Conatus Pharmaceuticals Inc.
Form 10-K
March 08, 2018

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2017

OR

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: 001-36003

CONATUS PHARMACEUTICALS INC.

(Exact name of registrant as specified in its charter)

Delaware	20-3183915
(State or Other Jurisdiction of	(I.R.S. Employer
Incorporation or Organization)	Identification No.)
16745 West Bernardo Dr., Suite 200	
San Diego, CA	92127
(Address of Principal Executive Offices)	(Zip Code)
(858) 376-2600	

(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, par value $0.0001 per share	The Nasdaq Global Market

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

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

Indicate by a check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934. Yes No

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate website, 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 No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

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

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

Emerging growth company
If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

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

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant as of the last business day of the registrant's most recently completed second fiscal quarter was approximately $160.8 million, based on the closing price of the registrant's common stock on the Nasdaq Global Market of $5.76 per share.

As of March 1, 2018, the registrant had 30,059,999 shares of common stock ($0.0001 par value) outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement to be filed with the Securities and Exchange Commission by April 30, 2018 pursuant to Regulation 14A in connection with the registrant's 2018 Annual Meeting of Stockholders are incorporated by reference into Part III of this report.

CONATUS PHARMACEUTICALS INC.

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PART I

FORWARD-LOOKING STATEMENTS AND MARKET DATA

This annual report on Form 10-K contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended. All statements other than statements of historical facts contained in this annual report, including statements regarding our future results of operations and financial position, business strategy, prospective products, product approvals, research and development costs, timing and likelihood of success, plans and objectives of management for future operations and future results of anticipated products, 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. This annual report on Form 10-K also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

In some cases, you can identify forward-looking statements by terms such as “may,” “will,” “should,” “expect,” “plan,” “anticipate,” “could,” “intend,” “target,” “project,” “contemplates,” “believes,” “estimates,” “predicts,” “potential” or “continu negative of these terms or other similar expressions. The forward-looking statements in this annual report are only predictions. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our business, financial condition and results of operations. These forward-looking statements speak only as of the date of this annual report and are subject to a number of risks, uncertainties and assumptions, including those described in Part I, Item 1A, “Risk Factors.” The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. Moreover, we operate in an evolving environment. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

We use our registered trademark, CONATUS PHARMACEUTICALS, in this annual report. This annual report also includes trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, trademarks and tradenames referred to in this annual report appear without the ® and ™ symbols, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or that the applicable owner will not assert its rights, to these trademarks and tradenames.

We maintain a website at www.conatuspharma.com, to which we regularly post copies of our press releases as well as additional information about us. Our filings with the Securities and Exchange Commission, or SEC, are available free of charge through our website as soon as reasonably practicable after being electronically filed with or furnished to the SEC. Interested persons can subscribe on our website to email alerts that are sent automatically when we issue press releases, file our reports with the SEC or post certain other information to our website. Information contained in our website does not constitute a part of this report or our other filings with the SEC.

ITEM 1. BUSINESS

Overview

We are a biotechnology company focused on the development and commercialization of novel medicines to treat liver disease. We are developing emricasan, a first-in-class, orally active pan-caspase protease inhibitor, for the treatment of patients with chronic liver disease. Emricasan is designed to reduce the activities of human caspases, which are

enzymes that mediate inflammation and apoptosis. We believe that by reducing the activity of these enzymes, caspase inhibitors have the potential to interrupt the progression of a variety of diseases.

In collaboration with Novartis Pharma AG, or Novartis, we plan to focus on advancing toward registration of emricasan for patients with fibrosis or cirrhosis due to nonalcoholic steatohepatitis, or NASH. Preclinical studies and clinical trials have yielded compelling results that suggest emricasan may have clinical utility in slowing the progression of liver disease regardless of the original cause of the disease. To date, emricasan has been studied in over 650 subjects in 16 completed clinical trials across a broad range of liver disease etiologies and stages of progression.

We are conducting three EmricasaN, a Caspase inhibitOR, for Evaluation clinical trials, or the ENCORE trials, designed to provide further information on doses leading to clinically relevant efficacy, including improvement in severe portal hypertension and hepatic function in patients with NASH cirrhosis and improvement in biopsy-proven fibrosis and inflammation in patients with NASH fibrosis. We are also conducting a trial of emricasan in post-orthotopic liver transplant, or POLT, recipients with hepatitis C virus, or HCV, who achieved viral clearance, known as sustained viral response, or SVR, but who have residual fibrosis or cirrhosis in the transplanted liver. These four trials are also designed to provide safety data to support the registration of emricasan for chronic administration. We expect these trials to build on the data from our completed clinical trials, which have demonstrated emricasan's ability to provide improvements in validated functional surrogate endpoints of portal hypertension and liver function.

Our current clinical program for emricasan includes the following:

Phase 2b POLT-HCV-SVR Clinical Trial: In May 2014, we initiated a randomized, double-blind, placebo-controlled Phase 2b clinical trial in approximately 60 POLT-HCV-SVR, patients with residual fibrosis or cirrhosis, classified as Ishak Fibrosis Score 2-6, who will receive 25 mg of emricasan or placebo orally twice daily for two years. The primary endpoint in this exploratory proof-of-concept trial is the change in the Ishak Fibrosis Score compared with placebo. The trial will also evaluate histological markers of inflammation, key serum biomarkers, and the safety and tolerability of emricasan. Top-line results are expected in the second quarter of 2018. This trial was initiated following the FDA granting orphan drug designation to emricasan in late 2013 for the treatment of POLT patients with reestablished fibrosis to delay the progression to cirrhosis and end-stage liver disease.

Phase 2b ENCORE-PH (Portal Hypertension) Clinical Trial: In November 2016, we initiated a randomized, double-blind, placebo-controlled Phase 2b clinical trial to evaluate the effect of emricasan in reducing hepatic venous pressure gradient, or HVPG, in approximately 240 compensated or early decompensated NASH cirrhosis patients with severe portal hypertension, established by baseline HVPG values of 12 mmHg or higher. Patients will be randomized 1:1:1:1 to receive 5 mg of emricasan, 25 mg of emricasan, 50 mg of emricasan, or placebo twice daily for 24 weeks. The primary endpoint is the mean change in HVPG from week 0 to week 24 for each dosing group compared with placebo. Top-line results are expected in the second half of 2018. In addition, this trial has an additional 24-week open-label extension period for patients after they complete the blinded 24-week stage of the trial.

Phase 2b ENCORE-NF (NASH Fibrosis) Clinical Trial: In January 2016, we initiated a Phase 2b clinical trial evaluating emricasan's potential long-term benefits for patients with liver fibrosis resulting from NASH. This randomized, double-blind, placebo-controlled clinical trial will evaluate the effect of emricasan in reducing fibrosis and steatohepatitis in approximately 330 patients with NASH fibrosis, but not cirrhosis. Patients will be randomized 1:1:1 to receive 5 mg of emricasan, 50 mg of emricasan, or placebo twice daily for 72 weeks. The primary endpoint is a biopsy-based change in fibrosis by at least one stage using the NASH Clinical Research Network Histologic Scoring System, without worsening of steatohepatitis. Top-line results are expected in the first half of 2019.

Phase 2b ENCORE-LF (Liver Function) Clinical Trial: In May 2017, we initiated a randomized, double-blind, placebo-controlled Phase 2b clinical trial to evaluate emricasan in approximately 210 patients with decompensated NASH cirrhosis. Patients will be randomized 1:1:1 to receive 5 mg of emricasan, 25 mg of emricasan, or placebo twice daily for at least 48 weeks. The primary endpoint is event-free survival for each treatment group compared with the placebo group. For the purposes of the trial, events are defined as all-cause mortality, new decompensation events, or a progression of ≥4 points in the Model for End-stage Liver Disease, or MELD, score. Key secondary endpoints include safety and tolerability, MELD and Child-Pugh-Turcotte, or CPT, scores, liver transplantation rates, liver metabolic function using the BreathID® Methacetin Breath Test, and health-related quality of life. An interim futility analysis may be conducted after a specific number of events have occurred. Top-line results are expected in the second half of 2019.

In addition, we recently initiated a non-treatment observational study pursuant to which subjects from the four trials above will be followed for an up to three-year safety follow-up.

In February 2016, we announced that the U.S. Food and Drug Administration, or the FDA, granted Fast Track designation to the emricasan development program for the treatment of liver cirrhosis caused by NASH. The Fast Track program provides greater access to the FDA in order to expedite review of drugs that are intended, alone or in combination with one or more drugs, to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition.

In May 2017, Novartis exercised its option under the Option, Collaboration and License Agreement, or the Collaboration Agreement, we entered into with Novartis in December 2016. Pursuant to such exercise, we granted Novartis an exclusive, worldwide license to our intellectual property rights relating to emricasan to collaborate with us for the global development and commercialization of products containing emricasan either as a single active ingredient or in combination with other Novartis compounds for liver cirrhosis or liver fibrosis, including but not limited to Farnesoid X receptor agonists that Novartis is currently developing for the treatment of chronic liver diseases. The license became effective upon our receipt of a $7.0 million option exercise payment in July 2017.

Pursuant to the Collaboration Agreement, we are responsible for completing the three ENCORE trials and the POLT-HCV-SVR trial described above. We share the costs of these four Phase 2b trials equally with Novartis. In addition, until the completion of the four Phase 2b trials, we will equally share the costs of the non-treatment observational study that will follow patients from the four Phase 2b trials. After the completion of the four Phase 2b trials, Novartis will assume 100% of the observational study costs. Novartis is responsible for 100% of certain expenses for required registration-supportive nonclinical activities. Novartis is also responsible for the development of emricasan beyond the four Phase 2b trials described above, including the Phase 3 development of emricasan single agent products and all development for emricasan combination products, and Novartis has agreed to use commercially reasonable efforts to develop and commercialize emricasan products. A joint steering committee comprised of representatives from our company and Novartis oversees the collaboration, development and commercialization of emricasan products.

Under the Collaboration Agreement, Novartis paid us an upfront payment of $50.0 million. Following Novartis' exercise of the option under the Collaboration Agreement, we received the additional $7.0 million option exercise payment and are eligible to receive up to an aggregate of $650.0 million in milestone payments over the term of the Collaboration Agreement, contingent on the achievement of certain development, regulatory and commercial milestones, as well as royalties. After the initiation of the first Phase 3 clinical trial for an emricasan product candidate, we have the right to elect to enter into a co-commercialization agreement with Novartis under which we would receive up to 30% of the commercial profits less the same percentage of the commercial losses, subject to certain reductions in milestone and royalty payments.

In June 2017, the FDA granted Orphan Drug Designation to our preclinical product candidate IDN-7314, a pan-caspase inhibitor, for the treatment of primary sclerosing cholangitis, or PSC, a disease affecting bile ducts in the liver, which can lead to cirrhosis and liver failure. In October 2017, the European Medicines Agency granted orphan designation to IDN-7314 for the treatment of PSC. We believe these orphan designations provide an opportunity to address an important unmet medical need and expand our development pipeline beyond emricasan. Pursuant to the Collaboration Agreement, Novartis will have a right of first negotiation prior to any offer for IDN-7314 by us to a third party, and we may not develop IDN-7314 in any pivotal registration clinical trials or commercialize IDN-7314 in liver disease until the earlier of five years after the first commercial sale of an emricasan product in the United States or major European market or ten years from the execution date of the Collaboration Agreement. We will continue to evaluate the potential of IDN-7314 as a product candidate as a component of our pipeline expansion plans.

We also plan to expand our development pipeline by internal development of new preclinical product candidates leveraging our caspase inhibition expertise or in-licensing or acquiring preclinical or clinical-stage product candidates consistent with our product development and regulatory expertise. In addition to liver disease, we may pursue the development of product candidates in other disease areas.

Our Team

Our senior management team includes former senior executives of Idun Pharmaceuticals, Inc., or Idun. At Idun, these senior executives discovered and led the development of Idun's lead asset emricasan, which was then known as IDN-6556, until the company was sold to Pfizer Inc. in July 2005. We acquired the global rights to emricasan from Pfizer, where it was known as PF-3491390, in July 2010. At both Idun and Pfizer, emricasan was being developed for the treatment of liver fibrosis. Due to our experience, we believe we can successfully develop emricasan for the treatment of one or more liver diseases, including NASH fibrosis and NASH cirrhosis. Furthermore, we believe our experience developing product candidates in liver disease, including but not limited to caspase inhibitors, will enable us to expand our development pipeline beyond emricasan.

Our Strategy

Our strategy is to develop and commercialize medicines to treat cirrhotic and fibrotic liver indications in areas of high unmet medical need. The key elements of our strategy are to:

- Focus initial development of emricasan on the treatment of liver diseases with high unmet medical need. We believe that by inhibiting the caspases responsible for inflammation and apoptosis in the liver, emricasan has the potential to stabilize and improve liver function and to slow liver disease progression in patients with liver cirrhosis or fibrosis. In collaboration with Novartis, we plan to focus on advancing emricasan toward registration for patients with cirrhosis or fibrosis.
- Increase the commercial potential of emricasan through the Novartis collaboration. We believe the collaboration with Novartis will increase the commercial potential of emricasan by leveraging the resources of a large pharmaceutical company with expertise in liver disease, experience in drug development and marketing application approval, and established sales and marketing capabilities and potentially by pursuing the development and commercialization of combination products containing emricasan along with compounds developed or acquired by Novartis.

- Develop, in-license or acquire new product candidates to expand our pipeline. Although we are currently focused on the development of emricasan, we plan to pursue additional product candidates in the future. We plan to expand our development pipeline by developing internal preclinical product candidates or by in-licensing or acquiring preclinical or clinical-stage product candidates. We may develop such product candidates independently or in collaboration with third parties.

Liver Disease and Apoptosis

The liver is the largest internal organ in the human body and its proper function is indispensable for many critical metabolic functions, including the regulation of lipid and sugar metabolism, the production of important proteins, including those involved in blood clotting, and purification of blood. There are over 100 described diseases of the liver, and because of its many functions, these can be highly debilitating and life-threatening unless effectively treated. Liver diseases can result from injury to the liver caused by a variety of insults, including HCV, hepatitis B virus, or HBV, obesity, chronic excessive alcohol use or autoimmune diseases. Regardless of the underlying cause of the disease, there are important similarities in the disease progression including increased inflammatory activity and excessive liver cell apoptosis, which if unresolved leads to fibrosis. Fibrosis, if allowed to progress, will lead to cirrhosis, or excessive scarring of the liver, and eventually reduced liver function. Some patients with liver cirrhosis have a partially functioning liver and may appear asymptomatic for long periods of time, which is referred to as compensated liver disease. Decompensated liver disease is when the liver is unable to perform its normal functions. Many people with active liver disease remain undiagnosed largely because liver disease patients are often asymptomatic for many years. The National Institutes of Health, or NIH, estimates that 5.5 million Americans have chronic liver disease or cirrhosis, and liver disease is the twelfth leading cause of death in the United States. According to the European Association for the Study of the Liver, 29 million Europeans have chronic liver disease, and liver disease represents approximately 2% of deaths annually. In the United States in 2016, there were more than 7,500 liver transplants performed. There are currently approximately 14,000 active candidates on the transplant waiting list in the United States. Furthermore, NASH is expected to be the leading cause of liver transplants in the next five to ten years.

The death of cells and resulting inflammation play an important role in the progression of many liver diseases. In general, cells can die by either of two major mechanisms, apoptosis, a form of programmed cell death, or necrosis, which is uncontrolled cell death caused by infection, toxins or trauma. Both of these mechanisms can produce a state of acute and/or chronic inflammation. High levels of noxious stimuli can rapidly overwhelm the cell’s natural protective mechanisms, leading to a rupture of the cell and subsequent release of its contents into the surrounding tissue. This process is known as necrosis and results in a highly pro-inflammatory response, further damaging the surrounding tissue. In contrast, the programmed cell death mechanism, termed apoptosis, is a highly controlled and tightly regulated process that involves the orderly condensation and dismantling of the cell leading to its subsequent rapid and specific removal from the surrounding tissue by specialized cells. However, under conditions of excessive stress as often observed in disease, the production of apoptotic cells outpaces the body’s ability to effectively remove them from the surrounding tissue. This results in an accumulation of shed cell fragments known as apoptotic bodies, which are taken up by surrounding cells and can stimulate additional cell death. Disease-driven excessive apoptosis results in the development of scar tissue or fibrosis, which can lead to tissue destruction and eventually reduce the capacity of an organ to function normally.

Liver disease is often first detected as hepatitis, which is defined as inflammation of the liver. Hepatitis is easily detected by a routine laboratory test to measure blood levels of the liver enzyme alanine aminotransferase, or ALT. ALT is an enzyme that is produced in liver cells and is naturally found in the blood of healthy individuals. In liver disease, liver cells are damaged and as a consequence, ALT is released into the blood, increasing ALT levels above the normal range. Physicians routinely test blood levels of ALT to monitor the health of a patient’s liver. ALT level is a clinically important biochemical marker of the severity of liver inflammation and ongoing liver disease. ALT is elevated in almost all early- to mid-stage liver diseases and represents an overall measure of liver inflammation and liver cell death. However, in later stage cirrhosis patients, ALT levels have been shown to not be elevated above the normal range. Aspartate aminotransferase, or AST, is a second enzyme found in the blood that is produced in the liver

and routinely measured by physicians along with ALT. As with ALT, AST is often elevated in liver disease and, like ALT, is considered an overall marker of liver inflammation. We have measured both ALT and AST levels in our clinical trials and have observed similar effects of emricasan on both enzymes.

NASH is typically suspected when a patient has elevated ALT or AST and no evidence or history of viral hepatitis or excessive alcohol use. As liver disease progresses, fibrotic scar tissue will begin to replace healthy liver tissue and over time will reduce the liver's ability to function properly. A liver biopsy is used to diagnose fibrosis and determine how much liver scarring has developed. If fibrosis is allowed to progress, it will lead to cirrhosis. As liver cirrhosis becomes progressively worse, all aspects of liver function will dramatically decline.

Another important marker of liver cell death is a protein fragment called cleaved Cytokeratin 18, or cCK18. During apoptosis, a key structural protein within the cell called Cytokeratin 18, or CK18, is specifically cleaved by caspases, which results in the release of cCK18 into the blood stream. cCK18 is easily detected in the blood with a commercially-available test and is a mechanism-specific biomarker of apoptosis and caspase activity. Unlike ALT, cCK18 is elevated in patients with advanced cirrhosis. Importantly, cCK18

is also present in healthy subjects and multiple studies have demonstrated an approximate basal level in healthy subjects. Numerous independent clinical trials and published studies have demonstrated the utility of cCK18 for detecting and gauging the severity of ongoing liver disease across a variety of disease etiologies. These studies have demonstrated correlations between disease and cCK18 levels in patients with liver cirrhosis, NASH, HCV and various other liver disease indications. For example, serum cCK18 levels corresponded well to an improvement in liver histology in two clinical trials of NASH in adults and children, respectively. Moreover, it has been shown that the severity of liver disease in HCV patients was associated with cCK18 levels and apoptosis, such that the more severe the disease, the higher the serum level of cCK18. In liver cirrhosis patients, studies have shown that cCK18 levels are elevated and correlate with liver inflammation and cholestasis. In POLT patients with recurrent HCV, it has been shown that cCK18 levels and apoptosis were significantly elevated in liver biopsies as determined by immunohistochemical analysis. We believe these studies demonstrate the relationship between elevated cCK18 levels and severity of liver disease and that cCK18 is an important biomarker of excessive apoptosis in liver disease.

Emricasan

Emricasan is a first-in-class, proprietary and orally active caspase protease inhibitor designed to slow or halt the progression of chronic liver disease caused by fibrosis and cirrhosis. To date, emricasan has been administered to over 650 subjects in eight completed Phase 1 and eight completed Phase 2 clinical trials and has been generally well-tolerated in both healthy volunteers and patients with liver disease. Emricasan has also been extensively profiled in in vitro tests and studied in many preclinical models of human disease. Recent clinical trial results have demonstrated emricasan’s ability to provide significant improvements in validated functional surrogate endpoints of portal hypertension and liver function across a variety of etiologies in the subgroups of liver cirrhosis patients with high medical need.

Mechanism of Action

Emricasan works by inhibiting caspases, which are a family of related enzymes that play an important role as modulators of critical cellular functions, including functions that result in apoptosis and inflammation. Caspase activation and regulation is tightly controlled through a number of mechanisms. All caspases are expressed as enzymatically inactive forms known as pro-caspases, which can be activated following a variety of cellular insults or stimuli. Seven caspases are specifically involved in the process of apoptosis while three caspases specifically activate pro-inflammatory cytokines and are not directly involved in apoptosis as shown in Figure 1.

Figure 1. Emricasan is a Potent Inhibitor of Apoptotic and Inflammatory Caspases

Caspase mediated apoptosis is driven primarily by the activity of caspases 3 and 7 which, by virtue of their enzymatic activity, cleave a wide variety of cellular proteins and result in dismantling of the cell. Other apoptotic caspase family members are principally involved in sensing and transmitting signals from either outside or inside the cell. These signals converge to activate pro-caspases 3 and 7, enabling them to carry out the process of apoptosis.

CK18 is one key structural protein that is cleaved by caspases 3 and 7 in a highly specific manner. The product of this cleavage is a small protein fragment, cCK18. This fragment is contained within the apoptotic cell fragments and is easily detected in serum using a commercially available monoclonal antibody assay. This monoclonal antibody, M30, is used routinely in clinical trials as a measure of apoptosis.

While healthy individuals have normal levels of apoptosis, excessive levels of apoptosis associated with disease can overwhelm the body’s normal clearance mechanisms. Reducing excessive levels of apoptosis reestablishes balance between apoptotic activity and normal clearance mechanisms and brings inflammation and other drivers of disease progression under control. As a result, we believe targeting caspases that drive both apoptosis and inflammation in disease offers a unique and potentially powerful therapeutic approach for the treatment of both acute and chronic liver disease.

Testing in vitro enzyme assays demonstrated that emricasan efficiently inhibits all human caspases at low nanomolar concentrations. Preclinical studies have demonstrated that emricasan is highly selective for the caspase family of enzymes with little to no activity against other enzyme systems. These studies have also shown that emricasan potently inhibits the apoptosis of cells regardless of the apoptotic stimuli and that it is a potent inhibitor of caspase-mediated pro-inflammatory cytokines. Emricasan has been examined in various preclinical models of liver disease. In these models, caspase activity was demonstrated to be inhibited, as determined by histological examination, in liver tissue. Based on our evaluation of emricasan in in vitro systems, cellular assays and disease models, we believe emricasan’s mechanism of action has been well characterized.

Clinical Data

To date, emricasan has been studied in over 650 subjects in eight completed Phase 1 clinical trials and eight completed Phase 2 clinical trials. This includes approximately 450 subjects with liver disease, 50 liver transplant subjects and 150 healthy volunteers receiving single or multiple doses of emricasan ranging from 1 to 500 mg per day orally or 0.1 to 10 mg/kg per day intravenously for up to 12 weeks. Emricasan has demonstrated evidence of a beneficial effect on serological biomarkers in patients with chronic liver disease independent of the cause of disease. Favorable changes have been observed in functional biomarkers of liver damage and inflammation, such as ALT and AST, and mechanistic biomarkers, such as cCK18 and caspase activity, indicating that emricasan works by the presumed mechanism of action of inhibiting apoptosis of liver cells. Importantly, clinical trials have also demonstrated that emricasan does not inhibit normal levels of caspase activity in healthy individuals. Recent emricasan clinical trial results have demonstrated emricasan's ability to provide significant improvements in validated functional surrogate endpoints of portal hypertension and liver function across a variety of etiologies in the subgroups of liver cirrhosis patients with high medical need. Emricasan has been generally well-tolerated in clinical trials completed to date.

Phase 2 Clinical Trials

We have conducted eight Phase 2 clinical trials in subjects with both single and multiple-dose administration of emricasan. The objective of these trials was to examine the safety, tolerability, pharmacokinetics, or PK, and, in some trials, the mechanistic pharmacodynamics, or PD, of emricasan. As shown in Figure 2 below, emricasan was generally well-tolerated in all eight Phase 2 clinical trials.

Figure 2. Emricasan Phase 2 Clinical Trial Summary

Trial Design	Subjects	Dosing/ Days	Outcome
Phase 2 Trial of IDN-6556 in Subjects with Liver Cirrhosis (Study IDN-6556-10)	86 (US)	BID/ 12 weeks	Well-tolerated; reduction in elevated markers of liver function and elevated biomarkers; trial included open-label extension
Phase 2 Trial of IDN-6556 in Cirrhotic Subjects with Portal Hypertension (Study IDN-6556-11)	23 (US)	BID/ 28 days	Well-tolerated; reduction in HVPG in patients with liver cirrhosis and severe portal hypertension
Phase 2 Trial of IDN-6556 in Subjects with NAFLD and Raised Transaminases (Study IDN-6556-06)	38 (US)	BID/ 28 days	Well-tolerated; reduction in ALT
Phase 2b Pharmacokinetic and Pharmacodynamic Clinical Trial in Acute-on-chronic Liver Failure Patients (Study IDN-6556-02)	21 (US, EU)	BID/ 28 days	Well-tolerated: dose-related responses in elevated biomarkers
Phase 2b Dose Response Trial in HCV Patients (Study A8491003)	204 (US)	BID/ 12 weeks	Well-tolerated; improved liver enzymes (ALT and AST)
Phase 2 Ascending Dose Trial in Patients with Hepatic Impairment (Study A8491004)	105 (US)	QD, BID, TID/ 14 days	Well-tolerated; improved liver enzymes (ALT)
Phase 2 Ascending Dose Crossover Trial in Patients with HCV and Liver Fibrosis (Study A8491010)	24 (US)	Various	Discontinued prematurely; formal statistical tests were not performed
Phase 2 Trial of IDN-6556 in Patients with Severe Alcoholic Hepatitis and Contradictions to Steroid Therapy (Study IDN-6556-04)	5 (US)	BID/ 28 days	Study closed; formal statistical tests were not performed

Phase 2 Clinical Trial of IDN-6556 in Subjects with Liver Cirrhosis

In January 2016, we announced results from the three-month, double-blind, placebo-controlled stage of the six-month Phase 2 clinical trial in patients with liver cirrhosis due to different etiologies, mild to moderate liver impairment and a MELD score of 11 to 18 during the screening period. The double-blind, placebo-controlled stage of this clinical trial was conducted at 26 U.S. sites and enrolled 86 patients. Among the 86 subjects enrolled and dosed, liver cirrhosis etiologies included alcohol (38%), HCV (29%), NASH (23%), and other causes (9%). Baseline MELD scores were ≤14 in 78% of enrolled subjects and ≥15 in 22% of enrolled subjects. Baseline CPT status was A (CPT score of 5-6) in 43% of subjects and B (CPT score of 7-9) in 56% of subjects.

These results showed a statistically significant reduction in cCK18 vs. placebo (p=0.04) at month three in the overall patient population when adjusted for differences between treatment and placebo groups in baseline MELD score and disease etiology as specified in the trial statistical analysis plan. cCK18 is a mechanism-specific biomarker of caspase-driven cell death. Multiple additional liver disease biomarkers achieved statistically significant reductions vs. placebo in the overall patient population after three months of treatment, including caspase 3/7 and ALT, while others achieved positive trends. Collectively, two key secondary endpoints and clinically relevant measures of liver function, MELD score and CPT score, along with other key liver function parameters, demonstrated favorable trends vs. placebo in the overall patient population after three months of treatment. The trends in the overall patient population were driven by statistically significant improvements in a subgroup of patients with baseline MELD scores ≥15. Additional endpoint results in various subgroups for the first three months are shown below in Figure 3.

Figure 3. Phase 2 Liver Cirrhosis Clinical Trial Secondary Endpoint Results

for the Mixed Etiology Patient Population with Baseline MELD Scores ≥15 and

by Etiology Regardless of Baseline MELD Score

	Treatment Difference at Month 3 (LS Mean)*			
	MELD≥15 (N=19)	NASH (N=20)	HCV (N=25)	Alcohol/Other (N=41)
MELD score	-2.19*	-1.63*	-0.60	-0.71
CPT score	-1.31*	-0.96*	-0.32	-0.75*
INR	-0.19*	-0.13*	-0.05	-0.10*
Total bilirubin	-0.79*	-0.40	-0.43	-0.45
Albumin	0.04	-0.06	-0.06	0.03
ALT (median)	-3.0	-2.0	-6.0	-3.0
AST (median)	-5.5*	-3.0	-12.0*	-3.0

*LS Mean treatment differences between emricasan and placebo for the change from baseline at Month 3 (LOCF) using Adjusted ANCOVA model including treatment group, adjusting for baseline value, baseline MELD category, etiology, and treatment by subgroup interaction terms. For ALT and AST, mean treatment difference reported using 1-way non-parametric ANOVA and Hodges-Lehmann estimation.

In May 2016, we announced top-line results from the three-month, open-label second stage of this trial. In the second stage, patients on emricasan in the first stage continued treatment for another three months, and patients on placebo in the first stage switched to emricasan for three months. In a mixed etiology subgroup of patients with baseline MELD scores ≥15, statistically significant emricasan treatment effects vs. placebo (improvement in the emricasan group vs. progression in the placebo group) after the first three months showed continued directional improvements after the second three months of treatment with emricasan. In patients whose liver cirrhosis was caused by NASH, statistically significant emricasan treatment effects vs. placebo (slower progression in the emricasan group than in the placebo group) on measures of liver function after the first three months showed continued directional improvement after the second three months of treatment with emricasan regardless of baseline MELD score. Other etiologies showed similar directional improvements after the first three months and continued during the second three months. We believe the

statistically significant treatment effects in the NASH patient subgroup, which applied regardless of baseline MELD scores, offer a range of options for future clinical trials in patients with NASH cirrhosis.

Emricasan was generally well-tolerated in the clinical trial, and the overall safety profile was similar in the emricasan and placebo groups with regard to both serious and other adverse events.

Phase 2 Clinical Trial of IDN-6556 in Cirrhotic Subjects with Portal Hypertension

We announced in September 2015 that the open-label Phase 2 clinical trial of emricasan in patients with liver cirrhosis due to different etiologies and portal hypertension confirmed by HVPG procedure upon enrollment met the following primary endpoints: a) a clinically meaningful and statistically significant change from baseline in HVPG in patients with liver cirrhosis and severe portal hypertension (HVPG ≥12 mmHg); and b) a statistically significant change from baseline in cCK18 in the total evaluable patient population. Portal hypertension was confirmed by HVPG measurement > 5 mmHg at baseline and measured again after treatment with 25 mg of emricasan orally twice daily for 28 days. Patients were divided according to the HVPG therapeutic threshold of 12 mmHg, which indicates more severe portal hypertension. Reducing the HVPG to below 12 mmHg or reducing HVPG by ≥10% or ≥20% has been strongly associated with clinical benefit in this patient population. The HVPG endpoint was analyzed in: a) patients with baseline HVPG values ≥12 mmHg (N=12); b) patients with baseline HVPG values <12 mmHg (N=10); and c) all evaluable patients (N=22). HVPG measurement was standardized, and tracings were evaluated by a single expert reader not otherwise involved in the trial. HVPG decreased by a mean of 3.7 mmHg from the mean baseline of 20.6 mmHg in the ≥12 mmHg baseline HVPG group ($p < 0.003$), with 8 of 12 patients achieving a ≥10% decrease, 4 of 12 patients achieving a ≥20% decrease, and 2 of 12 patients achieving

reductions below 12 mmHg. The changes from baseline HVPG were not statistically significant in the <12 mmHg baseline HVPG group (+1.9 mmHg mean increase from mean baseline of 8.1 mmHg; p=0.12) or the total evaluable patient population (-1.1 mmHg from mean baseline of 15.2 mmHg; p=0.26). Sensitivity analysis using an HVPG cutoff of 10 mmHg yielded similar results. The cCK18 endpoint, analyzed in the total evaluable patient population, showed a statistically significant reduction ($p < 0.03$) from baseline.

Consistent with results from prior trials, emricasan was safe and well-tolerated in the trial, with no dose-limiting toxicities and no drug-related serious adverse events. One subject discontinued the trial early for non-serious adverse events and one subject had three serious adverse events ten days after the last emricasan dose, assessed as unrelated to treatment. There were no significant changes in blood pressure or heart rate. ALT and AST levels decreased significantly in the entire group and in those with an HVPG ≥12 mmHg. This clinical trial was conducted at nine U.S. sites and enrolled 23 patients, 22 of whom were evaluable, with portal hypertension and compensated liver cirrhosis that was predominantly due to NASH or HCV, including patients with active HCV infection and patients who had an SVR to antiviral therapy.

Phase 2 Clinical Trial of IDN-6556 in Subjects with Nonalcoholic Fatty Liver Disease and Raised Transaminases

In March 2015, we announced top-line results from our Phase 2 double-blind, placebo-controlled clinical trial of emricasan in 38 patients with nonalcoholic fatty liver disease, or NAFLD, including the subset of NAFLD patients with NASH. The trial met its primary endpoint, showing a statistically significant ($p<0.05$) reduction in ALT in patients treated for 28 days with emricasan at 25 mg twice per day dosing compared to patients in the placebo control group. Reductions from baseline in ALT at Day 28 of approximately 39% in the emricasan treatment arm and approximately 14% in the placebo arm were similar to results observed in previous trials. Elevated baseline levels of three key serum biomarkers – cCK18, full-length cytokeratin 18, a biomarker of more generalized cell death, or flCK18, and caspase 3/7 – also showed statistically significant reductions from baseline in emricasan-treated patients at Day 28. A reduction from baseline in cCK18 at Day 28 of approximately 30% in the emricasan treatment arm and an increase from baseline of approximately 4% in the placebo arm were similar to results observed in previous trials. The reduction in serum cCK18 levels demonstrated that emricasan can effectively reduce inflammation and elevated levels of apoptosis in NAFLD/NASH patients. Emricasan was safe and well-tolerated in the NAFLD/NASH trial, with no dose-limiting toxicities and no drug-related serious adverse events. Treatment with emricasan also had no adverse effects on lipid levels or insulin sensitivity, important safety assessments in NAFLD/NASH patients who are at risk for cardiovascular disease.

Phase 2b Pharmacokinetic and Pharmacodynamic Clinical Trial in Acute-on-chronic Liver Failure Patients

In January 2015, we completed a Phase 2b dose ranging clinical trial in acute-on-chronic liver failure, or ACLF, patients. The ACLF clinical trial was designed to assess the PK and PD of emricasan, as well as biomarker and clinical responses, following twice daily, or BID, oral dosing of emricasan or placebo for 28 days. Patients were randomized to receive either placebo, 5 mg, 25 mg or 50 mg emricasan BID. The primary objective in this 28-day dosing trial was to evaluate the PK and PD together with the safety of emricasan to determine whether any dosing adjustments are needed in this critically ill patient population. We measured changes in liver function (creatinine, bilirubin and International Normalized Ratio), changes in biomarkers (ALT, cCK18, Caspase 3/7 and Interleukin 18, or IL-18), time to clinical worsening, or TTCW, which is defined as the first occurrence of liver transplant, progression to next organ failure or death and changes in extra-hepatic organ function. Twenty of 21 patients enrolled in the ACLF clinical trial had alcohol-associated liver disease, consistent with alcoholic liver disease being a major contributor to the ACLF patient population.

ALT levels were not increased in the ACLF patient population. By contrast, levels of mechanism-specific biomarkers of caspase activity and inflammation – cCK18, Caspase 3/7, IL-18 and flCK18 were all elevated at baseline, demonstrating their important role in the ACLF disease process. Dose-related responses to emricasan in elevated biomarkers were apparent with no response noted in the placebo cohort, limited or no response in the 5 mg BID

cohort, an initial rapid but transitory response in the 25 mg BID cohort, and a rapid and sustained response in almost all of the 50 mg BID cohort. Emricasan 25 mg and 50 mg BID oral dosing reduced cCK18, flCK18 and Caspase 3/7 levels within 24 hours post administration (Study Day 2) by at least 30%. More modest ~20% reductions in elevated IL-18 levels were also observed in the 25 mg and 50 mg BID cohorts by Day 7. Only the emricasan 50 mg dose resulted in sustained reductions in cCK18 over the entire dosing period in the majority of patients. The median reduction in the 50 mg BID cohort on Day 1 was 54% compared with a median reduction of 7%, 13% and 44% in the placebo, 5 mg and 25 mg cohorts, respectively. The observed reduction in cCK18 was maintained in the 50 mg BID cohort (median reduction of 56% and 50% on Day 4 and Day 7, respectively) but not maintained in the other cohorts. Emricasan exposure after the first dose was more than twice the exposure in patients with stable severe hepatic impairment. Emricasan was well-tolerated and there were no drug-related serious adverse events or dose-limiting toxicities. Adverse events observed were reflective of the patient populations being studied.

Phase 1 Clinical Trials

We have conducted eight Phase 1 clinical trials in subjects with both single and multiple-dose administration of emricasan. The objective of these trials was to examine the safety, tolerability, PK and, in some trials, the mechanistic PD of emricasan. As shown in Figure 4 below, emricasan was generally well-tolerated in all eight Phase 1 clinical trials.

Figure 4. Emricasan Phase 1 Clinical Trial Summary

Trial Design	Subjects	Dosing/Days	Outcome
Safety and PK Study in Healthy and Liver Impaired Subjects	76 (US)	QD/ 7 days	Well-tolerated; improved liver enzymes (ALT)
Randomized, Open-label, PK Dose Proportionality Study in Healthy Subjects	24 (US)	Single dose	Well-tolerated; PK profiled
Randomized, Placebo-controlled, Drug-drug Interaction, or DDI, Study with Ketoconazole in Healthy Subjects	24 (EU)	Single dose	Well-tolerated; no drug-drug-interaction with ketoconazole
Double-blind, Randomized, Placebo-controlled, PK Multiple (escalating) Dose Study in Healthy Subjects	32 (EU)	BID/ 14 days	Well-tolerated; PK profiled
Randomized, Double-blind, Parallel Group Placebo-controlled, PK Multiple (escalating) Dose Study in Healthy Asian Subjects	20 (EU, Asia)	BID/ 15 days	Well-tolerated; no difference in PK in Asian population
Randomized, Placebo-controlled, DDI Study with Cyclosporine and Measurement of cCK18 Levels in Healthy Subjects	15 (EU)	QD/BID/10 days	Well-tolerated; no effect on cyclosporine; no effect on cCK18 levels
PK and PD Study of IDN-6556 in Subjects with Hepatic Impairment and Matched Healthy Volunteers	36 (US)	Single dose	Well-tolerated; PK profiled; reduction of the PD markers, cCK18, flCK18 and caspase 3/7
PK and PD Study of IDN-6556 in Subjects with Severe Renal Impairment and Matched Healthy Volunteers	15 (US)	Single dose	Well-tolerated; no effect on cCK18 levels

Emricasan History

Emricasan was initially discovered and developed by researchers at Idun, where the company was developing a new class of drugs that modulate caspases involved in the apoptosis and inflammation pathways. Idun, co-founded by Nobel Prize winner H. Robert Horvitz, Ph.D. for his work in the apoptosis field, was uniquely positioned as a leading expert in translating apoptosis research into drug development candidates. Emricasan was Idun's lead program when Pfizer acquired the company for $298 million in 2005.

When we acquired emricasan through the acquisition of Idun from Pfizer in 2010, emricasan was on clinical hold in the United States due to an observation of inflammatory infiltrates in mice that Pfizer saw in a preclinical study and reported to the FDA in 2007. Pfizer performed additional preclinical studies attempting to characterize the nature of the inflammatory infiltrates, but did not carry out a formal carcinogenicity study to evaluate whether or not the infiltrates progressed to cancer. These infiltrates observed in mice were not observed in any other species. In 2008, Pfizer stopped work on the program. After acquiring emricasan in 2010, we conducted a thorough internal review of these studies and commissioned several independent experts to review all of the available data. The analysis provided

by these experts unanimously concluded that these inflammatory infiltrates did not represent pre-cancerous lesions, nor were these infiltrates likely to progress to cancer. Additionally, a comprehensive analysis of available apoptosis literature supported the conclusion that the infiltrates were not likely to be precursors to cancer.

In April 2011, we met with the FDA to discuss plans for reinitiating clinical development of emricasan. We proposed conducting a carcinogenicity study designed to reproduce the previously observed findings of inflammatory infiltrates and determine whether they progress to cancer. We proposed using the Tg.rasH2 transgenic mouse model, which is known to be predisposed toward tumor development. The FDA agreed with the study design and agreed that if the study reproduced the previously observed inflammatory infiltrates, but did not produce cancer, the issue that generated the clinical hold would be resolved.

This study was completed successfully in 2012. The inflammatory infiltrates were reproduced, and there was no evidence of tumor formation. In summary, treatment with emricasan for 26-weeks did not result in an increase in the incidence of tumors in Tg.rasH2 mice. The results were submitted to the FDA in preparation for a meeting in October 2012. The FDA reviewed the data and agreed with the study conclusion. We subsequently filed a new investigational new drug application, or IND, for emricasan for HCV-

POLT, which was formally cleared in January 2013. In addition, the FDA has accepted this Tg.rasH2 carcinogenicity study as one of two carcinogenicity studies required for registration. We are currently conducting a two-year rat carcinogenicity study as the second carcinogenicity study.

Our Clinical Development Plans

In collaboration with Novartis, we plan to focus on advancing toward registration of emricasan for patients with NASH fibrosis or NASH cirrhosis. We are conducting three trials, the ENCORE trials, designed to provide further information on doses leading to clinically relevant efficacy, including improvement in severe portal hypertension and hepatic function in patients with NASH cirrhosis and improvement in biopsy-proven fibrosis and inflammation in patients with NASH fibrosis. Together, we may pursue the development and commercialization of combination products containing emricasan along with compounds developed or acquired by Novartis, particularly for NASH indications. We are also conducting the POLT-HCV-SVR clinical trial of emricasan in liver transplant recipients cleared of their HCV but with residual fibrosis or cirrhosis. These four clinical trials are also designed to provide safety data to support the registration of emricasan for chronic administration in patients with fibrosis and cirrhosis.

Under the Collaboration Agreement, we granted Novartis an exclusive, worldwide license to our intellectual property rights relating to emricasan to collaborate with us for the global development and commercialization of products containing emricasan either as a single active ingredient or in combination with other Novartis compounds for liver cirrhosis or liver fibrosis. Pursuant to the Collaboration Agreement, we are responsible for completing the ENCORE trials and the POLT-HCV-SVR trial. We share the costs of these four Phase 2b trials equally with Novartis, as well as the non-treatment observational study until the completion of the four Phase 2b trials. Novartis is also responsible for 100% of certain expenses for required registration-supportive nonclinical activities. Novartis is responsible for the development of emricasan beyond these four Phase 2b trials, including the Phase 3 development of emricasan single agent products and all development for emricasan combination products, and Novartis has agreed to use commercially reasonable efforts to develop and commercialize emricasan products. A joint steering committee comprised of representatives from our company and Novartis oversees the collaboration, development and commercialization of emricasan products.

Emricasan in NASH Fibrosis

Medical Need and Market Opportunity

NASH is a progressive form of NAFLD where fat builds up in the liver and patients suffer from inflammation and damage ultimately leading to fibrosis and cirrhosis. Steatosis is caused by the accumulation of triglycerides within lipid droplets in hepatocytes and steatosis associated with inflammation, cell death, and fibrosis is referred to as NASH, which can progress to cirrhosis. According to the NIH, NASH affects 2-5% of people in the United States. NASH is one of the leading causes of cirrhosis in adults in the United States, and up to 25% of adults with NASH may have cirrhosis. The condition is more common in adults who are obese, diabetic, or have high cholesterol or high triglycerides. The current diagnosis rate for NASH is low because of the asymptomatic nature of NASH and low awareness of the disease. There are currently no drugs approved to treat NASH fibrosis.

Development Plans

Emricasan has demonstrated activity in preclinical models of both NASH and NAFLD. In preclinical models of NASH, emricasan inhibited apoptosis, fibrosis and inflammation associated with experimental NASH. In a preclinical model of NAFLD, emricasan reduced inflammation of adipose tissue, resolved hepatic steatosis and improved metabolic parameters by reducing fasting glucose and insulin levels. We believe that these preclinical data provide support for evaluating emricasan in patients with NASH. Our Phase 2 clinical trial in NAFLD/NASH demonstrated that emricasan can effectively reduce elevated levels of biomarkers related to apoptosis and inflammation.

In collaboration with Novartis, we plan to develop emricasan toward registration for patients with NASH fibrosis in parallel with our liver cirrhosis development plans. In January 2016, we initiated the ENCORE-NF trial, a Phase 2b clinical trial evaluating emricasan's potential long-term benefits for patients with liver fibrosis resulting from NASH. This randomized, double blind, placebo-controlled clinical trial will evaluate the effect of emricasan in reducing fibrosis and steatohepatitis in approximately 330 patients with NASH fibrosis but not cirrhosis. The primary endpoint will be a biopsy-based change in fibrosis by at least one stage using the NASH Clinical Research Network Histologic Scoring System, without worsening of steatohepatitis. Treatment will be twice daily for 18 months and patients will receive either emricasan at 50 mg, emricasan at 5 mg, or placebo. Top-line results from the ENCORE-NF clinical trial are expected in the first half of 2019.

In addition to emricasan as a single active ingredient for a product candidate for the treatment of NASH fibrosis, we believe that emricasan has the potential to be developed for use whereby emricasan is one of two or more active ingredients. Under the Collaboration Agreement with Novartis, we expect the development of emricasan with one or more Novartis compounds to be pursued as a combination product to treat NASH fibrosis or other liver diseases.

Emricasan in NASH Cirrhosis

Medical Need and Market Opportunity

The patients with chronic liver disease that we are studying suffer from compensated or decompensated liver cirrhosis, as well as potentially portal hypertension. Continual disease progression may eventually lead such patients to require liver transplantation, in which the diseased liver is replaced by a donor liver or part thereof. The cause of the chronic decompensation or liver failure may vary, and includes infections, such as subacute bacterial peritonitis, HCV or HBV, metabolic causes, such as NASH, autoimmune diseases and alcohol. Objectives for the management of patients with liver cirrhosis and portal hypertension include specific treatment of any identifiable causes of chronic liver function and prevention of the development or progression of signs of decompensation, including portal pressure, ascites, hepatic encephalopathy and esophageal varices, with or without hemorrhage, in order for the patient to be eligible for transplant. More than 38,000 patients died due to chronic liver disease and cirrhosis in the United States in 2014.

NASH is one of the leading causes of cirrhosis in adults in the United States, and up to 25% of adults with NASH may have cirrhosis. Furthermore, NASH is expected to be the leading cause of liver transplant in the next five to ten years. There are currently no approved drugs for the treatment of NASH cirrhosis.

Development Plans

Given its mechanism of action and recent clinical trial results, we believe emricasan has the potential to improve patients' ability to survive longer with cirrhosis while waiting for a liver transplant and potentially to improve their liver disease status such that they may no longer require a liver transplant. In collaboration with Novartis, we plan to focus on advancing toward registration of emricasan for patients with NASH cirrhosis in parallel with our NASH fibrosis development plans. In February 2016, we announced that the FDA granted Fast Track designation to the emricasan development program for the treatment of liver cirrhosis caused by NASH. Based on the recent clinical trial results in patients with cirrhosis and interactions with the FDA, we initiated the Phase 2b ENCORE-PH trial in November 2016 and the Phase 2b ENCORE-LF trial in May 2017.

The ENCORE-PH trial is a randomized, double-blind, placebo-controlled Phase 2b clinical trial to evaluate the effect of emricasan in reducing HVPG in approximately 240 compensated or early decompensated NASH cirrhosis patients with severe portal hypertension, established by baseline HVPG values of 12 mmHg or higher. Patients will be randomized 1:1:1:1 to receive 5 mg of emricasan, 25 mg of emricasan, 50 mg of emricasan, or placebo twice daily for 24 weeks. The primary endpoint is the mean change in HVPG from week 0 to week 24 for each dosing group compared with placebo. Key secondary endpoints include safety and tolerability, dose response, and percentage of patients achieving at least a 20% reduction in HVPG. Top-line results are expected in the second half of 2018. In addition, we amended the protocol for this trial to add a 24-week open-label extension period for patients after they complete the blinded 24-week stage of the trial. A basis for this trial was the clinical trial results from the previously completed exploratory, open-label Phase 2 clinical trial of emricasan in patients with liver cirrhosis due to different etiologies and portal hypertension confirmed by HVPG procedure upon enrollment, which demonstrated a clinically meaningful and statistically significant change from baseline in HVPG in patients with liver cirrhosis and severe portal hypertension (HVPG ≥12 mmHg).

The ENCORE-LF trial is a randomized, double-blind, placebo-controlled Phase 2b clinical trial to evaluate emricasan in approximately 210 patients with decompensated NASH cirrhosis. Patients will be randomized 1:1:1 to receive 5 mg

of emricasan, 25 mg of emricasan, or placebo twice daily for at least 48 weeks. The primary endpoint is event-free survival for each treatment group compared with the placebo group. For the purposes of the trial, events are defined as all-cause mortality, new decompensation events, or a progression of ≥4 points in MELD score. Key secondary endpoints include safety and tolerability, MELD and CPT scores, liver transplantation rates, liver metabolic function using the BreathID® Methacetin Breath Test, and health-related quality of life. Top-line results are expected in the second half of 2019.

Emricasan in POLT-HCV-SVR

Medical Need and Market Opportunity

Patients with HCV who receive liver transplants are at risk for recurrent HCV infections in the transplanted organs. Many of these patients will experience accelerated development of fibrosis and progression to cirrhosis of the transplanted liver due to the recurrence of HCV. Even after successful treatment with drugs designed to clear the HCV infection, fibrotic changes in the liver may persist for many years. The HCV landscape has dramatically changed in recent years and will continue to evolve in the future with the introduction of interferon-free regimens with greater efficacy and tolerability over the current antiviral therapies.

Development Plans

We were granted Orphan Drug Designation in late 2013 by the FDA for the treatment of POLT patients with reestablished fibrosis to delay the progression to cirrhosis and end-stage liver disease. Our clinical development strategy in the POLT patient population is to conduct a Phase 2b clinical trial tracking biomarkers and histology in POLT-HCV-SVR patients. Only approximately 30% of non-transplant HCV patients with fibrosis and SVR show histological signs of fibrosis improvement two years after virus clearance. In May 2014, we initiated the double-blind, placebo-controlled Phase 2b clinical trial in approximately 60 POLT-HCV-SVR patients with residual fibrosis or cirrhosis, classified as Ishak Fibrosis Score 2-6, who will receive 25 mg of emricasan or placebo orally twice daily for two years. The primary endpoint in this exploratory proof-of-concept trial is the change in the Ishak Fibrosis Score compared with placebo. The trial will also evaluate histological markers of inflammation, key serum biomarkers, and the safety and tolerability of emricasan. Top-line results are expected in the second quarter of 2018. If positive, we believe the results from this trial may serve as a basis for future trials in pre-transplant HCV-SVR patients, who are cured of their HCV but still have residual fibrosis or cirrhosis, as well as potentially in pre-transplant NASH cirrhosis patients and post-transplant NASH recurrent fibrosis or cirrhosis patients.

Future Indications for Emricasan

Due to its mechanism of action and the presence of apoptosis and inflammation in many liver diseases, we believe there may be several patient populations that could potentially benefit from emricasan, including those that have previously failed HCV treatment and those with early-stage NAFLD, viral hepatitis and other chronic liver diseases. If emricasan demonstrates the ability to halt the progression of fibrosis or cirrhosis in the patient populations we are studying, we believe that this could serve as a basis to evaluate emricasan for additional indications in patients at earlier stages of liver fibrosis resulting from diseases that we are not currently studying, such as pre-transplant HCV, HBV, chronic excessive alcohol use or autoimmune diseases.

Commercialization Strategy

Under the Collaboration Agreement, Novartis will be responsible for the commercialization of emricasan, and we are eligible to receive up to $650.0 million in milestone payments over the term of the Collaboration Agreement, contingent on the achievement of certain development, regulatory and commercial milestones, as well as royalties. After the initiation of the first Phase 3 clinical trial for an emricasan product candidate, we have the right to elect to enter into a co-commercialization agreement with Novartis under which we would receive up to 30% of the commercial profits less the same percentage of the commercial losses, subject to certain reductions in milestone and royalty payments.

Manufacturing

Pfizer completed a significant portion of the manufacturing process optimization needed to provide an efficient synthesis of active pharmaceutical ingredient, or API, and scale-up methodology for registration trials for emricasan. API was successfully produced under current Good Manufacturing Practices, or cGMP, conditions, and a strategy to scale up the API for commercialization is in development. We believe the quantities of API we acquired from Pfizer are sufficient to support our ongoing clinical trials. Although we believe the current quantities of API are sufficient to complete our ongoing clinical trials, additional API will potentially need to be manufactured for future clinical trials. We have identified a new third-party manufacturer of emricasan API for potential manufacturing needs in the future. Both the emricasan API and the drug product emricasan have demonstrated sufficient stability characteristics in our studies conducted to date. Furthermore, Novartis is responsible under the Collaboration Agreement for the manufacturing related to emricasan beyond the three Phase 2b ENCORE trials and the Phase 2b POLT-HCV-SVR trial.

Future Product Candidates

We are currently focused on the development of emricasan, but we plan to pursue additional product candidates in the future. We believe that a diversified portfolio will mitigate risks inherent in drug development and increase the likelihood of our success. We plan to expand our development pipeline by developing internal preclinical product candidates or by in-licensing or acquiring preclinical or clinical-stage product candidates. We may develop such product candidates independently or in partnership with third parties.

Competition

The biopharmaceutical industry is characterized by intense competition and rapid innovation. Although we believe that we hold a leading position in our understanding of caspase inhibition related to liver disease, our competitors may be able to develop other compounds or drugs that are able to achieve similar or better results. Our potential competitors include major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies and universities and other

research institutions. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. We believe the key competitive factors that will affect the development and commercial success of our product candidates are efficacy, safety and tolerability profile, reliability, convenience of dosing, price and reimbursement.

Although there are several product candidates in clinical development, there are currently no therapeutic products approved for the treatment of NASH cirrhosis, NASH fibrosis or POLT-HCV-SVR. There are a number of marketed therapeutics used in each of these diseases to try to remove the underlying cause of the disease, address symptoms or complications of the disease or prevent further liver injury. For example, if the liver damage is a result of HBV or HCV, marketed antiviral medications may be used to treat the virus that led to liver damage. However, we expect that there will continue to be a significant unmet need in the HCV-POLT patient population, including patients with fibrosis after antiviral treatments to clear their HCV infection. If the liver damage is a result of alcoholic hepatitis, marketed alcohol addiction drugs may be used. If the liver damage is a result of obesity, diet and exercise may be prescribed along with marketed therapeutics. If the liver damage is a result of NASH, which is expected to become the leading cause of liver transplants in the next five to ten years, currently marketed drugs are generally used, although none of these are approved for NASH. In addition to the marketed drugs for those indications, there are drugs in development for each of these indications. Although these marketed therapies and those in development may be efficacious, all of them take time to show an effect, and as long as the underlying conditions persist there will continue to be damage to the liver. In NASH, for example, drugs in development have differing mechanisms of action, and it is currently unknown whether any single drug will eliminate liver inflammation and halt liver disease progression into advanced fibrosis. For each of these indications, emricasan is the only product candidate we are aware of that is being developed specifically to reduce the level of apoptosis in the liver. As a result, if successfully developed and approved, emricasan may be used with these other therapies and may be included as an active ingredient in combination products developed and commercialized by Novartis under the Collaboration Agreement.

Material Contracts

Pfizer Inc.

In July 2010, we entered into a Stock Purchase Agreement with Pfizer pursuant to which we acquired all of the outstanding capital stock of Idun, a wholly-owned subsidiary of Pfizer at the time, in consideration for an upfront payment of $250,000 and a promissory note in the principal amount of $1.0 million. In July 2013, the promissory note was amended to become convertible into shares of our common stock following the completion of our initial public offering, at the option of the holder, at a price per share equal to the fair market value of our common stock on the date of conversion. We had the right to prepay the promissory note at any time, and in January 2017, we voluntarily prepaid the entire balance of the principal and accrued interest of the promissory note. The promissory note bore interest at a per annum interest rate equal to 7%, compounded quarterly, and interest was payable on a quarterly basis during the term of the promissory note. The promissory note was scheduled to mature in July 2020, subject to acceleration upon specified events of default, including a change of control transaction, our failure to timely pay any principal or interest when due, our failure to timely provide certain financial information to Pfizer, the creation of any lien on our property other than permitted liens, any disposition of our business or property other than permitted transfers, our payment of dividends or other distributions on our equity securities, our incurrence of any indebtedness other than permitted indebtedness, our involvement in liquidation, dissolution, bankruptcy or similar proceedings, our failure to notify Pfizer of certain material adverse events, our failure to repay any indebtedness that causes an aggregate of $2.0 million or more in such indebtedness to accelerate in maturity and the rendering of certain judgments against us. Pursuant to the Stock Purchase Agreement, we will be required to make additional payments to Pfizer totaling $18.0 million upon the achievement of specified regulatory milestones relating to emricasan.

Idun Sublicense Agreement

In January 2013, we conducted a spin-off of our subsidiary Idun, which we had acquired from Pfizer in the transaction described above, to our stockholders at that time. Immediately prior to the spin-off, all rights relating to emricasan were distributed to us pursuant to a distribution agreement.

In March 2013, we entered into a sublicense agreement with Idun in which we were granted the right to use the patent rights and know-how related to the screening and identification of emricasan. These rights were previously granted to Idun under license agreements with Thomas Jefferson University, or TJU. Under the sublicense, we are required to pay directly to TJU a royalty of less than 1% on net sales of emricasan. We also have the right to grant further sublicenses to third parties and are required to pay TJU a portion of any such sublicense revenue we receive. The sublicense agreement will expire upon the date which there are no longer any valid claims in any patents or patent applications sublicensed to us, unless earlier terminated. Idun may terminate the agreement if we substantially fail to perform or otherwise materially breach any of the material terms, covenants or provisions of the sublicense agreement, and we do not cure any such breach within 60 days of receipt of written notice from Idun specifying the breach. Our obligations under the agreement include, among others, using reasonable efforts to commercialize emricasan, timely paying the royalties set forth in the sublicense agreement and timely paying a portion of any sublicense revenue we receive if we grant further

sublicenses under the sublicense agreement. We are currently in full compliance with these obligations. The agreement may also be terminated if the underlying license agreements between Idun and TJU are terminated. The underlying license agreements may be terminated by either Idun or TJU if the other party substantially fails to perform or otherwise materially breaches any of the material terms, covenants or provisions of the underlying license agreements and the breaching party does not cure any such breach within 90 days of receipt of written notice from the non-breaching party specifying the breach. Idun may also elect upon 30 days' prior written notice to terminate its rights and obligations under one of the underlying license agreements with respect to any patent applications or patents licensed to it, or to terminate such underlying license agreement in its entirety. In the event that either of the underlying license agreements are terminated, Idun is obligated to assign and transfer to TJU all rights under sublicenses granted by Idun. We do not depend on the sublicense agreement for the further development or commercialization of emricasan, and we would not experience a material adverse effect if the sublicense agreement were terminated.

Novartis Pharma AG

In December 2016, we entered into the Collaboration Agreement with Novartis, pursuant to which we granted Novartis an exclusive option to collaborate with us to develop products containing emricasan. In May 2017, Novartis exercised its option under the Collaboration Agreement. Pursuant to such exercise, we granted Novartis an exclusive, worldwide license to our intellectual property rights relating to emricasan to collaborate with us for the global development and commercialization of products containing emricasan either as a single active ingredient or in combination with other Novartis compounds for liver cirrhosis or liver fibrosis, for the treatment, diagnosis and prevention of disease in all indications in humans. The license became effective upon our receipt of a $7.0 million option exercise payment in July 2017.

Under the Collaboration Agreement, we are responsible for completing the three ENCORE trials and the POLT-HCV-SVR trial. We share the costs of these four trials equally with Novartis. In addition, until the completion of the four Phase 2b trials, we will equally share the costs of the non-treatment observational study that will follow patients from the four Phase 2b trials. After the completion of the four Phase 2b trials, Novartis will assume 100% of the observational study costs. Novartis is also responsible for 100% of certain expenses for required registration-supportive nonclinical activities. Novartis is responsible for Phase 3 development of products containing only emricasan as an active ingredient, or Emricasan Only Products, and all development for products containing emricasan and one or more other Novartis active ingredients, or Combination Products. Emricasan Only Products and Combination Products are collectively referred to as Emricasan Products. A joint steering committee comprised of senior personnel from our company and Novartis oversees the collaboration, development and commercialization of the Emricasan Products.

Pursuant to the Collaboration Agreement, we received an upfront payment of $50.0 million and the option exercise payment of $7.0 million from Novartis. We are eligible to receive up to an aggregate of $650.0 million in milestone payments over the term of the Collaboration Agreement, contingent on the achievement of certain development, regulatory and commercial milestones. Novartis will be required to pay us tiered royalties ranging from the high-teens to the high-twenties as a percentage of net sales of Emricasan Only Products, and tiered royalties ranging from the high-single digits to the mid-teens as a percentage of net sales of Combination Products, subject to reduction in certain cases. We may elect, after the initiation of the first Phase 3 clinical trial for an Emricasan Product, to enter into a co-commercialization agreement with Novartis under which we would receive up to 30% of the commercial profits less the same percentage of the commercial losses for Emricasan Products in the United States, subject to certain reductions in milestone and royalty payments.

For the period from the execution date of Collaboration Agreement until the earlier of five years after the first commercial sale of an Emricasan Product in the United States or major European market or ten years from the execution date of the Collaboration Agreement, we have agreed not to develop in any pivotal registration clinical trials or commercialize any pan-caspase inhibitors in liver disease. For the period from the execution date of the

Collaboration Agreement until five years after the first commercial sale of an Emricasan Only Product, Novartis has agreed not to develop in any pivotal registration clinical trials or commercialize any pan-caspase inhibitors for the diagnosis, prevention or treatment of disease in all indications in humans. Novartis will have a right of first negotiation prior to any offer by us to any third party for future pan-caspase inhibitors that we may develop or acquire for the treatment of liver diseases or for certain retained pan-caspase inhibitors, provided that any license or collaboration that we enter into or propose to enter into must be on terms and conditions in the aggregate no more favorable to such third party than those last offered to Novartis.

The Collaboration Agreement will remain in effect on a product-by-product and country-by-country basis until Novartis' royalty obligations expire. Both parties have certain termination rights in the circumstances of an uncured material breach or insolvency by the other party. Novartis has certain termination rights in the event of a mandated clinical trial hold for any Emricasan Only Product. Novartis has the right to terminate the Collaboration Agreement without cause upon 180 days prior written notice to us. In such event, the license granted to Novartis will be terminated and revert to us, and Novartis will transfer any ongoing trials for the Emricasan Only Products to us and will cease development of the Emricasan Products. In the event Novartis terminates the Collaboration Agreement due to our uncured material breach or insolvency, the license granted to Novartis pursuant to the Collaboration Agreement will become irrevocable and Novartis will be required to continue to make all milestone and royalty payments otherwise due to us

under the Collaboration Agreement, provided that if we materially breach the Collaboration Agreement such that the rights licensed to Novartis or the commercial prospects of the Emricasan Products are seriously impaired, the milestone and royalty payments will be reduced by 50%. In the event of a change of control of Conatus, Novartis has the right to disband the joint steering committee and all decision-making power otherwise assigned to the joint steering committee will be assigned solely to Novartis.

Concurrent with the entry into the Collaboration Agreement, we entered into an Investment Agreement with Novartis whereby we agreed to sell and Novartis agreed to purchase, convertible promissory notes, in one or two closings, for an aggregate principal amount of up to $15.0 million. In February 2017, we issued to Novartis a convertible promissory note, or the Novartis Note, in the principal amount of $15.0 million. The maturity date of the Novartis Note is December 31, 2019. The Novartis Note bears interest on the unpaid principal balance at a rate of 6% per annum. We may prepay or convert the Novartis Note into shares of our common stock, at our option, until December 31, 2019. Novartis may convert the Novartis Note into shares of our common stock upon a change of control of Conatus or termination of the Collaboration Agreement in its entirety. If converted, the principal and accrued interest under the Novartis Note will convert into shares of our common stock at a conversion price equal to 120% of the 20-day trailing average closing price per share of the common stock immediately prior to the conversion date. Upon the occurrence of certain events of default, the Novartis Note requires us to repay the principal balance of the Novartis Note and any unpaid accrued interest.

Intellectual Property

The proprietary nature of, and protection for, our product candidates and discovery programs and know-how are important to our business. We have sought patent protection in the United States and internationally for emricasan, crystalline forms of emricasan and certain methods of treatment with emricasan. In addition, we have patent protection covering certain other preclinical stage compounds. Our policy is to pursue, maintain and defend patent rights whether developed internally or licensed from third parties and to protect the technology, inventions and improvements that are commercially important to the development of our business.

Our commercial success will depend in part on obtaining and maintaining patent protection and trade secret protection of our current and future product candidates and the methods used to develop and manufacture them, as well as successfully defending these patents against third-party challenges. Our ability to stop third parties from making, using, selling, offering to sell or importing our products depends on the extent to which we have rights under valid and enforceable patents that cover these activities. We cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our product candidates, discovery programs and processes. For this and more comprehensive risks related to our intellectual property, please see “Risk Factors—Risks Related to Our Intellectual Property.”

Our patent portfolio for emricasan contains patents directed to the composition of matter, crystalline forms and methods of use. As of December 31, 2017, we have received three United States patents and corresponding foreign patents and patent applications directed to the composition of matter. Foreign patents have been granted in Australia, Austria, Belgium, Canada, China, Denmark, Europe, Finland, France, Germany, Great Britain, Greece, Hong Kong, India, Ireland, Israel, Italy, Japan, Luxembourg, Mexico, Netherlands, Portugal, Singapore, South Africa, South Korea, Spain, Sweden and Switzerland. We expect that the composition of matter patent, if the appropriate maintenance, renewal, annuity or other governmental fees are paid, will expire in 2018 (United States) and 2019 (international). It is possible that the term of a composition of matter patent in the United States could be extended up to five additional years under the provisions of the Hatch-Waxman Act. Patent term extension may be available in certain foreign countries upon regulatory approval.

Our patent portfolio includes patents directed to crystalline forms and methods of use of emricasan. As of December 31, 2017, we have received one United States patent and corresponding foreign patents and patent application directed

to crystalline forms of emricasan. Foreign patents have been granted in Australia, Austria, Belgium, Canada, China, Czech Republic, Denmark, Europe, Finland, France, Germany, Great Britain, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Luxembourg, Mexico, Netherlands, Norway, Poland, Portugal, Romania, Singapore, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan and Turkey. Additional applications are pending in China, Hong Kong and Thailand. We expect that the crystalline forms and methods of use patent, if the appropriate maintenance, renewal, annuity or other governmental fees are paid, will expire in 2028 (United States) and 2027 (international). It is possible that the term of a crystalline forms patent in the United States could be extended up to five additional years under the provisions of the Hatch-Waxman Act. Patent term extension may be available in certain foreign countries upon regulatory approval.

Our patent portfolio includes patents and patent applications directed to certain methods of use of emricasan. As of December 31, 2017, we have received five United States patents and corresponding foreign patents and patent applications directed to methods of use of emricasan. Foreign patents have been granted in Europe, France, Germany, Great Britain, Ireland, Italy, Japan and Spain. We expect that the methods of use patents, if the appropriate maintenance, renewal, annuity or other governmental fees are paid, will expire in 2018. We also have pending international and provisional patent applications for certain methods of use of emricasan in patients with liver disease.

Government Regulation

Government authorities in the United States (at the federal, state and local level) and in other countries extensively regulate, among other things, the research, development, testing, manufacturing, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of drug products such as those we are developing. Emricasan and any other product candidates that we develop must be approved by the FDA before they may be legally marketed in the United States and by the appropriate foreign regulatory agency before they may be legally marketed in foreign countries.

United States Drug Development Process

In the United States, the FDA regulates drugs under the Federal Food, Drug and Cosmetic Act, or FDCA, and implementing regulations. Drugs are also subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval, may subject an applicant to administrative or judicial sanctions. FDA sanctions could include, among other actions, refusal to approve pending applications, withdrawal of an approval, a clinical hold, warning letters, product recalls or withdrawals from the market, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us. The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- Completion of extensive preclinical laboratory tests, preclinical animal studies and formulation studies in accordance with applicable regulations, including the FDA's Good Laboratory Practice, or GLP, regulations;
- Submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- Performance of adequate and well-controlled human clinical trials in accordance with applicable regulations, including the FDA's current good clinical practice regulations, or GCPs, to establish the safety and efficacy of the proposed drug for its proposed indication;
- Submission to the FDA of a new drug application, or NDA, for a new drug product;
- A determination by the FDA within 60 days of its receipt of an NDA to accept the NDA for filing and review;
- Satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the drug is produced to assess compliance with the FDA's cGMP, which are regulations to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;
- Potential FDA audit of the preclinical and/or clinical trial sites that generated the data in support of the NDA; and
- FDA review and approval of the NDA.

Before testing any compounds with potential therapeutic value in humans, a product candidate enters the preclinical testing stage. Preclinical tests include laboratory evaluations of drug chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs. The sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of an IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human studies. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions regarding the proposed clinical trials and places the IND on clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA may also impose clinical holds on a product candidate at any time before or during clinical trials due to safety concerns or non-compliance. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun,

issues will not arise that suspend or terminate such trials.

Clinical trials involve the administration of the product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the clinical trial sponsor's control, in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Further, each clinical trial must be

reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers issues such as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries.

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

- Phase 1: The drug is initially introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion, the side effects associated with increasing doses, and if possible, to gain early evidence of effectiveness. In the case of some drugs for severe or life-threatening diseases, especially when the drug may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.
- Phase 2: The drug is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the drug for specific targeted diseases or conditions and to determine dosage tolerance, optimal dosage and dosing schedule. Phase 2 clinical trials can be further divided into Phase 2a and Phase 2b clinical trials. Phase 2a clinical trials are typically smaller and shorter in duration and generally consist of patient exposure-response trials, which focus on proving the hypothesized mechanism of action. Phase 2b clinical trials are typically higher enrolling and longer in duration and generally consist of patient dose-ranging trials, which focus on finding the optimum dose at which the drug shows clinical benefit with minimal side effects.
- Phase 3: Clinical trials are undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population at geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the drug and provide an adequate basis for drug approval. Generally, two adequate and well-controlled Phase 3 clinical trials are required by the FDA for approval of an NDA. Phase 3 clinical trials usually involve several hundred to several thousand participants.
- Phase 4 or post-approval studies: Clinical trials may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, the FDA may mandate the performance of Phase 4 studies.

The FDCA permits the FDA and an IND sponsor to agree in writing on the design and size of clinical trials intended to form the primary basis of a claim of effectiveness in an NDA. This process is known as a Special Protocol Assessment, or SPA. An SPA agreement may not be changed by the sponsor or the FDA after the clinical trial begins except with the written agreement of the sponsor and the FDA, or if the FDA determines that a substantial scientific issue essential to determining the safety or effectiveness of the drug was identified after the testing began. For certain types of protocols, including carcinogenicity protocols, stability protocols and Phase 3 protocols for clinical trials that will form the primary basis of an efficacy claim, the FDA has agreed under its performance goals associated with the Prescription Drug User Fee Act, or PDUFA, to provide a written response on most protocols within 45 days of receipt. However, the FDA does not always meet its PDUFA goals, and additional FDA questions and resolution of issues leading up to an SPA agreement may result in the overall SPA process being much longer, if an agreement is reached at all.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA, and written IND safety reports must be submitted to the FDA and the investigators for serious and unexpected adverse events or any finding from tests in laboratory animals that suggests a significant risk for human subjects. Phase 1, Phase 2 and Phase 3 clinical trials may fail to be completed successfully within any specified period, if at all. The FDA, the IRB or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known

as a data safety monitoring board or data monitoring committee. This group provides authorization for whether or not a trial may move forward at designated checkpoints based on access to certain data from the clinical trial. A trial may also be suspended or terminated based on evolving business objectives and/or competitive climate.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the drug in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

FDA Review and Approval Processes

The results of drug development, preclinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the chemistry of a drug, proposed labeling and other relevant information, are submitted to the FDA as part of an NDA requesting approval to market the drug. The application includes both negative and ambiguous results of preclinical and clinical trials as well as positive findings. Data may come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a drug or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational product candidate to the satisfaction of the FDA. The submission of an NDA is subject to the payment of substantial user fees; a waiver of such fees may be obtained under certain limited circumstances.

In addition, under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan designation has been granted. However, if only one indication for a drug has orphan designation, a pediatric assessment may still be required for any applications to market that same drug for the non-orphan indication(s).

The FDA reviews all NDAs submitted before it accepts them for filing and may request additional information rather than accepting an NDA for filing. The FDA must make a decision on accepting an NDA for filing within 60 days of receipt. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has ten months from the 60-day filing date in which to complete its initial review of a standard NDA and respond to the applicant and six months for a priority NDA, if the drug is a new molecular entity. The FDA does not always meet its PDUFA goal dates for standard and priority NDAs, and the review process is often significantly extended by FDA requests for additional information or clarification.

After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the drug is safe and effective for its intended use and whether the drug is being manufactured in accordance with cGMP to assure and preserve the drug's identity, strength, quality and purity. The FDA may refer applications for drug or biological products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA will inspect the facilities at which the drug is manufactured. The FDA will not approve the drug unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the drug within required specifications. Additionally, before approving an NDA, the FDA may inspect one or more clinical sites to assure compliance with GCP requirements. After the FDA evaluates the application, manufacturing process and manufacturing facilities, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response Letter usually describes all of the specific deficiencies in the NDA identified by the FDA. The Complete Response Letter may require additional clinical data and/or an additional pivotal Phase 3 clinical trial(s) and/or other significant and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. If a Complete Response Letter is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter, or withdraw the application. Even if such data and information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive, and the FDA may interpret data differently than we interpret the same data.

If a drug receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the drug. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling or may condition the approval of the NDA on other changes to the proposed labeling, development of adequate controls and specifications or a commitment to conduct one or more post-market studies or clinical trials. For example, the FDA may require Phase 4 testing, which involves clinical trials designed to further assess a drug's safety and effectiveness, and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. The FDA may also determine that a risk evaluation and mitigation strategy, or REMS, is necessary to assure the safe use of the drug. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS; the FDA will not approve the NDA without an approved REMS, if required. A REMS could include medication guides, physician communication plans or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Following approval of an NDA with a REMS, the sponsor is responsible for marketing the drug in compliance with the REMS and must submit periodic REMS assessments to the FDA.

Orphan Drug Designation

In the United States, under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition. Such diseases and conditions are those that affect fewer than 200,000 individuals in the United States, or if they affect more than 200,000 individuals in the United States, there is no reasonable expectation that the cost of developing and making a drug available in the United States for these types of diseases or conditions will be recovered from sales of the drug. Orphan Drug Designation must be requested before submitting an NDA. If the FDA grants Orphan Drug Designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by that agency. Orphan Drug Designation does not convey any advantage in or shorten the duration of the regulatory review and approval process, but it can lead to financial incentives, such as opportunities for grant funding toward clinical trial costs, tax advantages and user-fee waivers.

If a drug that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the drug is entitled to orphan drug marketing exclusivity for a period of seven years. Orphan drug marketing exclusivity generally prevents the FDA from approving another application, including a full NDA, to market the same drug or biological product for the same indication for seven years, except in limited circumstances, including if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. For purposes of small molecule drugs, the FDA defines “same drug” as a drug that contains the same active chemical entity and is intended for the same use as the drug in question. A designated orphan drug may not receive orphan drug marketing exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. Orphan drug marketing exclusivity rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition.

We submitted applications for orphan drug designation for emricasan for the treatment of fibrosis in HCV-POLT patients in the United States and the EU. In late 2013, we received orphan drug designation from the FDA for the treatment of POLT patients with reestablished fibrosis in their liver to delay the progression to cirrhosis and end-stage liver disease. In the EU, we withdrew the application based on feedback from the applicable regulatory body that emricasan may have efficacy in fibrosis outside of the HCV-POLT patient population. In June 2017, the FDA granted Orphan Drug Designation to our preclinical product candidate IDN-7314 for the treatment of PSC, a disease affecting bile ducts in the liver, which can lead to cirrhosis and liver failure. In October 2017, IDN-7314 received orphan designation in the EU for the treatment of PSC.

Expedited Development and Review Programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs that meet certain criteria. Specifically, new drugs are eligible for Fast Track designation if they are intended, alone or in combination with one or more drugs, to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Fast Track designation applies to the combination of the product candidate and the specific indication for which it is being studied. If a product candidate receives Fast Track designation, the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable and the sponsor pays any required user fees upon submission of the first section of the NDA.

Any drug submitted to the FDA for approval, including a drug with a Fast Track designation, may also be eligible for other types of FDA programs intended to expedite development and review, such as Priority Review and Accelerated Approval. A drug is eligible for Priority Review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug designated for Priority Review in an effort to facilitate the review. Additionally, a drug

may be eligible for Accelerated Approval. Drugs studied for their safety and effectiveness in treating serious or life-threatening diseases or conditions may receive Accelerated Approval upon a determination that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving Accelerated Approval perform adequate and well-controlled post-marketing clinical trials. In addition, the FDA currently requires, as a condition for Accelerated Approval, pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the drug.

The FDA may also accelerate the approval of a designated Breakthrough Therapy, which is a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant

endpoints, such as substantial treatment effects observed early in clinical development. The sponsor of a Breakthrough Therapy may request the FDA to designate the drug as a Breakthrough Therapy at the time of, or any time after, the submission of an IND for the drug. If the FDA designates a drug as a Breakthrough Therapy, it must take actions appropriate to expedite the development and review of the application, which may include holding meetings with the sponsor and the review team throughout the development of the drug; providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable; involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review; assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor; and taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment.

Fast Track designation, Priority Review, Accelerated Approval and Breakthrough Therapy designation do not change the standards for approval but may expedite the development or approval process. We plan to explore expedited development and review opportunities for emricasan as appropriate for our targeted indications. In February 2016, we announced that the FDA granted Fast Track designation to the emricasan development program for the treatment of liver cirrhosis caused by NASH.

Post-Approval Requirements

Any drugs for which we receive FDA approvals are subject to continuing regulation by the FDA, including, among other things, record-keeping requirements, reporting of adverse experiences with the product, providing the FDA with updated safety and efficacy information, product sampling and distribution requirements and complying with FDA promotion and advertising requirements, which include, among other requirements, standards for direct-to-consumer advertising, restrictions on promoting drugs for uses or in patient populations that are not described in the drug's approved labeling (known as "off-label use"), limitations on industry sponsored scientific and educational activities and requirements for promotional activities involving the internet. Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such off-label uses.

In addition, quality control and manufacturing procedures must continue to conform to applicable manufacturing requirements after approval. We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our product candidates and products in accordance with cGMP regulations. cGMP regulations require among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer or holder of an approved NDA, including, among other things, recall or withdrawal of the product from the market. In addition, changes to the manufacturing process are strictly regulated and depending on the significance of the change, may require prior FDA approval before being implemented. Other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

The FDA also may require Phase 4 testing and surveillance to monitor the effects of an approved product or place conditions on an approval that could restrict the distribution or use of the product. Discovery of previously unknown problems with a product or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement, warning letters from the FDA, mandated corrective advertising or communications with doctors and civil or criminal penalties, among others. Newly

discovered or developed safety or effectiveness data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures, such as a REMS. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our product candidates under development.

United States Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our United States patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA plus the time between the submission date of an NDA and the approval of that application. Only one patent applicable to an

approved drug is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent. The United States Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA.

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

Other types of non-patent marketing exclusivity include orphan drug exclusivity under the Orphan Drug Act, which may offer a seven-year period of marketing exclusivity as described above, and pediatric exclusivity under the Best Pharmaceuticals for Children Act, which may add six months to existing exclusivity periods and patent terms. This six-month pediatric exclusivity may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued “Written Request” for such a trial.

Foreign Government Regulation

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials, marketing authorization, manufacturing and any commercial sales, promotion and distribution of our products.

Whether or not we obtain FDA approval for a product candidate, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like an IND prior to the commencement of human clinical trials. In the EU, for example, a clinical trial application, or CTA, must be submitted to each country’s national health authority and an independent ethics committee, much like the FDA and IRB requirements in the United States, respectively. Once the CTA is approved in accordance with a country’s requirements, clinical trials may proceed.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

In the European Economic Area, or EEA (comprised of the 28 EU Member States plus Iceland, Liechtenstein and Norway), medicinal products must be authorized for marketing by using either the centralized authorization procedure or national authorization procedures.

Centralized procedure: Under the centralized procedure, following the opining of the European Medicines Agency's, or EMA's, Committee for Medicinal Products for Human Use, or the CHMP, the European Commission issues a single marketing authorization valid across the EEA. The centralized procedure is compulsory for human medicines derived from biotechnology processes advanced therapy medicinal products (such as gene therapy, somatic cell therapy and tissue engineered products), products that contain a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders, diabetes, autoimmune diseases and other immune dysfunctions, viral diseases, and officially designated orphan medicines. For medicines that do not fall within these categories, an applicant has the option of submitting an application for a centralized marketing authorization to the EMA, as long as the medicine concerned contains a new active substance not yet authorized in the EEA, is a significant therapeutic, scientific or technical innovation, or if its authorization would be in the interest of public health in the EEA. Under the centralized procedure the maximum timeframe for the evaluation of a marketing authorization application, or MAA, by the

EMA is 210 days, excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP. Accelerated assessment might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, particularly from the point of view of therapeutic innovation. The timeframe for the evaluation of an MAA under the accelerated assessment procedure is 150 days, excluding clock stops.

National authorization procedures: There are also two other possible routes to authorize medicinal products in several countries, which are available for products that fall outside the scope of the centralized procedure:

- Decentralized procedure. Using the decentralized procedure, an applicant may apply for simultaneous authorization in more than one EU country of medicinal products that have not yet been authorized in any EU country and that do not fall within the mandatory scope of the centralized procedure.
- Mutual recognition procedure. In the mutual recognition procedure, a medicine is first authorized in one EU Member State, in accordance with the national procedures of that country. Following this, further marketing authorizations can be sought from other EU countries in a procedure whereby the countries concerned recognize the validity of the original, national marketing authorization.

In the EEA, new products authorized for marketing, or reference products, qualify for eight years of data exclusivity and an additional two years of market exclusivity upon marketing authorization. The data exclusivity period prevents generic or biosimilar applicants from relying on the preclinical and clinical trial data contained in the dossier of the reference product when applying for a generic or biosimilar marketing authorization in the EU during a period of eight years from the date on which the reference product was first authorized in the EU. The market exclusivity period prevents a successful generic or biosimilar applicant from commercializing its product in the EU until 10 years have elapsed from the initial authorization of the reference product in the EU. The 10-year market exclusivity period can be extended to a maximum of 11 years if, during the first eight years of those 10 years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

The criteria for designating an “orphan medicinal product” in the EEA are similar in principle to those in the United States. In the EEA, a medicinal product may be designated as orphan if (a) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (b) either (i) such condition affects no more than five in 10,000 persons in the EU when the application is made, or (ii) the product, without the benefits derived from orphan status, would not generate sufficient return in the EU to justify investment; and (c) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the EU, or if such a method exists, the product will be of significant benefit to those affected by the condition. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. During this ten-year orphan market exclusivity period, no similar medicinal product for the same indication may be placed on the market. An orphan product can also obtain an additional two years of market exclusivity in the EU for pediatric studies. The ten-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if the: (a) second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior; (b) applicant consents to a second orphan medicinal product application; or (c) applicant cannot supply enough orphan medicinal product.

If we fail to comply with applicable foreign regulatory requirements, we may be subject in those countries to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Coverage and Reimbursement

Sales of our products will depend, in part, on the extent to which our products will be covered by third-party payors, such as government health care programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly limiting coverage and/or reducing reimbursements for medical products and services. In addition, the United States government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures and adoption of more restrictive policies in jurisdictions with existing controls and measures could further limit our net revenue and results. Decreases in third-party reimbursement for our product candidates or a decision by a third-party payor not to cover our product candidates could reduce physician usage of our products once approved and have a material adverse effect on our sales, results of operations and financial condition.

Healthcare Reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medical products, implementing reductions in Medicare and other healthcare funding, and applying new payment methodologies. For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the Affordable Care Act, was enacted, which, among other things, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; introduced a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care plans; imposed mandatory discounts for certain Medicare Part D beneficiaries as a condition for manufacturers' outpatient drugs coverage under Medicare Part D; subjected drug manufacturers to new annual fees based on pharmaceutical companies' share of sales to federal healthcare programs; created a new Patient Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and establishment of a Center for Medicare Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending.

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the Affordable Care Act. We expect that the current presidential administration and U.S. Congress will likely continue to seek to modify, repeal, or otherwise invalidate all, or certain provisions of, the Affordable Care Act. Most recently, the Tax Cuts and Jobs Act was enacted, which, among other things, removes penalties for not complying with the Affordable Care Act's individual mandate to carry health insurance. There is still uncertainty with respect to the impact President Trump's administration and the U.S. Congress may have, if any, and any changes will likely take time to unfold, and could have an impact on coverage and reimbursement for healthcare items and services covered by plans that were authorized by the Affordable Care Act. However, we cannot predict the ultimate content, timing or effect of any healthcare reform legislation or the impact of potential legislation on us.

In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act to reduce healthcare expenditures. These changes include aggregate reductions of Medicare payments to providers of 2% per fiscal year that, due to subsequent legislative amendments, will remain in effect through 2025 unless additional action is taken by Congress. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Recently there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed bills designed to, among other things, reform government program reimbursement methodologies. Individual states in the United States have also become increasingly active in implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Fraud and Abuse Laws

We will also be subject to healthcare fraud and abuse laws and other regulations and enforcement by the federal government as well as the state and foreign governments in which we will conduct our business once emricasan or another product candidate developed by us is approved and commercialization of such product candidate begins. Such laws include, without limitation, state and federal anti-kickback, false claims, privacy and security and physician sunshine laws and regulations. Violations of any of such laws or any other governmental regulations may result in penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of operations, the

exclusion from participation in federal and state healthcare programs and individual imprisonment.

Employees

As of March 1, 2018, we had 35 employees, 33 of whom are full-time, 11 of whom hold Ph.D. or M.D. degrees, 21 of whom were engaged in research and development activities and 14 of whom were in general and administrative positions. None of our employees are subject to a collective bargaining agreement. We consider our relationship with our employees to be good.

Research and Development

We have invested $43.2 million, $20.3 million and $16.3 million in research and development for the years ended December 31, 2017, 2016 and 2015, respectively.

About Conatus

We were incorporated under the laws of the state of Delaware in 2005. Our principal executive offices are located at 16745 West Bernardo Dr., Suite 200, San Diego, California 92127, and our telephone number is (858) 376-2600. Our website address is www.conatuspharma.com. The information in or accessible through our website is not incorporated into and is not considered part of this filing.

Financial Information about Segments

We operate only in one business segment, which is the commercialization and development of pharmaceutical products. See note 2 to our financial statements included in this annual report on Form 10-K. For financial information regarding our business, see “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and our financial statements and related notes.

Available Information

We file electronically with the Securities and Exchange Commission, or SEC, our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended. We make available on our website at www.conatuspharma.com, free of charge, copies of these reports, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. The public may read or copy any materials we file with the SEC at the SEC’s Public Reference Room at 100 F Street NE, Washington, D.C. 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains a website that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC. The address of that website is www.sec.gov. The information in or accessible through the SEC and our website are not incorporated into, and are not considered part of, this filing. Further, our references to the URLs for these websites are intended to be inactive textual references only.

ITEM 1A. RISK FACTORS

You should carefully consider the following risk factors, together with the other information contained in this annual report on Form 10-K, including our financial statements and the related notes and “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” before making a decision to purchase or sell shares of our common stock. We cannot assure you that any of the events discussed in the risk factors below will not occur. These risks could have a material and adverse impact on our business, results of operations, financial condition and growth prospects. If that were to happen, the trading price of our common stock could decline. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations or financial condition.

Risks Related to Our Business and Industry

Our business is dependent on the success of a single product candidate, emricasan, which will require significant additional clinical testing before we can seek regulatory approval and potentially launch commercial sales.

Our future success depends on our ability to obtain regulatory approval for, and then successfully commercialize, our only product candidate, emricasan. We have not completed the development of any product candidates. We currently generate no revenues from sales of any drugs, and we may never be able to develop a marketable drug. Emricasan will require additional clinical and non-clinical development, regulatory review and approval in multiple jurisdictions,

substantial investment, access to sufficient commercial manufacturing capacity and significant marketing efforts before we can generate any revenues from product sales. We entered into an Option, Collaboration and License Agreement, or the Collaboration Agreement, with Novartis Pharma AG, or Novartis, pursuant to which we granted Novartis an exclusive license to collaborate with us to develop products containing emricasan either as a single active ingredient or in combination with other Novartis compounds for liver cirrhosis or liver fibrosis. Novartis is responsible for Phase 3 development of emricasan single agent products and all development for emricasan combination products as well as the manufacturing and commercialization for all emricasan products. Neither we, nor Novartis, are permitted to market or promote emricasan before emricasan receives regulatory approval from the United States Food and Drug Administration, or FDA, or comparable foreign regulatory authorities, and emricasan may never receive such regulatory approvals.

Our registration strategy is to develop emricasan for patients with fibrosis or cirrhosis due to non-alcoholic steatohepatitis, or NASH. Our four ongoing trials are a Phase 2b clinical trial in patients with NASH cirrhosis and severe portal hypertension, a Phase 2b clinical trial in patients with decompensated NASH cirrhosis, a Phase 2b clinical trial in patients with NASH fibrosis, and a Phase 2b clinical trial in post-orthotopic liver transplant, or POLT, recipients with reestablished liver fibrosis post-transplant as a result of recurrent hepatitis C virus, or HCV, infection who have successfully achieved a sustained viral response, or SVR, following HCV antiviral therapy, or POLT-HCV-SVR, patients with residual fibrosis or cirrhosis.

There is no guarantee that our current or future clinical trials will be completed on time or at all or that any future clinical trials will commence on time or at all, and the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials. Even if such regulatory authorities agree with the design and implementation of our clinical trials, we cannot guarantee you that such regulatory authorities will not change their requirements in the future. In addition, even if our clinical trials are successfully completed, we cannot guarantee that the FDA or foreign regulatory authorities will interpret the results as we do, and more trials would likely be required before we submit emricasan for approval. To the extent that the results of the clinical trials are not satisfactory to the FDA or foreign regulatory authorities for support of a marketing application, approval of emricasan may be significantly delayed, or we may be required to expend significant additional resources, which may not be available to us, to conduct additional trials in support of potential approval of emricasan.

We cannot anticipate when or if we will seek regulatory review of emricasan for any indication. We have not previously submitted a new drug application, or NDA, to the FDA, or similar drug approval filings to comparable foreign authorities. An NDA must include extensive preclinical and clinical data and supporting information to establish the product candidate's safety and effectiveness for each desired indication. The NDA must also include significant information regarding the chemistry, manufacturing and controls for the product. Obtaining approval of an NDA is a lengthy, expensive and uncertain process and may not be obtained. We have not received marketing approval for any product candidate, and we cannot be certain that emricasan will be successful in future clinical trials or receive regulatory approval for any indication. If we do not receive regulatory approvals for and successfully commercialize emricasan on a timely basis or at all, we may not be able to continue our operations. Even if we successfully obtain regulatory approvals to market emricasan, our revenues will be dependent, in part, on Novartis' ability to commercialize emricasan as well as the size of the markets in the territories for which we gain regulatory approval and have commercial rights. If the markets for the treatment of liver cirrhosis, including NASH cirrhosis, NASH fibrosis or POLT-HCV-SVR are not as significant as we estimate, our business and prospects will be harmed.

Emricasan was the subject of a clinical hold imposed by the FDA while under development by Pfizer Inc. due to a preclinical observation. Although the clinical hold has been lifted, any adverse side effects or other safety risks associated with emricasan could delay or preclude approval of the product candidate, cause us to suspend or discontinue our clinical trials or limit the commercial profile of emricasan.

When we acquired emricasan from Pfizer in 2010, emricasan was on clinical hold in the United States due to an observation of inflammatory infiltrates in mice that Pfizer saw in a preclinical study and reported to the FDA in 2007. Pfizer performed additional preclinical studies attempting to characterize the nature of the inflammatory infiltrates, but did not carry out a formal carcinogenicity study to evaluate whether or not the infiltrates progressed to cancer. These infiltrates observed in mice were not observed in any other species. In 2008, Pfizer stopped work on the program. After acquiring emricasan, we conducted a thorough internal review of these studies, commissioned several independent experts to review the data and, based on guidance from the FDA, conducted a 6-month carcinogenicity study in the Tg.rasH2 transgenic mouse model, which is known to be predisposed toward tumor development. This study was completed in 2012. There was no evidence of drug-related tumorgenicity in our carcinogenicity study, and after further discussions with the FDA, we were cleared in January 2013 to proceed with our previously planned HCV-POLT clinical trial, formally lifting emricasan from clinical hold in the United States. Emricasan was never placed on clinical hold outside the United States. We cannot assure you that emricasan will not be placed on clinical hold in the future for similar or unrelated reasons.

In addition, undesirable side effects caused by emricasan could result in the delay, suspension or termination of our clinical trials by us, the FDA or other regulatory authorities or institutional review boards, or IRBs, for a number of reasons. To date, over 650 subjects have received emricasan in Phase 1 and Phase 2 clinical trials. The most commonly reported treatment-related adverse events in emricasan-treated subjects were dizziness, headache, fatigue, nausea and diarrhea. Although most of the adverse events reported in relation to emricasan in these trials were mild to moderate, results of our ongoing and future trials could reveal a high and unacceptable severity and prevalence of these or other side effects, including, potentially, more severe side effects. In such an event, our trials could be

suspended or terminated, and the FDA or comparable foreign regulatory authorities could order us to cease further development of, or deny approval of, emricasan for any or all targeted indications. In addition, the drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the clinical trial or result in potential product liability claims. Even if regulatory authorities granted approval of emricasan, if adverse events caused regulatory authorities to impose a restrictive label or if physicians' perceptions of emricasan's safety caused them to limit their use of the drug, our ability to generate sufficient sales of emricasan could be limited. Any of these occurrences may harm our business, prospects, financial condition and results of operations significantly.

Clinical drug development involves uncertain outcomes, and results of earlier studies and trials may not be predictive of future trial results.

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. For example, in late 2011 we ceased clinical development of a product candidate, CTS-1027, for which we had incurred $31.3 million in research and development expenses prior to such time. The results of preclinical studies

and early clinical trials of emricasan may not be predictive of the results of later-stage clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or safety profiles, notwithstanding promising results in earlier trials.

Emricasan has been the subject of eight competed Phase 1 and eight competed Phase 2 clinical trials. Although we believe emricasan has demonstrated evidence of a beneficial effect in patients with chronic liver disease independent of the cause of disease in these clinical trials, we are now seeking to evaluate emricasan in targeted indications within liver disease, initially NASH cirrhosis and NASH fibrosis, and we have not previously evaluated the safety and efficacy of emricasan in these and other planned indications. Previously, the development program for emricasan focused primarily on the treatment of HCV patients and the evaluation of the product candidate in liver disease generally. We cannot be certain that any of our ongoing and planned clinical trials will be successful, and failure in one indication may have negative consequences for the development of emricasan for other indications. Any such failure may harm our business, prospects and financial condition.

The FDA regulatory approval process is lengthy and time-consuming, and if we experience significant delays in the clinical development and regulatory approval of emricasan, our business will be substantially harmed.

We may experience delays in commencing and completing clinical trials of emricasan. For example, based on data in 2013 regarding a new HCV antiviral being developed by another company, we chose to delay and change our previously planned Phase 2b/3 HCV-POLT clinical trial to a Phase 2b POLT-HCV-SVR clinical trial. We may also experience delays in commencing and completing other clinical trials of emricasan. We do not know whether planned clinical trials will begin on time, need to be redesigned, enroll patients on time or be completed on schedule, if at all. Any of our ongoing and planned clinical trials may be delayed for a variety of reasons, including delays related to:

- the availability of financial resources for us to commence and complete our planned clinical trials;
- reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites;
- obtaining IRB approval at each clinical trial site;
- obtaining regulatory approval for clinical trials in each country;
- recruiting suitable patients to participate in clinical trials;
- having patients complete a clinical trial or return for post-treatment follow-up;
- clinical trial sites deviating from trial protocol or dropping out of a trial;
- adding new clinical trial sites;
- developing one or more new formulations or routes of administration; or
- manufacturing sufficient quantities of our product candidate for use in clinical trials.

Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the clinical trial, the design of the clinical trial, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating. In addition, significant numbers of patients who enroll in our clinical trials may drop out during the clinical trials as a result of being offered a liver transplant in the case of liver cirrhosis or portal hypertension patients, a potential curative therapy or other reasons. We believe we have appropriately accounted for such increased risk of dropout rates in our trials when determining expected clinical trial timelines in our ongoing clinical trials, but we cannot assure you that our assumptions are correct, or that we will not experience higher numbers of dropouts than anticipated, which would result in the delay of completion of such trials beyond our expected timelines. For example, our previous Phase 2b ACLF clinical trial experienced lower than expected enrollment rates, and we elected to complete the trial prior to reaching the initial targeted number of patients.

We could encounter delays if physicians encounter unresolved ethical issues associated with enrolling patients in clinical trials of emricasan in lieu of prescribing existing treatments that have established safety and efficacy profiles. Further, a clinical trial may be suspended or terminated by us, the IRBs in the institutions in which such trials are being conducted, the data monitoring committee for such trial, or by the FDA or other regulatory authorities due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to

demonstrate a benefit from using a product candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. If we experience termination of, or delays in the completion of, any clinical trial of emricasan, the commercial prospects for emricasan will be harmed, and our ability to generate product revenues will be delayed. In addition, any delays in completing our clinical trials will increase our costs, slow down our product development and approval process and jeopardize our ability to commence product sales and generate revenues. Any of these occurrences may harm our business, prospects, financial condition and results of operations significantly. Furthermore, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of emricasan.

The clinical trials for emricasan involve a high degree of uncertainty and risk of failure, and some of our development activities involve indications with little or no previous product candidate development activities as well as patient populations with critical illnesses and potential challenges for enrollment and participation in clinical trials.

Our business involves the development of new drugs, which is a highly risky undertaking and involves a lengthy process and high degree of uncertainty. Some of our clinical trials for emricasan may involve indications and patient populations that have had little or no previous development activities by us or others in our industry.

In connection with clinical trials, we face risks that:

- IRBs may delay approval of, or fail to approve, a clinical trial at a prospective site;
- there may be a limited number of, and significant competition for, suitable patients for enrollment in the clinical trials;
- there may be slower than expected rates of patient recruitment and enrollment;
- patients may fail to complete the clinical trials;
- there may be an inability or unwillingness of patients or medical investigators to follow our clinical trial protocols;
- there may be an inability to monitor patients adequately during or after treatment;
- there may be termination of the clinical trials by one or more clinical trial sites;
- unforeseen ethical or safety issues may arise;
- conditions of patients may deteriorate rapidly or unexpectedly, which may cause the patients to become ineligible for a clinical trial or may prevent emricasan from demonstrating efficacy or safety;
- patients may die or suffer other adverse effects for reasons that may or may not be related to emricasan being tested;
- we may not be able to sufficiently standardize certain of the tests and procedures that are part of our clinical trials because such tests and procedures are highly specialized and involve a high degree of expertise;
- emricasan may not prove to be efficacious in all or some patient populations;
- the results of the clinical trials may not confirm the results of earlier trials;
- the results of the clinical trials may not meet the level of statistical significance required by the FDA or other regulatory agencies; and
- emricasan may not have a favorable risk/benefit assessment in the disease areas studied.

We cannot assure you that our ongoing clinical trials or any future clinical trial for emricasan will be started or completed on schedule, or at all. Any failure or significant delay in completing clinical trials for emricasan would harm the commercial prospects for emricasan and adversely affect our financial results. Difficulties and failures can occur at any stage of clinical development, and we cannot assure you that we will be able to successfully complete the development and commercialization of emricasan in any indication.

If we are unable to obtain regulatory approval of emricasan, we will not be able to commercialize this product candidate and our business will be adversely impacted.

We have not obtained regulatory approval for any product candidate. If we fail to obtain regulatory approval to market emricasan, our only product candidate, we will be unable to sell emricasan, which will significantly impair our ability to generate revenues. To receive approval, we must, among other things, demonstrate with substantial evidence from clinical trials that the product candidate is both safe and effective for each indication for which approval is sought, and failure can occur in any stage of development. Satisfaction of the approval requirements typically takes several years, and the time and money needed to satisfy them may vary substantially, based on the type, complexity and novelty of the pharmaceutical product. We have not commenced any Phase 3 clinical trials of emricasan to date, and we cannot predict if, or when, our future clinical trials will generate the data necessary to support an NDA and if, or when, we might receive regulatory approvals for emricasan.

The FDA generally requires two confirmatory clinical trials for approval of an NDA. Under the FDA's Accelerated Approval Program, the FDA may grant "accelerated approval" to product candidates that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. Accelerated approval provides a pathway for an investigational product to be approved on the basis of adequate and well-controlled clinical studies establishing that the product candidate has an effect on a surrogate endpoint that the FDA considers reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. The Accelerated Approval Program does not change the statutory requirements for marketing approval. In addition, as a condition of approval, the FDA may require that a sponsor of a drug receiving accelerated approval perform adequate and well-controlled post-marketing clinical studies. The FDA also generally requires pre-approval of promotional materials as a condition of accelerated approval.

We are using change in hepatic venous pressure gradient, or HVPG, as the primary endpoint in our ongoing Phase 2b ENCORE-PH trial in compensated or early decompensated NASH cirrhosis with severe portal hypertension. Decreasing HVPG has been identified by the FDA as a validated, objective measure that potentially could be acceptable as a surrogate endpoint for clinical trials of patients with liver cirrhosis. We do not know if the FDA will agree with the use of a surrogate endpoint for accelerated approval of emricasan for the treatment of liver cirrhosis. In the event emricasan does receive accelerated approval for the treatment of liver cirrhosis, we would be required to conduct one or more post-approval clinical outcomes trials to confirm the clinical benefit of emricasan.

Emricasan could fail to receive regulatory approval for many reasons, including the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that emricasan is safe and effective for any of its proposed indications;
- the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate that emricasan's clinical and other benefits outweigh its safety risks;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- the data collected from clinical trials of emricasan may not be sufficient to the satisfaction of the FDA or comparable foreign regulatory authorities to support the submission of an NDA or other comparable submission in foreign jurisdictions or to obtain regulatory approval in the United States or elsewhere;
- the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and

- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

This lengthy approval process as well as the unpredictability of future clinical trial results may result in our failure to obtain regulatory approval to market emricasan, which would significantly harm our business, prospects, financial condition and results of operations. In addition, even if we were to obtain approval, regulatory authorities may grant approval contingent on the performance of costly post-marketing clinical trials or the imposition of a risk evaluation and mitigation strategy, or REMS, requiring substantial additional post-approval safety measures. Moreover, any approvals that we obtain may not cover all of the clinical indications for which we are seeking approval or could contain significant limitations in the form of narrow indications, warnings, precautions or contra-indications with respect to conditions of use. In such event, our ability to generate revenues would be greatly reduced and our business would be harmed.

Even if we obtain and maintain regulatory approval for emricasan in one jurisdiction, we may never obtain regulatory approval for emricasan in any other jurisdiction, which would limit our market opportunities and adversely affect our business.

Obtaining and maintaining regulatory approval for emricasan in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction. For example, even if the FDA grants marketing approval for a product candidate, comparable regulatory authorities in foreign countries must also approve the manufacturing, marketing and promotion of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the United States, including additional preclinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our products is also subject to approval. We expect to submit a marketing authorization application, or MAA, to the European Medicines Agency, or EMA, for approval of emricasan in the European Union, or the EU. As with the FDA, obtaining approval of an MAA from the EMA is a similarly lengthy and expensive process, and the EMA has its own procedures for approval of product candidates. Even if a product is approved, the FDA or the EMA, as the case may be, may limit the indications for which the product may be marketed, require extensive warnings on the product labeling, require a REMS or require expensive and time-consuming clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and the EU also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not ensure approval in any other country, while a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory approval process in others. Also, regulatory approval for any product candidate may be withdrawn. If we fail to comply with the regulatory requirements in international markets and/or receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of emricasan will be harmed, which would adversely affect our business, prospects, financial condition and results of operations.

Even if we receive regulatory approval for emricasan, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense. Additionally, emricasan, if approved, could be subject to labeling and other restrictions and market withdrawal, and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with emricasan.

Any regulatory approvals that we receive for emricasan may be subject to limitations on the approved indicated uses for which emricasan may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the safety and efficacy of the product candidate. The FDA may also require a REMS in order to approve emricasan, which could entail requirements for a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA or a comparable foreign regulatory authority approves emricasan, the manufacturing processes, labeling, packaging,

distribution, adverse event reporting, storage, advertising, promotion, import, export and recordkeeping for emricasan will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with current good manufacturing practices, or cGMPs, and good clinical practice regulations, or GCPs, for any clinical trials that we conduct post-approval. Later discovery of previously unknown problems with emricasan, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of emricasan, withdrawal of the product from the market, or voluntary or mandatory product recalls;
- fines, warning letters or holds on clinical trials;
- refusal by the FDA or comparable foreign regulatory authorities to approve pending applications or supplements to approved applications filed by us or suspension or revocation of license approvals;

- product seizure or detention, or refusal to permit the import or export of emricasan; and
- injunctions or the imposition of civil or criminal penalties.

The FDA's and other regulatory authorities' policies may change, and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of emricasan. For example, in December 2016, the 21st Century Cures Act, or Cures Act, was signed into law. The Cures Act, among other things, is intended to modernize the regulation of drugs and spur innovation, but its ultimate implementation is unclear. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations.

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. For example, certain policies of the Trump administration may impact our business and industry. Namely, the Trump administration has taken several executive actions, including the issuance of a number of executive orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. It is difficult to predict how these executive orders will be implemented and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on the FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

Even if we obtain regulatory approval for emricasan, the product may not gain market acceptance among physicians, patients, tertiary care centers, transplant centers and others in the medical community.

If emricasan is approved for commercialization, its acceptance will depend on a number of factors, including:

- the clinical indications for which emricasan is approved;
    - physicians, major operators of tertiary care centers and transplant centers and patients considering emricasan as a safe and effective treatment;
- the potential and perceived advantages of emricasan over alternative treatments;
- the prevalence and severity of any side effects;
- product labeling or product insert requirements of the FDA or other regulatory authorities;
- the timing of market introduction of emricasan as well as competitive products;
- the cost of treatment in relation to alternative treatments;
- the availability of adequate reimbursement and pricing by third-party payors and government authorities;
- relative convenience and ease of administration; and
- the effectiveness of our sales and marketing efforts.

If emricasan is approved but fails to achieve market acceptance among physicians, patients or others in the medical community, we will not be able to generate significant revenues, which would have a material adverse effect on our business, prospects, financial condition and results of operations.

Coverage and reimbursement may be limited or unavailable in certain market segments for emricasan, which could make it difficult for us to sell emricasan profitably.

Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which drugs they will cover and the amount of reimbursement. Reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;

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- cost-effective; and
- neither experimental nor investigational.

Obtaining coverage and reimbursement approval for a product from a government or other third-party payor is a time-consuming and costly process that could require us to provide to the payor supporting scientific, clinical and cost-effectiveness data for the use of our products. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If reimbursement of our future products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, we may be unable to achieve or sustain profitability.

We intend to seek approval to market emricasan in both the United States and in select foreign jurisdictions. If we obtain approval in one or more foreign jurisdictions for emricasan, we will be subject to rules and regulations in those jurisdictions. In some foreign countries, particularly those in the EU, the pricing of prescription pharmaceuticals and biologics is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after obtaining marketing approval for a product candidate. In addition, market acceptance and sales of emricasan will depend significantly on the availability of adequate coverage and reimbursement from third-party payors for emricasan and may be affected by existing and future health care reform measures.

In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In particular, in 2010, the Affordable Care Act, was enacted, which, among other things, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees on manufacturers of certain branded prescription drugs, required manufacturers to participate in a discount program for certain outpatient drugs under Medicare Part D and promoted programs that increase the federal government's comparative effectiveness research, which will impact existing government healthcare programs and will result in the development of new programs. An expansion in the government's role in the United States healthcare industry may further lower rates of reimbursement for pharmaceutical products.

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the Affordable Care Act. We expect that the current presidential administration and U.S. Congress will likely continue to seek to modify, repeal, or otherwise invalidate all, or certain provisions of, the Affordable Care Act. Most recently, the Tax Cuts and Jobs Act was enacted, which, among other things, removes penalties for not complying with the Affordable Care Act's individual mandate to carry health insurance. There is still uncertainty with respect to the impact President Trump's administration and the U.S. Congress may have, if any, and any changes will likely take time to unfold, and could have an impact on coverage and reimbursement for healthcare items and services covered by plans that were authorized by the Affordable Care Act. However, we cannot predict the ultimate content, timing or effect of any healthcare reform legislation or the impact of potential legislation on us.

Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. On August 2, 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2025 unless additional Congressional action is taken. On January 2, 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

There have been, and likely will continue to be, legislative and regulatory proposals at the federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. For instance, there have recently been public hearings in the U.S. Congress concerning pharmaceutical product pricing, which have resulted in several Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for pharmaceutical products. Individual states in the United States have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. We cannot predict the initiatives that may be adopted in the future. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and/or impose price controls may adversely affect:

- the demand for emricasan, if we obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to generate revenues and achieve or maintain profitability;
- the level of taxes that we are required to pay; and
- the availability of capital.

Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors, which may adversely affect our future profitability.

We currently have no marketing and sales organization and have no experience in marketing products. If our collaborator fails to market and sell emricasan and if we are unable to establish marketing and sales capabilities or enter into agreements with third parties to market and sell emricasan, we may not be able to generate product revenues.

We currently do not have a commercial organization for the marketing, sales and distribution of pharmaceutical products. We entered into the Collaboration Agreement with Novartis for the development and commercialization of emricasan. Under the Collaboration Agreement, Novartis is responsible for the commercialization of emricasan worldwide. If emricasan is approved, we will have limited control over the marketing and sales efforts of Novartis, and our revenues from product sales may be lower than if we had commercialized emricasan ourselves.

If the Collaboration Agreement with Novartis is terminated, we may need to build our marketing, sales, distribution, managerial and other non-technical capabilities to commercialize emricasan or make arrangements with third parties to perform these services. We expect that the majority of all liver cirrhosis and POLT-HCV-SVR patients will be treated at tertiary care centers and transplant centers, and therefore our marketing and sales efforts can be addressed with a targeted sales force. We may build our own commercial infrastructure in North America and the EU to target these centers. The establishment and development of our own sales force or the establishment of a contract sales force to market emricasan would be expensive and time-consuming and could delay any commercial launch. Moreover, we cannot be certain that we will be able to successfully develop this capability. We would have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain marketing and sales personnel. We would also face competition in our search for third parties to assist us with the sales and marketing efforts of emricasan. We may also consider other opportunities to partner with a pharmaceutical company that has global capabilities to develop and commercialize.

To the extent we rely on Novartis or any other third parties to commercialize emricasan, if approved, we may have little or no control over the marketing and sales efforts of such third parties, and our revenues from product sales may be lower than if we had commercialized emricasan ourselves. In the event we are unable to develop our own marketing and sales force or collaborate with a third-party marketing and sales organization, we would not be able to commercialize emricasan.

A variety of risks associated with marketing emricasan internationally could materially adversely affect our business.

We plan to seek regulatory approval for emricasan outside of the United States and, accordingly, we expect that we will be subject to additional risks related to operating in foreign countries if we obtain the necessary approvals, including:

- differing regulatory requirements in foreign countries;
- the potential for so-called parallel importing, which occurs when a local seller, faced with high or higher local prices, opts to import goods from a foreign market (with low or lower prices) rather than buying them locally;
- unexpected changes in tariffs, trade barriers, price and exchange controls and other regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;

- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- difficulties staffing and managing foreign operations;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- potential liability under the Foreign Corrupt Practices Act of 1977 or comparable foreign regulations;
- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism.

These and other risks associated with our international operations may materially adversely affect our ability to attain or maintain profitable operations.

If we fail to develop and commercialize any other product candidates, we may be unable to grow our business.

We plan to develop and commercialize product candidates in addition to emricasan, which is currently our only product candidate. In order to develop and commercialize any additional product candidates, we may be required to invest significant resources to acquire or in-license the rights to such product candidates or to conduct drug discovery activities. In addition, any other product candidates will require additional, time-consuming development efforts prior to commercial sale, including preclinical studies, extensive clinical trials and approval by the FDA and applicable foreign regulatory authorities. All product candidates are prone to the risks of failure that are inherent in pharmaceutical product development, including the possibility that the product candidate will not be shown to be sufficiently safe and/or effective for approval by regulatory authorities. In addition, we cannot assure you that we will be able to acquire, discover or develop any additional product candidates, or that any additional product candidates we may develop will be approved, manufactured or produced economically, successfully commercialized or widely accepted in the marketplace or be more effective than other commercially available alternatives. Research programs to identify new product candidates require substantial technical, financial and human resources whether or not we ultimately identify any candidates. If we are unable to develop or commercialize emricasan or any other product candidates, our business and prospects will suffer.

We cannot be certain that emricasan or any other product candidates that we develop will produce commercially viable drugs that safely and effectively treat liver or other diseases. Even if we are successful in completing preclinical and clinical development and receiving regulatory approval for one commercially viable drug for the treatment of one disease, we cannot be certain that we will also be able to develop and receive regulatory approval for other product candidates for the treatment of other forms of that disease or other diseases. If we fail to develop a pipeline of potential product candidates other than emricasan, we will not have any prospects for commercially viable drugs should our efforts to develop and commercialize emricasan be unsuccessful, and our business prospects would be harmed significantly.

We face significant competition from other biotechnology and pharmaceutical companies, and our operating results will suffer if we fail to compete effectively.

The biopharmaceutical industry is characterized by intense competition and rapid innovation. Although we believe that we hold a leading position in our understanding of caspase inhibition related to liver disease, our competitors may be able to develop other compounds or drugs that are able to achieve similar or better results. Our potential competitors include major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations and well-established sales forces. Smaller or early-stage companies may

also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis drug products that are more effective or less costly than emricasan. We believe the key competitive factors that will affect the development and commercial success of our product candidates are efficacy, safety and tolerability profile, reliability, convenience of dosing, price and reimbursement.

There are currently no therapeutic products approved for the treatment of NASH cirrhosis, POLT-HCV-SVR or NASH fibrosis. There are a number of marketed therapeutics used in each of these diseases to try to remove the underlying cause of the disease and prevent further liver injury. For example, if the liver damage is a result of hepatitis B virus or HCV infection, marketed antiviral medications may be used to treat the virus that led to liver damage. If the liver damage is a result of alcoholic hepatitis, marketed alcohol addiction drugs may be used. If the liver damage is a result of obesity, diet and exercise may be prescribed along with marketed therapeutics. If the liver damage is a result of NASH, currently marketed drugs may be used, although none of these are approved for NASH. In addition to the marketed drugs for those indications, there are drugs in development for each of these indications. Although these marketed therapies and those in development may be efficacious, all of them take time to show an effect, and as long as the underlying conditions persist there will continue to be damage to the liver. In NASH for example, drugs in development have differing mechanisms of action, and it is currently unknown whether any single product candidate will eliminate liver inflammation and halt liver disease progression into advanced fibrosis. For each of these indications, emricasan is the only therapeutic we are aware of that is being developed specifically to reduce the level of apoptosis in the liver, and as a result it may be used with these other therapies. Our estimates of disease prevalence consider the presence of these other treatments. In addition, the HCV landscape has dramatically changed in recent years and will continue to evolve in the future with the introduction of interferon-free regimens with greater efficacy and tolerability over the current antiviral therapies.

Even if we obtain regulatory approval for emricasan, the availability and price of our competitors' products could limit the demand and the price we are able to charge for emricasan. We will not achieve our business plan if the acceptance of emricasan is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to emricasan, or if physicians switch to other new drug products or choose to reserve emricasan for use in limited circumstances. Our inability to compete with existing or subsequently introduced drug products would have a material adverse impact on our business, prospects, financial condition and results of operations.

Established pharmaceutical companies may invest heavily to accelerate discovery and development of novel compounds or to in-license novel compounds that could make emricasan less competitive. In addition, any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and safety in order to overcome price competition and to be commercially successful. Accordingly, our competitors may succeed in obtaining patent protection, receiving FDA approval or discovering, developing and commercializing medicines before we do, which would have a material adverse impact on our business.

We may not be able to obtain orphan drug exclusivity for emricasan or IDN-7314 for any indication.

In the United States, under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition. Such diseases and conditions are those that affect fewer than 200,000 individuals in the United States, or if they affect more than 200,000 individuals in the United States, there is no reasonable expectation that the cost of developing and making a drug product available in the United States for these types of diseases or conditions will be recovered from sales of the product. Orphan Drug Designation must be requested before submitting an NDA. If the FDA grants Orphan Drug Designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by that agency. Orphan Drug Designation does not convey any advantage in or shorten the duration of the regulatory review and approval process, but it can lead to financial incentives, such as opportunities for grant funding toward clinical trial costs, tax advantages and user-fee waivers.

If a drug that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the drug is entitled to orphan drug marketing exclusivity for a period of seven years. Orphan drug marketing exclusivity generally prevents the FDA from approving another application, including a full NDA, to market the same drug or biological product for the same indication for seven years, except in limited circumstances, including if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. For purposes of small molecule drugs, the FDA defines "same drug" as a drug that contains the same active chemical entity and is intended for the same use as the drug in question. A designated orphan drug

may not receive orphan drug marketing exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. Orphan drug marketing exclusivity rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition.

The criteria for designating an orphan medicinal product in the EU are similar in principle to those in the United States. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five in 10,000 persons in the EU when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the EU to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the EU, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years

of market exclusivity for the approved therapeutic indication. The application for orphan designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the marketing authorization application if the orphan designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The ten-year market exclusivity in the EU may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

- the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;
- the applicant consents to a second orphan medicinal product application; or
- the applicant cannot supply enough orphan medicinal product.

We originally applied for Orphan Drug Designation for emricasan for the treatment of fibrosis in HCV-POLT patients in the United States and the EU. In late 2013, the FDA granted an Orphan Drug Designation for emricasan for the treatment of POLT patients with reestablished fibrosis to delay the progression to cirrhosis and end-stage liver disease. In the EU, we withdrew the application based on feedback from the applicable regulatory body that emricasan may have efficacy in fibrosis outside of the HCV-POLT patient population. In June 2017, the FDA granted Orphan Drug Designation for our preclinical product candidate IDN-7314 for the treatment of primary sclerosing cholangitis, or PSC. In October 2017, the EMA granted orphan designation to IDN-7314 for the treatment of PSC. We cannot assure you that we will be able to obtain orphan drug exclusivity for emricasan or IDN-7314 in any jurisdiction for the target indications in a timely manner or at all or that a competitor will not obtain orphan drug exclusivity that could block the regulatory approval of emricasan or IDN-7314 for several years. If we are unable to obtain Orphan Drug Designation in the United States or in the EU, we will not receive market exclusivity, which might affect our ability to generate sufficient revenues. If a competitor is able to obtain orphan exclusivity that would block emricasan's or IDN-7314's regulatory approval, our ability to generate revenues could be significantly reduced, which could harm our business prospects, financial condition and results of operations.

We may be unable to maintain or effectively utilize orphan drug exclusivity for emricasan or IDN-7314 for any indication.

We received Orphan Drug Designation from the FDA for emricasan for the treatment of POLT patients with reestablished fibrosis to delay the progression to cirrhosis and end-stage liver disease. We also received Orphan Drug Designation from the FDA and orphan designation from the EMA for IDN-7314 for the treatment of PSC. We may be unable to obtain regulatory approval for emricasan or IDN-7314 for these orphan populations or any other orphan population, or we may be unable to successfully commercialize emricasan or IDN-7314 for such orphan populations due to risks that include:

- the orphan patient populations may change in size;
- there may be changes in the treatment options for patients that may provide alternative treatments to emricasan or IDN-7314;
- the development costs may be greater than projected revenue of drug sales for the orphan indications;
- the regulatory agencies may disagree with the design or implementation of our clinical trials;
- there may be difficulties in enrolling patients for clinical trials;
- emricasan or IDN-7314 may not prove to be efficacious in the respective orphan patient populations;
- clinical trial results may not meet the level of statistical significance required by the regulatory agencies; and
- emricasan or IDN-7314 may not have a favorable risk/benefit assessment in the respective orphan indication.

If we are unable to obtain regulatory approval for emricasan or IDN-7314 for any orphan population or are unable to successfully commercialize emricasan or IDN-7314 for such orphan population, it could harm our business prospects, financial condition and results of operations.

A Fast Track or Breakthrough Therapy designation for emricasan may not lead to a faster development or review process, or we may be unable to maintain or effectively utilize such a designation.

In February 2016, we announced that the FDA granted Fast Track designation to the emricasan development program for the treatment of liver cirrhosis caused by NASH. This Fast Track designation does not guarantee that we will qualify for or be able to take advantage of the expedited review procedures or that we will ultimately obtain regulatory approval of emricasan. Even though we have received this Fast Track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw the Fast Track designation if it believes that the Fast Track designation is no longer supported by data from our clinical development program. We may also seek Fast Track designation for additional liver disease indications, and we may not be successful in securing such additional designation or in expediting development if such designations were received.

The Fast Track program is intended to expedite or facilitate the process for reviewing new product candidates that meet certain criteria. Specifically, new drugs are eligible for Fast Track designation if they are intended, alone or in combination with one or more drugs, to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Fast Track designation applies to the combination of the product candidate and the specific indication for which it is being studied. Unique to a Fast Track product candidate, the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable and the sponsor pays any required user fees upon submission of the first section of the NDA.

We may also seek a Breakthrough Therapy designation for emricasan for various liver disease indications. The Breakthrough Therapy designation is for a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The sponsor of a Breakthrough Therapy may request the FDA to designate the drug as a Breakthrough Therapy at the time of, or any time after, the submission of an IND for the drug. If the FDA designates a drug as a Breakthrough Therapy, it must take actions appropriate to expedite the development and review of the application, which may include holding meetings with the sponsor and the review team throughout the development of the drug; providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable; involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review; assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor; and taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment.

The FDA has broad discretion is determining whether to grant a Fast Track or Breakthrough Therapy designation for a drug. Obtaining a Fast Track or Breakthrough Therapy designation does not change the standards for product approval, but may expedite the development or approval process. There is no assurance that the FDA will grant either such designation. Even if the FDA does grant either such designation for emricasan, it may not actually result in faster clinical development or regulatory review or approval. Furthermore, such a designation does not increase the likelihood that emricasan will receive marketing approval in the United States.

We entered into the Collaboration Agreement with Novartis, and we may form or seek additional strategic alliances or collaborations in the future. Such alliances and collaborations may inhibit future opportunities, or we may not realize the benefits of such collaborations or alliances.

We entered into the Collaboration Agreement with Novartis for the development of emricasan, and we may form or seek strategic alliances, joint ventures or collaborations or enter into licensing arrangements with other third parties that we believe will complement or augment our development and commercialization efforts with respect to future product candidates that we may develop. In connection with entering into the Collaboration Agreement, we incurred non-recurring and other charges and issued a convertible note in the amount of $15.0 million. In addition, for the period from the execution date of the Collaboration Agreement until the earlier of five years after the first commercial sale of an emricasan product in the United States or major European market or ten years from the execution date of the Collaboration Agreement, we have agreed not to develop in any pivotal registration clinical trials or commercialize any pan-caspase inhibitors in liver disease. Further, Novartis will have a right of first negotiation prior to any offer by us to any third party for future pan-caspase inhibitors that we may develop or acquire for the treatment of liver diseases or for certain retained pan-caspase inhibitors, provided that any license or collaboration that we enter into or propose to enter into must be on terms and conditions in the aggregate no more favorable to such third party than those last offered to Novartis. These provisions, and similar provisions in agreements we may enter into in the future, may inhibit our ability to develop and commercialize other pan-caspase inhibitors, including IDN-7314, or enter into future alliances or collaborations to develop or commercialize other pan-caspase inhibitors, including IDN-7314.

Future efforts for additional alliances or collaborations may also require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing stockholders or disrupt our management and business. In addition, we face significant competition in seeking appropriate strategic partners, and the negotiation process is time-consuming and complex. Furthermore, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and company culture. We cannot be certain that, following a strategic transaction or license, we will achieve the revenues or specific net income that justifies such transaction.

We are highly dependent on our key personnel, and if we are not successful in attracting and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

Our ability to compete in the highly competitive biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on our management, scientific and medical personnel. The loss of the services of any of our executive officers or other key employees and our inability to find suitable replacements could potentially harm our business, prospects, financial condition or results of operations.

Our scientific team has expertise in many different aspects of drug discovery and development. We conduct our operations at our leased facility in San Diego, California. This region is headquarters to many other biopharmaceutical companies and many academic and research institutions. Competition for skilled personnel in our market is very intense and may limit our ability to hire and retain highly qualified personnel on acceptable terms. In order to induce valuable employees to remain with our company, in addition to salary and cash incentives, we have provided stock options that vest over time. The value to employees of stock options that vest over time may be significantly affected by movements in our stock price that are beyond our control and may at any time be insufficient to counteract more lucrative offers from other companies.

Despite our efforts to retain valuable employees, members of our management, scientific and development teams may terminate their employment with us on short notice. Although we have employment agreements with our key employees, these employment agreements provide for at-will employment, which means that any of our employees could leave our employment at any time, with or without notice. We do not maintain “key man” insurance policies on the lives of these individuals or the lives of any of our other employees. Our success also depends on our ability to continue to attract, retain and motivate highly skilled junior, mid-level and senior managers as well as junior, mid-level and senior scientific and medical personnel.

Many of the other biotechnology and pharmaceutical companies that we compete against for qualified personnel have greater financial and other resources, different risk profiles and a longer history in the industry than we do. They may also provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high quality candidates than what we can offer. If we are unable to continue to attract and retain high quality personnel, our ability to advance the development of emricasan and obtain regulatory approval and potentially commercialize this product candidate will be limited.

We may need to grow the size of our organization, and we may experience difficulties in managing this growth.

As of March 1, 2018, we had 35 employees, 33 of whom are full-time. As our development and commercialization plans and strategies develop, we expect to need additional managerial, operational, sales, marketing, financial or other personnel. Future growth would impose significant added responsibilities on members of management, including:

- identifying, recruiting, integrating, maintaining and motivating additional employees;
- managing our internal development efforts effectively, including the clinical and FDA review process for emricasan, while complying with our contractual obligations to contractors and other third parties; and
- improving our operational, financial and management controls, reporting systems and procedures.

Our future financial performance and our ability to commercialize emricasan will depend, in part, on our ability to effectively manage any future growth, and our management may also have to divert a disproportionate amount of its attention away from day-to-day activities in order to devote a substantial amount of time to managing these growth activities. To date, we have used the services of outside vendors to perform tasks including clinical trial management, statistics and analysis, regulatory affairs, formulation development and other drug development functions. Our growth strategy may also entail expanding our group of contractors to implement these tasks going forward. Because we rely on numerous contractors, effectively outsourcing many key functions of our business, we will need to be able to effectively manage these contractors to ensure that they successfully carry out their contractual obligations and meet expected deadlines. However, if we are unable to effectively manage our outsourced activities or if the quality or accuracy of the services provided by contractors is compromised for any reason, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for emricasan or otherwise advance our business. There can be no assurance that we will be able to manage our existing contractors or find other competent contractors on economically reasonable terms, or at all. If we are not able to effectively expand our organization by hiring new employees and expanding our group of contractors, we may not be able to successfully implement the tasks necessary to further develop and commercialize emricasan. Accordingly, we may not achieve our research, development and commercialization goals for emricasan.

Our business and operations would suffer in the event of system failures.

Despite the implementation of security measures, our internal computer systems and those of our current and future CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such material system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Likewise, we rely on third parties to manufacture emricasan and conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development and commercialization of emricasan could be delayed.

Business disruptions could seriously harm our future revenues and financial condition and increase our costs and expenses.

Our operations could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or manmade disasters or business interruptions, for which we are predominantly self-insured. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses. We rely on third-party manufacturers to produce emricasan. Our ability to obtain clinical supplies of emricasan could be disrupted if the operations of these suppliers are affected by a man-made or natural disaster or other business interruption. Our corporate headquarters is located in California near major earthquake faults and fire zones. The ultimate impact on us, our significant suppliers and our general infrastructure of being located near major earthquake faults and fire zones and being consolidated in certain geographical areas is unknown, but our operations and financial condition could suffer in the event of a major earthquake, fire or other natural disaster.

We rely significantly on information technology, which face certain risks, and any failure, inadequacy, interruption or security lapse of that technology, including any cybersecurity incidents, could harm our ability to operate our business effectively.

We rely significantly on our information technology to effectively manage and conduct our business and operations. Any failure, inadequacy or interruption of that infrastructure or security lapse of that technology, including cybersecurity incidents, could harm our ability to operate our business effectively. In the ordinary course of business, we collect, store and transmit confidential information, and it is critical that we do so in a secure manner in order to maintain the confidentiality and integrity of such confidential information. Significant disruptions to our information technology systems or breaches of information security could adversely affect our business. Our information technology systems are potentially vulnerable to service interruptions and security breaches from inadvertent or intentional actions by our employees, partners, vendors, or from attacks by malicious third parties. Maintaining the secrecy of this confidential, proprietary, and/or trade secret information is important to our competitive business position. While we have taken steps to protect such information and invested in information technology, there can be no assurance that our efforts will prevent service interruptions or security breaches in our systems or the unauthorized or inadvertent wrongful access or disclosure of confidential information that could adversely affect our business operations or result in the loss, dissemination, or misuse of critical or sensitive information. Cybersecurity attacks in particular are evolving and include, but are not limited to, malicious software, attempts to gain unauthorized access to data and other electronic security breaches that could lead to disruptions in systems, misappropriation of our confidential or otherwise protected information and corruption of data. A breach of our security measures or the accidental loss, inadvertent disclosure, unapproved dissemination or misappropriation or misuse of trade secrets, proprietary information, or other confidential information, whether as a result of theft, hacking, or other forms of

deception, or for any other cause, could enable others to produce competing products, use our proprietary technology and/or adversely affect our business position. Further, a breach in security, unauthorized access resulting in misappropriation, theft, or sabotage with respect to our proprietary and confidential information, including research or clinical data, could require significant capital investments to remediate and could adversely affect our business, financial condition and results of operations.

Our employees, independent contractors, principal investigators, consultants, commercial collaborators, service providers and other vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk that our employees, independent contractors, principal investigators, consultants, commercial collaborators, service providers and other vendors may engage in fraudulent or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violates FDA laws and regulations, including those laws that require the reporting of true, complete and accurate information to the FDA, manufacturing standards, federal and state healthcare fraud and abuse laws and regulations, or laws that require the true, complete and accurate reporting of financial information or data. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws

and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Activities subject to these laws also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a code of business conduct and ethics, but it is not always possible to identify and deter third-party misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

If emricasan is approved, we may be subject to healthcare laws, regulation and enforcement. Our or our collaborators' failure to comply with those laws could have a material adverse effect on our results of operations and financial condition.

Although we currently do not have any products on the market, if emricasan or another product candidate developed by us is approved, once commercialization of such product candidate begins, we and our collaborators may be subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which we conduct our business. Such laws include, without limitation:

- the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information;
- the federal healthcare programs' Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;
- federal false claims laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent;
- federal criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation;
- the federal Physician Payment Sunshine Act, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to the government information related to payments or other "transfers of value" made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, and requires applicable manufacturers and group purchasing organizations to report annually to the government ownership and investment interests held by the physicians described above and their immediate family members and payments or other "transfers of value" to such physician owners (manufacturers are required to submit reports to the government by the 90th day of each calendar year); and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the

relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures and pricing information; and state and foreign laws governing the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by the Health Insurance Portability and Accountability Act, thus complicating compliance efforts.

If our or our collaborators' operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and individual imprisonment, any of which could adversely affect our ability to operate our business and our results of operations.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of emricasan.

We face an inherent risk of product liability as a result of the clinical testing of emricasan and will face an even greater risk if we commercialize any products. For example, we may be sued if emricasan allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of emricasan. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for emricasan;
- injury to our reputation;
- withdrawal of clinical trial participants;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources;
- the inability to commercialize emricasan; and
- a decline in our share price.

Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop. Although we maintain product liability insurance covering our clinical trials, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. If we determine that it is prudent to increase our product liability coverage due to the commercial launch of any approved product, we may be unable to obtain such increased coverage on acceptable terms, or at all. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

Risks Related to Our Reliance on Third Parties

If Novartis terminates the Collaboration Agreement, we may not receive additional payments under the Collaboration Agreement, and we may not be able to enter into a similar agreement on favorable terms, or at all.

Pursuant to the Collaboration Agreement, Novartis has certain termination rights in the circumstances of an uncured material breach or insolvency by us and in the event of a mandated clinical trial hold for any products containing only emricasan as an active ingredient, or Emricasan Only Products. Additionally, Novartis has the right to terminate the Collaboration Agreement without cause upon 180 days prior written notice to us. In such event, the license granted to Novartis will be terminated and revert to us, and Novartis will transfer any ongoing trials for the Emricasan Only Products to us and will cease development of emricasan products. In the event Novartis terminates the Collaboration Agreement due to our uncured material breach or insolvency, the license granted to Novartis pursuant to the Collaboration Agreement will become irrevocable and Novartis will be required to continue to make all milestone and royalty payments otherwise due to us under the Collaboration Agreement, provided that if we materially breach the Collaboration Agreement such that the rights licensed to Novartis or the commercial prospects of emricasan products are seriously impaired, the milestone and royalty payments will be reduced by 50 percent. If Novartis terminates the Collaboration Agreement, we will not receive additional milestones under the Collaboration Agreement, and we may be unable to raise the additional capital required to further develop and commercialize emricasan or enter into a collaboration agreement with another pharmaceutical company with equivalent or comparable terms, or at all. Further, any delays in entering into new strategic partnership agreements related to emricasan could delay the development and commercialization of emricasan, which would harm our business, prospects, financial condition and results of operations.

We depend on Novartis to develop and commercialize emricasan, and we have limited control over how Novartis will conduct development and commercialization activities for emricasan.

Under the Collaboration Agreement, we rely on Novartis for a substantial portion of the financial resources and for the development, regulatory, and commercialization activities for emricasan, and we have limited control over the amount and timing of resources that Novartis devotes to emricasan. In addition, payments associated with development, regulatory and commercial milestones that we may be eligible to receive, as well as royalties and profit and loss sharing, will be dependent upon further advancement of emricasan by Novartis. If these milestones are not met and if emricasan is not commercialized, we will not receive future revenues from our collaboration with Novartis. Novartis may fail to develop or effectively commercialize emricasan for a variety of reasons, including because: it does not have sufficient resources or decides not to devote the necessary resources due to internal constraints such as limited cash or human resources or a change in strategic focus; it decides to pursue a competitive product developed outside of the collaboration; or it cannot obtain the necessary regulatory approvals.

Our dependence on Novartis and the Collaboration Agreement subjects us to a number of risks, including:

- Novartis may not commit sufficient resources to the development, regulatory approval, marketing or distribution of emricasan;
- Novartis may be unable to successfully complete the clinical development of emricasan or obtain all necessary approvals from the FDA and similar foreign regulatory agencies required to market emricasan;
- Novartis may fail to manufacture emricasan in compliance with requirements of the FDA and similar foreign regulatory agencies and in commercial quantities sufficient to meet market demand;
- there may be disputes between us and Novartis, including disagreements regarding the Collaboration Agreement, that may result in (1) the delay of (or prevent entirely) the achievement of development, regulatory and commercial objectives that would result in milestone payments, (2) the delay or termination of the development or commercialization of emricasan, and/or (3) costly litigation or arbitration that diverts our management’s attention and resources;
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- Novartis may not comply with applicable regulatory guidelines with respect to developing or commercializing emricasan, which could adversely impact the development of or sales of emricasan and could result in administrative or judicially imposed sanctions, including warning letters, civil and criminal penalties, injunctions, product seizures or detention, product recalls, total or partial suspension of production and refusal to approve any new drug applications;
- Novartis may experience financial difficulties;
- business combinations or significant changes in Novartis' business strategy may also adversely affect Novartis' ability to perform its obligations under the Collaboration Agreement;

- Novartis may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation; and
- notwithstanding certain non-competition requirements in the Collaboration Agreement, Novartis could independently move forward with a competing product candidate developed either independently or in collaboration with others, including our competitors.

If Novartis does not perform in the manner we expect or fulfill its responsibilities in a timely manner, or at all, the development, regulatory approval, and commercialization efforts related to emricasan could be delayed. It may be necessary for us to assume the responsibility at our own expense for the development of emricasan. In that event, we would likely need to seek additional funding and our potential to generate future revenues from emricasan could be significantly reduced and our business could be materially and adversely harmed.

We rely on third parties to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize emricasan, and our business could be substantially harmed.

We have and anticipate that we will continue to engage one or more third-party CROs in connection with our ongoing and future clinical trials for emricasan. We rely heavily on these parties for execution of our clinical trials, and we control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our trials is conducted in accordance with applicable protocol, legal, regulatory and scientific standards, and our reliance on our CROs does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with GCPs, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for product candidates in clinical development. Regulatory authorities enforce these GCPs through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of these CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable, and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, such regulatory authorities will determine that any of our clinical trials comply with the GCPs. In addition, our clinical trials must be conducted with drug product produced under cGMP regulations and will require a large number of test subjects. Our failure or any failure by our CROs to comply with these regulations or to recruit a sufficient number of patients may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of our CROs violate federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws.

Our CROs are not our employees and, except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our ongoing preclinical, clinical and nonclinical programs. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities, which could affect their performance on our behalf. Our clinical trials may be extended, delayed or terminated if CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons. As a result, we may not be able to complete development of, obtain regulatory approval for or successfully commercialize emricasan. Therefore, our financial results and the commercial prospects for emricasan would be harmed, our costs could increase and our ability to generate revenues could be delayed.

Switching or adding CROs involves substantial cost and requires extensive management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Although we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, prospects, financial condition and results of operations.

We rely completely on third parties to manufacture our preclinical and clinical drug supplies, and we intend to rely on third parties to produce commercial supplies of emricasan, if approved. The development and commercialization of emricasan could be stopped, delayed or made less profitable if those third parties fail to obtain and maintain regulatory approval of their facilities, fail to provide us with sufficient quantities of drug product or fail to do so at acceptable quality levels or prices.

We do not currently have nor do we plan to acquire the infrastructure or capability internally to manufacture our clinical drug supplies for use in the conduct of our clinical trials, and we lack the resources and the capability to manufacture emricasan on a clinical or commercial scale. Instead, we rely on contract manufacturers for such production.

We acquired quantities of active pharmaceutical ingredient, or API, of emricasan from Pfizer as part of our acquisition of the rights to the product candidate. We believe the quantities we acquired from Pfizer are sufficient to support our ongoing clinical trials. Pursuant to the Collaboration Agreement, Novartis is responsible for the manufacturing of emricasan beyond our ongoing Phase 2b clinical trials. If Novartis terminates the Collaboration Agreement, we will be required to qualify a new API manufacturer prior to commercialization of emricasan and potentially prior to the initiation or completion of future clinical trials. Any delay in qualifying the new manufacturer of API could delay the potential commercialization of emricasan, and in the event that we do not have sufficient API to complete our ongoing clinical trials, it could delay such trials.

In addition, we do not currently have a long-term commitment for the production of finished emricasan drug product. Metrics, Inc., a contract manufacturer, has performed formulation and finished goods manufacturing for us based on purchase orders. We expect to continue to purchase finished drug product from Metrics, but currently have no long-term supply commitment with Metrics. If Metrics is unable to produce the amount of finished drug product we need, we may need to identify and qualify other third-party manufacturers of finished drug product in order to complete the clinical development and commercialization of emricasan if Novartis terminates the Collaboration Agreement. Metrics' inability to produce the amount of finished drug product we need or any delay in identifying and qualifying another manufacturer of finished drug product could delay our clinical trials and the potential commercialization of emricasan.

The facilities used by our contract manufacturers to manufacture emricasan must be approved by the applicable regulatory authorities, including the FDA, pursuant to inspections that will be conducted after an NDA or comparable foreign regulatory marketing application is submitted. We do not control the manufacturing process of emricasan and are completely dependent on our contract manufacturing partners for compliance with the FDA's requirements for manufacture of both the API and finished drug product. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the FDA's strict regulatory requirements, they will not be able to secure or maintain FDA approval for the manufacturing facilities. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or any other applicable regulatory authorities does not approve these facilities for the manufacture of emricasan or if it withdraws any such approval in the future, or if our suppliers or contract manufacturers decide they no longer want to supply or manufacture for us, we may need to find alternative manufacturing facilities, in which case we might not be able to identify manufacturers for clinical or commercial supply on acceptable terms, or at all, which would significantly impact our ability to develop, obtain regulatory approval for or market emricasan.

In addition, the manufacture of pharmaceutical products is complex and requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling up and validating initial production and absence of contamination. These problems include difficulties with production costs and yields, quality control, including stability of the product, quality assurance testing, operator error, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. Furthermore, if contaminants are discovered in our supply of emricasan or in the manufacturing facilities in which emricasan is made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination. We cannot assure you that any stability or other issues relating to the manufacture of emricasan will not occur in the future. Additionally, our manufacturers may experience manufacturing difficulties due to resource constraints or as a result of labor disputes or unstable political environments. If our manufacturers were to encounter any of these difficulties, or otherwise fail to comply with their contractual obligations, our ability to provide our product candidate to patients in clinical trials would be jeopardized. Any delay or interruption in the supply of clinical trial supplies could delay the completion of clinical trials, increase the costs associated with maintaining clinical trial programs and, depending upon the period of delay, require us to commence new clinical trials at additional expense or terminate clinical trials completely.

If our third-party manufacturers use hazardous and biological materials in a manner that causes injury or violates applicable law, we may be liable for damages.

Our research and development activities involve the controlled use of potentially hazardous substances, including chemical and biological materials by our third-party manufacturers. Our manufacturers are subject to federal, state and local laws and regulations in the United States governing the use, manufacture, storage, handling and disposal of medical, radioactive and hazardous materials. Although we believe that our manufacturers' procedures for using, handling, storing and disposing of these materials comply with legally prescribed standards, we cannot completely eliminate the risk of contamination or injury resulting from medical, radioactive or hazardous materials. As a result of any such contamination or injury, we may incur liability. Furthermore, local, city, state or federal authorities may curtail the use of these materials and interrupt our business operations. In the event of an accident, we could be held liable for damages or penalized with fines, and the liability could exceed our resources. We do not have any insurance for liabilities arising from medical, radioactive or hazardous materials. Compliance with applicable environmental laws and regulations is expensive, and current or future environmental regulations may impair our research, development and production efforts, which could harm our business, prospects, financial condition or results of operations.

Risks Related to Our Financial Position and Capital Requirements

We have a limited operating history, have incurred significant operating losses since our inception and anticipate that we will continue to incur losses for the foreseeable future.

Our operations began in 2005, and we have only a limited operating history upon which you can evaluate our business and prospects. Our operations to date have been limited to conducting product development activities and performing research and development with respect to our clinical and preclinical programs. In addition, as an early-stage company, we have limited experience and have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the pharmaceutical area. Nor have we demonstrated an ability to obtain regulatory approval for or to commercialize a product candidate. Consequently, any predictions about our future performance may not be as accurate as they would be if we had a history of successfully developing and commercializing pharmaceutical products.

We have incurred significant operating losses since our inception, including net losses of $17.4 million, $29.7 million and $24.1 million for the years ended December 31, 2017, 2016 and 2015, respectively. As of December 31, 2017, we had an accumulated deficit of $168.0 million. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. Our losses have resulted principally from costs incurred in our research and development activities. We anticipate that we will continue to incur operating losses over the next several years as we execute our plan to expand our research, development and commercialization activities, including the clinical development of emricasan, and continue to incur the costs of operating as a public company. In addition, if we obtain regulatory approval of emricasan, we may incur significant sales and marketing expenses. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or whether or when we will become profitable, if ever.

We have not generated any revenues to date from product sales. We may never achieve or sustain profitability, which could depress the market price of our common stock and could cause our stockholders to lose all or a part of their investment.

Our ability to become profitable depends on our ability to develop and commercialize emricasan. To date, we have no products approved for commercial sale and have not generated any revenues from sales of any product candidate, and we do not know when, or if, we will generate revenues in the future. We do not anticipate generating revenues, if any, from sales of emricasan for at least the next several years, and we will never generate revenues from emricasan if we or Novartis does not obtain regulatory approval of emricasan. Our ability to generate future revenues depends heavily on our success in:

- developing and commercializing emricasan in collaboration with Novartis, including relying on Novartis for Phase 3 development and commercialization;
- developing and securing United States and/or foreign regulatory approvals for emricasan;
- manufacturing commercial quantities of emricasan at acceptable cost;
- achieving broad market acceptance of emricasan in the medical community and with third-party payors and patients;
- commercializing emricasan, assuming we receive regulatory approval; and
- pursuing clinical development of emricasan in additional indications.

Even if we do generate product sales, we may never achieve or sustain profitability. Our failure to become and remain profitable would depress the market price of our common stock and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations.

If Novartis terminates the Collaboration Agreement and we fail to obtain additional financing, we may be unable to complete the development and commercialization of emricasan.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts to continue the clinical development of emricasan, including our ongoing clinical trials. We believe the payments under the Collaboration Agreement and our existing capital resources will fund our share of the development costs for emricasan. If Novartis terminates the Collaboration Agreement, we will require significant additional amounts in order to continue clinical development and, if approved, launch and commercialize emricasan. To date, our operations have been primarily funded through the proceeds from the issuance of our common and preferred stock, including the proceeds from our initial public offering, or IPO, completed in July 2013 and follow-on public offerings completed in April 2015 and May 2017. In addition, we have funded our operations through proceeds from sales of common stock under an At Market Issuance Sales Agreement, or the Sales Agreement, with MLV & Co. LLC, or MLV, pursuant to which we sold 6,305,526 shares of our common stock pursuant to the Sales Agreement at a weighted average price per share of $2.35 and received net proceeds of $14.2 million, after deducting offering-related transaction costs and commissions. We terminated the Sales Agreement in December 2016. We expect to fund our near-term operations primarily with the upfront payment of $50.0 million that we received from Novartis in December 2016 pursuant to the Collaboration Agreement and proceeds from the issuance of a convertible promissory note in the principal amount of $15.0 million, which we issued to Novartis in February 2017.

We believe that our existing cash, cash equivalents and marketable securities will be sufficient to fund our operations for at least the next 12 months from the date of the filing of this Form 10-K. However, changing circumstances may cause us to consume capital significantly faster than we currently anticipate, and we may need to spend more money than currently expected because of circumstances beyond our control. We will require additional capital for the development and commercialization of product candidates other than emricasan.

We may seek to obtain additional financing in the future through the issuance of our common stock in public offerings, through other equity or debt financings or through collaborations or partnerships with other companies. We cannot be certain that additional funding will be available on acceptable terms, or at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of emricasan or other research and development initiatives.

Any of the above events could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common stock to decline.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidate.

We may seek additional capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interests of our stockholders will be diluted, and the terms may include liquidation or other preferences that adversely affect the rights of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and could involve certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies or product candidate, or grant licenses on terms unfavorable to us.

Our ability to utilize our net operating loss, or NOL, carryforwards and certain other tax attributes may be limited.

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an “ownership change” (generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period), the corporation’s ability to use its pre-change NOL carryforwards and other pre-change tax attributes to offset its post-change income may be limited. During 2017, we completed a Section 382 analysis to determine if our historical NOLs and research and development credits are limited due to an ownership change. Based on this analysis, we experienced an ownership change as a result of our Series A financing in October 2006 and our IPO in July 2013. We may also experience “ownership changes” in the future as a result of subsequent shifts in our stock ownership. At December 31, 2017, we had federal and state NOL carryforwards of $94.6 million and $76.4 million, respectively, net of a de minimis amount of federal NOLs that were determined to be limited for future utilization by Section 382. We also had federal and state research and development credits of $5.0 million and $2.0 million, respectively, net of a de minimis amount of research and development credits that were determined to be limited for future utilization by Section 382. Furthermore, under recently enacted U.S. tax legislation, although the treatment of tax losses generated in taxable years ending before December 31, 2017 has generally not changed, tax losses generated in taxable years beginning after December 31, 2017 may only be utilized to offset 80% of taxable income annually. This change may require us to pay federal income taxes in future years despite generating a loss for federal income tax purposes in prior years.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and stock price.

As widely reported, global credit and financial markets have experienced extreme disruptions in the past several years, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, or do not improve, it may make any necessary equity or debt financing more difficult, more costly and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive these difficult economic times, which could directly affect our ability to attain our operating goals on schedule and on budget.

At December 31, 2017, we had $74.9 million of cash, cash equivalents and marketable securities. While we are not aware of any downgrades, material losses, or other significant deterioration in the fair value of our cash equivalents and marketable securities since December 31, 2017, no assurance can be given that deterioration of the global credit and financial markets would not negatively impact our current portfolio of cash equivalents or marketable securities or our ability to meet our financing objectives. Furthermore, our stock price may decline due in part to the volatility of the stock market.

Risks Related to Our Intellectual Property

If our efforts to protect the proprietary nature of the intellectual property related to our technologies are not adequate, we may not be able to compete effectively in our market.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our technologies. Any disclosure to or misappropriation by third parties of our confidential proprietary information could enable competitors to quickly duplicate or surpass our technological achievements, thus eroding our competitive position in our market.

Composition-of-matter patents on the API and crystalline forms are generally considered to be the strongest form of intellectual property protection for pharmaceutical products, as such patents provide protection without regard to any method of use. We cannot be certain that the claims in our patent applications covering composition-of-matter and crystalline forms of emricasan will be considered patentable by the United States Patent and Trademark Office, or the USPTO, courts in the United States, or by the patent offices and courts in foreign countries. Method-of-use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products “off-label.” Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent or prosecute.

The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. Some of our patents related to emricasan were acquired from a predecessor owner and were therefore not written by us or our attorneys, and we did not have control over the drafting and prosecution of these patent applications. Further, the former patent owners might not have given the same attention to the drafting and early prosecution of these patents and applications as we would have if we had been the owners of the patents and applications and had control over the drafting and prosecution. In addition, the former patent owners may not have been completely familiar with United States patent law, possibly resulting in inadequate disclosure and/or claims. This could result in findings of invalidity or unenforceability of the patents we own or patents issuing with reduced claim scope. Under the Collaboration Agreement, Novartis is responsible for the prosecution and maintenance of jointly owned patents and patent applications. Therefore, these patent applications may not be written by us or our attorneys, and we will not control the drafting, prosecution and maintenance of these patent applications and patents. Novartis might not give the same attention to the drafting and prosecution of these applications as we would if we controlled the drafting and prosecution. This could result in findings of invalidity or unenforceability of such patents or such patent applications issuing with reduced claim scope.

In addition, the patent applications that we own or that we may license may fail to result in issued patents in the United States or in other foreign countries. Even if the patents do successfully issue, third parties may challenge the validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated or held unenforceable. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims. If the breadth or strength of protection provided by the patent applications we hold with respect to emricasan is threatened, it could dissuade Novartis from developing emricasan and threaten the ability to commercialize emricasan. Further, if there are delays in our clinical trials, the period of time during which emricasan is marketed under patent protection would be reduced.

Since patent applications in the United States and most other countries are confidential for a period of time after filing, we cannot be certain that we are the first to file any patent application related to emricasan. Furthermore, for applications in which all claims are entitled to a priority date before March 16, 2013, an interference proceeding can be provoked by a third-party or instituted by the USPTO to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. For applications containing a claim not entitled to priority before March 16, 2013, the passage of the America Invents Act changed the priority of invention to a “first to file” system in the United States. This requires us to be cognizant going forward of the time from invention to filing of a patent application.

In addition to the protection afforded by patents, we seek to rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our drug discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. Although we require all of our employees to assign their inventions to us, and require all of our employees, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot be certain that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Furthermore, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent unauthorized material disclosure of our intellectual property to third parties, we will not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, operating results and financial condition.

Third-party claims of intellectual property infringement may prevent or delay our drug discovery and development efforts.

Our commercial success depends in part on our and our collaborators avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation involving patents and other intellectual property rights in the biotechnology and pharmaceutical industries, as well as administrative proceedings for challenging patents, including interference and reexamination proceedings before the USPTO or oppositions and other comparable proceedings in foreign jurisdictions. Under United States patent reform, new procedures including inter partes review and post grant review have been implemented. As stated above, this reform brings uncertainty to the possibility of challenge to our patents in the future. Numerous United States and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we or our collaborators are developing emricasan. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that emricasan may give rise to claims of infringement of the patent rights of others.

Third parties may assert that we or our collaborators are employing their proprietary technology without authorization. There may be third-party patents of which we or our collaborators are currently unaware with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of emricasan. Because patent applications can take many years to issue, there may be currently pending patent applications that may later result in issued patents that emricasan may infringe. In addition, third parties may obtain patents in the future and claim that use of our or our collaborators' technologies infringes upon these patents. Under the Collaboration Agreement, we will cooperate with Novartis in the defense of the patent rights under the Collaboration Agreement in the event any patent or patent application is challenged by a third party. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of emricasan, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block the ability to commercialize the product candidate unless we or our collaborators obtain a license under the applicable patents, or until such patents expire or they are finally determined to be held invalid or unenforceable. Similarly, if any third-party patent were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy or patient selection methods, the holders of any such patent may be able to block the ability to develop and commercialize the product candidate, unless we or our collaborators obtain a license or until such patent expires or is finally determined to be held invalid or unenforceable. In either case, such a license may not be available on commercially reasonable terms or at all. If we or our collaborators are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, or at all, our ability to commercialize emricasan may be impaired or delayed, which could in turn significantly harm our business.

Parties making claims against us may seek and obtain injunctive or other equitable relief, which could effectively block the ability to further develop and commercialize emricasan. Defense of these claims, regardless of their merit,

would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing products, which may be impossible or require substantial time and monetary expenditure. We cannot predict whether any such license would be available at all or whether it would be available on commercially reasonable terms. Furthermore, even in the absence of litigation, we or our collaborators may need to obtain licenses from third parties to advance our research or allow commercialization of emricasan. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we or our collaborators would be unable to further develop and commercialize emricasan, which could harm our business significantly.

We or our collaborators may be involved in lawsuits to protect or enforce our patents, which could be expensive, time-consuming and unsuccessful.

Competitors may infringe our patents. To counter infringement or unauthorized use, we or our collaborators may be required to file infringement claims, which can be expensive and time-consuming. Under the Collaboration Agreement, Novartis will have the first right to bring and control any legal action in connection with a third party infringement relating to patent rights under the Collaboration Agreement. In an infringement proceeding, a court may decide that one or more of our patents is not valid or is unenforceable or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated, held unenforceable, or interpreted narrowly and could put our patent applications at risk of not issuing. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we or our collaborators may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing products, which may be impossible or require substantial time and monetary expenditure.

Interference proceedings provoked by third parties or brought by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent misappropriation of our trade secrets or confidential information, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees on any issued patent are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. In such an event, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We may be subject to claims that our employees or independent contractors have wrongfully used or disclosed confidential information of third parties.

We have received confidential and proprietary information from third parties. In addition, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we

or our employees or independent contractors have inadvertently or otherwise used or disclosed confidential information of these third parties or our employees' former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial cost and be a distraction to our management and employees.

Risks Related to Ownership of our Common Stock

The price of our stock may be volatile.

Prior to our IPO, there was no public market for our common stock. Since the commencement of trading in connection with our IPO in July 2013 through March 1, 2018, the sale price per share of our common stock on the Nasdaq Global Market, or Nasdaq, has ranged from a low of $1.40 to a high of $15.67. The trading price of our common stock is likely to continue to be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control, including limited trading volume. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this annual report, these factors include:

- the commencement, enrollment or results of our ongoing clinical trials of emricasan or any future clinical trials we may conduct, or changes in the development status of emricasan;
- any delay in our regulatory filings for emricasan and any adverse development or perceived adverse development with respect to the applicable regulatory authority's review of such filings, including without limitation the FDA's issuance of a "refusal to file" letter or a request for additional information;
- adverse results or delays in clinical trials;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- adverse regulatory decisions, including failure to receive regulatory approval for emricasan;
- changes in laws or regulations applicable to our product candidate or products, including but not limited to clinical trial requirements for approvals;
- adverse developments concerning our manufacturers;
- our inability to obtain adequate product supply for any approved drug product or inability to do so at acceptable prices;
- our inability to establish collaborations if needed;
- our failure to commercialize emricasan;
- additions or departures of key scientific or management personnel;
- unanticipated serious safety concerns related to the use of emricasan;
- introduction of new products or services offered by us or our competitors;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors;
- announcements by Novartis relating to the development or commercialization of emricasan;
- our ability to effectively manage our growth;
- the size and growth, if any, of the NASH cirrhosis, POLT-HCV-SVR and NASH fibrosis markets and other targeted markets;
- our ability to successfully enter new markets;
- actual or anticipated variations in quarterly operating results;
- our cash position;
- our failure to meet the estimates and projections of the investment community or that we may otherwise provide to the public;
- publication of research reports about us or our industry or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- changes in the market valuations of similar companies;
- overall performance of the equity markets;
- sales of our common stock by us or our stockholders in the future;
- trading volume of our common stock;
- changes in accounting practices;
- ineffectiveness of our internal controls;

- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- significant lawsuits, including patent or stockholder litigation;
- general political and economic conditions; and
- other events or factors, many of which are beyond our control.

In addition, the stock market in general, and Nasdaq and biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance. The realization of any of the above risks or any of a broad range of other risks, including those described in this "Risk Factors" section and elsewhere in this annual report on Form 10-K, could have a dramatic and material adverse impact on the market price of our common stock.

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We have never declared or paid any cash dividend on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock.

Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.

As of December 31, 2017, our executive officers, directors, 5% stockholders and their affiliates owned approximately 17% of our outstanding voting stock. Therefore, these stockholders have the ability to influence us through this ownership position. These stockholders may be able to determine all matters requiring stockholder approval. For example, these stockholders may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that our stockholders may feel are in their best interests.

We are an emerging growth company, and we cannot be certain if the reduced reporting requirements applicable to emerging growth companies will make our common stock less attractive to investors.

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements and exemptions from the requirements of holding nonbinding advisory votes on executive compensation and stockholder approval of any golden parachute payments not previously approved. We could be an emerging growth company for up to five years following 2013, the year in which we completed our IPO, although circumstances could cause us to lose that status earlier, including if the market value of our common stock held by non-affiliates exceeds $700.0 million as of any June 30 before that time or if we have total annual gross revenue of $1.0 billion or more during any fiscal year before that time, in which cases we would no longer be an emerging growth company as of the following December 31 or if we issue more than $1.0 billion in non-convertible debt during any three year period before that time, in which case we would cease to be an emerging growth company immediately. Even after we no longer qualify as an emerging growth company, we may qualify as a "smaller reporting company," which would allow us to take advantage of many of the same exemptions from disclosure requirements including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these

exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies. As a result, changes in rules of United States generally accepted accounting principles or their interpretation, the adoption of new guidance or the application of existing guidance to changes in our business could significantly affect our financial position and results of operations.

We incur significant increased costs as a result of operating as a public company, and our management is required to devote substantial time to compliance initiatives.

As a public company, we incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act, as well as rules subsequently adopted by the Securities and Exchange Commission, or the SEC, and Nasdaq to implement provisions of the Sarbanes-Oxley Act, imposes significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. Further, in July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas such as “say on pay” and proxy access. Current legislation permits emerging growth companies to implement many of these requirements over a longer period and up to five years following their IPO. We are taking advantage of this legislation but cannot guarantee that we will not be required to implement these requirements sooner than budgeted or planned and thereby incur unexpected expenses. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate.

The rules and regulations applicable to public companies may substantially increase our legal and financial compliance costs and make some activities more time-consuming and costly. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition and results of operations. The increased costs will decrease our net income or increase our net loss and may require us to reduce costs in other areas of our business or increase the prices of our products or services. For example, these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required to incur substantial costs to maintain the same or similar coverage. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers.

Sales of a substantial number of shares of our common stock by our existing stockholders in the public market could cause our stock price to fall.

Persons who were our stockholders prior to our IPO in July 2013 continue to hold a substantial number of shares of our common stock that they are able to sell in the public market, subject in some cases to certain legal restrictions. Significant portions of these shares are held by a small number of stockholders. If these stockholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline. The perception in the market that these sales may occur could also cause the trading price of our common stock to decline. As of March 1, 2018, we had 30,059,999 shares of common stock outstanding.

In addition, shares of common stock that are either subject to outstanding options or reserved for future issuance under our equity incentive plans will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 and Rule 701 under the Securities Act of 1933, or the Securities Act. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

The holders of 791,547 shares of our common stock as of March 1, 2018 (including shares issuable upon exercise of options and warrants) are entitled to rights with respect to the registration of their shares under the Securities Act. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares held by affiliates, as defined in Rule 144 under the Securities Act. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock.

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

We expect that significant additional capital may be needed in the future to continue our planned operations, including conducting clinical trials, commercialization efforts, expanded research and development activities and costs associated with operating a public company. To raise capital, we may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities, our stockholders may be materially diluted by subsequent sales, and new investors could gain rights preferences and privileges senior to the holders of our common stock.

Pursuant to our 2013 equity incentive award plan, or the 2013 Plan, which became effective on the business day prior to the public trading date of our common stock, our management is authorized to grant stock options to our employees, directors and consultants. The number of shares available for future grant under the 2013 Plan will automatically increase each year by an amount equal to the least of (1) 1,000,000 shares of our common stock, (2) 5% of the outstanding shares of our common stock as of the last day of our immediately preceding fiscal year, or (3) such other amount as our board of directors may determine. Unless our board of directors elects not to increase the number of shares available for future grant each year, our stockholders may experience additional dilution, which could cause our stock price to fall.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

Anti-takeover provisions under our charter documents and Delaware law could delay or prevent a change of control, which could limit the market price of our common stock and may prevent or frustrate attempts by our stockholders to replace or remove our current management.

Our amended and restated certificate of incorporation and amended and restated bylaws contain provisions that could delay or prevent a change of control of our company or changes in our board of directors that our stockholders might consider favorable. Some of these provisions include:

- a board of directors divided into three classes serving staggered three-year terms, such that not all members of the board will be elected at one time;
- a prohibition on stockholder action through written consent, which requires that all stockholder actions be taken at a meeting of our stockholders;
- a requirement that special meetings of stockholders be called only by the chairman of the board of directors, the chief executive officer, the president or by a majority of the total number of authorized directors;
- advance notice requirements for stockholder proposals and nominations for election to our board of directors;
- a requirement that no member of our board of directors may be removed from office by our stockholders except for cause and, in addition to any other vote required by law, upon the approval of not less than two-thirds of all outstanding shares of our voting stock then entitled to vote in the election of directors;
- a requirement of approval of not less than two-thirds of all outstanding shares of our voting stock to amend any bylaws by stockholder action or to amend specific provisions of our certificate of incorporation; and
- the authority of the board of directors to issue preferred stock on terms determined by the board of directors without stockholder approval and such preferred stock may include rights superior to the rights of the holders of common stock.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporate Law, which may prohibit certain business combinations with stockholders owning 15% or more of our outstanding voting stock. These anti-takeover provisions and other provisions in our amended and restated certificate of incorporation and amended and restated bylaws could make it more difficult for stockholders or potential acquirors to obtain control of our board of directors or initiate actions that are opposed by the then-current board of directors and could also delay or impede a merger, tender offer or proxy contest involving our company. These provisions could also discourage proxy contests and make it more difficult for our stockholders to elect directors of their choosing or cause us to take other corporate actions desired by certain stockholders. Any delay or prevention of a change of control transaction or changes in our board of directors could cause the market price of our common stock to decline.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our stock price and trading volume could decline.

The trading market for our common stock depends in part on the research and reports that securities or industry analysts publish about us or our business. We currently have limited research coverage by securities and industry analysts. In the event one or more of the analysts who covers us downgrades our stock or publishes inaccurate or unfavorable research about our business, our stock price may decline. If one or more of these analysts ceases coverage of our company or fails to publish reports on us regularly, demand for our stock could decrease, which might cause our stock price and trading volume to decline.

ITEM 1B. UNRESOLVED STAFF COMMENTS
None.

ITEM 2. PROPERTIES
We lease 13,225 square feet of space for our headquarters in San Diego, California under an agreement that expires in September 2020.

ITEM 3. LEGAL PROCEEDINGS
We are currently not a party to any material legal proceedings.

ITEM 4. MINE SAFETY DISCLOSURES
Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Market Information

Our common stock has been traded on the Nasdaq Global Market since July 25, 2013 under the symbol "CNAT." Prior to such time, there was no public market for our common stock. The following table sets forth, for the quarterly periods indicated, the high and low sale prices for our common stock on the Nasdaq Global Market.

	High	Low
Year Ended December 31, 2017		
First Quarter	$6.43	$4.06
Second Quarter	$9.40	$4.65
Third Quarter	$7.05	$4.80
Fourth Quarter	$6.18	$3.88

	High	Low
Year Ended December 31, 2016		
First Quarter	$4.05	$1.40
Second Quarter	$3.45	$1.88
Third Quarter	$2.44	$1.68
Fourth Quarter	$6.30	$1.45

Holders of Common Stock

As of March 1, 2018, there were 30,059,999 shares of our common stock outstanding and 27 holders of record of our common stock. This number was derived from our shareholder records and does not include beneficial owners of our common stock whose shares are held in the name of various dealers, clearing agencies, banks, brokers and other fiduciaries.

Dividend Policy

We have never declared or paid any cash dividend on our common stock. We currently anticipate that we will retain future earnings, if any, for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any future determination related to our dividend policy will be made at the discretion of our board of directors.

Equity Compensation Plan Information

The following table summarizes securities available under our equity compensation plans as of December 31, 2017.

	Equity Compensation Plan Information		
Plan category	Number of securities to be	Weighted-average	Number of securities remaining

	issued upon exercise of outstanding options, warrants and rights (a)	exercise price of outstanding options, warrants and rights (b)	available for future issuance under equity compensation plans (excluding securities reflected in column (a)) (c)
Equity compensation plans approved by security holders	4,831,172	$ 5.05	1,140,171
Equity compensation plans not approved by security holders	—	—	—
Total	4,831,172	$ 5.05	1,140,171

Performance Graph

The information contained in this Performance Graph section shall not be deemed “soliciting material” or to be “filed” with the Securities and Exchange Commission, or the SEC, for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liabilities under that Section, and shall not be deemed to be incorporated by reference into any filing of Conatus Pharmaceuticals Inc. under the Securities Act of 1933, as amended, or the Exchange Act.

The following graph shows a comparison from July 25, 2013, the date our common stock commenced trading on the Nasdaq Global Market, through December 31, 2017 of cumulative total return for our common stock, the Nasdaq Composite Index and the Nasdaq Biotechnology Index. Such returns are based on historical results and are not intended to suggest future performance. The graph assumes the investment of $100 on July 25, 2013 in our stock at the opening trading price of $11.00 and in the indices at the opening trading prices, with the reinvestment of dividends, although dividends have not been declared on our common stock.

	7/25/13	12/31/13	12/31/14	12/31/15	12/31/16	12/31/17
Conatus Pharmaceuticals Inc.	$ 100	$ 59	$ 64	$ 26	$ 48	$ 42
Nasdaq Composite	$ 100	$ 116	$ 132	$ 140	$ 150	$ 192
Nasdaq Biotechnology	$ 100	$ 117	$ 157	$ 175	$ 137	$ 166

ITEM 6. SELECTED FINANCIAL DATA

The following tables set forth a summary of our historical financial data as of, and for the periods ended on, the dates indicated. We have derived the statement of operations data and balance sheet data from our audited financial statements. You should read the selected financial data in conjunction with the related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations," both of which are included elsewhere in this report. Our historical results for any prior period are not necessarily indicative of our future results.

	Year Ended December 31,				
	2017	2016	2015	2014	2013
Statement of Operations Data:					
Revenues:					
Collaboration revenue	$35,376,796	$799,046	$—	$—	$—
Total revenues	35,376,796	799,046	—	—	—
Operating expenses:					
Research and development	43,220,446	20,293,632	16,297,617	14,908,843	6,947,439
General and administrative	9,706,834	10,337,182	7,833,085	7,379,339	4,650,807
Total operating expenses	52,927,280	30,630,814	24,130,702	22,288,182	11,598,246
Loss from operations	(17,550,484)	(29,831,768)	(24,130,702)	(22,288,182)	(11,598,246)
Other income (expense):					
Interest income	892,178	138,413	67,885	57,616	22,144
Interest expense	(662,395)	(70,000)	(70,000)	(70,000)	(462,570)
Other (expense) income	(75,712)	29,914	(15,809)	(19,325)	(1,070)
Other financing expense	—	—	—	—	(3,576,750)
Total other income (expense)	154,071	98,327	(17,924)	(31,709)	(4,018,246)
Net loss	$(17,396,413)	$(29,733,441)	$(24,148,626)	$(22,319,891)	$(15,616,492)
Net loss per share applicable to common stockholders, basic and diluted	$(0.61)	$(1.31)	$(1.30)	$(1.44)	$(0.63)
Weighted average shares outstanding used in computing net loss per share applicable to common stockholders, basic and diluted	28,586,625	22,649,911	18,617,537	15,478,999	7,358,201

	December 31,				
	2017	2016	2015	2014	2013
Balance Sheet Data:					
Cash, cash equivalents and marketable securities	$74,853,247	$77,015,124	$36,508,109	$37,071,946	$56,352,987
Working capital	51,081,683	40,892,572	34,507,442	33,693,531	54,081,487
Total assets	81,940,890	82,323,840	39,727,268	38,447,881	56,935,954
Note payable	—	1,000,000	1,000,000	1,000,000	1,000,000
Convertible note payable	13,157,534	—	—	—	—
Deferred revenue, less current portion	12,518,667	20,803,762	—	—	—

Other long-term liabilities	126,030	171,544	204,224	58,699	—
Total stockholders' equity	27,996,312	21,788,546	34,540,346	33,213,949	53,118,950

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

Overview

We are a biotechnology company focused on the development and commercialization of novel medicines to treat liver disease. We are developing emricasan, a first-in-class, orally active pan-caspase protease inhibitor, for the treatment of patients with chronic liver disease. Emricasan is designed to reduce the activities of human caspases, which are enzymes that mediate inflammation and apoptosis. We believe that by reducing the activity of these enzymes, caspase inhibitors have the potential to interrupt the progression of a variety of diseases.

We plan to continue advancing toward registration of emricasan for patients with fibrosis or cirrhosis due to nonalcoholic steatohepatitis, or NASH. Our current clinical program for emricasan includes the following randomized, double-blind, placebo-controlled Phase 2b clinical trials:

- Phase 2b POLT-HCV-SVR Clinical Trial: In May 2014, we initiated a clinical trial in approximately 60 post-orthotopic liver transplant, or POLT, recipients with reestablished liver fibrosis post-transplant as a result of recurrent hepatitis C virus, or HCV, infection who have successfully achieved a sustained viral response, or SVR, following HCV antiviral therapy, or POLT-HCV-SVR, patients with residual fibrosis or cirrhosis, classified as Ishak Fibrosis Score 2-6. Top-line results are expected in the second quarter of 2018.
- Phase 2b ENCORE-PH (Portal Hypertension) Clinical Trial: In November 2016, we initiated a clinical trial to evaluate the effect of emricasan in approximately 240 compensated or early decompensated NASH cirrhosis patients with severe portal hypertension. Top-line results are expected in the second half of 2018.
- Phase 2b ENCORE-NF (NASH Fibrosis) Clinical Trial: In January 2016, we initiated a clinical trial to evaluate emricasan in approximately 330 patients with liver fibrosis resulting from NASH. Top-line results are expected in the first half of 2019.
- Phase 2b ENCORE-LF (Liver Function) Clinical Trial: In May 2017, we initiated a clinical trial to evaluate emricasan in approximately 210 patients with decompensated NASH cirrhosis. Top-line results are expected in the second half of 2019.

In addition, we recently initiated a non-treatment observational study pursuant to which subjects from the four trials above will be followed for an up to three-year safety follow-up.

In May 2017, Novartis Pharma AG, or Novartis, exercised its option under the Option, Collaboration and License Agreement, or the Collaboration Agreement, we entered into with Novartis in December 2016. Pursuant to such exercise, we granted Novartis an exclusive, worldwide license to our intellectual property rights relating to emricasan to collaborate with us for the global development and commercialization of products containing emricasan either as a single active ingredient or in combination with other Novartis compounds for liver cirrhosis or liver fibrosis, for the treatment, diagnosis and prevention of disease in all indications in humans. The license became effective upon our receipt of a $7.0 million option exercise payment in July 2017.

Pursuant to the Collaboration Agreement, we are responsible for completing the three ENCORE trials and the POLT-HCV-SVR trial described above. We share the costs of these four Phase 2b trials equally with Novartis. In addition, until the completion of the four Phase 2b trials, we will equally share the costs of the non-treatment observational study that will follow patients from the four Phase 2b trials. After the completion of the four Phase 2b trials, Novartis will assume 100% of the observational study costs. Novartis is responsible for 100% of certain expenses for required registration-supportive nonclinical activities. Novartis is also responsible for the development of emricasan beyond the four Phase 2b trials and the observational study described above, including the Phase 3 development of emricasan single agent products and all development for emricasan combination products, and Novartis has agreed to use commercially reasonable efforts to develop and commercialize emricasan products. A joint steering committee comprised of representatives from our company and Novartis oversees the collaboration, development and commercialization of emricasan products.

Under the Collaboration Agreement, Novartis paid us an upfront payment of $50.0 million and the option exercise payment of $7.0 million. In addition, we are eligible to receive up to an aggregate of $650.0 million in milestone payments, as well as royalties.

In June 2017, the U.S. Food and Drug Administration granted Orphan Drug Designation to our preclinical product candidate IDN-7314, a pan-caspase inhibitor, for the treatment of primary sclerosing cholangitis, or PSC, a disease affecting bile ducts in the liver, which can lead to cirrhosis and liver failure. In October 2017, the European Medicines Agency granted orphan designation to IDN-7314 for the treatment of PSC. We believe these orphan designations

provide an opportunity to address an important unmet medical need and expand our development pipeline beyond emricasan. Pursuant to the Collaboration Agreement, Novartis will have a right of first negotiation prior to any offer for IDN-7314 by us to a third party, and we may not develop IDN-7314 in any pivotal registration clinical trials or commercialize IDN-7314 in liver disease until the earlier of five years after the first commercial sale of an emricasan product in the United States or major European market or ten years from the execution date of the Collaboration Agreement. We will continue to evaluate the potential of IDN-7314 as a product candidate as a component of our pipeline expansion plans. We also plan to expand our development pipeline by internal development of new preclinical product candidates leveraging our expertise with caspase inhibition or by in-licensing or acquiring preclinical or clinical product candidates consistent with our product development and regulatory expertise. In addition to liver disease, we may pursue the development of product candidates in other disease areas.

Since our inception, our primary activities have been organizational activities, including recruiting personnel, conducting research and development, including clinical trials, and raising capital. We have no products approved for sale, and we have not generated any revenues from product sales to date. We have funded our operations since inception primarily through sales of equity securities and convertible promissory notes and payments made under the Collaboration Agreement, and we have incurred significant operating losses since our inception. We have never been profitable and have incurred net losses of $17.4 million, $29.7 million and $24.1 million in the years ended December 31, 2017, 2016 and 2015, respectively. As of December 31, 2017, we had an accumulated deficit of $168.0 million.

We expect to continue to incur significant operating losses and negative cash flows from operating activities for the foreseeable future as we continue the clinical development of emricasan and seek regulatory approval for and, if approved, pursue commercialization of emricasan. In May 2017, we completed a public offering of 5,980,000 shares of our common stock at a public offering price of $5.50 per share. We received net proceeds of $30.6 million, after deducting underwriting discounts and commissions and offering-related transaction costs. Immediately following the offering, we used $11.2 million of the net proceeds to repurchase and retire 2,166,836 shares of our common stock from funds affiliated with Advent Private Equity, or Advent, at a price of $5.17 per share.

As of December 31, 2017, we had cash, cash equivalents and marketable securities of $74.9 million. Although it is difficult to predict future liquidity requirements, we believe that our existing cash, cash equivalents and marketable securities will be sufficient to fund our operations for at least the next 12 months from the date of the filing of this Form 10-K. We will need to raise additional capital to fund further operations, including the development of internally developed and/or in-licensed product candidates other than emricasan or the co-commercialization of emricasan with Novartis. We may obtain additional financing in the future through the issuance of our common stock in future public offerings, through other equity or debt financings or through collaborations or partnerships with other companies.

Successful transition to profitability is dependent upon achieving a level of revenues adequate to support our cost structure. We cannot assure you that we will ever be profitable or generate sustained positive cash flow from operating activities and, unless and until we do, we will need to raise substantial additional capital through equity or debt financings or through collaborations or partnerships with other companies. We may not be able to raise additional capital on terms acceptable to us, or at all, and any failure to raise capital as and when needed could have a material adverse effect on our results of operations, financial condition and our ability to execute on our business plan.

JOBS Act

In April 2012, the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, was signed into law. The JOBS Act contains provisions that, among other things, reduce certain reporting requirements for an “emerging growth company.” As an “emerging growth company,” we are electing not to take advantage of the extended transition period afforded by the JOBS Act for the implementation of new or revised accounting standards, and as a result, we will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-emerging growth companies. Section 107 of the JOBS Act provides that our decision not to take advantage of the extended transition period is irrevocable. In addition, we are in the process of evaluating the benefits of relying on the other exemptions and reduced reporting requirements provided by the JOBS Act. Subject to certain conditions set forth in the JOBS Act, if as an “emerging growth company” we choose to rely on such exemptions, we may not be required to, among other things, (i) provide an auditor’s attestation report on our system of internal control over financial reporting pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, (ii) provide all of the compensation disclosure that may be required of non-emerging growth public companies under the Dodd-Frank Wall Street Reform and Consumer Protection Act, (iii) comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor’s report providing additional information about the audit and the financial statements (auditor discussion and analysis) and (iv) disclose certain executive compensation-related items such as the correlation between executive compensation and performance and comparisons of the Chief Executive Officer’s compensation to median employee compensation. These exemptions will apply for a period of five years following the completion of our initial public offering, or IPO,

or until we no longer meet the requirements of being an “emerging growth company,” whichever is earlier.

Financial Overview

Revenues

Our revenues to date have been generated primarily from the Collaboration Agreement with Novartis. Under the terms of the Collaboration Agreement, we received an upfront payment of $50.0 million. In May 2017, Novartis exercised its option, and we received a $7.0 million option exercise payment in July 2017. We are eligible to receive up to $650.0 million in additional payments for development, regulatory and commercial sales milestones, as well as royalties or profit and loss sharing on future product sales in the United States, if any.

We currently have no products approved for sale, and we have not generated any revenues from product sales to date. We have not submitted any product candidate for regulatory approval. If we fail to achieve clinical success in the development of emricasan in a timely manner and/or obtain regulatory approval for this product candidate, or to successfully develop other product candidates, our ability to generate future revenues would be materially adversely affected.

Research and Development Expenses

The majority of our operating expenses to date have been incurred in research and development activities. Starting in late 2011, research and development expenses have been focused on the development of emricasan. Since acquiring emricasan in 2010, we have incurred $108.8 million in the development of emricasan through December 31, 2017. Our business model is currently focused on the development of emricasan in various liver diseases and is dependent upon our continuing to conduct research and a significant amount of clinical development. Our research and development expenses consist primarily of:

- expenses incurred under agreements with contract research organizations, or CROs, investigative sites and consultants that conduct our clinical trials and our preclinical studies;
- employee-related expenses, which include salaries and benefits;
- the cost of finalizing our chemistry, manufacturing and controls, or CMC, capabilities and providing clinical trial materials; and
- costs associated with other research activities and regulatory approvals.

Research and development costs are expensed as incurred.

At this time, due to the inherently unpredictable nature of preclinical and clinical development, we are unable to estimate with any certainty the costs we will incur in the continued development of emricasan. Clinical development timelines, the probability of success and development costs can differ materially from expectations.

The costs of clinical trials may vary significantly over the life of a project owing to factors that include but are not limited to the following:

- per patient trial costs;
- the number of patients that participate in the clinical trials;
- the number of sites included in the clinical trials;
- the countries in which the clinical trials are conducted;
- the length of time required to enroll eligible patients;
- the number of doses that patients receive;
- the drop-out or discontinuation rates of patients;
- potential additional safety monitoring or other studies requested by regulatory agencies;
- the duration of patient follow-up; and
- the efficacy and safety profile of the product candidate.

We are currently focused on advancing emricasan in multiple indications, and our future research and development expenses will depend on its clinical success. In addition, we cannot forecast with any degree of certainty to what extent Novartis will develop and commercialize emricasan under the Collaboration Agreement.

Research and development expenditures will continue to be significant as we continue clinical development of emricasan over at least the next several years. We expect to incur significant development costs as we conduct our ongoing Phase 2b trials of emricasan and develop product candidates other than emricasan.

We do not expect emricasan to be commercially available, if at all, for at least the next several years.

General and Administrative Expenses

General and administrative expenses consist principally of salaries and related costs for personnel in executive, finance, business development and administrative functions. Other general and administrative expenses include costs related to being a public company, as well as insurance, facilities, travel, patent filing and maintenance, legal and consulting expenses.

If we exercise our option to co-commercialize emricasan pursuant to the Collaboration Agreement, we may incur expenses associated with activities related to commercializing emricasan. Some expenses may be incurred prior to receiving regulatory approval of emricasan. We do not expect to receive any such regulatory approval for at least the next several years.

Interest Income

Interest income consists primarily of interest income earned on our cash, cash equivalents and marketable securities.

Interest Expense

Interest expense consists of accrued interest on our $15.0 million convertible promissory note payable to Novartis, or the Novartis Note, and coupon interest on our $1.0 million promissory note payable to Pfizer Inc., or the Pfizer Note.

Other Income (Expense)

Other income (expense) includes non-operating transactions such as those caused by currency fluctuations between transaction dates and settlement dates and the conversion of account balances held in foreign currencies to U.S. dollars.

Critical Accounting Policies and Significant Judgments and Estimates

Our management’s discussion and analysis of financial condition and results of operations is based on our financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States, or GAAP. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported revenues and expenses during the reporting periods. These items are monitored and analyzed by us for changes in facts and circumstances, and material changes in these estimates could occur in the future. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Changes in estimates are reflected in reported results for the period in which they become known. Actual results may differ materially from these estimates under different assumptions or conditions.

While our significant accounting policies are more fully described in the notes to our audited financial statements appearing elsewhere in this annual report, we believe that the following accounting policies are critical to the process of making significant judgments and estimates in the preparation of our financial statements and understanding and evaluating our reported financial results.

Revenue Recognition

We recognize revenue when each of the following four criteria is met: (i) persuasive evidence of an arrangement exists; (ii) products are delivered or as services are rendered; (iii) the sales price is fixed or determinable; and (iv) collectability is reasonably assured.

Multiple-element arrangements, such as the Collaboration Agreement, may include (i) grants of licenses, or options to obtain licenses, to intellectual property, (ii) research and development services, (iii) participation on joint research and/or joint development committees, and/or (iv) manufacturing or supply services. The payments we may receive under these arrangements typically include one or more of the following: non-refundable, upfront license fees; option exercise fees; funding of research and/or development efforts; amounts due upon the achievement of specified objectives; and/or royalties on future product sales.

Multiple-element arrangements require the separability of deliverables included in an arrangement into different units of accounting and the allocation of arrangement consideration to the units of accounting. The evaluation of multiple-element arrangements requires management to make judgments about (i) the identification of deliverables, (ii) whether such deliverables are separable from the other aspects of the contractual relationship, (iii) the estimated selling price of each deliverable, and (iv) the expected period of performance for each deliverable.

To determine the units of accounting under a multiple-element arrangement, management evaluates certain separation criteria, including whether the deliverables have stand-alone value, based on the relevant facts and circumstances for each arrangement. Management then estimates the selling price for each unit of accounting and allocates the arrangement consideration to each unit using the relative selling price method. The allocated consideration for each unit of accounting is recognized based on the method most appropriate for that unit of account and in accordance with the revenue recognition criteria detailed above.

If there are deliverables in an arrangement that are not separable from other aspects of the contractual relationship, they are treated as a combined unit of accounting, with the allocated revenue for the combined unit recognized in a manner consistent with the revenue recognition applicable to the final deliverable in the combined unit. Payments received prior to satisfying the relevant revenue recognition criteria are recorded as deferred revenue in the accompanying balance sheets and recognized as revenue when the related revenue recognition criteria are met.

The Collaboration Agreement provides for non-refundable milestone payments. We recognize revenue that is contingent upon the achievement of a substantive milestone in its entirety in the period in which the milestone is achieved. A milestone is considered substantive when the consideration payable to us for such milestone (i) is consistent with our performance necessary to achieve the milestone or the increase in value to the collaboration resulting from our performance, (ii) relates solely to our past performance and (iii) is reasonable relative to all of the other deliverables and payments within the arrangement. In making this assessment, we consider all facts and circumstances relevant to the arrangement, including factors such as the scientific, regulatory, commercial and other risks that must be overcome to achieve the milestone, the level of effort and investment required to achieve the milestone and whether any portion of the milestone consideration is related to future performance or deliverables.

We periodically reviewed the estimated performance periods under the Collaboration Agreement, which provides for non-refundable upfront payments and fees. We adjusted the periods over which revenue was recognized when appropriate to reflect changes in assumptions relating to the estimated performance periods. In the first quarter of 2018, we will adopt new accounting guidance that will change future patterns of revenue recognition.

We record revenues related to the reimbursement of costs incurred under the Collaboration Agreement where we act as a principal, control the research and development activities and bear credit risk. Under the Collaboration Agreement, we are reimbursed for associated out-of-pocket costs and for a certain amount of our full-time equivalent, or FTE, costs based on an agreed-upon FTE rate. The gross amount of these pass-through reimbursed costs is reported as revenue in the accompanying statements of operations and comprehensive loss, while the actual expenses for which we are reimbursed are reflected as research and development costs. In the first quarter of 2018, we will adopt new accounting guidance that will change future patterns of revenue recognition.

Accrued Research and Development Expenses

As part of the process of preparing our financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing contracts and purchase orders, reviewing the terms of our vendor agreements, communicating with our applicable personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual cost. The majority of our service providers invoice us monthly in arrears for services performed. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time.

Examples of estimated accrued research and development expenses include:

- fees paid to CROs in connection with clinical trials;
- fees paid to investigative sites in connection with clinical trials;
- fees paid to vendors in connection with preclinical development activities; and

- fees paid to vendors related to product manufacturing, development and distribution of clinical supplies.

We base our expenses related to clinical trials on our estimates of the services received and efforts expended pursuant to contracts with multiple research institutions and CROs that conduct and manage clinical trials on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows and expense recognition. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual accordingly. Our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in our reporting changes in estimates in any particular period. We have not experienced any significant adjustments to our estimates to date. In the years ended December 31, 2017, 2016 and 2015, we increased our clinical trial activities, and we expect our clinical trial activities to continue to be significant in the next several years.

Stock-Based Compensation

Stock-based compensation expense for stock option grants under our stock option plans is recorded at the estimated fair value of the award as of the grant date and is recognized as expense on a straight-line basis over the requisite service period of the stock-based award, and forfeitures are recognized as they occur. Stock-based compensation expense for employee stock purchases under our 2013 Employee Stock Purchase Plan, or the ESPP, is recorded at the estimated fair value of the purchase as of the plan enrollment date and is recognized as expense on a straight-line basis over the applicable six-month ESPP offering period. We estimate the fair value of our stock-based awards to employees and directors using the Black-Scholes model. The Black-Scholes model requires the input of subjective assumptions, including the risk-free interest rate, expected dividend yield, expected volatility, expected term and the fair value of the underlying common stock on the date of grant, among other inputs. We account for stock options granted to non-employees using the fair value approach. Stock options granted to non-employees are subject to periodic revaluation over their vesting terms.

Net Operating Loss and Research and Development Tax Credit Carryforwards

At December 31, 2017, we had federal and state net operating loss, or NOL, carryforwards of $94.6 million and $76.4 million, respectively. The federal loss carryforwards begin to expire in 2025, and the state carryforwards began to expire in 2015. As a result, state loss carryforwards of $4.2 million generated in 2007 were removed from our 2017 ending NOL balance. At December 31, 2017, we also had federal and state research credit carryforwards of $5.0 million and $2.0 million, respectively. The federal research credit carryforwards will begin expiring in 2026 unless previously utilized. The state research credit will carry forward indefinitely.

During 2017, we completed a Section 382 analysis to determine if our historical NOLs and research and development credits are limited due to an ownership change. The Section 382 analysis showed an ownership change at the Series A financing in October 2006 and at the IPO in July 2013. The Section 382 change resulted in a forfeiture of a de minimis amount of NOLs from 2006 and a research and development credit of a de minimis amount from 2006. All remaining NOLs and credits are eligible to be used during the carryforward period. We utilized $13.1 million of NOLs to offset our 2017 taxable income. We have recorded a valuation allowance on all of our deferred tax assets, including our deferred tax assets related to our NOL and research and development tax credit carryforwards.

Results of Operations

Comparison of the Years Ended December 31, 2017, 2016 and 2015

Total Revenues

Total revenues were $35.4 million for the year ended December 31, 2017, as compared to $0.8 million for the same period in 2016. The increase of $34.6 million was primarily due to recognition of a complete year of collaboration revenue related to the Collaboration Agreement with Novartis, which was executed in December 2016.

Total revenues were $0.8 million for the year ended December 31, 2016, as compared to $0.0 million for the same period in 2015. For the year ended December 31, 2016, total revenues consisted of collaboration revenue related to the Collaboration Agreement with Novartis, which was executed in December 2016.

We recognized collaboration revenue on the license portion of deferred revenue on a straight-line basis between the inception of the agreement (or with respect to the option exercise fee, upon exercise of the option) through November 2019 – the estimated period over which we expect to perform the research and development services. Due to the inherently unpredictable nature of product development activities, we periodically reviewed the performance period of the research and development services and adjusted the period over which revenue was recognized when appropriate. In the first quarter of 2018, we will adopt new accounting guidance that will change future patterns of revenue

recognition.

Research and Development Expenses

Research and development expenses were $43.2 million for the year ended December 31, 2017, as compared to $20.3 million for the same period in 2016. The increase of $22.9 million was primarily due to an increase in external costs related to emricasan and new product candidate development and higher personnel costs. In 2017, external research and development expenses for emricasan were $34.0 million, compared to $13.7 million in 2016. The increase of $20.3 million was primarily due to the ramp up of our ENCORE-NF, ENCORE-PH and ENCORE-LF clinical trials. In 2017, external research and development expenses not related to emricasan were $1.3 million, compared to $0.0 million in 2016. Research and development related personnel expenses were $7.6 million in 2017 and $6.3 million in 2016. The increase of $1.3 million was primarily due to higher employee salaries and benefits and stock compensation.

Research and development expenses were $20.3 million for the year ended December 31, 2016, as compared to $16.3 million for the same period in 2015. The increase of $4.0 million was primarily due to an increase in external costs related to emricasan and higher personnel costs. In 2016, external research and development expenses for emricasan were $13.7 million, compared to $10.4 million in 2015. The increase of $3.3 million was primarily due to higher spending on the ENCORE trials, partially offset by lower spending on the completed Phase 2 liver cirrhosis trial and Phase 2 portal hypertension trial. Research and development related personnel expenses were $6.3 million in 2016 and $5.6 million in 2015. The increase of $0.7 million was primarily due to higher employee salaries and benefits.

General and Administrative Expenses

General and administrative expenses were $9.7 million for the year ended December 31, 2017, as compared to $10.3 million for the same period in 2016. The decrease of $0.6 million was primarily due to lower consulting and legal fees related to the Collaboration Agreement in 2017 as compared to 2016. General and administrative related personnel expenses were $5.5 million in 2017 and $5.4 million in 2016. The increase of $0.1 million was primarily due to higher stock compensation.

General and administrative expenses were $10.3 million for the year ended December 31, 2016, as compared to $7.8 million for the same period in 2015. The increase of $2.5 million was primarily due to higher consulting fees, personnel costs and legal fees. The increase in consulting and legal fees was primarily due to the execution of the Collaboration Agreement. General and administrative related personnel expenses were $5.4 million in 2016 and $4.6 million in 2015. The increase of $0.8 million was primarily due to higher employee salaries and benefits.

Changes in components of Other Income (Expense) were as follows:

Interest Income

Interest income was $892,000, $138,000 and $68,000 for the years ended December 31, 2017, 2016 and 2015, respectively. Interest income consisted of interest earned on our cash, cash equivalents and marketable securities and fluctuates based on changes in investment balances and interest rates.

Interest Expense

Interest expense was $662,000, $70,000 and $70,000 for the years ended December 31, 2017, 2016 and 2015, respectively. The increase was due to higher interest expense related to the Novartis Note, which was issued in February 2017, partially offset by lower interest expense related to the Pfizer Note, which was voluntarily prepaid in January 2017.

Other (Expense) Income

Other expense was $76,000 for the year ended December 31, 2017. Other income was $30,000 for the year ended December 31, 2016. Other expense was $16,000 for the year ended December 31, 2015. Other (expense) income represents non-operating transactions such as those caused by currency fluctuations between transaction dates and settlement dates and the conversion of account balances held in foreign currencies to U.S. dollars.

Liquidity and Capital Resources

We have incurred losses since inception and negative cash flows from operating activities for the years ended December 31, 2017 and 2015. For the year ended December 31, 2016, we had positive net cash flows from operating activities due to the upfront payment related to the Collaboration Agreement with Novartis. As of December 31, 2017, we had an accumulated deficit of $168.0 million. We anticipate that we will continue to incur net losses for the foreseeable future as we continue the development and potential commercialization of emricasan.

Prior to our IPO in July 2013, we funded our operations primarily through private placements of equity and convertible debt securities. In July 2013, we completed our IPO of 6,000,000 shares of common stock at an offering price of $11.00 per share. We received net proceeds of $58.6 million, after deducting underwriting discounts and commissions and offering-related transaction costs.

In August 2014, we entered into an At Market Issuance Sales Agreement, or the Sales Agreement, with MLV & Co. LLC, or MLV, pursuant to which we could sell from time to time, at our option, up to an aggregate of $50.0 million of shares of our common stock through MLV, as sales agent. We terminated the Sales Agreement in December 2016. We sold 6,305,526 shares of our common stock pursuant to the Sales Agreement at a weighted average price per share of $2.35 and received net proceeds of $14.2 million, after deducting offering-related transaction costs and commissions.

In April 2015, we completed a public offering of 4,025,000 shares of our common stock at a public offering price of $5.75 per share. We received net proceeds of $21.4 million, after deducting underwriting discounts and commissions and offering-related transaction costs. In May 2017, we completed a public offering of 5,980,000 shares of our common stock at a public offering price of $5.50 per share. We received net proceeds of $30.6 million, after deducting underwriting discounts and commissions and offering-related transaction costs. Immediately following the offering, we used $11.2 million of the net proceeds to repurchase and retire 2,166,836 shares of our common stock from Advent at a price of $5.17 per share, which is equal to the net proceeds per share we received from the offering, before expenses, pursuant to a stock purchase agreement we entered into with Advent in May 2017.

In December 2016, we entered into the Collaboration Agreement with Novartis pursuant to which we granted Novartis an exclusive option to collaborate with us for the global development and commercialization of emricasan. Under the Collaboration Agreement, Novartis paid us an upfront payment of $50.0 million. In May 2017, Novartis exercised its option, and we received a $7.0 million option exercise payment in July 2017. Concurrent with the entry into the Collaboration Agreement, we entered into an Investment Agreement with Novartis whereby we agreed to sell and Novartis agreed to purchase, convertible promissory notes, in one or two closings, for an aggregate principal amount of up to $15.0 million. In February 2017, we issued the Novartis Note in the principal amount of $15.0 million. The maturity date of the Novartis Note is December 31, 2019. The Novartis Note bears interest on the unpaid principal balance at a rate of 6% per annum. We may prepay or convert the Novartis Note into shares of our common stock, at our option, until December 31, 2019. Novartis may convert the Novartis Note into shares of our common stock upon a change of control of our company or termination of the Collaboration Agreement by Novartis pursuant to certain provisions. If converted, the principal and accrued interest under the Novartis Note will convert into shares of our common stock at a conversion price equal to 120% of the 20-day trailing average closing price per share of the common stock immediately prior to the conversion date. Upon the occurrence of certain events of default, the Novartis Note requires us to repay the principal balance and any unpaid accrued interest.

At December 31, 2017, we had cash, cash equivalents and marketable securities of $74.9 million. We believe our existing cash, cash equivalents and marketable securities will be sufficient to fund our operations for at least the next 12 months from the date of the filing of this Form 10-K. To fund further operations, we will need to raise additional capital. We plan to continue to fund losses from operations and capital funding needs through future equity and debt financing, as well as potential collaborations. The sale of additional equity or convertible debt could result in additional dilution to our stockholders. The incurrence of indebtedness would result in debt service obligations and could result in operating and financing covenants that would restrict our operations. No assurances can be provided that financing will be available in the amounts we need or on terms acceptable to us, if at all. If we are not able to secure adequate additional funding, we may be forced to make reductions in spending, extend payment terms with suppliers, liquidate assets where possible, and/or suspend or curtail planned programs. Any of these actions could materially harm our business, results of operations and future prospects.

The following table sets forth a summary of the net cash flow activity for each of the periods set forth below:

	Year Ended December 31,		
	2017	2016	2015
Net cash (used in) provided by operating activities	$(33,210,041)	$26,997,001	$(22,546,185)
Net cash (used in) provided by investing activities	(39,871,250)	3,582,797	4,119,640
Net cash provided by financing activities	31,076,718	13,627,521	22,389,961
Net (decrease) increase in cash and cash equivalents	$(42,004,573		