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