild to moderate gastrointestinal tolerability issues were observed with CAT-2003 at higher doses with an uncoated soft gelatin capsule and were improved but not eliminated with a coated soft gelatin capsule formulation. Given the superior distribution of CAT-2054 to the liver, we have chosen to prioritize the development of CAT-2054 over CAT-2003 for the treatment of hyperlipidemias.

CAT-4001

CAT-4001 is a SMART linker conjugate of monomethyl fumarate and DHA 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 Friedreich's ataxia and ALS, two diseases of the central nervous system in which the Nrf2 and NF-κB pathways have been implicated. Nrf2, or Nuclear factor (erythroid-derived 2)-like 2, 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. The Nrf2 and NF-κB pathways have been implicated in Friedreich's ataxia and ALS.

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 Friedreich's ataxia 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 2016, we plan to continue preclinical evaluation of CAT-4001 in animal models of Friedreich's ataxia as well as ALS, and to conduct IND-enabling activities for CAT-4001. If we are successful in these activities, we intend to advance CAT-4001 into a Phase 1 clinical trial in 2017.

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Friedreich's Ataxia

Friedreich's ataxia is a rare genetic disease that causes nervous system damage and compromises motor coordination. Friedreich's ataxia 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 Friedreich's ataxia causes a reduction in the production of the frataxin protein and iron levels in mitochondria become poorly regulated. In Friedreich's ataxia, iron overload in mitochondria affects metabolism, causing oxidative stress and ultimately damaging mitochondrial DNA. Progressive degeneration of central and peripheral nervous systems in Friedreich's ataxia 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.

Friedreich's ataxia 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 Friedreich's ataxia in the US and up to 15,000 Friedreich's ataxia 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 Friedreich's ataxia.

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 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.

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. We intend to commercialize CAT-1004 in North America ourselves and commercialize CAT-1004 outside of North America either ourselves or with a collaborator. We intend to seek a partner for the CAT-2054 program prior to initiating Phase 3 clinical trials. 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, for each of the bioactives and for the linker. 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

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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.

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.

CAT-1004 for Duchenne Muscular Dystrophy

There are currently no therapies approved for the treatment of DMD in the United States. Although not approved for the treatment of DMD, corticosteroid therapy is often prescribed to treat the inflammation underlying DMD and to delay loss of ambulation. Marathon Pharmaceuticals has announced that it is conducting clinical trials to support approval of deflazacort, a corticosteroid, in DMD and that it anticipates filing an NDA for deflazacort with the FDA in 2016.

A number of companies are developing therapies to treat DMD in patients with specific mutations in the dystrophin gene. PTC Therapeutics has received conditional approval for ataluren (Translarna) in the European Union for DMD patients with nonsense mutations and reported in January 2016 the completion of a rolling NDA submission to the FDA for marketing approval in the United States. In February 2016, PTC received a Refuse to File letter for ataluren from the FDA. BioMarin Pharmaceutical and Sarepta Therapeutics each have product candidates in clinical development based on a different scientific approach, which is referred to as exon-skipping. BioMarin received a complete response letter from the FDA in January 2016 for drisapersen (Kyndrisa). BioMarin has yet to announce next steps for the program. Sarepta is conducting Phase 3 clinical trials of its lead product candidate eteplirsen and has submitted an NDA to the FDA, with a PDUFA date of May 26, 2016. Based on the prevalence of the specific mutations that these product candidates are designed to address, they would be expected to be effective in an aggregate of approximately 26% of DMD patients. Other companies have alternative therapeutic approaches to the treatment of DMD in late stage clinical development. Santhera Pharmaceuticals has announced positive effects on respiratory function in a Phase 3 clinical trial of idebenone (Raxone® in the European Union and Catena® in the United States). Santhera has announced that it plans to submit filings to the FDA and EMA in 2016 to support regulatory approval of idebenone for the treatment of DMD in the United States and Europe. Eli Lilly conducted a Phase 3 trial of the product tadalafil (Cialis®), which is currently approved for marketing for the treatment of erectile dysfunction, to assess whether Cialis will delay the loss of ambulatory function in patients with DMD. Eli Lilly reported negative results from this trial in February 2016. A number of companies have products in earlier stages of clinical development for

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DMD, including Akashi Therapeutics, Bristol Myers Squibb, Capricor Therapeutics, Cardero Therapeutics, Pfizer, Phrixus Pharmaceuticals, Summit Plc, and Taiho Pharmaceuticals. If successfully developed, some of these alternative therapeutic approaches may be applicable to all DMD patients.

CAT-2054 for Hypercholesterolemia

There are many widely available products, including statins and cholesterol absorption inhibitors, approved for the treatment of patients with hypercholesterolemia. The market and development pipeline for cholesterol regulating therapies is especially large and competitive. If CAT-2054 is approved for the treatment of hypercholesterolemia, either as monotherapy or in combination therapies, it will face intense competition from current approved therapies as well as a number of therapeutic approaches in development, including:

Anti-PCSK9 monoclonal antibodies and RNAi therapeutics. The PCSK9 monoclonal antibodies alirocumab (Praluent) marketed by Sanofi and Regeneron and evolocumab (Repatha) marketed by Amgen were approved by the FDA and the EMA in 2015 for the treatment of hypercholesterolemia in the United States and the European Union. PCSK9 inhibitors represent the first major new class of LDL-C reducing agents approved for the treatment of hyperlipidemia since statins. These agents are highly efficacious and well tolerated but are injectable and priced at a premium to current branded oral agents in this category. Industry analysts project that Praluent and Repatha will achieve combined global sales of $4.4 billion in 2020, based on the ability of these agents to lower LDL-C by more than 50%.

Cholesterol ester transfer protein (CETP) inhibitors. CETP inhibitors are intended to reduce the risk of atherosclerosis by both raising high-density lipoprotein cholesterol and reducing LDL-C. Multiple CETP inhibitor programs have been terminated due to safety (Pfizer's torcetrapib) or lack of efficacy (Roche's dalcetrapib and Eli Lilly's evecetrapib). Merck's anacetrapib (MK-0859) is being studied in a Phase 3 outcomes trial expected to be completed in 2017. Amgen/Dezima's CETP inhibitor TA-8995 has completed a Phase 2b clinical trial.

Other mechanisms. Esperion Therapeutics is developing bempedoic acid, or ETC-1002, an inhibitor of ATP citrate lyase that is currently in Phase 3 clinical trials for the treatment of hypercholesterolemia. Madrigal Pharmaceuticals is developing MGL-3196, an inhibitor of thyroid hormone receptors that has completed Phase 1 clinical trials in healthy volunteers.

Other SREBP inhibitors. In October 2015, Medivation, Inc. announced initiation of a Phase 1 clinical trial in normal healthy volunteers with its oral SREBP inhibitor, MDV-4463.

Intellectual Property

We strive to protect the proprietary technologies that we believe are important to our business, including pursuing and maintaining patent protection intended to cover the composition of matter of our product candidates, their methods of use, related technologies and other inventions that are important to our business. In addition to patent protection, we also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection, including certain aspects of our SMART linker drug discovery platform.

Our commercial success depends in part upon our ability to obtain and maintain patent and other proprietary protection for commercially important technologies, inventions and know-how related to our business, defend and enforce our intellectual property rights, in particular, our patent rights, preserve the confidentiality of our trade secrets and operate without infringing valid and enforceable intellectual property rights of others.

The patent positions for biotechnology and pharmaceutical companies like us are generally uncertain and can involve complex legal, scientific and factual issues. In addition, the coverage claimed

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in a patent application can be significantly reduced before a patent is issued, and its scope can be reinterpreted and even challenged after issuance. As a result, we cannot guarantee that any of our product candidates will be protected or remain protectable by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties.

As of December 31, 2015, our patent estate included 14 issued U.S. patents, over 20 issued foreign patents, over 25 pending U.S. patent applications, and over 100 pending foreign patent applications.

With regard to CAT-1004, we have four issued U.S. patents with composition of matter and method of use claims directed to CAT-1004 and its use. The issued U.S. patents are expected to expire in 2029, without taking a potential patent term extension into account. In addition, we have patents that have been granted in nine different countries including Australia, China, Japan, Mexico and New Zealand, which are expected to expire in 2029, without taking potential patent term extensions into account, and at least 20 pending patent applications in various other countries and regions in North America, South America, Europe, and Asia, which, if issued, are expected to expire in 2029, without taking potential patent term extensions into account.

With regard to CAT-2003 and CAT-2054, we have two issued U.S. patents with composition of matter and method of use claims directed to CAT-2003 and CAT-2054 and their use. These U.S. patents are scheduled to expire in 2030 and 2031, without taking potential patent term extensions into account. In addition, we have patents that have been granted in eight different countries including Australia, Mexico, China, Japan and New Zealand, which are expected to expire in 2030, without taking potential patent term extensions into account and at least 20 pending applications in various other countries and regions including North and South America, Europe, and Asia, which, if issued, are expected to expire in 2030, without taking patent term extensions into account. In addition, we have a pending U.S. patent application covering CAT-2054, which, if issued, is expected to expire in 2033, without taking a potential patent term extension into account. We have at least 10 counterpart patent applications pending in various countries and regions in North America, South America, Europe and Asia, which, if issued, are expected to expire in 2033, without taking potential patent term extensions into account.

With regard to CAT-4001, we have one granted U.S. patent and one allowed U.S. patent application with composition of matter and method of use claims directed to CAT-4001 and its use. This U.S. patent is scheduled to expire in 2031, without taking a potential patent term extension into account. In addition, we have patents that have been granted in five different countries including Japan, New Zealand and Taiwan, which are expected to expire in 2031, without taking potential patent term extensions into account, and at least 20 pending patent applications in various other countries and regions in North America, South America, Europe and Asia, which, if issued, are expected to expire in 2031, without taking potential patent term extensions into account.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application.

In the United States, the term of a patent covering an FDA-approved drug may be eligible for a patent term extension under the Hatch-Waxman Act as compensation for the loss of patent term during the FDA regulatory review process. The period of extension may be up to five years beyond the expiration of the patent, but cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval. Only one patent among those eligible for an extension may be extended. Similar provisions are available in Europe and in certain other jurisdictions to extend the term of a patent that covers an approved drug. It is possible that issued U.S. patents covering

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CAT-1004, CAT-2003, CAT-2054 and CAT-4001 may be entitled to patent term extensions. If our product candidates receive FDA approval, we intend to apply for patent term extensions, if available, to extend the term of patents that cover the approved product candidates. We also intend to seek patent term extensions in any jurisdictions where they are available, however, there is no guarantee that the applicable authorities, including the FDA, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions.

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

Government Regulation and Product Approvals

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

Review and Approval of Drugs in the United States

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The failure to comply with applicable U.S. requirements at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must take effect before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;

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preparation and submission to the FDA of an NDA;

review of the product by an FDA advisory committee, where appropriate or if applicable;

satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;

satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;

payment of user fees and securing FDA approval of the NDA; and

compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies, or REMS, and post-approval studies required by the FDA.

Preclinical Studies

Preclinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as *in vitro* and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to a proposed clinical trial and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA can place an IND on clinical hold at any point in development, and depending upon the scope of the hold, clinical trial(s) may not restart until resolution of the outstanding concerns to the FDA's satisfaction.

In addition, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct a continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on their ClinicalTrials.gov website.

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Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

Phase 1. The drug is initially introduced into healthy human subjects or, in certain indications such as cancer, patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.

Phase 2. The drug 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 diseases and to determine dosage tolerance and optimal dosage.

Phase 3. The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Submission of an NDA to the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of most NDAs is additionally subject to an application user fee, currently exceeding $2.3 million, and the sponsor of an approved NDA is also subject to annual product and establishment user fees, currently exceeding $114,000 per product and $585,000 per establishment. These fees are typically increased annually.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs the sponsor by the 74th day after the FDA's receipt of the submission to determine whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Most such applications are meant to be reviewed within ten months from the date of filing, and most applications for "priority review" products are meant to be reviewed within six months of filing. The review process may be extended by the FDA for three additional months to consider new information or clarification

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provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including drug component manufacturing (such as active pharmaceutical ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

The FDA is required to refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Fast Track, Breakthrough Therapy and Priority Review Designations

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

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

Second, in 2012, Congress enacted the Food and Drug Administration Safety and Innovation Act, or FDASIA. This law established a new regulatory scheme allowing for expedited review of products

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

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

Accelerated Approval Pathway

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

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

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of drugs for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit.

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

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

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 often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. 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 severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

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

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

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Abbreviated New Drug Applications for Generic Drugs

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

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug..."

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

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product. The FDA typically makes decisions about awards of data exclusivity shortly before a product is approved.

Hatch-Waxman Patent Certification and the 30-Month Stay

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

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

the required patent information has not been filed;

the listed patent has expired;

the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or

the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method

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of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the ANDA applicant is not seeking approval).

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With enactment of the FDASIA in 2012, sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in FDASIA. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

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

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition (generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product). A company must request orphan product designation before submitting an NDA. If the request is granted, the FDA will disclose the

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identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product with orphan status receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will be receiving orphan product exclusivity. Orphan product exclusivity means that the FDA may not approve any other applications for the same product for the same indication for seven years, except in certain limited circumstances. Competitors may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product but for a different indication. If a drug or drug product designated as an orphan product ultimately receives marketing approval for an indication broader than what was designated in its orphan product application, it may not be entitled to exclusivity.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted is typically 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 ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The U.S. Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Review and Approval of Drug Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, the company would need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Procedures Governing Approval of Drug Products in the European Union

Pursuant to the European Clinical Trials Directive, a system for the approval of clinical trials in the European Union has been implemented through national legislation of the member states. Under this system, an applicant must obtain approval from the competent national authority of a European Union member state in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial after a competent ethics committee has issued a favorable opinion. Clinical trial application must be accompanied by an investigational medicinal product dossier with supporting information prescribed by the European Clinical Trials Directive and corresponding national laws of the member states and further detailed in applicable guidance documents.

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To obtain marketing approval of a product under European Union regulatory systems, an applicant must submit a marketing authorization application, or MAA, either under a centralized or decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization by the EC that is valid for all European Union member states. The centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the EMA is responsible for conducting the initial assessment of a product. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days.

The decentralized procedure is available to applicants who wish to market a product in various European Union member states where such product has not received marketing approval in any European Union member states before. The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one member state designated by the applicant, known as the reference member state. Under this procedure, an applicant submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference member state and concerned member states. The reference member state prepares a draft assessment report and drafts of the related materials within 210 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report and related materials, each concerned member state must decide whether to approve the assessment report and related materials.

If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the European Commission, whose decision is binding on all member states.

Data and Market Exclusivity in the European Union

In the European Union, new chemical entities qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application for eight years, after which generic marketing authorization can be submitted, and the innovator's data may be referenced, but not approved for two years. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity and the sponsor is able to gain the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company can complete a full MAA with a complete database of pharmaceutical test, preclinical tests and clinical trials and obtain marketing approval of its product.

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In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of drug products. Whether or not it obtains FDA approval for a product, the company would need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Periods of Authorization and Renewals

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

Orphan Drug Designation and Exclusivity

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

Regulation 847/2000 sets out criteria and procedures governing designation of orphan drugs in the European Union. Specifically, an application for designation as an orphan product can be made any time prior to the filing of an application for approval to market the product. Marketing authorization for an orphan drug leads to a ten-year period of market exclusivity. This period may, however, be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan drug designation, for example because the product is sufficiently profitable not to justify market exclusivity. Market exclusivity can be revoked only in very selected cases, such as consent from the marketing authorization holder, inability to supply sufficient quantities of the product, demonstration of "clinically relevant superiority" by a similar medicinal product, or, after a review by the Committee for Orphan Medicinal Products, requested by a member state in the fifth year of the

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marketing exclusivity period (if the designation criteria are believed to no longer apply). Medicinal products designated as orphan drugs pursuant to Regulation 141/2000 shall be eligible for incentives made available by the European Community and by the member states to support research into, and the development and availability of, orphan drugs.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of products will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage, and establish adequate reimbursement levels for, such products. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged for medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Third-party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on investment in product development.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of drugs have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results.

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

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular drug candidate to currently available therapies. For example, the European Union provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a drug product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce

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pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements.

Healthcare Law and Regulation

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with third-party payors and customers are subject to broadly applicable fraud and abuse and other healthcare laws and regulations. Such restrictions under applicable federal and state healthcare laws and regulations, include the following:

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

- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

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

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, which also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;

- the federal transparency requirements under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or the Affordable Care Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report to the Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals and physician ownership and investment interests; and

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

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

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Healthcare Reform

There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, government control and other changes to the healthcare system in the United States.

By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the United States Congress enacted the Affordable Care Act, which, among other things, includes changes to the coverage and payment for drug products under government health care programs. The Affordable Care Act:

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

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

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

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

Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2024 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare.

Employees

As of December 31, 2015, we had 37 employees, 23 of whom were primarily engaged in research and development activities. A total of 16 employees have Ph.D. degrees. None of our employees is represented by a labor union and we believe our relations with our employees are good.

Our Corporate Information

We were incorporated under the laws of the State of Delaware on June 26, 2008 under the name Catabasis Pharmaceuticals, Inc. Our executive offices are located at One Kendall Square, Bldg. 1400E, Suite B14202, Cambridge, Massachusetts 02139, and our telephone number is (617) 349-1971. Our website address is www.catabasis.com. The information contained on, or that can be accessed through,

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our website is not a part of this prospectus. We have included our website address in this prospectus solely as an inactive textual reference.

Available Information

Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and any amendments to these reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, are available free of charge on our website located at www.catabasis.com as soon as reasonably practicable after they are filed with or furnished to the Securities and Exchange Commission (the "SEC"). These reports are also available at the SEC's Internet website at www.sec.gov. The public may also read and copy any materials filed with the SEC at the SEC's Public Reference Room at 100 F Street, N.E., Washington D.C. 20549. Information on the operation of the Public Reference Room may be obtained by calling the SEC at 1-800-SEC-0330.

A copy of our Corporate Governance Guidelines, Code of Business Conduct and Ethics and the charters of the Audit Committee, Compensation Committee and Nominating and Corporate Governance Committee are posted on our website, www.catabasis.com, under "Corporate Governance" and are available in print to any person who requests copies by contacting us by calling (617) 349-1971 or by writing to Catabasis Pharmaceuticals, Inc., One Kendall Square, Bldg. 1400E, Suite B14202, Cambridge, Massachusetts 02139.

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Item 1A. Risk Factors

We operate in a dynamic and rapidly changing business environment that involves risks and substantial uncertainty. The following discussion addresses risks and uncertainties that could cause, or contribute to causing, actual results to differ from expectations in material ways. In evaluating our business, investors should pay particular attention to the risks and uncertainties described below and in other sections of this Annual Report on Form 10-K and in our subsequent filings with the Securities and Exchange Commission, or SEC. These risks and uncertainties, or other events that we do not currently anticipate or that we currently deem immaterial also may affect our results of operations, cash flows and financial condition. The trading price of our common stock could also decline due to any of these risks, and you could lose all or part of your investment.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since inception and expect to incur significant and increasing losses for at least the next several years. We may never achieve or maintain profitability.

We have incurred significant annual net operating losses in every year since our inception. We expect to continue to incur significant and increasing operating losses for at least the next several years. Our net losses were $32.6 million, $21.9 million and $18.1 million for the years ended December 31, 2015, 2014 and 2013, respectively. As of December 31, 2015, we had an accumulated deficit of $108.0 million. We have not generated any revenues from product sales, have not completed the development of any product candidate and may never have a product candidate approved for commercialization. We have financed our operations to date primarily through our initial public offering of common stock, private placements of our preferred stock and debt financing, and have devoted substantially all of our financial resources and efforts to research and development, including preclinical studies and our clinical development programs. Our net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity (deficit) and working capital.

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