Esperion Therapeutics, Inc.
Form 10-K
March 10, 2015

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 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, 2014

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: 001-35986

Esperion Therapeutics, Inc.

(Exact Name of Registrant as Specified in its Charter)

Delaware	**26-1870780**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
3891 Ranchero Drive, Suite 150 Ann Arbor, Michigan 48108	**48108**
(Address of Principal Executive Offices)	(Zip Code)

(734) 887-3903
(Registrant's Telephone Number, Including Area Code)

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	NASDAQ Stock Market LLC

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

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

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

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 (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. o

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 ý	Non-accelerated filer o (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 Act). Yes o No ý

The aggregate market value of the voting stock held by non-affiliates of the registrant on June 30, 2014, based upon the closing price of $15.84 of the registrant's common stock as reported on the NASDAQ Global Market, was $244.4 million. Shares of the registrant's common stock held by each officer and director and each person known to the registrant to own 10% or more of the outstanding voting power of the registrant have been excluded in that such persons may be deemed affiliates. This determination of affiliate status is not a determination for other purposes.

As of March 1, 2015, there were 20,425,860 shares of the registrant's common stock, $0.001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report on Form 10-K incorporates by reference information from the definitive Proxy Statement for the registrant's 2015 Annual Meeting of Shareholders, which is expected to be filed with the Securities and Exchange Commission not later than 120 days after the Registrant's fiscal year ended December 31, 2014.

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Forward-Looking Statements

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, objectives of management and expected market growth, are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements.

The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," 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 ability to obtain regulatory approval for ETC-1002, including statements related to specific clinical studies or clinical observations that will be required for such approval;
- the timing and outcome of our ongoing or future Phase 2 clinical studies of ETC-1002;
- the timing and outcome of our Phase 3 clinical program of ETC-1002;
- our ability to replicate positive results from a completed clinical study in a future clinical study;
- our ability to fund our development programs with existing capital or our ability to raise additional capital in the future;
- the potential benefits, effectiveness or safety of ETC-1002, as compared to statins and other LDL-cholesterol lowering therapies, either those currently available or those in development;
- our ability to respond and adhere to changes in regulatory requirements, including any requirement to conduct additional, unplanned clinical studies in connection with our pursuit of ETC-1002 as an LDL-cholesterol lowering therapy;
- the progress, timing and amount of costs associated with our development of ETC-1002;
- guidelines relating to LDL-cholesterol levels and cardiovascular risk that are generally accepted within the medical community, including recent changes and any future changes to such guidelines;
- reimbursement policies, including any future changes to such policies or related government legislation, and their impact on our ability to market, distribute and obtain payment for ETC-1002, if approved;
- the accuracy of our estimates of the size and growth potential of the LDL-cholesterol lowering market and the rate and degree of ETC-1002's market acceptance, if approved;
- our ability to obtain and maintain intellectual property protection for ETC-1002 without infringing on the intellectual property rights of others;

the loss of any of our key scientific or management personnel;

our intention to seek to establish strategic relationships or partnerships; and

our ability to compete with other companies that are, or may be, developing or selling products that may compete with ETC-1002, if approved.

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These forward-looking statements are only predictions and we may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, so 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 based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our business, financial condition and operating results. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in Item 1.A. Risk Factors, that could cause actual future 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, joint ventures or investments we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to the 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 statements whether as a result of new information, future events or otherwise, except as required by applicable law.

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PART I

All brand names or trademarks appearing in this report are the property of their respective holders. Unless the context requires otherwise, references in this report to "Esperion" the "Company," "we," "us," and "our" refer to Esperion Therapeutics, Inc.

Item 1. Business

Overview

We are an emerging pharmaceutical company focused on developing and commercializing first-in-class, oral, low-density lipoprotein cholesterol (LDL-cholesterol) lowering therapies for the treatment of patients with hypercholesterolemia and other cardiometabolic risk markers. ETC-1002, our lead product candidate, is a first-in-class, orally available, once-daily small molecule designed to lower LDL-cholesterol levels and avoid the side effects associated with other LDL-cholesterol lowering therapies currently available. ETC-1002 is being developed for patients with hypercholesterolemia. One completed Phase 2b clinical study and a second that is nearing completion build upon a successful and comprehensive Phase 1 and Phase 2 clinical development program for ETC-1002. We plan to hold an End-of-Phase 2 meeting with the Food and Drug Administration (FDA) in the middle of 2015 and we expect to initiate our Phase 3 program for ETC-1002 by year-end. We own the exclusive worldwide rights to ETC-1002.

Statins are the current standard of care for LDL-cholesterol lowering for approximately 35 million patients in the United States. However, it is estimated that 2 - 7 million U.S. adults are intolerant of statin therapy due to muscle pain or weakness associated with their use. We believe that ETC-1002, if approved, has the potential to become the preferred once-daily, oral therapy for patients who are unable to tolerate statin therapy. Additionally, because symptoms of muscle pain or weakness occur in up to 20% of patients on statin therapy in clinical practice, we believe that the size of the statin intolerant market is poised to expand as effective and better tolerated non-statin therapies, such as ETC-1002, become available.

On October 1, 2014, we announced top-line results for our Phase 2b ETC-1002-008 clinical study. ETC-1002-008 was a 12-week Phase 2b clinical study in 349 randomized patients across 65 participating clinical recruitment sites in the United States. The primary endpoint of this clinical study was to assess the LDL-cholesterol lowering efficacy of ETC-1002 monotherapy versus ezetimibe monotherapy in 349 patients with hypercholesterolemia with or without statin intolerance. Secondary endpoints included characterization of ETC-1002 dose response, assessment of the effect of ETC-1002 on additional lipid and cardiometabolic biomarkers, characterization of safety, tolerability, and rates of muscle-related adverse events, or AEs, and assessment of LDL-cholesterol lowering efficacy of ETC-1002 and ezetimibe combination therapy versus ezetimibe alone. The full results of the ETC-1002-008 study have been accepted for presentation at the 64th Annual Scientific Session of the American College of Cardiology on Saturday March 14, 2015. The top-line results of this Phase 2b clinical study are summarized as follows:

LDL-cholesterol Percent Change from Baseline to Week 12 Endpoint

Treatment Group	Number of Patients	LDL-cholesterol Baseline Mean (SD) mg/dL	LDL-cholesterol Week 12 Endpoint Mean (SD) mg/dL	Average Percent Change from Baseline	
				LS Mean (SE)	P Value vs. ezetimibe
ETC-1002 120mg	97	164 (28)	119 (30)	27% (1.3)	0.0008
ETC-1002 180mg	99	166 (24)	115 (25)	30% (1.3)	<0.0001
ezetimibe 10mg	98	165 (25)	129 (20)	21% (1.3)	
ETC-1002 120mg + ezetimibe 10mg	24	161 (26)	92 (29)	43% (2.6)	<0.0001
ETC-1002 180mg + ezetimibe 10mg	22	164 (27)	86 (21)	48% (2.8)	<0.0001

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hsCRP Nonparametric Analysis

Treatment	N	Baseline Level (mg/L)	Percent Change from Baseline Median Change	P Value vs. ezetimibe
ETC-1002 120mg	92	1.60	30%	≤0.01
ETC-1002 180mg	86	2.50	40%	≤0.01
ezetimibe 10mg	94	2.60	10%	NS
ETC-1002 120mg + ezetimibe 10mg	20	1.85	38%	NS
ETC-1002 180mg + ezetimibe 10mg	21	1.25	26%	≤0.05

LS = least squares; SD = standard deviation; SE = standard error; mITT population

LDL-cholesterol levels after 12 weeks of treatment of ETC-1002, the primary endpoint of the study, were reduced up to 30% for patients dosed with ETC-1002 only, compared to an average reduction of 21% for patients dosed with ezetimibe ($p<0.0001$).

LDL-cholesterol levels were lowered up to 48% in the ETC-1002 plus ezetimibe combination treatment versus 21% for ezetimibe alone ($p<0.0001$).

hsCRP, a marker of inflammation in coronary disease, was reduced by 30% ($p \leq 0.01$) with ETC-1002 120 mg; by 40% ($p \leq 0.01$) with ETC-1002 180 mg; versus a 10% reduction with ezetimibe.

Discontinuation rates and muscle related adverse events with ETC-1002 were comparable to ezetimibe.

In an exploratory analysis of the data, there was comparable LDL-cholesterol lowering with ETC-1002 between patients who are statin intolerant and those who are statin tolerant.

Consistent with prior clinical studies with ETC-1002, no clinically relevant changes in high-density lipoprotein cholesterol or triglycerides were observed.

We were founded in January 2008 by former executives of and investors in the original Esperion Therapeutics, Inc., a biopharmaceutical company, which was primarily focused on the research and development of therapies to regulate high-density lipoprotein cholesterol, or HDL-cholesterol. After successfully completing a Phase 2a clinical study with its synthetic HDL-cholesterol therapy ETC-216, the original Esperion was acquired by Pfizer Inc. in 2004. ETC-1002 was first discovered at the original Esperion and we subsequently acquired the rights to the product from Pfizer in 2008.

ETC-1002

ETC-1002, our lead product candidate, is a first-in-class, orally available, once-daily small molecule designed to lower LDL-cholesterol levels and avoid many of the side effects associated with other LDL-cholesterol lowering therapies currently available, including muscle-related adverse events. ETC-1002 is being developed primarily for patients with hypercholesterolemia.

ETC-1002 is a first-in-class, orally available, once-daily LDL-cholesterol lowering small molecule therapy that is differentiated from statins because it acts at an earlier step in the cholesterol biosynthetic pathway. ETC-1002 is converted to the CoA form in the liver and works primarily by inhibiting the ATP citrate lyase (ACL) enzyme upstream of HMG-CoA reductase, whereas statins directly inhibit the rate-limiting enzyme, HMG-CoA reductase. Reductions in LDL-cholesterol levels resulting from statin therapy are ultimately due to reduced cholesterol synthesis and an increase in the number of LDL receptors in the liver. Experts believe that the muscle-related side effects experienced by some patients taking statins could result from inhibition of cholesterol synthesis in skeletal muscle

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tissue. The CoA form of ETC-1002 achieves LDL-cholesterol lowering due to reduced cholesterol synthesis and an increase in the number of LDL receptors in the liver but is not active in skeletal muscle tissue. ETC-1002 has been shown to provide incremental lowering of LDL-cholesterol when used in combination with both ezetimibe and statins.

Cardiovascular Disease and Hypercholesterolemia

Cardiovascular disease, which results in heart attacks, strokes and other cardiovascular events, represents the number one cause of death and disability in western societies. The American Heart Association estimates that approximately 800,000 deaths in the United States were caused by cardiovascular disease in 2009.

Elevated LDL-cholesterol is well-accepted as a significant risk factor for cardiovascular disease and the CDC estimates that 71 million U.S. adults have elevated levels of LDL-cholesterol. A consequence of elevated LDL-cholesterol is atherosclerosis, which is a disease that is characterized by the deposition of excess cholesterol and other lipids in the walls of arteries as plaque. The development of atherosclerotic plaques often leads to cardiovascular disease. The risk relationship between elevated LDL-cholesterol and cardiovascular disease was first defined by the Framingham Heart Study, which commenced in 1948 to define the factors that contributed to the development of cardiovascular disease. The study enrolled participants who did not have any form of cardiovascular disease and followed them over a long period of time. Elevated LDL-cholesterol and elevated blood pressure were identified early on as key risk factors for the eventual development of cardiovascular disease.

The hypothesis that lowering elevated levels of LDL-cholesterol would translate into reduced risk of cardiovascular disease was first proven in 1984 with the publication of the Lipid Research Clinics Coronary Primary Prevention Trial. In this study, treatment with cholestyramine, a bile acid sequestrant, showed a 20% reduction in LDL-cholesterol and, importantly, a 19% reduction in risk of cardiovascular disease death or nonfatal myocardial infarction, or heart attack. This was the first major clinical study to demonstrate a direct relationship between lowering LDL-cholesterol levels and reduced risk of major cardiovascular events.

The first marketed statin, lovastatin, was approved for use in the United States in 1987 based on its ability to significantly lower elevated LDL-cholesterol levels. That same year, the National Cholesterol Education Program issued its first guidelines for the diagnosis and treatment of patients with hypercholesterolemia. Over the subsequent 22 years, seven more statins were approved for use to lower elevated LDL-cholesterol levels.

In 1994, the first clinical outcomes study with a statin was published. This study demonstrated a significant reduction in risk for total mortality and major cardiovascular events. A series of additional clinical outcomes studies with statins have each shown that lowering elevated LDL-cholesterol translated into reduced major cardiovascular events. The relationship between the extent of LDL-cholesterol lowering and reduction in cardiovascular risk appeared to be linear, which has supported a "lower is better" hypothesis. This hypothesis was tested and proven in the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) study where an on-treatment LDL-cholesterol level of 62 mg/dL associated with atorvastatin treatment translated into a statistically significant 16% reduction in risk of major cardiovascular events as compared with the 95 mg/dL on-treatment LDL-cholesterol level associated with pravastatin.

Most recently, in November 2014 the results of the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study was presented at the Scientific Sessions of the American Heart Association. 18,144 patients with acute coronary syndrome were enrolled in IMPROVE-IT and were randomized to receive either 40 mg of simvastatin or 10 mg ezetimibe/40 mg of simvastatin, and were followed until >5,250 events (cardiovascular death, heart attack, documented unstable angina requiring hospitalization, coronary revascularization or stroke) occurred. The addition

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of ezetimibe to simvastatin resulted in a 6.4% relative risk reduction (p=0.016) in the aggregate of the events described above. This was the first study to demonstrate incremental clinical benefit with a non-statin added to a statin. The positive results of IMPROVE-IT also showed that "even lower is even better", i.e., reducing LDL-cholesterol levels below the levels achieved in previous studies translated into reduction in risk of cardiovascular events, and reaffirmed the LDL-cholesterol hypothesis that reducing LDL-cholesterol reduces risk for major cardiovascular events.

The direct relationship between lower LDL-cholesterol levels and reduced risk for major cardiovascular events has been consistently demonstrated for more than a decade in 14 clinical studies involving more than 90,000 patients. As a result, physicians are highly focused on lowering LDL-cholesterol levels in their patients, and we believe there is a trend towards even more aggressive LDL-cholesterol lowering. For example, in the United States, increasing attention has been placed on aggressive LDL-cholesterol management by organizations such as the National Cholesterol Education Program, or NCEP, the American Heart Association, and the American College of Cardiology. Additionally, both the Canadian Cardiovascular Society and the Joint British Societies have supported even lower LDL-cholesterol treatment targets for high-risk patients. This has led to the combination of statins with other treatments, such as Zetia.

In July 2004, the NCEP issued an update to its Adult Treatment Panel III (ATP III) clinical practice guidelines on cholesterol management, advising physicians to consider new, more intensive treatment options for people at very high risk, high risk and moderately high risk for cardiovascular disease. The LDL-cholesterol goals in these updated clinical practice guidelines, which are presented below, contemplate initiating drug therapy at lower LDL-cholesterol thresholds, expanding the number of potential patients for LDL-cholesterol lowering therapy.

NCEP ATP III Clinical Practice Guidelines

Patient Cardiovascular Disease Risk	LDL-cholesterol Goal
Very High Risk	< 70 mg/dL
Cardiovascular Disease and Cardiovascular Disease Risk Equivalent	< 100 mg/dL
Multiple (2+) Risk Factors	< 130 mg/dL
0 - 1 Risk Factor	< 160 mg/dL

In November 2013, the American College of Cardiology and the American Heart Association issued new guidelines for the treatment of elevated cholesterol. For the first time in more than 20 years, the new guidelines do not include specific, numerical LDL-cholesterol treatment goals for patients with hypercholesterolemia. However, the guidelines strongly recommend the use of more potent statins and intensive statin therapy in patients with hypercholesterolemia. The new guidelines also significantly expanded the number of patients eligible for statin therapy, including patients with a history of cardiovascular disease including stroke, patients with both Type 1 and Type 2 diabetes, all patients with LDL-cholesterol ≥ 190 mg/dL and patients with a 10-year risk of > 7.5% of developing cardiovascular disease. Also for the first time, the guidelines acknowledge the existence of statin intolerance, and incorporate statin intolerance into the consideration of treatment choices and into the evaluation of statin safety.

Other organizations continue to utilize goals of treatment in their guidelines. The National Lipid Association guidelines established < 100 mg/dL as the LDL-cholesterol goal of treatment for patients at low, moderate and high risk. Patients considered to be at very high risk have a goal of < 70 mg/dL of LDL-cholesterol. The International Atherosclerosis Society has recommended optimal LDL-cholesterol levels of < 100 mg/dL for patients who have not had a cardiovascular event, and < 70 mg/dl for patients who have had a cardiovascular event.

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Currently Approved Therapies

The following table illustrates common therapies used to treat hypercholesterolemia:

Class of Therapy	Labeled Indication	Average LDL-cholesterol Change from Baseline	Key Issues/Side Effects
Statins	Reduction in LDL-cholesterol	Up to 63%	Skeletal muscle effects (e.g., myopathy and rhabdomyolysis) FDA recently warned that the use of statins is associated with increases in HbA1c and fasting serum glucose levels
Fixed combination therapies	Reduction in LDL-cholesterol	Up to 63%	Includes a statin as one of the underlying therapies and therefore contains the same side effects outlined above
Bile acid sequestrants	Reduction in LDL-cholesterol[(1)]	Up to 20%	Limited LDL-cholesterol lowering Gastrointestinal disorders
Cholesterol absorption inhibitors	Reduction in LDL-cholesterol	Up to 18%	Limited LDL-cholesterol lowering
Niacin	Reduction in LDL-cholesterol; Reduction in recurrent myocardial infarction	Up to 17%	Flushing (i.e., warmth or redness) hepatic toxicity and skeletal muscle effects Limited LDL-cholesterol lowering
Fibrates	Reduction in triglycerides and LDL-cholesterol	Up to 21%	Gallstones, skeletal muscle effects and liver disorders Limited LDL-cholesterol lowering

(1) Welchol, a bile acid sequestrant, is also approved for improving glycemic control in adults with type 2 diabetes.

Other Approved Therapies for Specific Populations

A small subpopulation of patients with extremely elevated levels of LDL-cholesterol, estimated to be approximately 300 patients in the U.S., suffer from homozygous familial hypercholesterolemia, or HoFH. HoFH is a serious and rare genetic disease and patients with HoFH lack or have dysfunctional LDL receptors and cannot remove LDL particles and LDL-cholesterol from the blood. As a result, untreated HoFH patients typically have LDL-cholesterol levels in the range of 450 mg/dL to 1,000 mg/dL. Microsomal transfer protein (MTP) inhibitors and ApoB antisense drugs are approved therapies to treat patients with a clinical or laboratory diagnosis of HoFH. Given the serious safety concerns with these therapies, specifically hepatotoxicity, the FDA has restricted their usage to this narrow subpopulation.

Statin Therapy

Statins are the cornerstone of lipid treatment today and are highly effective at lowering LDL-cholesterol. This class of drugs includes atorvastatin calcium, marketed as Lipitor®, the most prescribed LDL-cholesterol lowering drug in the world and the best-selling pharmaceutical drug in history. Approximately 25% of Americans over the age of 45 from 2005 to 2008 were treated for

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elevated LDL-cholesterol levels with statin therapy, according to a National Health and Nutrition Examination Survey.

Statins are selective, competitive inhibitors of HMG-CoA reductase, a rate-limiting enzyme in the cholesterol biosynthesis pathway, and work primarily in liver cells. Statin inhibition of cholesterol synthesis increases the number of LDL receptors on the surface of liver cells. This increase in LDL receptors enhances uptake of LDL particles into liver cells from the circulation, thus lowering LDL-cholesterol levels. Statins are also thought to have the potential to inhibit cholesterol synthesis in skeletal muscle. This inhibition could be linked to the myalgia associated with statin use as seen in patients with statin intolerance.

The benefits of statin use in lowering LDL-cholesterol levels and improving cardiovascular outcomes are well documented. Despite the effectiveness of statins and their broad market acceptance, there is a significant subset of patients who are unable to tolerate statins due to muscle pain or weakness, memory loss or increased glucose levels, or who are otherwise unable to reach their LDL-cholesterol goal on statin therapy alone. In rare but extreme cases, statins can lead to muscle breakdown, kidney failure and death. In addition, the FDA has recently warned that statins can cause hyperglycemia, an increase in blood sugar levels and create an increased risk of worsening of glycemic control and of new onset diabetes. There are approximately 37 million U.S. adults with elevated LDL-cholesterol levels who are not on an LDL-cholesterol lowering therapy. For these reasons, we believe there is a need for unique therapies to treat patients with hypercholesterolemia.

Statin Intolerance Initial Market Opportunity for ETC-1002

We are initially pursuing the development of ETC-1002 as a therapy for patients with primary hypercholesterolemia. Upon approval, we will focus our commercialization efforts on patients with hypercholesterolemia who are intolerant of statins. Based upon our communications with the FDA, statin intolerance is defined as the inability to tolerate at least two statins, one of which was taken at the lowest approved dose, due to skeletal muscle pain, aches, weakness or cramping, that manifested or increased during statin therapy and stopped upon the discontinuation of statin usage.

Muscle pain or weakness is the most common side effect experienced by statin users and the most common cause for discontinuing therapy. According to the USAGE survey, an approximately 10,000 patient academic study of current and former statin users published during 2012 in the Journal of Clinical Lipidology, 12% of patients on statins discontinue therapy and 62% of these patients cited side effects as the reason for discontinuation. More than 86% of patients who discontinued therapy because of side effects cited muscle pain or weakness as the reason. Based upon these data, approximately 6% of statin users, or more than 3 million adults in the United States, ceased therapy because of muscle pain or weakness and are therefore statin intolerant.

Moreover, a significant proportion of patients remain on statin therapy despite experiencing muscle-related side effects. The rate of occurrence in the clinical setting, as highlighted by the USAGE survey, is significantly higher than the up to 5% rate reported by subjects in the controlled environment of clinical studies. The USAGE survey reported that 25% of patients currently on statins have muscle-related side effects. Similarly, a study published in the Journal of General Internal Medicine in August 2008 estimated that up to 20% of statin-treated patients in clinical practice complained of muscle pain. Accordingly, we believe that in the presence of a safe and effective non-statin, oral, once-daily, small molecule LDL-cholesterol lowering therapy, the statin intolerant market could grow substantially.

Patients with Hypercholesterolemia Subsequent Market Opportunity for ETC-1002

We expect ETC-1002 may also be used by patients and physicians as an add-on therapy for patients with hypercholesterolemia who are unable to reach their recommended LDL-cholesterol goals despite the use of a statin or other LDL-cholesterol lowering therapy. The severity of

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hypercholesterolemia in these patients, their level of cardiovascular disease risk and their therapeutic options all vary widely.

Additional Therapies in Development

PCSK9 Inhibitors

A number of larger biopharmaceutical companies are currently developing a new class of biologic therapies that target proprotein convertase subtilisin/kexin type 9, or PCSK9, an enzyme that binds LDL receptors. These PCSK9 inhibitors are injectable, fully-human antibodies that are being evaluated as potential therapies to lower LDL-cholesterol, including in patients who are statin intolerant or who are statin resistant. In January 2015, Sanofi and Regeneron Pharmaceuticals Inc. announced that the FDA had accepted for priority review the Biologics License Application (BLA) application for alirocumab, their PCSK9 inhibitor. The FDA is expected to finish its regulatory review for alirocumab in late July of 2015. In August 2014, Amgen Inc. announced that the FDA had accepted for review the BLA for evolocumab, their PCSK9 inhibitor. The FDA is expected to finish its regulatory review for evolcumab in late August of 2015. Also in 2013, Pfizer Inc. announced the initiation of Phase 3 studies of bococizumab, their PCSK9 inhibitor. In monotherapy clinical studies to date, PCSK9 inhibitors have demonstrated reductions of LDL-cholesterol, up to 56%. The PCSK9 inhibitors, if approved, could be an effective therapeutic alternative for statin intolerant patients or as an add-on to statin therapy. Notwithstanding the LDL-cholesterol lowering efficacy of PCSK9 inhibitors, we believe their adoption by patients, physicians, and payors could be adversely impacted by their higher cost as injectable biologics, their inconvenient route of administration, and their inability to positively impact other important cardiometabolic risk markers.

CETP Inhibitors

A number of larger biopharmaceutical companies are currently developing a class of therapies that target cholesteryl ester transfer protein (CETP), which mediates the transfer of cholesteryl esters from HDL particles to apolipoprotein B containing particles. CETP inhibitors were initially designed to raise levels of HDL-cholesterol and are required by FDA to complete clinical outcomes studies in Phase 3 prior to approval. Pfizer brought the first drug in this class, torcetrapib, into clinical development but terminated development activities in December 2006 due to an increase in all-cause mortality and cardiovascular events in the ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events) study. A second CETP inhibitor, dalcetrapib, from Roche, terminated development in May 2012 due to insufficient efficacy in the dal-OUTCOMES study. Two additional CETP inhibitors are being developed and are currently in Phase 3 clinical outcomes studies. Anacetrapib is being developed by Merck and evacetrapib is being developed by Lilly. Both product candidates have been shown to significantly raise levels of HDL-cholesterol and to lower LDL-cholesterol. The Phase 3 outcomes studies are expected to complete by 2017.

Clinical Experience

To date, ETC-1002 has been studied in eleven completed clinical studies across five patient populations: healthy volunteers; patients with elevated LDL-cholesterol levels; patients with type 2 diabetes and elevated LDL-cholesterol levels; patients with elevated LDL-cholesterol levels and a history of statin intolerance; and patients with elevated LDL-cholesterol levels taking 10 mg of atorvastatin. These clinical studies consisted of five Phase 2 clinical studies and three Phase 1 clinical studies. The first six clinical studies compared ETC-1002 monotherapy to placebo. In ETC-1002-007, ETC-1002 was administered as an add-on to a 10 mg dose of atorvastatin. In ETC-1002-008 we evaluated the efficacy and safety of ETC-1002, ezetimibe, and the combination of ETC-1002 and ezetimibe in patients with hypercholesterolemia with or without statin intolerance. The individual design and results of each of our completed clinical studies are summarized below.

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Completed Clinical Studies

To date, we have completed the following clinical studies of ETC-1002:

Description	Title	Treatment Duration	Subjects	
			Total	Treated
ETC-1002-008	**Phase 2b Clinical Study of Safety Efficacy in Patients with Hypercholesterolemia, with or without a history of statin intolerance** A randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of ETC-1002 monotherapy, ezetimibe monotherapy, and the combination of ETC-1002 and ezetimibe in patients with hypercholesterolemia, with or without statin intolerance	12 Weeks	348	249
ETC-1002-007	**Phase 2a Clinical Study of Safety and Pharmacokinetic Interaction in Patients with Hypercholesterolemia on a Background of Atorvastatin 10 mg** Placebo-controlled, randomized, double-blind, drug interaction study to evaluate the safety, tolerability and effect on atorvastatin pharmacokinetics of ETC-1002 added to atorvastatin 10 mg/day in patients with hypercholesterolemia	8 Weeks	58	42
ETC-1002-006	**Phase 2a Proof-of-Concept Clinical Study in Patients with Hypercholesterolemia and a History of Statin Intolerance** Placebo-controlled, randomized, double-blind, multicenter study to evaluate the efficacy and safety of ETC-1002 in patients with hypercholesterolemia and a history of intolerance to statin therapy	8 Weeks	56	37
ETC-1002-005	**Phase 2a Proof-of-Concept Clinical Study in Patients with Hypercholesterolemia and Type 2 Diabetes** Placebo-controlled, randomized, double-blind, single site clinical study to evaluate the LDL-cholesterol lowering efficacy and safety of ETC-1002 in patients with type 2 diabetes	4 Weeks	60	30

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Description	Title	Treatment Duration	Subjects Total	Subjects Treated
ETC-1002-004	**Phase 1b Multiple-Dose Tolerance Greater Than 120 mg Clinical Study** Multiple ascending dose clinical study to evaluate safety, tolerability and pharmacokinetics (PK) of ETC-1002 in doses greater than 120 mg once-daily in healthy subjects	2 Weeks	24	18
ETC-1002-003	**Phase 2a Proof-of-Concept Clinical Study in Patients with hypercholesterolemia** Placebo-controlled, randomized, double-blind, parallel group, multicenter clinical study to evaluate the LDL-cholesterol lowering efficacy and safety of ETC-1002 in patients with hypercholesterolemia and either normal or elevated triglycerides	12 Weeks	177	133
ETC-1002-002	**Phase 1b Multiple-Dose Tolerance Clinical Study** Multiple ascending dose clinical study to evaluate safety, tolerability, PK and pharmacodynamics (PD) of ETC-1002 in doses of up to 120 mg once-daily in healthy subjects	2 Weeks / 4 Weeks	53	39
ETC-1002-001	**Phase 1a Single-Dose Tolerance Clinical Study** First-in-human single-dose clinical study to evaluate safety, tolerability and PK of ETC-1002 in healthy subjects	Single Dose	18	18
Overall, ETC-100				