Seres Therapeutics, Inc.
Form 10-K
March 06, 2019

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, 2018

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: 001-37465

Seres Therapeutics, Inc.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	27-4326290
(State or Other Jurisdiction of Incorporation or Organization)	(IRS Employer Identification No.)

200 Sidney Street – 4th Floor

Cambridge, Massachusetts	02139
(Address of Principal Executive Offices)	(Zip Code)

(617) 945-9626

(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 $0.001 per share	The Nasdaq Global Select Market

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

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

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. 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 every Interactive Data File required to be submitted 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 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 the "large accelerated filer," "accelerated filer," "non-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	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 Act). Yes No

The aggregate market value of common stock held by non-affiliates of the registrant based on the closing price of the registrant's common stock as reported on the Nasdaq Global Select Market on June 29, 2018, was $177,045,629.

As of February 28, 2019, there were 41,048,360 shares of the registrant's common stock, par value $0.001 per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement relating to its 2019 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission are incorporated by reference into Part III of this Annual Report on Form 10-K.

TABLE OF CONTENTS

FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements. We intend such forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. All statements other than statements of historical facts contained in this Annual Report on Form 10-K, 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.

In some cases, you can identify forward-looking statements by terms such as “may,” “will,” “should,” “expect,” “plan,” “anticipate,” “could,” “intend,” “target,” “project,” “contemplate,” “believe,” “estimate,” “predict,” “potential” or “continue” o of these terms or other similar expressions. The forward-looking statements in this Annual Report on Form 10-K 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 report and are subject to a number of important factors that could cause actual results to differ materially from those in the forward-looking statements, including the risks, uncertainties and assumptions described under the sections in this report titled “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and elsewhere in this report. These forward-looking statements are subject to numerous risks, including, without limitation, the following:

- our status as a clinical-stage company and our expectation to incur losses in the future;
- our future capital needs and our need to raise additional funds;
- our ability to build a pipeline of product candidates and develop and commercialize drugs;
- our unproven approach to therapeutic intervention;
- our ability to enroll patients in clinical trials, timely and successfully complete those trials and receive necessary regulatory approvals;
- our ability to establish our own manufacturing facilities and to receive or manufacture sufficient quantities of our product candidates;
- our ability to protect and enforce our intellectual property rights;
- federal, state, and foreign regulatory requirements, including U.S. Food and Drug Administration regulation of our product candidates;
- our ability to obtain and retain key executives and attract and retain qualified personnel; and
- our ability to successfully manage our growth.

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.

You should read this Annual Report on Form 10-K and the documents that we reference in this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements. 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.

TRADEMARKS, SERVICE MARKS AND TRADENAMES

We have proprietary rights to trademarks used in this Annual Report on Form 10-K, including Ecobiotic, which are important to our business and many of which are registered under applicable intellectual property laws. Solely for convenience, the trademarks, service marks, logos and trade names referred to in this Annual Report on Form 10-K are without the ® and ™ symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights to these trademarks, service marks and trade names. This Annual Report on Form 10-K contains additional trademarks, service marks and trade names of others, which are the property of their respective owners. All trademarks, service marks and trade names appearing in this Annual Report on Form 10-K are, to our knowledge, the property of their respective owners. We do not intend our use or display

of other companies' trademarks, service marks, copyrights or trade names to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

PART I

Item 1. Business

Overview

We are a microbiome therapeutics platform company developing a novel class of biological drugs, which we refer to as Ecobiotic® microbiome therapeutics. The human microbiome is an ecosystem of microorganisms, including bacteria, fungi and viruses, that, when unhealthy, or dysbiotic, can leave the body more susceptible to infections, metabolic disorders, allergies, autoimmune disease, inflammation and other serious conditions. Our drug candidates are designed to restore health by repairing the function of a dysbiotic microbiome. We are initially focused on implementing our microbiome therapeutics platform to develop Ecobiotic microbiome therapeutics that treat dysbiosis in the colonic microbiome, one of the most diverse microbial ecologies in the human body.

The human microbiome is one of the richest and most diverse ecosystems on earth, with a population of approximately 30 – 50 trillion microorganisms that live in our intestines, mouth, skin and elsewhere in or on the body. In a healthy, symbiotic state the colonic microbiome plays an important role in human health, helping the body digest food, resist pathogens, regulate the metabolic systems, develop and regulate the immune system and synthesize essential nutrients and vitamins. However, the colonic microbiome may change in composition for a variety of reasons, including in response to antibiotics or following gastrointestinal infection. These changes in composition may result in the loss of key commensal microbes and/or the gain of pathogenic microbes, resulting in a state of dysbiosis, and associated loss or gain of metabolic and/or immune function. While the study of the human microbiome is not new, the scientific community's understanding of the microbiome, and the colonic microbiome in particular, has been significantly advanced through metagenomics, which has enabled the broader understanding of the human microbiome at the organismal, functional and community level. Scientific research has correlated dysbiosis in the colonic microbiome with various conditions, including: infectious diseases, metabolic diseases, and inflammatory and immune diseases and cancer.

We are developing a new approach to treating disease by modulation of the dysbiotic colonic microbiome by using our Ecobiotic microbiome therapeutics to improve patient outcomes. Our approach is premised on the hypothesis that the proximal cause of many diseases is a dysbiosis in the natural state of the colonic microbiome. We believe that the restoration of a dysbiotic colonic microbiome using Ecobiotic microbiome therapeutics represents a paradigm shift in the approach to treating underlying disease. There are currently no therapeutics approved by the U.S. Food and Drug Administration, or the FDA, that are designed to restore the microbiome to a healthy state.

Our approach to discovery and design is based on an iterative bedside-to-bench-to-bedside drug discovery strategy, i.e. reverse translation that begins with data on the human microbiome that we gather from clinical studies. From these clinical data, we identify the microbiological and functional differences between a healthy and a diseased microbiome, which we then use to design potential Ecobiotic microbiome therapeutics. After further in-lab preclinical testing, selected Ecobiotic microbiome therapeutic candidates are then studied in clinical trials. We apply a comparative genomic systems biology framework that leverages proprietary computational, microbiological and screening capabilities to design lead candidates that target the microbiological and functional deficiencies identified in the setting of human disease. We are able to apply this framework and experience to clinical data sets from published studies and those generated with our collaborators, as well as to the proprietary clinical data set we have generated through our clinical trials. We believe we can utilize our knowledge and data to design Ecobiotic microbiome therapeutics to treat various medical conditions. We also have advanced capabilities in pharmacokinetic and pharmacodynamic analytics, and the production and formulation of colonic bacteria as well as spore forms of bacteria into therapeutics. We believe that the combination of experience, proprietary data and proprietary know-how that comprise our microbiome therapeutics platform provides us with a competitive advantage in the design and development of microbiome therapeutics. Further, our approach and platform, which enable the design, testing, optimization, manufacturing and formulation of Ecobiotic microbiome therapeutic candidates, provide a framework

that we believe can significantly reduce the time typically required to advance therapeutics to the clinic.

Using our microbiome therapeutics platform, we are focusing our resources on obtaining clinical results from our highest-priority, clinical programs in ulcerative colitis, or UC, a form of inflammatory bowel disease, or IBD, with SER-287, Clostridium difficile infection, or CDI, with SER-109, and our recently initiated Phase 1b study with SER-401 in patients with metastatic melanoma, as well as our preclinical SER-301 program in UC.

The clinical development of SER-287 to treat UC, is supported by successful clinical and preclinical studies. Preclinical colitis animal models and in vitro screens provide evidence that SER-287 administration has the potential to result in reduced pathology and modulation of inflammatory and immunological functional pathways. Published clinical reports also suggest that modulation of the microbiome through repetitive fecal microbiota transplantation, or FMT may lead to meaningful clinical response in UC patients.

We completed our Phase 1b clinical study for our UC drug candidate, SER-287, in subjects with active mild to moderate UC who were failing current therapies. The results of the SER-287 Phase 1b study, a randomized, double-blinded, placebo-controlled, multiple-dose, induction study enrolled patients with active mild-to-moderate UC, with Total Modified Mayo scores of 4 to 10 were positive. The study enrolled 58 subjects who exhibited pre-study disease activity despite treatment with standard-of-care therapeutics. SER-287 safety and tolerability was a primary study endpoint. The study showed no imbalance in adverse events in SER-287-treated patients as compared to patients treated with placebo and no drug-related serious adverse events were observed.

Analyses of microbiome data, a co-primary endpoint of the trial, showed that SER-287 induced regimen-dependent engraftment of SER-287 derived bacterial species into the colonic microbiome of patients treated with SER-287. Patients administered vancomycin pre-treatment followed by daily administration of SER-287 had the highest level of SER-287 engraftment, which was statistically significant. This patient cohort corresponded with the study arm where the most significant clinical benefits were observed, including clinical remission and endoscopic improvement. Differences in the composition of the microbiome post treatment were also associated with clinical remission. Bacterial engraftment signatures were durable throughout the dosing period of the trial and were also observed at four weeks post administration of the final SER-287 dose. The pharmacologic impact of the SER-287 engraftment was supported by metabolomic and transcriptomic data. Analysis of metabolites and gene expression signatures associated with inflammation and immune modulation, were observed to be correlated with remission in SER-287 treated subjects.

Based on these encouraging data from the Phase 1b trial, in December 2018, we initiated our Phase 2b trial, ECO-RESET, evaluating SER-287 in patients with active mild-to-moderate UC. Based on feedback obtained from the FDA on the SER-287 Phase 2b study design, we believe the study could serve as one of two required pivotal trials supporting potential future registration of SER-287. The Phase 2b study is a three-arm placebo-controlled trial of approximately 200 patients with active mild-to-moderate UC. Two groups of patients will receive different doses of SER-287, both following pretreatment with a short course of oral vancomycin. A third study arm will receive placebo. The study's primary endpoint will evaluate clinical remission measured after 10 weeks of SER-287 administration. Endoscopic improvement will be measured as a secondary efficacy measure. We expect to complete trial enrollment by mid-2020.

Our Phase 3 clinical candidate, SER-109, is designed to rapidly and durably correct dysbiosis in the colonic microbiome in the setting of recurrent CDI. CDI is most often caused by the use of broad spectrum antibiotics which create a dysbiosis of the microbiome, thus increasing susceptibility to infection by Clostridium difficile, or C. difficile, a spore forming bacterium. C. difficile expresses toxins leading to debilitating diarrhea in affected individuals, and which can also cause more severe outcomes, such as inflammation of the colon (colitis), toxic megacolon and death. The U.S. Centers for Disease Control, or CDC, has identified CDI as one of the top three most urgent antibiotic-resistant bacterial threats in the United States. It is the most common cause of hospital acquired infection in the United States and has overtaken methicillin-resistant Staphylococcus aureus, or MRSA in incidence of disease. CDI is responsible for the deaths of approximately 29,000 Americans each year. Based on an epidemiological study conducted by the CDC, the incidence of CDI in the United States, was estimated to be 453,000 (95% confidence interval, 397,100 to 508,500) (Lessa et. al., Burden of Clostridium difficile Infection in the United States, New England J. of Medicine, 2015). While the epidemiological data are varied outside the United States due to the widespread use of antibiotics, CDI is a growing global disease. The standard of care for CDI is to treat with antibiotics. In many cases, antibiotic treatments may resolve the acute infection caused by C. difficile. However, these antibiotic treatments kill beneficial bacteria indiscriminately, inducing a dysbiosis of the microbiome and potentially making patients more susceptible to a recurrence of CDI. For those patients who experience a CDI recurrence, it is likely that dysbiosis of the microbiome is the proximal cause of disease. Published data suggests that the risk of

recurrence is approximately 25% after the primary CDI, 40% after a first recurrence and as high as 60% for those experiencing two or more recurrences.

SER-109 is a donor-derived, purified bacterial spore-based microbiome therapeutic candidate consisting of an average of approximately 50 bacterial species purified from healthy donor stool. SER-109 is designed to prevent further recurrences of CDI in patients with recurrent CDI by restructuring the dysbiotic microbiome to a state that resists C. difficile growth and colonization. If approved by the FDA, SER-109 could be a first-in-field oral microbiome drug. We initiated a Phase 3 clinical study of SER-109 in approximately 320 patients with multiply recurrent CDI. The on-going study is designed to evaluate patients for 24 weeks with the primary endpoint of comparing the C. difficile recurrence rate in subjects who receive SER-109 verses placebo at up to eight weeks after dosing.

We continue to enroll the SER-109 Phase 3 study for patients with recurrent CDI despite the widespread use of FMT to treat CDI. As interference from this uncontrolled, understudied and unapproved product has impacted the enrollment rate of our SER-109 placebo-controlled clinical trial, we are evaluating modification of the study design to expedite clinical results.

Our SER-301 program is in preclinical discovery and bioprocess development. SER-301 is being rationally designed by utilizing our reverse translational microbiome therapeutics platform to incorporate learnings from our SER-287 and SER-262 clinical studies. We have identified specific bacterial species that engraft and are associated with clinical remission, and further we have identified metabolites made by these bacteria that correlate with clinical efficacy. We also have gene expression data from patient mucosal biopsies showing which genes and pathways are favorably altered by SER-287 treatment. All of these data are being leveraged in the design of SER-301.

We are also developing SER-401, for use with checkpoint inhibitors, or CPIs, in patients with solid tumors to enhance efficacy and improve survival. SER-401 is a microbiome therapeutic candidate sourced from healthy individuals who have been identified to have a microbiome signature that is similar to that observed in cancer patient responders to CPIs. CPIs block the mechanisms by which cancers evade detection and destruction by the immune system. Observational studies of humans by a group led by our collaborator, Dr. Jennifer Wargo of MD Anderson Cancer Center, or MD Anderson, suggest that microbiome composition impacts response to CPIs. This has been supported by mouse model studies conducted by us and at MD Anderson that show that colonization with human responder microbes affected tumor response to CPI treatment, versus mice colonized with CPI non-responder microbes. These effects are thought to be a result of a specific microbiome "signature" enriched in certain members of the Firmicutes phylum of bacteria. We are working in collaboration with MD Anderson and the Parker Institute for Cancer Immunotherapy, or the Parker Institute, to evaluate the potential of SER-401, based upon this signature, and to modulate the immunological tone of subjects to improve response in patients with metastatic melanoma to CPI treatment. MD Anderson granted Seres an exclusive option, with pre-defined financial terms, to license intellectual property rights from them related to the use of bacteria in combination with CPIs. In collaboration with the Parker Institute and MD Anderson, we initiated a Phase 1b study of SER-401 in patients with metastatic melanoma. Patients will be treated with either CPI alone, or in combination with SER-401, and observed for tumor regression and biomarkers of response to CPI. We expect to obtain Phase 1b study results in 2020.

On February 7, 2019, we announced corporate changes to focus our resources. We will now concentrate on completing the recently-initiated SER-287 Phase 2b study in mild-to-moderate UC, obtaining results from the ongoing SER-109 Phase 3 study for recurrent CDI and advancing the SER-401 Phase 1b study, in collaboration with the Parker Institute and MD Anderson, to evaluate augmenting CPI response in patients with metastatic melanoma. We will also continue to pursue focused preclinical activity on SER-301, a rationally-designed microbiome therapeutic candidate for UC, leveraging learnings obtained from our prior clinical study results. In connection with the prioritization of these therapeutic candidates, we made changes to our management team and committed to a workforce reduction plan to reduce headcount by approximately 30 employees.

Other Programs

In July 2016, we initiated a SER-262 Phase 1b dose-escalating study, the first clinical trial conducted using a rationally designed, fermented consortium of bacteria. SER-262 was rationally designed to be used following antibiotic treatment to prevent an initial recurrence of CDI. We have established various capabilities to enable the development of rationally designed microbiome therapeutics including metagenomic and metabolomic profiling, use of curated reference computational databases and proprietary in silico algorithms for drug design, an extensive proprietary bacterial library, advanced manufacturing processes, and capabilities to conduct pharmacokinetics and pharmacodynamics analyses in clinical studies. SER-262 contains a consortium of 12 bacterial strains derived from a manufacturing process using fermentation and does not require human donor material.

The Phase 1b clinical study was a 24-week, randomized, placebo-controlled, dose-escalation trial. The primary endpoints of the study were safety and tolerability and a comparison of the CDI recurrence rate in the SER-262 and placebo groups. Key secondary endpoints included analysis of SER-262 bacterial strain engraftment. Top line clinical and microbiome results from the study are available. No drug-related serious adverse events were observed. No significant differences were observed in the recurrence rates in patients administered SER-262 as compared to placebo. However, we observed a statistically significant reduction in CDI recurrence rates in patients pretreated with vancomycin followed by SER-262, as compared to those treated with metronidazole followed by SER-262. This observation corresponded with an increase in SER-262 microbiome engraftment in patients pretreated with vancomycin. We believe the analyses of clinical data from both the SER-262 and SER-287 Phase 1b studies suggests

that vancomycin pretreatment may augment engraftment of our microbiome therapeutic candidates.

We are also designing SER-155, a rationally designed, fermented microbiome therapeutic candidate designed to correct dysbiosis in patients following allogeneic hematopoietic stem cell transplants, or allo-HSCT, or solid organ transplants. This preclinical program is based on published clinical evidence from our collaborators at Memorial Sloan Kettering Cancer Center showing that allo-HSCT patients with dysbiosis are far more likely to die due to infection and/or lethal graft versus host disease, or GvHD. In November 2017, we were awarded a highly-competitive grant from Combating Antibiotic-Resistant Bacteria Accelerator, or CARB-X, to support continued preclinical research and early development work for SER-155. The CARB-X grant provides us with up to $2.5 million of research funding with potential for an additional $3.1 million for manufacture and investigational new drug application, or IND, upon completion of milestones.

We continue to evaluate microbiome pharmacokinetic and pharmacodynamic data from the SER-262 Phase 1b study, in addition to insights gained from research efforts with our other rationally designed Ecobiotic microbiome therapeutic candidates, in order to determine next steps in the development of both SER-262 and SER-155.

We have completed early stages of researching Ecobiotic microbiome therapeutics for the treatment of metabolic diseases, such as non-insulin dependent diabetes, non-alcoholic steatohepatitis, or NASH, and metabolic syndrome. Research in these indications

has focused on identifying microbiome signatures associated with various disease states and early discovery efforts to identify Ecobiotic consortia that could impact specific functional defects in the microbiome.

We have assembled a world class group of scientists, clinicians, directors and investors, who have established our leadership in the field of microbiome therapeutics. We were co-founded by Drs. Noubar Afeyan, David Berry and Geoffrey von Maltzahn of Flagship Pioneering. Through Flagship Pioneering's contribution of foundational scientific concepts and intellectual property, assembly of our management team and critical early-stage support, we launched as the first company focused on the ecological nature of the microbiome. Led by Eric Shaff, our President and Chief Executive Officer, our experienced management team possesses core capabilities in microbiome therapeutics, drug development, commercialization, chemistry, manufacturing and controls, or CMC, public company management and finance. Our management team has extensive experience in microbial ecology, microbiology and live biological products, with over 25 years of experience studying the microbiome and over 60 published papers on the science of the microbiome. Additionally, our team has extensive experience in building out commercial capabilities in specialty diseases and has a track record for success in the commercialization of vaccine products, which have analogous manufacturing processes to that of Ecobiotic microbiome therapeutics.

Our Strategy

Our goal is to remain the leading biopharmaceutical company developing and commercializing microbiome therapeutics to address significant unmet medical needs. We intend to focus in the near term on the highest priority clinical programs which we believe will optimally advance our pipeline: SER-287 for UC; SER-109 for recurrent CDI; and the SER-401 immuno-oncology program. We also intend to continue to strengthen our next generation of rationally designed, fermented microbiome therapeutic approach with SER-301 for UC being our lead candidate. The critical components of our strategy include:

Advancing our Programs

- Continuing clinical development of SER-287 for the treatment of UC. The clinical development of SER-287 to treat UC is supported by both clinical and preclinical studies in multiple animal models of colitis that provide evidence that SER-287 administration may result in reduced inflammation. Published clinical reports suggest that modulation of the microbiome through repetitive FMT may lead to meaningful clinical response in certain UC patients. In December 2015, we initiated a Phase 1b clinical trial evaluating SER 287 in patients with mild to moderate UC who were failing current therapies. In October 2017, we announced positive topline results from our Phase 1b clinical trial of SER-287 in patients with UC. The SER-287 Phase 1b study, a randomized, double-blinded, placebo-controlled, multiple-dose, induction study enrolled patients with active mild-to-moderate UC, with Total Modified Mayo scores of 4 to 10. The study enrolled 58 patients at 20 sites across the United States. Study subjects exhibited pre-study disease activity despite use of current therapies in a majority of subjects, which included 5-amino-salacylic acid, low dose corticosteroids, or immunomodulatory therapy. Based on the encouraging data from the Phase 1b trial, in December 2018, we initiated our Phase 2b trial, ECO-RESET, evaluating SER-287 in patients with active mild-to-moderate UC. Based on feedback obtained from the FDA on the SER-287 Phase 2b study design, the study could serve as one of two required pivotal trials supporting potential future registration of SER-287. The Phase 2b study is a three-arm placebo-controlled trial of approximately 200 patients with active mild-to-moderate UC. Two groups of patients will receive different doses of SER-287, both following pretreatment with a short course of oral vancomycin. A third study arm will receive placebo. The study's primary endpoint will evaluate clinical remission measured after 10 weeks of SER-287 administration. Endoscopic improvement will be measured as a secondary efficacy measure. SER-287 has been awarded Orphan Drug Designation designation for pediatric UC.
- Advancing the development of our lead product candidate, SER-109, for the prevention of further recurrences of CDI in patients with recurrent CDI. SER-109 has been granted both Orphan Drug and Breakthrough Therapy designation by the FDA for the treatment of CDI. Breakthrough Therapy designation provides for intensive guidance from the FDA in an effort to expedite the drug development process. In our randomized, double-blind, placebo-controlled Phase 2 clinical study, 44% of subjects (26 of 59) who received SER-109 experienced a recurrence at the 8-week

endpoint compared to 53% of subjects (16 of 30) who received placebo, a result that was not statistically significant. Based on a detailed analysis of clinical, microbiome and CMC factors that may have contributed to the outcome of this study, as well as our earlier Phase 1b/2 clinical study and following discussions with the FDA, a new SER-109 clinical study in approximately 320 patients with multiply recurrent CDI was initiated in June 2017. Study participants are being randomized 1:1 between SER-109 and placebo and receiving a total dose that is approximately 10-fold higher than in the Phase 2 study, administered over three consecutive days.

- Developing SER-401 for use with CPIs in patients with solid tumors. We are developing SER-401 for administration in combination with CPI treatment to increase efficacy in patients with solid tumors. The design is being driven by insights from our collaborators at MD Anderson and recent published data in a number of high-profile scientific journals from other international research groups that suggest that the microbiome may impact patients' response to CPI treatment.

Together with our collaborators, we have initiated a Phase 1b multicenter study in metastatic melanoma patients as part of our collaboration with MD Anderson and the Parker Institute.

- Developing SER-301 for the treatment of IBD. We are designing and developing SER-301, a rationally designed, fermented, Ecobiotic microbiome therapeutic candidate for the treatment of IBD leveraging pharmacokinetic and pharmacodynamic data from our SER-287 clinical trial, our knowledge of modulation of dysbioses seen in patients with UC, as well as insights from our SER-262 clinical study.

Advancing Our Capabilities

- Leveraging our leading reverse translation microbiome therapeutics platform to develop additional innovative and novel Ecobiotic microbiome therapeutics across a range of serious medical conditions with high unmet need including infectious and inflammatory disease and disease associated with modulation of host immunity. We believe that the combination of experience, proprietary data and proprietary know-how related to the microbiome and of the production of microbial strains provides us a competitive advantage in the design and development of microbiome therapeutics. Our platform enables us to build upon our existing and growing clinical experience to rationally design treatments for acute and complex chronic diseases. We intend to leverage this advantage to develop additional innovative Ecobiotic microbiome therapeutics.
- Developing manufacturing capabilities sufficient to support commercialization of any approved Ecobiotic microbiome therapeutic candidates. Ecobiotic microbiome therapeutic manufacturing will require capabilities that are distinct from other biologic drugs. We have made strategic investments in manufacturing capabilities to help ensure that we maintain control of our know-how and also because we believe these capabilities will be necessary and highly advantageous for the development of future Ecobiotic microbiome therapeutic candidates. Our bioprocess and manufacturing personnel are focused on creating a platform of manufacturing expertise that will set the stage for further advances in the emerging field of microbiome therapeutics.

Understanding the Microbiome and Its Impact on Disease

Among the various microbial ecosystems in the human body, the colonic microbiome is the most diverse microbial communities with about 100 billion bacterial cells per milliliter. In a healthy, symbiotic state the colonic microbiome enables the body to function normally. However, the colonic microbiome can change in composition, such as in response to long-term or high-dose exposure to antibiotics or following a gastrointestinal infection. As a result, there can be a loss of key microbes that results in a state of dysbiosis. Dysbiosis of the microbiome is associated with a wide range of disease and infections.

Although bacteria are often associated with infection and disease, much of the bacteria that colonize the human body are essential for life. Until recently, few scientific studies focused on the benefits of the bacteria comprising the microbiome. In 2005, the National Institutes of Health funded the Human Microbiome Project, or HMP, which had as one of its goals the characterization of the microbiome with enough specificity to enable the study of variations in the microbiome and their influence on disease.

Historically, researchers studied microbes in patients by isolating pathogens and growing them in culture. This process typically identifies only a limited diversity of microbial species. The HMP used metagenomic sequencing technologies to analyze 5,000 samples, representing more than 3.5 terabases of genome sequence data, to identify specific genetic sequences found only in bacteria. The most recent studies estimate that 30-50 trillion bacterial cells comprising more than 1,000 unique bacterial species occupy the human ecosystem. Importantly, HMP researchers have discovered that different consortia of microbes may accomplish the same metabolic activity, and the presence of those metabolic activities is more important than the exact species of microbe providing the function. Results from the HMP have provided a robust baseline microbiome against which disease states can be compared.

Complementing the HMP baseline data, numerous scientific studies are emerging in both animals and humans, suggesting that many human diseases are correlated with dysbiosis of the microbiome. These include infections, such as CDI or vancomycin-resistant Enterococcus, or VRE; inflammatory diseases, such as UC, Crohn’s disease and pouchitis; autoimmune disease and cancer, including immune-oncology related applications; and further metabolic

disorders, such as early-stage, non-insulin dependent diabetes, obesity and non-alcoholic fatty liver disease, or NAFLD/NASH. Examples of some studies include:

- A study published in PLOS Pathogens in 2012 suggested that a mixture of six different bacteria found naturally in the gastrointestinal system of mice, when isolated from stool and reintroduced into the infected mice, was effective at suppressing CDI (Lawley et al., PLOS Pathogens, 2012). Researchers in the study found that a single treatment of the bacteria was sufficient and that the suppression lasted for months. We observed that SER-262, our clinical consortium of human-derived bacterial species formulated as spores, protected mice from disease in a CDI model.

- A placebo-controlled, randomized, blinded clinical study published in Gastroenterology in 2015 showed that repetitive FMT delivered via enema weekly for 6 weeks induced clinical remissions in 24% of patients with active UC compared to 5% receiving placebo (Moayyedi et al., Gastroenterology, 2015). This study utilized endoscopy, a direct visualization of the colon, before and after treatment to assess the efficacy of FMT, thus demonstrating the role of the microbiome in treating active UC. A subsequent randomized, placebo controlled, blinded study of FMT delivered via enema 5 days per week for 8 weeks demonstrated similar clinical remission rates: 27% receiving FMT and 8% receiving placebo (Paramsothy et al., Lancet, 2017). Most recently, a study of FMT delivered by a colonoscopy followed by 2 enemas to UC patients resulted in similar outcomes: 32% receiving donor-FMT and 9% receiving autologous control (Costello et al, JAMA, 2019). We announced top-line clinical data from our Phase 1b clinical trial for SER-287 in October 2017. In this trial, patients with mild-to-moderate UC, receiving a vancomycin pre-treatment followed by a daily oral dose of SER-287 for 8 weeks achieved a 40% rate of clinical remission compared to no clinical remission for treatment with placebo. This analysis followed the intent-to-treat, or ITT, "worst case" analysis used for drug registration studies in which missing data is counted as failure.
- Data from cancer patients undergoing allo-HSCT show the influence of the microbiome on patient survival. An observational study of allo-HSCT patients following allo-HSCT demonstrated that 3-year survival in patients with a low diversity microbiome was 36% whereas survival in patients with a medium to high diversity microbiome was ≥60%. Excess mortality in the low diversity subset was driven by deaths due to infection and GvHD, not the underlying cancer itself (Taur et al, Blood, 2014). A follow up from the same researchers looked at allo-HSCT patients receiving transplants who are at highest risk of GvHD and showed a greater than 5-fold increase in mortality was correlated with microbiome composition. (Jenq et al., Biol of Blood and Marrow Transplant, 2015).
- Two studies in mouse cancer models, both published in Science in 2015, demonstrated that the anti-tumor response to immune CPIs could be enhanced by altering the microbiome (Velizou et al., Science 2015; Slvan et al., Science 2015). More recently, independent groups from MD Anderson, the Institute Gustave Roussy in Paris, France, and the University of Chicago have published data from human studies showing that cancer patients who successfully respond to immune CPIs tend to have a distinct microbiome from patients who do not respond. Moreover, when human fecal samples from responding and non-responding patients are transferred into mice, these have been shown to exhibit the same response to CPIs in tumor model experiments as their human donors (Golpalakrishnan et al, Science, 2017; Routy et al, Science, 2017; Matson et al, Science, 2018). Taken together, these results suggest that microbiome therapies might improve the efficacy of CPIs in treating cancer.

There are currently no microbiome therapeutics approved by the FDA. We believe that the ability to develop drugs that are able to modulate the microbiome and return a dysbiotic microbiome to its healthy state presents a significant opportunity to improve human health.

Our Microbiome Therapeutics Platform

We have developed the leading microbiome therapeutics platform, which we believe enables us to significantly reduce the time typically required to advance therapeutics to the clinic, and ultimately, to the market. We use reverse translation, the practice of driving discovery based on human data sets to improve the translatability of a preclinical program. Specifically, we start with data sets from both healthy subjects and patients to delineate at high-resolution the composition of the microbiome and physiological state of subjects and identify specific signatures in the microbiome that associate with disease or the onset of disease; these in-human insights are leveraged in preclinical drug design and development.

Our discovery process begins with human data derived from clinical trials and cohort studies, which we use as a basis for designing our Ecobiotic microbiome therapeutic candidates. We compare healthy, normal colonic microbiomes to those in an unhealthy dysbiotic or disease state, revealing the ecological and functional differences between various states of disease and during the transition from health to disease or vice versa. We then develop our Ecobiotic microbiome therapeutic candidates to target these differences. Our clinical data from the SER-109, SER-262 and SER-287 programs, and microbiome data generated with external collaborators, serve to instruct us on how the

introduction of certain keystone microbes have the potential to restructure a dysbiotic colonic microbiome and shift it to a non-disease state.

We have developed a proprietary suite of bioinformatics and computational tools, which facilitate our insights into the human microbiome. Using whole metagenomic shotgun sequencing, and our proprietary, curated, reference database of novel bacterial genomes, our algorithms enable us to track changes in the microbiome at the level of bacterial species and individual strains. We have also developed tools integrating gene profiling and metabolomics data (the small molecules made by the microbiome) with genomic data (the collection of bacteria defined by sequencing) to understand the functions related groups of organisms contribute to the state of disease or health. Further, we have established de novo analytics for pharmacokinetic and pharmacodynamic assessments of microbiome therapeutics.

Our proprietary strain library of over 35,000 bacterial isolates from healthy donors and patients enables us to translate computational insights into defined compositions. It includes the majority of the HMP's "most wanted" and many novel species not described in other databases or the scientific literature. Using proprietary assays and full-genome sequences, we characterize the functional capabilities of the bacteria in our strain library, based on both metabolomics and how the bacteria interact with human colonic epithelial cells and human immune cells. We also seek to understand how these microbes improve the health of barrier cells in the gut and how this may impact immune responses.

We select bacteria from our library with specific predicted properties using novel algorithms for functional design and grow the compositions in the lab to be tested both in vitro and in vivo animal models. Our animal models include conventional mice, germ-free mice, and "humanized" mice that possess only bacteria derived from humans, which we developed to minimize confounding variables presented by murine microbes. Data from our in vitro and in vivo screens are analyzed and used to optimize compositional designs; introducing new bacterial strains and optimizing existing strains until we identify a lead composition suitable for clinical testing.

Finally, we manufacture the bacterial composition under current Good Manufacturing Practices, or cGMP, which are required by FDA and European regulators. We believe our unique manufacturing capacities position us to exploit the insights of our proprietary human data and the novel biology of species and strains that have not previously been used for therapeutics. We have optimized fermentation conditions to generate spores and enhance bacterial yields in anaerobic fermentation and have in-house capabilities to formulate both spores and live non-spore bacteria. Our manufacturing facility in Cambridge, Massachusetts was designed to be fit-for-purpose and is highly differentiated compared to the offerings of commercial contract research organizations. We address quality control requirements for our Ecobiotic microbiome therapeutic candidates using proprietary microbiological and sequence-based testing schemes, including high-throughput quantitative analytics to assess the identity, potency and purity of the final product. These methods have been qualified to meet regulatory standards for live biotherapeutic products.

Taken together, we believe our platform, spanning drug discovery, preclinical translation, and novel manufacturing and quality control approaches, has enabled a field leading pipeline across a range of therapeutics areas.

Disease Overview and Our Product Pipeline

We believe our Ecobiotic microbiome therapeutic candidates represent a novel approach with potential application across a broad range of human diseases. SER-287 is under development for the treatment of active mild-to-moderate UC and has completed a Phase 1b study in the United States. SER-287 has been designated an Orphan Drug for pediatric UC by the FDA. We are designing SER-301, a rationally-designed, fermented Ecobiotic microbiome therapeutic candidate, for the treatment of IBD. Our most advanced drug development program, SER-109, focuses on recurrent CDI. SER-109 has been designated as a Breakthrough Therapy and an Orphan Drug by the FDA. Based on feedback received from the FDA, we have initiated a Phase 3 SER-109 clinical study in approximately 320 patients with multiply recurrent CDI. We are designing SER-401 for combination therapy with immune CPIs in cancer. We have also conducted early stage research on potential Ecobiotic microbiome therapeutic candidates for the treatment of metabolic disorders, such as early-stage, non-insulin dependent diabetes, NASH, and metabolic syndrome. Research in these indications is focused on developing Ecobiotic drugs that address specific functional defects in the microbiome, including the specific metabolic products made by the microbes. We believe this approach may enable pursuit of a range of disorders including various forms of liver disease and rare genetic diseases of metabolism.

Ulcerative Colitis, SER-287 and SER-301

UC is a relapsing-remitting chronic inflammatory disorder affecting the mucosal surface of the colon, leading to episodes of bloody diarrhea, urgency and mucosal inflammation (Danese and Fiocchi, 2011), which generally begins in young adulthood and endures for life. As the disease mostly affects young and middle-aged individuals, a time of peak reproductive and economic productivity, the disease leads to decreased quality of life in those affected by the

condition, high morbidity, and significant health economic burden. (Ghosh and Mitchell, 2007; Kappelman et al., 2008; Rubin et al., 2014; Theede et al., 2015) The incidence of UC is rising worldwide and the prevalence of the disease is highest in the United States, Canada, and Europe. In the United States alone, the prevalence of UC in adults is estimated to be 263 per 100,000, while in the pediatric population (age <20 years), prevalence of the disease is estimated to be 33.9 per 100,000. (Kappelman et al., 2013)

UC is characterized by recurring episodes of inflammation limited to the mucosal layer of the colon. The severity of symptoms, diarrhea associated with blood and abdominal pain, may range from mild disease to severe disease with more than 10 stools per day with severe cramps and continuous bleeding. The severity, extent, and duration of disease are also risk factors for developing colon cancer, which occurs at a rate as high as 0.5-1.0% per year, an important complication given the young age at which the disease strikes. Patients with UC also experience increased risk of CDI and primary sclerosing cholangitis, compared to the general population.

The pathogenesis of UC is unclear but thought to arise from an aberrant immune response to a change in the colonic luminal environment in a genetically susceptible individual. The key features of UC include diffuse mucosal inflammation in a continuous pattern starting distally in the rectum to more proximal disease in the left colon to pancolitis.

Symptoms of UC include rectal bleeding, tenesmus, increased stool frequency, urgency, incontinence, fever, fatigue and malaise, which negatively impact quality of life, physical and mental health and productivity. A subset of patients has extra-intestinal manifestations ranging from iron deficiency anemia to primary sclerosing cholangitis with implications for increased morbidity. In pediatric patients, the symptoms of UC have a more damaging impact, as they affect children's growth and lead to delayed puberty. These patients also suffer from weight loss, anemia and joint symptoms and current therapy itself adversely impacts normal growth and development. (Kelsen et al., 2008). Treatment of UC with corticosteroids and immunosuppressive agents adds further medical complications to these vulnerable patients, including corticosteroid toxicity and increased risk of invasive infections and malignancy. Both environmental and genetic factors contribute to the etiology of the disease. Environmental factors may induce an ongoing immune response and inflammation in the genetically predisposed host. Efforts to identify specific environmental factors has implicated commensal bacteria or their products as key determinants of the inflammatory response in UC patients (Xavier et al., 2007). Thus, we believe SER-287 may target an "underlying cause" of UC rather than its symptoms.

Current and developing treatment alternatives and their limitations

Currently, patients with UC require life-long therapy. The goals of medical therapy are to induce and maintain clinical and endoscopic remission. Endoscopic remission is recognized as a key treatment goal since it better predicts short- and long-term clinical outcomes than symptomatic improvement alone. Attainment of these goals is generally associated with improved quality of life and decreased need for corticosteroids, and lower risk of hospitalization, colectomy, and colon cancer.

Although the etiology of UC is not fully understood, much progress has been made in the understanding of pathogenesis. Under homeostatic conditions, there is a balance between pro-inflammatory and anti-inflammatory cytokine signals mediated by epithelial and immune cells in the gastrointestinal tract. However, UC is characterized by dysregulated mucosal immune responses and translocation of inflammatory mediators of microbiological origin across a disrupted gastrointestinal barrier that may cause or perpetuate inflammation leading to chronic inflammatory disease. Migration of innate and adaptive immune cells into gut mucosal tissues is potentiated by locally produced cytokines and chemokines, and by the expression of integrins that enhance cellular trafficking into the gut lamina propria. Inhibition of the immune response, via antibodies and proteins that sequester pro-inflammatory cytokines or block the function of integrins, has been an important target of UC drug development over the past decade.

Current management of UC includes medications that decrease general inflammation (e.g., 5-aminosalicylate derivatives, or 5-ASA, corticosteroids) or dampen specific components of the host immune response (e.g., immunomodulators, inhibitors of tumor necrosis factor, anti-integrin antibodies).

For mild-to-moderate disease, the 5-ASA derivatives are the standard of care for both induction and remission. 5-ASA derivatives achieve clinical remission in only 25-40% of patients during induction and approximately one-third of responders have disease flares during the first year of maintenance therapy, necessitating additional treatment interventions such as corticosteroids and immunomodulators (e.g. 6-mercaptopurine, methotrexate, azathioprine). Corticosteroids are not recommended by guideline panels for chronic therapy since these drugs are ineffective for maintaining remission and are associated with significant adverse events. Patients taking thiopurines require ongoing monitoring for hepatotoxicity, myelosuppression, and opportunistic infections, as well as counseling on the potential risk of lymphoma.

Current medical therapies for the treatment of UC suppress the immune system rather than reducing the triggers of immune activation. We believe there remains an unmet need for safer agents with novel non-immunosuppressive mechanisms of action. Moreover, alternative therapy is needed for patients with mild-to-moderate UC who experience frequent flares or are intolerant to the aminosalicylate class of medication or where there are safety concerns relating to the use of immunomodulator or steroid therapy.

SER-287

Given the dysbiosis seen in UC patients, studies have explored the use of FMT to treat UC. (Angelberger et al., 2013; Colman and Rubin, 2014; Kump et al., 2013; Kunde et al., 2013; Moayyedi et al., 2015; Rossen et al., 2015; Paramsothy et al., 2017). Early reports of enhanced clinical remission and endoscopic improvement with repetitive FMT compared to placebo motivated the preclinical development and clinical testing of SER-287. SER-287 is a donor-derived, microbiome therapeutic candidate composed of the spore-forming fraction of the intestinal microbiota that is underrepresented in UC patients. We initiated our Phase 1b clinical study in December 2015 in subjects with mild-to-moderate UC to evaluate the safety and efficacy of SER-287 added to standard of care treatment. This SER-287 Phase 1b study, a randomized, double-blinded, placebo-controlled, multiple-dose, induction study enrolled patients with active mild-to-moderate UC, with Total Modified Mayo scores of 4 to 10. The study enrolled 58 patients at 20 sites across the United States. Study subjects exhibited pre-study disease activity despite use of current therapies in a majority of subjects, which included 5-ASA, low dose corticosteroids, or immunomodulatory therapy. Three SER-287 drug product lots, based on human donor material obtained from three separate individuals, were used in the Phase 1b study.

The primary endpoints of the study were to evaluate the safety and tolerability of SER-287, compare the change in the microbiome composition versus placebo and determine engraftment of SER-287 bacteria following SER-287 treatment. The study evaluated clinical response, complete remission, and endoscopic improvement, as well as metabolomic and immunological findings.

In October 2017, we announced positive topline results from our Phase 1b clinical trial of SER-287 in patients with UC. Study results showed no imbalance in adverse events in SER-287 treated patients, as compared to patients treated with placebo. No drug related serious adverse events were observed.

Analyses of study patients' microbiome data, a primary endpoint, indicated that SER-287 induced dose-dependent engraftment of SER-287-derived bacterial species into the colonic microbiome of the patients treated with SER-287. The cohort of patients that received vancomycin pre-treatment followed by daily administration of SER-287 showed the highest level of SER-287 engraftment. We also observed the most meaningful clinical benefit in this patient cohort. Differences in the composition of the microbiome post treatment were also associated with clinical remission. Bacterial engraftment signatures were durable throughout the dosing period of the trial and were also observed at four weeks post administration of the final SER-287 dose. The pharmacologic impact of the SER-287 engraftment was supported by metabolomic and transcriptomic data. Analysis of metabolites and gene expression signatures associated with inflammation and immune modulation, were observed to be correlated with remission in SER-287 treated subjects.

Microbiome results showed engraftment of SER-287-derived bacterial species in patients pre-treated with vancomycin who received SER-287, with daily dosing providing the most rapid and robust change in patients' microbiome. Engraftment observed in these patients was maintained during the entire dosing period and was observed four weeks after the last dose of SER-287 was administered. Thus, engraftment was durable. Vancomycin pre-treatment, as compared to placebo pre-treatment, led to an immediate reduction of microbiome diversity followed by rapid and robust engraftment of SER-287-derived bacterial species. We believe these data suggest that vancomycin pre-treatment may open ecological niches for SER-287 engraftment in the human microbiome of patients with UC.

In December 2017, the FDA granted Orphan Drug Designation to SER-287 for treatment of UC in pediatric patients.

Further Details of Phase 1b clinical study design.

The Phase 1b clinical study was a multicenter, randomized, double-blind, placebo-controlled multiple dose study utilizing weekly or daily dosing with SER-287. We enrolled eligible subjects at approximately 20 sites in the United States. The Phase 1b clinical study was designed to enroll adults 18 years of age and older who had mild-to-moderate UC as defined by a Total Modified Mayo score between 4 and 10, inclusive, with a modified Mayo endoscopic subscore ≥ 1, who were failing current therapies.

Patients were randomized to one of four study arms:

- Pre-treatment with placebo for 6 days, followed by weekly dosing of SER-287 for 8 weeks
- Pre-treatment with placebo for 6 days, followed by daily dosing with placebo for 8 weeks
- Pre-treatment with vancomycin for 6 days, followed by daily dosing of SER-287 for 8 weeks
- Pre-treatment with vancomycin for 6 days, followed by weekly dosing of SER-287 for 8 weeks

The primary objectives of the study were to evaluate the safety and tolerability of SER-287 compared to placebo; to compare the baseline composition of the intestinal microbiome to the composition at 8 weeks post-initiation of SER-287 or placebo; and to determine the engraftment of SER-287 bacteria into the intestinal microbial community in each of the SER-287 arms compared to the placebo arm.

The secondary objectives of the study were to determine the proportion of subjects in each of the treatment arms who at eight weeks post-initiation of treatment achieve a clinical response, complete remission, and endoscopic improvement; to assess changes in serum and fecal biomarkers from baseline throughout treatment; to determine the

complement of metabolic pathways; and to compare the changes in exploratory biomarkers from mucosal biopsies and stool in each of the treatment arms from baseline through eight weeks.

This study was designed to provide evidence of safety of SER-287 compared to placebo for the UC population, describe the changes in the microbiome as a result of treatment with SER-287 and provide potential predictive biomarkers for future studies. UC is characterized by a decrease in microbial diversity and richness, with a lower prevalence of spore-forming organisms within the phylum Firmicutes. Preliminary data using FMT suggest that microbial interventions can affect clinical outcomes in UC, and this study evaluated whether the ecology of bacterial spores in SER-287 could correct the dysbiosis in UC, increase microbial diversity and safely lead to a clinical response in UC patients with mild-to-moderate disease.

Phase 1b clinical study results

Results were analyzed using the ITT "missing equals failure" analysis and the ITT "observed case" analysis methods. The ITT "missing equals failure" analysis, included all 58 randomized subjects. For this analysis, incalculable clinical endpoints due to missing data, UC medication added due to UC flare during the treatment period and discontinuation from the trial prior to Day 48 were considered as not achieving the clinical endpoints (worst outcome). However, if the end-of-trial endoscopy at Day 48, or later, was available, and the subject did not take additional UC medication due to UC flare, then the observed data was used to define success or failure for the subject. A period of 48 days of microbiome therapy was considered sufficient treatment to estimate the outcome of clinical endpoints and was prespecified. The ITT "observed case" analysis included 53 of 58 subjects randomized, excluding those who were missing their end-of-treatment endoscopies and used the observed data to define success or failure for each subject in the analysis.

Clinical Efficacy Results

In the "missing equals failure" analysis, remission showed a statistically significant improvement in the vancomycin pre-treatment / SER-287 once-daily dosing arm as compared to the placebo/placebo daily arm: 40% (6 of 15 in SER-287) vs 0% (0 of 11 in placebo); change from placebo of 40.0% (95% confidence interval: 15.2%, 64.8%), (p-value, 0.0237). (See Figure 1).

The SER-287 weekly treatment arms also showed an improvement over placebo in both remission and endoscopic improvement but the effect was less than with the daily dosing regimen, showing a dose-response to SER-287 in these efficacy endpoints. Addition of vancomycin to the SER-287 weekly dosing regimen did not clearly alter efficacy results, although we believe this may be due to the small size of the study.

Clinical response (data not shown), showed a numeric increase in the vancomycin/SER287 daily treatment arm compared to placebo but did not reach statistical significance.

Figure 1:SER-287 Phase 1b Clinical Study Efficacy Data – Missing Equals Failure

Legend: Δ = change from placebo; Remission was defined as a Total Modified Mayo score of less than or equal to 2, and an endoscopic sub-score of 0 or 1; Endoscopic improvement was defined as a decrease in endoscopic sub score of greater than or equal to 1. Endoscopy measures were analyzed by a Central Reader.

Clinical Safety Results

The primary safety objective (short-term safety) was to evaluate the safety and tolerability of SER-287 in adults with active mild-to-moderate UC up to 92 days after randomization as determined by clinical and laboratory safety assessments.

The treatment-emergent adverse events, or TEAEs, were balanced across all the treatment arms. No drug-related serious adverse events, or SAEs, were reported. All adverse events, or AEs, were considered mild to moderate in

intensity. Gastrointestinal, or GI, disorders had the greatest number of AEs compared to other system organ classes, with the most efficacious treatment arm (vancomycin/SER-287 daily) experiencing the lowest percentage of GI AEs.

SER-287 was observed to be well-tolerated in all treatment arms, showing a safety profile consistent with the placebo arm. The safety profile, when evaluating GI AEs, showed an improvement in the vancoymycin/SER-287 treatment arm compared to vancomycin/placebo and the vancomycin/SER-287 weekly treatment arms.

Diverse analyses of microbiome data of patients in this trial, a primary endpoint, was completed after completion of the trial. Analyses of study patients' microbiome data, a co-primary study endpoint of the trial, indicate that SER-287 induced dose-dependent engraftment of SER-287-derived bacterial species into the colonic microbiome of the patients treated with SER-287. Patients administered vancomycin pre-treatment followed by daily administration of SER-287 had the highest level of SER-287 engraftment, which was statistically significant. This patient cohort corresponded with the study arm where the most significant clinical benefits were observed, including clinical remission and endoscopic improvement. Differences in the composition of the microbiome post treatment were also associated with clinical remission. Bacterial engraftment signatures were durable throughout the dosing period of the trial and were also observed at four weeks post administration of the final SER-287 dose. The SER-287 Phase 1b study microbiome data support the previously reported clinical results.

Microbiome results showed engraftment of SER-287-derived bacterial species in patients pre-treated with vancomycin who received SER-287. The degree of SER-287 engraftment, as measured by the number of detectable SER-287-derived bacterial species, increased in a dose-dependent manner, with daily dosing providing the most rapid and robust change in patients' microbiome. Engraftment was maintained during the entire dosing period and was observed four weeks after the last dose of SER-287 was administered. Thus, engraftment was durable. Changes in the composition of the GI microbiome were associated with clinical remission and further associated with changes in metabolite and gene expression signatures associated with inflammation and immune modulation. Vancomycin pre-treatment, as compared to placebo pre-treatment, led to an immediate reduction of microbiome diversity followed by rapid and robust engraftment of SER-287-derived bacterial species. These data suggest that vancomycin pre-treatment opens ecological niches for SER-287 engraftment in the human microbiome of patients with UC.

Phase 2b Clinical Study Design

Based on feedback from the FDA, we believe that the results from the SER-287 Phase 2b ECO-RESET study in conjunction with data from a second pivotal study, could enable submission of a SER-287 Biologics License Application.

The Phase 2b study, initiated in December 2018, is a three-arm placebo-controlled trial of approximately 200 patients with active mild-to-moderate UC. Two groups of patients will receive different doses of SER-287, both following pretreatment with a short course of oral vancomycin. A third study arm will receive placebo. The study's primary endpoint will evaluate clinical remission measured after 10 weeks of SER-287 administration. Endoscopic improvement will be measured as a secondary efficacy measure.

SER-301

Our SER-301 program is in preclinical discovery and bioprocess development. SER-301 is being rationally designed by utilizing our reverse translational platforms to incorporate learnings from our SER-287 clinical study, as well as our SER-262 clinical study. We have identified specific bacterial species that engraft and are associated with clinical remission, and further we have identified metabolic products made by these bacteria that have correlated with clinical efficacy. We also have gene expression data from patient mucosal biopsies showing which genes and pathways are favorably altered by SER-287 treatment. All of these data are being leveraged in the design of SER-301.

CDI Overview and SER-109

Clostridium difficile Infection

C. difficile is a Gram-positive, toxin-producing, spore forming bacterium that may cause debilitating diarrhea in infected individuals, but can also lead to more severe outcomes, such as inflammation of the colon, or colitis, toxic megacolon and death. C. difficile bacteria express toxins that disrupt the structural architecture of cells causing leakage of fluids through the GI epithelium. The cells disrupted by these toxins eventually undergo apoptosis and die, releasing their contents into the colon, resulting in inflammation of the colon, severe and persistent diarrhea and, in the most serious cases, death.

CDI is most often associated with the prior use of antibiotics, although age and poor immune status are important risk factors as well. Antibiotics are thought to decrease resistance to CDI by causing dysbiosis in the microbiome. Since C. difficile spores are able to survive for long periods of time outside the body, and because healthcare settings are often sites of significant antibiotic use, CDI transmission rates in hospitals, long-term acute care facilities and nursing homes have been increasing. CDI is also a cause of morbidity and mortality among hospitalized cancer patients and bone marrow transplant patients as their immune systems are suppressed by cytotoxic drugs, which are drugs that inhibit or prevent the function of cells including cells of the immune system, and they may be heavily treated with antibiotics to prevent or treat infections. More recently, the rise of community-acquired CDI has been recognized as a growing problem.

The CDC has identified C. difficile as one of the top three most urgent antibiotic-resistant bacterial threats in the United States. It is the most common cause of hospital acquired infection in the United States, having overtaken MRSA. CDI is responsible for the deaths of approximately 29,000 Americans each year. CDI is also costly to the healthcare system. According to a study published in Clinical Infectious Diseases, the economic burden of CDI in 2008 in U.S. acute care facilities alone was estimated to be as much as $4.8 billion. In addition, a summary of studies published in 2009 in The Journal of Hospital Infection, calculated that the treatment cost per episode of primary CDI was as much as $5,000 and as much as $18,000 per recurrence of CDI (Ghantoji et al., 2010). Further, according to a 2014 article in the American Journal of Infection Control, from 2001 to 2010, incidence of CDI per 1,000 patients discharged increased from 4.5 to 8.2 with an average hospital stay of eight days. Research suggests that the risk of recurrence is approximately 25% after primary CDI, 40% after a first recurrence and greater than 60% for those experiencing two or more recurrences (Higa & Kelly, New Drugs and Strategies for Management of Clostridium difficile Colitis, J. of Intensive Care Medicine, 2013). Based on an epidemiological study conducted by the CDC, the incidence of CDI in the United States, based on a positive toxin or molecular assay in patients who did not have a positive result in the previous 8 weeks, was estimated to be 453,000 (95% confidence interval, 397,100 to 508,500) (Lessa et. al., Burden of Clostridium difficile Infection in the United States, New England J. of Medicine, 2015).

Current and developing treatment alternatives and their limitations

Patients with CDI utilize antibiotics, FMT, unapproved over-the-counter probiotics, and antibodies. Several therapeutic vaccines are also being developed.

Antibiotics. According to the Infectious Disease Society of America, or IDSA, guidelines, the current standard of care for primary CDI is to treat with antibiotics, such as fidaxomicin or vancomycin. Metronidazole is only recommended for mild disease or where access to other drugs is limited. In addition, while fidaxomicin is recommended to treat primary CDI, it does not have a label claim to reduce or prevent CDI recurrence. No antibiotic therapeutics are currently approved for treatment of recurrent CDI.

Recurrent CDI, defined as the presence of diarrhea and a positive C. difficile stool assay within two to eight weeks following the initial episode, is not well addressed by any of the available antibiotics. When a patient has recurred two or more times after the initial occurrence, CDI recurrence rates are greater than 60% and the probability of additional recurrences increases with successive cycles. In extreme cases, patients are treated continuously for years with vancomycin, even while they continue to experience gastrointestinal symptoms including diarrhea and abdominal discomfort.

The primary limitation of antibiotics is that their use appears to exacerbate dysbiosis, resulting in increased risk of future CDI. Research in animal models has shown that antibiotic use not only eliminates many healthy bacteria in the GI tract, but also leads to the release of nutrients that facilitate the growth of C. difficile. Antibiotics have also been shown to change the ratio of primary versus secondary bile acids in the colon by killing bacteria required to metabolize bile acids. This shift to a predominance of primary bile acids further facilitates the growth of C. difficile, as it requires primary bile acids for germination of its spores. As a result, antibiotic use may induce a lasting dysbiosis that makes it possible for C. difficile to colonize a person and then cause, or further perpetuate, disease.

Fecal microbiota transplantation. FMT, also known as a stool transplantation, is a procedure during which donated stool, including fecal microbes, is typically instilled via colonoscopy into a patient with CDI. We believe that the efficacy of FMT, which has resulted in cure rates for recurrent CDI of 81% in a randomized controlled study reported in 2013 in the New England Journal of Medicine, supports the role of dysbiosis as a cause of CDI recurrence. However, FMT presents several challenges for effective treatment of the disease. FMT has the potential to transmit infectious or allergenic agents between hosts, involves the transmission of potentially hundreds of unknown strains of bacteria, fungi and viruses from donor to subject, and is difficult to perform on a mass scale. Additionally, FMT is inherently non-standardized so that different desired and/or undesired material may be transmitted in any given donation. FMT is not approved by the FDA and we believe that, as currently practiced by clinical centers in the

United States, it may be unable to gain such approval since the product, to our knowledge, cannot be characterized according to current regulatory requirements for identity, potency, purity and safety and has not been tested in rigorous, placebo controlled, randomized and blinded clinical studies. Commercial providers of FMT must meet FDA regulatory requirements for a biologics license and must produce FMT material using cGMP.

Probiotic therapies. Probiotics represent a group of products typically available over the counter in supplements and in some foods, which contain a small number of species of bacteria. However, to date there have been no clinical studies that have established the ability of probiotics to repair a dysbiosis of the microbiome. Further, there is neither a legally recognized definition of, nor a standard of identity for, the term probiotic in the United States or Europe. The European Food Safety Authority has rejected many of the claims of health benefits associated with probiotics because the microbes had not been sufficiently characterized, the claimed effect was not considered beneficial and human studies in support of the claims had not been made available. As a result, after December 14, 2012, food and nutritional supplements companies were no longer allowed to communicate health benefits for their products on account of probiotic content in the EU.

Antibodies. Bezlotoxumab a fully human monoclonal antibody directed against C. difficile toxin B was approved in the United States in October 2016 and in Europe in 2017 for the treatment of CDI. The antibody demonstrated 10% absolute risk reduction in preventing recurrence of CDI. Antibodies bind toxins to alleviate the symptoms of CDI, but they do not address the underlying dysbiosis of the microbiome, which we believe is the cause of recurrent CDI. Bezlotoxumab requires intravenous infusion.

Vaccines. The efficacy of vaccines in treating CDI in humans currently remains under investigation. In addition, it is difficult to define and access a target population for a CDI vaccine, given that the at-risk patient population is largely elderly individuals who typically respond less robustly to vaccination therapies.

SER-109

SER-109 is an investigational, donor-derived ecology of bacteria in spore form purified from fecal donations obtained from healthy screened donors. SER-109 consists of an average of approximately 50 bacterial species and is designed to reduce recurrences of CDI in patients suffering from recurrent CDI by restoring a dysbiotic microbiome to a state of health. In our open label Phase 1b/2 clinical study of SER-109, we evaluated the effect of treatment with SER-109 in patients with three or more occurrences of CDI in a 12-month period. Of the 30 patients enrolled in the trial, 87% of patients (26 of 30) met the predefined endpoint and 97% (29 of 30), achieved a clinical cure, which we defined as the absence of CDI requiring antibiotic treatment during the eight-week period after SER-109 dosing. A subsequent randomized, double-blind, placebo-controlled Phase 2 clinical study was conducted in 89 subjects to evaluate the safety, tolerability and efficacy of SER-109 in adults with recurrent CDI. In that study, 44% of subjects (26 out of 59) who received SER-109 experienced a recurrence at the 8-week endpoint compared to 53% of subjects (16 out of 30) who received placebo, a result that did not show a statistically significant difference between the two treatment arms. SER-109 was generally safe and well tolerated in both the Phase 1b/2 and Phase 2 clinical studies. In each study we also performed an analysis of the microbiome using next-generation sequencing technology and microbiological analysis. These studies demonstrated a re-establishment of keystone organisms and a rapid increase in bacterial diversity, which enable the restoration of the microbiome to a healthy state.

SER-109 is formulated as oral capsules for administration after completion of antibiotics. Four capsules of SER-109 is comprised of about 30 million SCFU that are delivered in four oral capsules. The spores in SER-109 are intended to germinate in the GI tract and compete for the same nutrients required by C. difficile.

Phase 1b/2 clinical study design. The Phase 1b/2 clinical study was a two-part trial designed to evaluate the safety and efficacy of SER-109 in 30 patients with recurrent CDI. Part 1 of the study evaluated a single dose of SER-109 administered orally in 30 capsules over two days, with a dose that varied between 3×10^7 and 2×10^{10}. Part 2 of the study evaluated a single dose of SER-109 administered orally in a range of one to 7 capsules over one day. The target dose in Part 2 was $1x10^8$ spores per dose, which was approximately 17-fold lower than the mean dose in Part 1.

Phase 1b/2 clinical study results. The primary efficacy measure was the absence of CDI (defined in this study as more than three unformed bowel movements in a 24-hour period with laboratory confirmation of a positive C. difficile stool test) during the eight weeks after initiating therapy. Twenty-six of 30 patients, or 87% of patients, in the Phase 1b/2 clinical study achieved the primary efficacy endpoint, consisting of 13 patients in each of Part 1 and Part 2 of the study. Among the 26 patients was one patient who experienced an initial recurrence on Day 26 and was re-treated, per protocol, with a dose from the same donor. Following re-treatment, this patient also achieved the primary efficacy endpoint. Of the patients who did not meet the primary efficacy endpoint, one had a recurrence of CDI on Day 5 and

did not receive a second treatment with SER-109 and the three other patients were determined by their attending investigator to be recovering from their diarrheal episode by the time they submitted their stool sample for CDI testing. The three patients were determined to be clinically CDI free at eight weeks. As a result, the clinical cure rate for the study, which we defined as the absence of CDI requiring antibiotic treatment during the eight-week period after SER-109 dosing, was 97%, or 29 of 30 patients. SER-109 was observed to be well tolerated in this study. The most common AEs were diarrhea, nausea, and abdominal pain. The majority of TEAEs were mild in severity and consistent with post-antibiotic recovery from CDI.

Phase 2 clinical study design. The Phase 2 clinical study was a randomized, double-blinded, placebo-controlled, parallel-group two arm trial that enrolled a total of 89 patients with a history of multiply-recurrent CDI, defined as 3 or more CDI episodes within 9 months. Subjects were randomized at a 2:1 ratio with 59 subjects receiving SER-109 and 30 subjects receiving placebo. SER-109 was administered orally as a single dose of $1x10^8$ bacterial spores, following the completion of antibiotic treatment for CDI. The study was conducted at 36 centers across the United States. The primary endpoint was the absence of recurrence of C. difficile positive diarrhea requiring antibiotic treatment up to 8 weeks following treatment with SER-109 or placebo.

Phase 2 clinical study results. The predefined study primary efficacy endpoint was the relative risk of CDI recurrence up to 8 weeks after treatment with SER-109 compared to treatment with placebo. CDI recurrence was defined as diarrhea for 2 or more consecutive days, a positive CDI test, and the requirement for antibiotic treatment. Based on 8-week data, CDI recurrence occurred in 44% of subjects (26 of 59) who received SER-109, compared to 53% of subjects (16 of 30) who received placebo. The relative risk of CDI recurrence for the placebo population compared to the SER-109 population was not statistically significant.

The most commonly reported AEs in both the SER-109 and placebo arms were in the GI category, and were diarrhea (25% vs 14%), abdominal pain (22% vs 14%), flatulence (12% vs 3%), and nausea (10% vs 10%), for SER-109 and placebo, respectively. No drug-related SAEs were observed. The SER-109 analyses were shared with the FDA. Based on feedback received from the FDA, a new Phase 3 SER-109 clinical study in approximately 320 patients with multiply recurrent CDI was initiated. Study participants are randomized 1:1 between SER-109 and placebo and receive a total dose that is approximately 10-fold higher than in the Phase 2 study, administered over three consecutive days. Diagnosis of CDI for both study entry and for endpoint analysis is confirmed by C. difficile cytotoxin assay, compared to the first Phase 2, where most patients were diagnosed by polymerase chain reaction, or PCR. The primary endpoint will compare the C. difficile recurrence rate in subjects who receive SER-109 verses placebo at up to eight weeks after dosing. The FDA has agreed that this new trial may qualify as a pivotal study with achievement of a persuasive clinical effect and addressing FDA requirements, including clinical and statistical factors, an adequately sized safety database, and certain CMC parameters.

Analysis of Phase 1b/2 and Phase 2 clinical study results. In our Phase 2 clinical study, the study's primary endpoint of reducing the relative risk of CDI recurrence at up to 8 weeks after treatment was not achieved. In order to understand the difference in outcome between Phase 1b/2 and Phase 2 clinical studies, we conducted an analysis of the available clinical, microbiome and CMC data. This root-cause investigation looked at the clinical trial population, study conduct, and diagnostic testing used for study inclusion and endpoint analysis, assessed clinical specimens for genomic and metabolomic biomarkers that might give insight into SER-109 efficacy and potency, reviewed manufacturing procedures and processes, performed retrospective analysis using high-resolution whole metagenomics sequencing of Phase 1b/2 clinical study stool samples, and reviewed analytical methods, that may have differed between the Phase 1b/2 and Phase 2 clinical studies. We identified key factors that potentially explain the Phase 2 clinical study results, including issues related to both the accurate diagnosis of C. difficile recurrent infection, and potential suboptimal dosing of subjects in the trial.

The key factors include:

- The diagnostic test for entry may not have differentiated subjects with active CDI disease from those with other disease but who had C. difficile carriage (e.g., irritable bowel syndrome)
- The diagnostic test for CDI recurrence during the study (the primary endpoint) overestimated recurrences, as PCR was the most common test performed.
- The difference in recurrence rates by age in the placebo arm was confounded by the small number of placebo subjects (30) and the likely inclusion of subjects with irritable bowel syndrome rather than recurrent CDI, or RCDI
- The safety profile of SER-109, which may include diarrhea in the first week following dosing, led to SER-109 subjects presenting for evaluation of recurrence at a time when they were likely to be colonized with C. difficile leading to mistaken diagnosis of RCDI
- The dose and dosing regimen used in the study may not have been optimal in the Phase 2 clinical study based upon an assessment of the microbiome response using whole metagenomics shotgun sequencing.

We performed an analysis of the microbiome of our Phase 2 clinical study and a reanalysis of our Phase 1b/2 clinical study using whole metagenomics shotgun sequencing and microbiological analysis to evaluate long-term changes in the microbiome, including the restoration of bacterial diversity in the colon of patients. This demonstrated a rapid increase in bacterial diversity and a restructuring of the microbiome towards a healthy state. Upon introduction,

SER-109 appears to engraft its bacterial species into the microbiome, with some of these species persisting in the patient's GI tract for at least 24 weeks after dosing. In addition, in some patients we noted the repopulation of organisms that were not in SER-109 and had not been detected in the patient prior to treatment. We believe this phenomenon, which we refer to as augmentation, is an important element for restoration of bacterial diversity and repair of dysbiosis. We did not observe any dose-dependent effect on engraftment, augmentation, or the clinical resolution of CDI in the Phase 1b/2 clinical study.

Phase 3 clinical study design. In June 2017 we initiated a Phase 3 clinical study of SER-109 in approximately 320 patients with multiply recurrent CDI. Study participants are being randomized 1:1 between SER-109 and placebo. Diagnosis of CDI for both study entry and for endpoint analysis utilizes a C. difficile cytotoxin assay, compared to the Phase 2 clinical study, where most patients were diagnosed by PCR. Patients in the SER-109 arm receive a total SER-109 dose, administered over three days, approximately 10-fold higher than the dose used in the Phase 2 clinical study. The study evaluates patients for 24 weeks and the primary endpoint is to compare the C. difficile recurrence rate in subjects who receive SER-109 verses placebo at up to eight weeks after dosing. CDI recurrence is defined as diarrhea (>3 unformed bowel movements/day for 2 or more consecutive days), a positive CDI toxin test, and the decision by the primary investigator that antibiotic treatment is warranted. The study is being conducted at approximately 100 sites in the United States and Canada.

Manufacturing. SER-109 is a purified ecology of spores produced through a process of extraction from a natural human stool source, obtained from qualified, highly screened donors. The donor raw material is collected in a controlled setting, under a protocol that ensures that donors meet appropriate qualification criteria.

Donors are required to be in good health, and to possess a medical history that minimizes the risk of exposure to and transmission of an infectious disease. Donors are tested for infectious agents and screened for GI and other health factors. Donors are monitored for health status changes during the donation period. At the end of the donation period, the qualification assessment is repeated to help ensure the donor has maintained their health status. After successful completion of an exit screening, donations are released for use in manufacturing.

We initially process the donor material in a Cambridge manufacturing facility, and then transfer the process intermediate to a contract manufacturing organization, or CMO, to isolate and concentrate SER-109 for finishing to the oral capsule dosage form. The purified drug substance is tested for identity, potency and purity, and subsequently formulated into drug product where it is again tested for identity, potency, purity, and pharmaceutical properties in our Cambridge facility. The final drug product dosage form is four hard capsules for oral administration. Steps are specifically built into the process to remove and kill non-spore microbes. We have conducted validation studies demonstrating the ability of the process to inactivate and clear hypothetical extraneous pathogens of concern, and we believe we have sufficient data from these studies to support ongoing and proposed clinical trials.

Raw materials, intermediates, drug substance and drug product are tested using cGMP assays developed with our know-how to assess the key quality attributes of identity, potency and purity of the product. Identity testing has been developed to assure the presence of specific live spore forms in the product. Potency assays assure the intended dose of spores and assess stability of the spores during storage. Stability of the dosage form is also confirmed. Proprietary microbiological purity assays have been developed to enable testing for microbial contaminants in the presence of the live spore product.

We believe we can address market demand with a relatively small-scale manufacturing process. If approved, we anticipate that we will be able to produce a sufficient commercial supply of SER-109 to meet estimated demand in the United States using donations from a modest number of donors.

Other Programs

SER-401

We are also developing SER-401, for use with CPIs in patients with solid tumors to enhance efficacy and improve survival. SER-401 is a microbiome therapeutic candidate sourced from healthy individuals who have been identified

to have a microbiome signature that is similar to that observed in cancer patient responders to CPIs. CPIs block the mechanisms by which cancers evade detection and destruction by the immune system. Observational studies of humans by a group led by our collaborator Dr. Jennifer Wargo of MD Anderson suggest that microbiome composition impacts response to CPIs. This has been supported by mouse model studies conducted by us and at MD Anderson that show that colonization with human responder microbes affected tumor response to CPI treatment, versus mice colonized with CPI non-responder microbes. These effects are thought to be a result of a specific microbiome 'signature' that is enriched with certain members of the Firmicutes phylum of bacteria. We are working in collaboration with MD Anderson and the Parker Institute to evaluate the potential of SER-401, based upon this signature, to modulate the immunological tone of subjects to improve response in patients with metastatic melanoma to CPI treatment. MD Anderson granted us an exclusive option, with pre-defined financial terms, to license intellectual property rights from them related to the use of bacteria in combination with CPIs. In collaboration with the Parker Institute and MD Anderson, we have initiated a study of SER-401 in patients with metastatic melanoma. Patients will be treated with either CPI alone, or in combination with SER-401, and observed for tumor regression and immunological markers of response to CPI.

SER-262

In July 2016, we initiated a SER-262 Phase 1b dose-escalating study, the first clinical trial conducted using a rationally designed, fermented ecology of bacteria. SER-262 was designed to be used following CDI antibiotic treatment to prevent an initial recurrence of CDI. We have established various capabilities to enable the development of rationally designed microbiome therapeutics including metagenomic and metabolomic profiling, use of curated reference computational databases and proprietary in silico algorithms for drug design, an extensive proprietary bacterial library, advanced manufacturing processes, and capabilities to conduct pharmacokinetics and pharmacodynamics analyses in clinical studies. SER-262 contains a consortium of 12 bacterial strains derived from a manufacturing process that utilizes in vitro fermentation and does not require human donor material.

The Phase 1b clinical study was a 24-week, randomized, placebo-controlled, dose-escalation trial. The primary endpoints of the study were safety and tolerability and a comparison of the CDI recurrence rate in the SER-262 and placebo groups. Key secondary endpoints included analysis of SER-262 bacterial strain engraftment. Top-line clinical and microbiome results from the study are available. No drug-related SAEs were observed. No significant differences were observed in the recurrence rates in patients administered SER-262 as compared to placebo. However, we observed a statistically significant reduction in CDI recurrence rates in patients pretreated with vancomycin followed by SER-262, as compared to those treated with metronidazole followed by SER-262. This observation corresponded with an increase in SER-262 microbiome engraftment in patients pretreated with vancomycin. Clinical data from both the SER-262 and SER-287 studies suggest that vancomycin pretreatment supports robust engraftment of our microbiome therapeutic candidates.

SER-155

We are also designing SER-155, a rationally designed product candidate to prevent infections and improve GI barrier function (including the consequences of GvHD) in patients following allo-HSCT liver transplants. This preclinical program is based on published clinical evidence from our collaborators at Memorial Sloan Kettering Cancer Center showing that allo-HSCT patients with reduced microbiome diversity are far more likely to die due to infection and/or lethal GvHD (Taur et al., Blood, 2014; Jenq et al, Biology of Blood and Marrow Transplantation, 2015). The selection of the patient population will be based on preclinical data, and the assessment of our clinical development plan, regulatory path and market opportunities. We plan to conduct studies in animal models as well as conduct further in vitro characterization of individual strains, in order to define and nominate a composition for clinical development In November 2017, we announced that we were awarded a grant from CARB-X (Combating Antibiotic-Resistant Bacteria Accelerator) to support continued preclinical research and early development work for SER-155. The CARB-X grant provides us with up to $2.5 million of research funding with potential for an additional $3.1 million for manufacture and IND upon completion of milestones.

We continue to evaluate microbiome pharmacokinetic and pharmacodynamic data from the SER-262 Phase 1b study, in addition to insights gained from research efforts with our other rationally designed Ecobiotic microbiome therapeutic candidates, in order to determine future steps in the development of both SER-262 and SER-155.

Sales and Marketing

If SER-109 is approved in the United States and Canada, we believe it can be commercialized with a focused specialty sales force of 100 or fewer sales representatives that will target gastrointestinal and infectious disease physicians,

which are the two primary groups of physicians who treat multiply recurrent CDI patients.

In January 2016, we entered into an agreement with Nestec Ltd., or NHS, for the development and commercialization outside of the United States and Canada of our product candidates in development for CDI and IBD, including UC and Crohn's disease. The agreement will support the development of our portfolio of products for CDI and IBD in markets outside of the United States and Canada and provide financial support for our ongoing research and development.

Manufacturing

The production of live bacterial products is highly specialized. Owing to their hardiness and environmental persistence, production of spore-forming organisms poses unique considerations for product, personnel, and facility protection. Manufacturing activities with spores are subject to specialized regulations. We expect that a typical commercial fermentation will yield on the order of hundreds or thousands of doses per liter depending on the product and its composition. Additionally, because a given total dose is split between several strains, the per-strain requirements for production may be even lower. As a result, we believe the high productivity relative to the dose level will enable production scales for both clinical and commercial supply to be modest.

We have developed supply chains for producing and testing materials to ensure the availability of future clinical trial supplies. Our development processes are designed to ensure that the raw materials, process technologies and analytical tests we use are scalable and transferable to a cGMP manufacturing environment. These include the following core elements:

- Fermentation. We are using microscale screening to optimize culture of the bacterial strains of interest in our current and foreseeable product candidates. These screens are designed to identify the fermentation platform that is best-suited for optimization and scale-up of the strains. Small-scale fermentation systems (0.1 L to 50 L) enable the optimization of a wide variety of culture conditions and have been demonstrated to be scalable to larger fermentation processes and enable technology transfer to clinical and final manufacturing sites. We employ platform fermentation processes as starting points for cGMP production processes and develop strain specific processes as required. To develop master cell banks, working cell banks, and bulk drug substance for commercial product, we are using bacterial strains originating from a unique research cell bank precursor, so we expect the research cell banks and final drug product should be genetically and physiologically similar.
- Purification. Similar to fermentation, we believe small-scale purification operations are available for assessing large-scale cGMP manufacturing of live cells, and to quickly assess downstream process yield, quality and robustness. For our oral products, purification is typically less complex than for parenteral biologics such as monoclonal antibodies that must purify away very similar components from the culturing process. Separation of viable microbes from soluble fermentation broth components is typically much simpler.
- Formulation. Our Ecobiotic microbiome therapeutic candidates are combinations of live bacteria and can be administered by a number of methods and by different routes. The primary goal in developing a formulation is to deliver live bacteria to the intended location in a condition where they are able to replicate and correct dysbiosis. Formulation development generally uses approved excipients and preservatives, and will include screening of liquid, solid, and suspension formulations to maximize the opportunity for extended stability with minimal cold-chain requirements. Dosage forms for oral products may be capsules, tablets, sachets, or liquid containers.
- Analytical. We are addressing quality control requirements for our Ecobiotic microbiome therapeutic candidates using proprietary microbiological, chemical, biochemical, and molecular sequence-based testing schemes. We have available and are further developing quality control and in-process analytical tools that can quantitatively measure the composition of spore, vegetative microbe and spore/vegetative combinations, which we believe enable a wide variety of drug products to be manufactured. Throughout the bioprocess and formulation development platform we use and will expand on high- throughput quantitative analytics to assess the identity, potency and purity of the final product.

We currently have two internal manufacturing facilities; a small-scale 7,000 ft^2 unit at our Kendall Square location in Cambridge, Massachusetts, where we conduct cGMP manufacture of Ecobiotic therapeutic candidates to support drug substance and drug product for early phase and small-scale clinical supplies, and a larger 10,000 ft^2 cGMP manufacturing facility at our headquarters, with the ability to perform both drug substance and drug product manufacturing for early and late-phase clinical development and at larger scales of operation. We may establish further manufacturing facilities that will serve late-phase clinical and commercial supply for our product candidates. We may do this by expanding our current facilities, or by purchasing or building additional facilities. We also use contract manufacturing and testing organizations to supplement our internal capacity.

Material Agreements

In January 2016, we entered into the Collaboration and License Agreement, or the License Agreement, with NHS, an affiliate of Nestlé Health Science US Holdings, Inc., a significant stockholder of ours, for the development and commercialization of certain product candidates in development for the treatment and management of CDI and IBD, including UC and Crohn’s disease. The License Agreement will support the development of our portfolio of products for CDI and IBD in markets outside of the United States and Canada, or the Licensed Territory. We have retained full commercial rights to our entire portfolio of product candidates with respect to the United States and Canada.

Under the License Agreement, we granted to NHS an exclusive, royalty-bearing license to develop and commercialize, in the Licensed Territory, certain products based on our microbiome technology that are being developed for the treatment of CDI and IBD, including SER-109, SER-262, SER-287 and SER-301, or collectively, the NHS Collaboration Products. The License Agreement sets forth our and NHS' respective obligations for development, commercialization, regulatory and manufacturing and supply activities for the NHS Collaboration Products with respect to the licensed fields and the Licensed Territory.

In exchange for the license, NHS made an upfront cash payment to us of $120.0 million. NHS also agreed to pay us tiered royalties, at percentages ranging from the high single digits to high teens, of net sales of NHS Collaboration Products in the Licensed Territory. Under the License Agreement we are eligible to receive up to $285.0 million in development milestone payments, $375.0 million in regulatory payments and up to an aggregate of $1,125.0 million for the achievement of certain commercial milestones related to the sales of NHS Collaboration Products.

In November 2018, we executed a letter agreement with NHS, or the Letter Agreement, modifying certain terms of the License Agreement. Under the Letter Agreement, NHS agreed to accelerate the payment of the $20.0 million Phase 3 commencement milestone to be payable upon the commencement of the Phase 2b study for SER-287. Further, based on the results of the Phase 2b study, the Letter Agreement modifies certain terms and conditions related to the extent and timing of expense reimbursement associated with the ongoing SER-287 clinical trials. The Phase 2b study was initiated and the $40.0 million of milestone payments were received in December 2018.

To date, we have received $70.0 million in development milestones under the License Agreement and the Letter Agreement.

Intellectual Property

We strive to protect the proprietary technology that is important to our business, including seeking and, if granted, maintaining patents intended to cover our product candidates and compositions, their methods of use and processes for their manufacture and any other aspects of inventions that are commercially important to the development of our business. We also utilize regulatory exclusivity as well as trade secrets to protect aspects of our business.

We plan to continue to expand our intellectual property estate by filing patent applications directed to compositions, methods of treatment, methods of manufacture and methods for patient selection created or identified from our ongoing development of our product candidates. Our success will depend on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, defend and enforce any patents that we may obtain, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and proprietary rights of third parties. We also rely on know-how and continuing technological innovation to develop and maintain our proprietary position and, in the future, may rely on or leverage in-licensing opportunities. We seek to obtain domestic and international patent protection, and endeavor to promptly file patent applications for new commercially valuable inventions.

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent may be challenged in courts after issuance. Moreover, many jurisdictions permit third parties to challenge issued patents in administrative proceedings, which may result in further narrowing or even cancellation of patent claims. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or at all, whether the claims of any patent applications, should they issue, will cover our product candidates, or whether the claims of any issued patents will provide sufficient protection from competitors or otherwise provide any competitive advantage.

Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months or potentially even longer, and because publication of discoveries in the scientific or patent literature often lags behind actual discoveries and patent application filings, we cannot be certain of the priority of inventions covered by pending patent applications. Accordingly, we may not have been the first to invent the subject matter disclosed in some of our patent applications or the first to file patent applications covering such subject matter, and we may have to participate in interference proceedings or derivation proceedings declared by the United States Patent and Trademark Office, or USPTO, to determine priority of invention.

Our patent portfolio includes issued U.S. patents and patent applications in various stages of prosecution, including ex-U.S. international counterparts. We believe that issued claims will provide protection for our microbiome therapeutic candidates.

Patent term

The base term of a U.S. patent is 20 years from the filing date of the earliest-filed non-provisional, patent application from which the patent claims priority. The term of a U.S. patent can be lengthened by patent term adjustment, which

compensates the owner of the patent for administrative delays at the USPTO. In some cases, the term of a U.S. patent is shortened by terminal disclaimer that reduces its term to that of an earlier-expiring patent.

The term of a U.S. patent may be eligible for patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act, to account for at least some of the time the drug is under development and regulatory review after the patent is granted. With regard to a drug for which FDA approval is the first permitted marketing of the active ingredient, the Hatch-Waxman Act allows for extension of the term of one U.S. patent that includes at least one claim covering the composition of matter of such an FDA-approved drug, an FDA- approved method of treatment using the drug and/or a method of manufacturing the FDA-approved drug. The extended patent term cannot exceed the shorter of five years beyond the non-extended expiration of the patent or fourteen years from the date of the FDA approval of the drug, and a patent cannot be extended more than once or for more than a single product. During the period of extension, if granted, the scope of exclusivity is limited to the approved product for approved uses. Some foreign jurisdictions, including Europe and Japan, have analogous patent term extension provisions, which allow for extension of the term of a patent that covers a drug approved by the applicable foreign regulatory agency. In the

future, if and when our product candidates receive FDA approval, we expect to apply, if appropriate, for patent term extension on patents covering those product candidates, their methods of use and/or methods of manufacture.

Trade secrets

In addition to patents, we rely on trade secrets and know-how to develop and maintain our competitive position. We typically utilize trade secrets to protect aspects of our business. We protect trade secrets and know-how by establishing confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and collaborators. These agreements provide that all confidential information developed or made known during the course of an individual or entities' relationship with us must be kept confidential during and after the relationship. These agreements also provide that all inventions resulting from work performed for us or relating to our business and conceived or completed during the period of employment or assignment, as applicable, shall be our exclusive property. In addition, we take other appropriate precautions, such as physical and technological security measures, to guard against misappropriation of our proprietary information by third parties.

Competition

The development and commercialization of new drug and biologic products is highly competitive and is characterized by rapid and substantial technological development and product innovations. We face competition with respect to our current product candidates and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. We are aware of a number of large pharmaceutical and biotechnology companies, as well as smaller, early-stage companies, that are pursuing the development of products, including microbiome therapeutics, and disease indications we are targeting. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources, established presence in the market and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors.

These third parties compete with us in recruiting and retaining qualified scientific, clinical, manufacturing sales and marketing and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

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

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market, especially for any competitor developing a microbiome therapeutic which will likely share our same regulatory approval requirements. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of lower cost products.

Government Regulation

The FDA and other regulatory authorities at federal, state and local levels, as well as in foreign countries, extensively regulate, among other things, the research, development, testing, manufacture, quality control, import, export, safety, effectiveness, labeling, packaging, storage, distribution, record keeping, approval, advertising, promotion, marketing, post-approval monitoring and post-approval reporting of drugs and biologics such as those we are developing. We, along with our contract manufacturers, will be required to navigate the various preclinical, clinical and commercial approval requirements of the governing regulatory agencies of the countries in which we wish to conduct studies or seek approval for our product candidates. The process of obtaining regulatory approvals and ensuring subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources.

In the United States, the FDA regulates drug and biologic products under the Federal Food, Drug and Cosmetic Act, its implementing regulations and other laws, including, in the case of biologics, the Public Health Service Act. Our product candidates are subject to regulation by the FDA as biologics. Biologics require the submission of a biologics license application, or BLA, and approval by the FDA before being marketed in the United States. None of our product candidates has been approved by the FDA for marketing in the United States, and we currently have no BLAs pending. If we fail to comply with applicable FDA or other requirements at any time during product development, clinical testing, the approval process or after approval, we may become subject to administrative or judicial sanctions. These sanctions could include the FDA's refusal to approve pending applications, suspension or revocation of approved applications, warning letters, product recalls, product seizures, total or partial suspensions of manufacturing or distribution, injunctions, fines, civil penalties or criminal prosecution. Any FDA enforcement action could have a material adverse effect on us.

The process required by the FDA before our biologic product candidates may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests and animal studies performed in accordance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must become effective before clinical trials in the United States may begin;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the product candidate for each proposed indication, conducted in accordance with the FDA's good clinical practice, or GCP, regulations;
- submission to the FDA of a BLA;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP regulations; and
- FDA review and approval of the BLA prior to any commercial marketing, sale or shipment of the product.

The testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

Preclinical and Clinical Trials

Once a product candidate is identified for development, it enters the preclinical testing stage. Preclinical studies include laboratory evaluations of drug chemistry, formulation and stability, as well as studies to evaluate toxicity in animals, which must be conducted in accordance with GLP requirements. The results of the preclinical studies, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions about the conduct of the clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. Submission of an IND may result in the FDA not allowing clinical trials to commence or not allowing clinical trials to commence on the terms originally specified in the IND. A separate submission to an existing IND must also be made for each successive clinical trial conducted during product development, and the FDA must grant permission, either explicitly or implicitly by not objecting, before each clinical trial can begin.

Clinical trials involve the administration of the product candidate to human subjects under the supervision of qualified investigators. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial and the parameters and criteria to be used in monitoring safety and evaluating effectiveness. Each protocol must be submitted to the FDA as part of the IND. An independent institutional review board, or IRB, for each investigator site proposing to participate in a clinical trial must also review and approve the clinical trial before it can begin at that site, and the IRB must monitor the clinical trial until it is completed. The FDA, the IRB, or the sponsor may suspend or discontinue a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive GCP requirements, including requirements for

informed consent.

For purposes of BLA approval, clinical trials are typically conducted in three sequential phases, which may overlap or be combined.

- Phase 1 — Phase 1 clinical trials involve initial introduction of the investigational product into healthy human subjects or patients with the target disease or condition. These studies are typically designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the investigational product in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.
- Phase 2 — Phase 2 clinical trials typically involve administration of the investigational product to a limited patient population with a specified disease or condition to evaluate the preliminary efficacy, optimal dosages and dosing schedule and to identify possible adverse side effects and safety risks.

- Phase 3 — Phase 3 clinical trials typically involve administration of the investigational product to an expanded patient population to further evaluate dosage, to provide statistically significant evidence of clinical efficacy and to further test for safety, generally at multiple geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the investigational product and to provide an adequate basis for product approval.

In some cases, the FDA may condition approval of a BLA on the sponsor's agreement to conduct additional clinical trials to further assess the biologic's safety and effectiveness after BLA approval. Such post-approval clinical trials are typically referred to as Phase 4 clinical trials.

Although most clinical research performed in the United States in support of a BLA must be authorized in advance by the FDA, under the IND regulations and procedures described above, there are certain circumstances under which clinical trials can be conducted without submission of an IND. For example, a sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. Similarly, the FDA may exercise enforcement discretion to permit sponsors to conduct certain types of clinical investigations without an IND. Pursuant to the FDA guidance document "Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies" (July 2013), the FDA announced its intention to exercise enforcement discretion and not apply the IND requirements for the use of FMT to treat CDI not responsive to standard therapies, provided that the treating physician obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products. In March 2014, the FDA issued a draft guidance document to clarify its Enforcement Policy in the July 2013 guidance. In the March 2014 draft guidance, the FDA noted that since the issuance of its Enforcement Policy in July 2013, it has continued to review its policies in this area and it intends to continue to exercise enforcement discretion in more narrow circumstances than previously identified. Specifically, the March 2014 draft guidance indicated the FDA's intent to limit enforcement discretion in circumstances where the licensed health care professional treating the patient obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products; the FMT product is obtained from a donor known to either the patient or the licensed health care provider; and the stool donor and stool are qualified by screening and testing performed under the discretion of the licensed health care provider for the purposes of providing the FMT product. Following receipt of public comments on the March 2014 draft guidance proposing to modify the July 2013 Enforcement Policy, the FDA issued a new draft guidance in March 2016 announcing its intention to further modify its approach to enforcement discretion for INDs for the use of FMT products. In this draft guidance, the FDA indicated that it intends to continue to exercise enforcement discretion, provided that the licensed health care professional treating the patient obtains adequate informed consent for use of the FMT product; the FMT product is not obtained from a stool bank; and the stool donor and stool are qualified by screening and testing performed under the direction of the licensed health care provider for purposes of providing the FMT product to treat his or her patient. The FDA further clarified in the March 2016 that, when finalized, the policy would supersede the final Enforcement Policy espoused in the July 2013 Guidance. However, to date, the FDA has not finalized the March 2016 draft guidance. The FDA provided confirmation to us that it intended to exercise enforcement discretion with respect to our Phase 1b/2 clinical study of SER-109, and accordingly, we did not conduct this trial under an IND. However, we have conducted and will continue to conduct all subsequent clinical studies of SER-109 under an IND.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the biologic and finalize a process for manufacturing the biologic in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and manufacturers must develop, among other things, methods for testing the identity, strength, quality and purity of the final biological product. 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.

BLA Submission and FDA Review

The results of preclinical studies and clinical trials, together with other detailed information, including extensive manufacturing information and information on the composition of the biologic, are submitted to the FDA in the form of a BLA requesting approval to market the biologic for one or more specified indications. The submission of a BLA requires payment of a substantial user fee unless a waiver is granted. However, an orphan-designated product, such as our SER-109, is not subject to an application user fee unless the human drug application includes an indication for other than a rare disease or condition. Each BLA submitted to the FDA is reviewed for administrative completeness and reviewability within 60 days of the FDA's receipt of the application. If the BLA is found to be complete, the FDA will file the BLA, triggering a full review of the application. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission.

Once a BLA has been accepted for filing, by law the FDA has 180 days to review the application and respond to the applicant. However, the review process is often significantly extended by FDA requests for additional information or clarification. Under the Prescription Drug User Fee Act, the FDA has a goal of reviewing BLAs within ten months of the 60-day filing date for standard review or six months for priority review, but the overall timeframe is often extended by FDA requests for additional information or clarification. The FDA reviews a BLA to determine, among other things, whether the biological product is safe, pure and potent and whether the facility or facilities in which it is manufactured meet standards designed to assure the product's continued safety, purity and potency. The FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. Before approving a BLA, the FDA will inspect the facility or the facilities at which the biologic product is manufactured and will not approve the product unless cGMP compliance is satisfactory. The FDA may also inspect the sites at which the clinical trials were conducted to assess their compliance with GCP requirements and will not approve the biologic unless compliance with such requirements is satisfactory.

The FDA may deny approval of a BLA if the applicable statutory and regulatory criteria are not satisfied, or it may require additional preclinical or clinical data. Even if such data are submitted, the FDA may ultimately decide that the BLA does not satisfy the criteria for approval. Data from clinical trials are not always conclusive and the FDA may interpret data differently than sponsors. Once the FDA approves a BLA, such approval defines the indicated uses for which the biologic may be marketed. The FDA may also require implementation of a Risk Evaluation and Mitigation Strategy, or REMS, which can include a medication guide, communication plan, or elements to assure safe use, such as restricted distribution methods, physician training, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling claims or the development of adequate controls and specifications. Once approved, the FDA may withdraw the product approval if compliance with pre- and post-marketing regulatory standards is not maintained or if problems occur after the product reaches the market. The FDA may require one or more Phase 4 post-market studies and surveillance to further assess and monitor the product's safety and effectiveness after commercialization and may limit further marketing based on the results of these post-marketing studies.

The biologic testing and approval processes encompasses significant risk, and requires substantial time, effort and financial resources, and each may take several years to complete. The FDA may not grant approval on a timely basis, or at all. Even if we believe a clinical trial has demonstrated safety and efficacy of one of our product candidates for the treatment of a disease or condition, the results may not be satisfactory to the FDA. Preclinical and clinical data may be interpreted by the FDA in different ways, which could delay, limit or prevent regulatory approval. We may encounter difficulties or unanticipated costs in our efforts to secure necessary governmental approvals which could delay or preclude us from marketing our product candidates. The FDA may limit the indications for use or place other conditions on any approvals that could restrict the commercial application of our products. After approval, certain changes to the approved biologic, such as adding new indications, manufacturing changes or additional labeling claims, are subject to further FDA review and approval. Depending on the nature of the change proposed, a BLA supplement must be filed and approved before the change may be implemented. For many proposed post-approval changes to a BLA, the FDA has up to 180 days to review the application. As with new BLAs, the review process is often significantly extended by the FDA requests for additional information or clarification.

Expedited Development and Review Programs

The FDA maintains several programs intended to facilitate and expedite development and review of new drugs and biologics to address unmet medical needs in the treatment of serious or life- threatening diseases or conditions. These programs include Fast Track designation, Breakthrough Therapy designation, Priority Review designation and Accelerated Approval, and the purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures.

A new drug or biologic is eligible for fast track designation if it is intended to treat a serious or life- threatening disease or condition and demonstrates the potential to address unmet medical needs for such disease or condition. Fast Track designation provides increased opportunities for sponsor meetings with the FDA during preclinical and clinical development, in addition to the potential for rolling review once a marketing application is filed, meaning that the agency may review portions of the marketing application before the sponsor submits the complete application, as well as Priority Review, discussed below. In addition, a new drug or biologic may be eligible for breakthrough therapy designation if it is intended 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. Breakthrough Therapy designation provides all the features of Fast Track designation in addition to intensive guidance on an efficient drug development program beginning as early as Phase 1, and FDA organizational commitment to expedited development, including involvement of senior managers and experienced review staff in a cross-disciplinary review, where appropriate.

Any product submitted to the FDA for approval, including a product with Fast Track or Breakthrough Therapy designation, may also be eligible for additional FDA programs intended to expedite the review process, including Priority Review designation and accelerated approval. A product is eligible for Priority Review if it has the potential to provide a significant improvement in safety or effectiveness in the treatment, diagnosis or prevention of a serious disease or condition. Additionally, products are eligible for accelerated approval if they can be shown to have an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or an effect on a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality which 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. Accelerated approval is usually contingent on a sponsor's agreement to conduct additional post-approval studies to verify and describe the product's clinical benefit. In addition, unless otherwise informed by the FDA, the FDA currently requires, as a condition for accelerated approval that all advertising and promotional materials that are intended for dissemination or publication within 120 days following marketing approval be submitted to the agency for review during the pre-approval review period, and that after 120 days following marketing approval, all advertising and promotional materials must be submitted at least 30 days prior to the intended time of initial dissemination or publication.

Fast Track designation, Breakthrough Therapy designation, Priority Review designation and Accelerated Approval do not change the standards for approval but may expedite the development or review process. We have received Breakthrough Therapy designation for SER-109, and we may apply for one or more of the FDA's expedited programs for our other product candidates. The FDA may find that our product candidates no longer satisfy the criteria for such programs for which we have already obtained the relevant designation or approval, such programs may fail to result in expedited development or review timelines, or the FDA may ultimately refuse to approve our product candidates despite their inclusion in any expedited programs. In addition, if the Breakthrough Therapy designation for SER-109 is no longer supported by subsequent data, FDA may rescind the designation.

Post-Approval Requirements

Approved biologics that are manufactured or distributed in the United States are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product distribution, advertising and promotion and reporting of adverse experiences with the product. There also are continuing, annual user fee requirements for products marketed pursuant to approved applications.

Any biologics manufactured or distributed by us or our contract manufactures pursuant to FDA approvals would be subject to continuing regulation by the FDA, including recordkeeping requirements and reporting of adverse experiences associated with the product. Manufacturers and their subcontractors 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 ongoing regulatory requirements, including cGMP, which impose certain procedural and documentation requirements upon us and our contract manufacturers. Failure to comply with statutory and regulatory requirements can subject a manufacturer to possible legal or regulatory action, such as warning letters, suspension of manufacturing, product seizures, injunctions, civil penalties or criminal prosecution. We cannot be certain that we or our present or future third-party manufacturers or suppliers will be able to comply with the cGMP regulations and other ongoing FDA regulatory requirements. If we or our present or future third-party manufacturers or suppliers are not able to comply with these requirements, the FDA may halt our clinical trials, require us to recall a product from distribution or withdraw approval of the BLA for that product.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information, requirements for post-market studies or clinical trials to assess new safety risks, or imposition of distribution or other restrictions under a REMS. Other potential consequences include, among other things:

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

The FDA closely regulates the post-approval marketing and promotion of biologics, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities, and promotional activities involving the internet and social media. A company can make only those claims relating to safety and efficacy that are approved by the FDA. Physicians may prescribe legally available biologics for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, impose stringent restrictions on manufacturers' communications regarding off-label use. Failure to comply with these requirements can result in adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties.

Biosimilars and Regulatory Exclusivity

We believe that any of our product candidates approved under a BLA should qualify for a 12-year period of exclusivity against biosimilar competition currently permitted by the Biologics Price Competition and Innovation Act, or BPCIA. Specifically, as part of the Patient Protection and Affordable Care Act enacted in 2010, as amended by the Health Care and Education Affordability Reconciliation Act, collectively the ACA, the BPCIA established an abbreviated pathway for the approval of biosimilar and interchangeable biological products. The abbreviated regulatory pathway provides legal authority for the FDA to review and approve biosimilar biologics based on their similarity to an existing brand product, referred to as a reference product, including the possible designation of a biosimilar as interchangeable with a brand product. Under the BPCIA the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biological drug products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing. The BPCIA is complex and continues to be interpreted and implemented by the FDA. As a result, its ultimate impact, implementation and meaning is subject to uncertainty. While it is uncertain when any such processes may be fully adopted by the FDA, any such processes that operate to limit the scope or length of exclusivity afforded by the BPCIA could have a material adverse effect on the future commercial prospects for our biological products. In addition, the period of exclusivity provided by the BPCIA only operates against third parties seeking approval via the abbreviated pathway but would not prevent third parties from pursuing approval via the traditional approval pathway. In addition, foreign regulatory authorities may also provide for exclusivity periods for approved biological products. For example, biological products in the EU may be eligible for at least a ten-year period of exclusivity.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biologic intended to treat a rare disease or condition, which is a disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States, there is no reasonable expectation that the cost of developing and making the product available in the United States for the disease or condition will be recovered from sales of the product. Orphan designation must be requested before submitting a BLA. Orphan designation does not convey any advantage in or shorten the duration of the regulatory review and approval process, though companies developing orphan products are eligible for certain incentives, including tax credits for qualified clinical testing and waiver of application fees.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to a seven-year period of marketing exclusivity during which the FDA may not approve any other applications to market the same therapeutic agent for the same indication, except in limited circumstances, such as a subsequent product's showing of clinical superiority over the product with orphan exclusivity or where the original applicant cannot produce sufficient quantities of product. Competitors, however, may receive approval of different therapeutic agents for the indication for which the orphan product has exclusivity or obtain approval for the same therapeutic agent for a different indication than that for which the orphan product has

exclusivity. Orphan product exclusivity could block the approval of one of our products for seven years if a competitor obtains approval for the same therapeutic agent for the same indication before we do, unless we are able to demonstrate that our product is clinically superior. Further, if a designated orphan product receives marketing approval for an indication broader than the rare disease or condition for which it received orphan designation, it may not be entitled to orphan exclusivity.

In August 2015, the FDA granted orphan drug designation to SER-109 for the treatment of recurrent CDI. In December 2017, the FDA granted Orphan Drug Designation to SER-287 for treatment of UC in pediatric patients.

We may seek additional orphan designation for one or more of our product candidates, but the FDA may disagree with our analysis of the prevalence of a disease or condition or other criteria for designation and refuse to grant orphan status. We cannot guarantee that we will obtain designation or approval for any product candidate, or that we will be able to secure orphan product exclusivity if we do obtain approval.

Government Regulation Outside of the United States

To market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, manufacturing, commercial sales and distribution of our products.

For instance, in the 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 EMA's Committee for Medicinal Products for Human Use, or, 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, 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 an 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 (i.e., 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 ten years have elapsed from the initial authorization of the reference product in the EU. The ten-year market exclusivity period can be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

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 (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. 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 marketing authorization application shall be accepted, and no marketing authorization shall be granted for a similar medicinal product for the same indication. 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 (i) the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior; (ii) the applicant consents to a second orphan medicinal product application; or (iii) the applicant cannot supply enough orphan medicinal product.

Other Healthcare Laws

In addition to FDA restrictions on marketing of pharmaceutical and biological products, other healthcare regulatory laws restrict business practices in the biotechnology industry, which include, but are not limited to, anti-kickback, false claims, physician payment and pricing transparency and data privacy and security laws. The federal Anti-Kickback Statute prohibits the offer, receipt, or payment of remuneration in exchange for or to induce the referral of patients or the use of products or services that would be paid for in whole or part by Medicare, Medicaid or other federal healthcare programs. Remuneration has been broadly interpreted to include anything of value, including cash, improper discounts and free or reduced-price items and services. The government has enforced the Anti-Kickback Statute to reach large settlements with healthcare companies based on sham research or consulting and other financial arrangements with physicians. Further, 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. In addition, the government may assert that a claim including items or services resulting from a violation of the Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act (discussed below). Many states have similar laws that apply to their state healthcare programs as well as private payors.

The federal false claims and civil monetary penalties laws, including the False Claims Act, or FCA, impose liability on persons who, among other things, knowingly present or cause to be presented, a false, fictitious or fraudulent claim for payment to, or approval by, the federal government, knowingly make, use, or cause to be made or used a false record or statement material to a false or fraudulent claim to the federal government, or knowingly make a false statement to avoid, decrease or conceal an obligation to pay money to the U.S. federal government. The FCA has been used to prosecute persons submitting claims for payment that are inaccurate or fraudulent, that are for services not provided as claimed, or for services that are not medically necessary. Actions under the FCA may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Violations of the FCA can result in significant monetary penalties and treble damages. The federal government is using the FCA, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies throughout the country, for example, in connection with the promotion of products for unapproved uses and other sales and marketing practices. The government has obtained multi-million and multi–billion-dollar settlements under the FCA in addition to individual criminal convictions under applicable criminal statutes. In addition, companies have been forced to implement extensive corrective action plans and have often become subject to consent decrees or corporate integrity agreements, severely restricting the manner in which they conduct their business. Given the significant size of actual and potential settlements, it is expected that the government authorities will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit, among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. 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 in order to have committed a violation.

We may also be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, which impose specified requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal

penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same requirements, thus complicating compliance efforts.

In addition, there has been a recent trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The ACA, among other things, imposed new reporting requirements through the Physician Payments Sunshine Act on certain manufacturers of drugs covered by a federal healthcare program for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians, certain other healthcare professionals and their immediate family members. Failure to submit required information may result in civil monetary penalties for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Manufacturers must submit reports by the 90th day of each calendar year. Certain states also mandate implementation of compliance programs, impose restrictions on drug manufacturer marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians, and pricing information and marketing expenditures.

To the extent that any of our product candidates, once approved, are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or other transfers of value to healthcare professionals.

The shifting commercial compliance environment and the need to build and maintain robust systems to comply with different compliance and/or reporting requirements in multiple jurisdictions increase the possibility that a healthcare company may violate one or more of the requirements. If our 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, without limitation, civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs, reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement, and imprisonment, any of which could adversely affect our ability to operate our business and our financial results.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we obtain regulatory approval. In both domestic and foreign markets, sales and reimbursement of any approved products will depend, in part, on the extent to which third-party payors, such as government health programs, commercial insurance and managed healthcare organizations provide coverage, and establish adequate reimbursement levels for, such products. Third-party payors are increasingly challenging the prices charged for medical products and services and imposing controls to manage costs. Third-party payors may limit, or hinder, coverage to specific products on an approved list, also known as a formulary, which might not include all of the FDA-approved products for a particular indication. Additionally, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the cost-effectiveness of our products, as well as provide rebates and discounts which may impact the net selling price of our products. If third-party payors do not consider our products to be cost-effective compared to other therapies, the payors may not cover our products as a benefit under their plans or, if they do, the level of reimbursement may not be sufficient to allow us to sell our products on a profitable basis.

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

Outside the United States, ensuring adequate coverage and payment for our products will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of our product candidates or products to other available therapies. Conducting such a clinical trial could be expensive and result in delays in our commercialization efforts. Third-party payors are challenging the prices charged for medical products and services, and many third-party payors limit reimbursement for newly approved healthcare products. Recent budgetary pressures in many countries are also causing governments to consider or implement various cost-containment measures, such as price freezes, increased price cuts and rebates. If budget pressures continue, governments may implement additional cost-containment measures. Cost-control initiatives could decrease the price we might establish for products that we may develop or sell, which would result in lower product revenues or royalties payable to us. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products.

Healthcare Reform

In the United States, there have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biological products, government control and other changes to the healthcare system. It is uncertain what legislative proposals will be adopted or what actions federal, state or private payors for medical goods and services may take in response to any healthcare reform proposals or legislation. We cannot predict the effect medical or healthcare reforms may have on our business, and no assurance can be given that any such reforms will not have a material adverse effect.

By way of example, in March 2010, the ACA was signed into law, which, among other things, includes changes to the coverage and payment for pharmaceutical and biological products under government health care programs. Among other things, the ACA:

- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of ''average manufacturer price,'' or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices;
- extended Medicaid drug rebates, previously due only on fee-for-service utilization, to Medicaid managed care utilization, and created an alternate rebate formula for new formulations of certain existing products that is intended to increase the amount of rebates due on those drugs;
- expanded the types of entities eligible for the 340B drug discount program that mandates discounts to certain hospitals, community centers and other qualifying providers. With the exception of children's hospitals, these newly eligible entities will not be eligible to receive discounted 340B pricing on orphan drugs. In addition, because 340B pricing is determined based on AMP and Medicaid drug rebate data, the revisions to the Medicaid rebate formula and AMP definition described above could cause the required 340B discounts to increase; and
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 70% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D.

There have been judicial and Congressional challenges to certain aspects of the ACA, as well as efforts to repeal or replace certain aspects of the ACA. For example, the Tax Cuts and Jobs Act was enacted, which, among other things, removes the penalties for not complying with the ACA's individual mandate to carry health insurance. On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, ruled that the individual mandate is a critical and inseverable feature of the ACA, and therefore, because it was repealed as part of the Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. While the current Presidential administration and the Centers for Medicare & Medicaid Services, or CMS, have both stated that the ruling will have no immediate effect, it is unclear how this decision, subsequent appeals, if any, and other efforts to repeal and replace the ACA will impact the ACA and our business. Similarly, we expect there will be additional challenges and amendments to the ACA in the future, particularly in light of the current Presidential administration and U.S. Congress.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In For example, the Budget Control Act of 2011, enacted in August 2011, among other things, included reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013 and, due to subsequent legislative amendments, will remain in effect through 2027 unless additional Congressional action is taken. In January 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, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. More recently, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which have resulted in several Congressional inquiries and proposed and enacted legislation 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 and biological products. Individual states in the United States have also become increasingly active in passing legislation and 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. Adoption of other new legislation at the federal or state level could further limit reimbursement for pharmaceuticals, including our product candidates if approved.

Employees

As of December 31, 2018, we had 145 full-time permanent employees. Twenty-three employees work in administration and operations and 122 work in research and development.

32

Our Corporate Information

We were incorporated in the State of Delaware in 2010 under the name Newco LS21, Inc. In October 2011, we changed our name to Seres Health, Inc., and in May 2015, we changed our name to Seres Therapeutics, Inc. Our principal executive offices are located at 200 Sidney Street, Cambridge, Massachusetts 02139 and our telephone number is (617) 945-9626. Our website address is www.serestherapeutics.com. The information contained in, or accessible through, our website does not constitute a part of this annual report on Form 10-K.

We are subject to the informational requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and, accordingly, file reports, proxy statements and other information with the Securities and Exchange Commission. The Securities and Exchange Commission maintains a web site (http://www.sec.gov) that contains material regarding issuers that file electronically, such as ourselves, with the Securities and Exchange Commission.

We make available free of charge on our website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission.

Item 1A. Risk Factors

Our business faces significant risks and uncertainties. Accordingly, in evaluating our business, you should carefully consider the risk factors discussed below, as well as the other information in this Annual Report on Form 10-K, including our consolidated financial statements and the related notes and "Management's Discussion and Analysis of Results of Operations and Financial Condition." The occurrence of any of the events or developments described below or elsewhere in this report could harm our business, financial condition, results of operations or growth prospects.

Risks Related to Our Financial Position and Need for Additional Capital

We are a development-stage company and have incurred significant losses since our inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability. As a result, there is substantial doubt about our ability to continue as a going concern.

Since inception, we have incurred significant operating losses. Our net loss was $98.9 million for the year ended December 31, 2018, $89.4 million for the year ended December 31, 2017, and $91.6 million for the year ended December 31, 2016. As of December 31, 2018, we had an accumulated deficit of $389.4 million. To date, we have financed our operations through the initial public offering of our common stock, private placements of our preferred stock, milestone payments under the licensing agreement with Nestec, Ltd., or NHS, and loan financing. We have devoted substantially all of our financial resources and efforts to developing our microbiome therapeutics platform, identifying potential product candidates and conducting preclinical studies and clinical trials. We have not completed development of any of our product candidates, which we call Ecobiotic microbiome therapeutics, or other drugs or biologics. We expect to continue to incur significant expenses and operating losses for the foreseeable future. We anticipate that our expenses may increase substantially as we:

- continue the clinical development of SER-109, our lead product candidate, in the Phase 3 clinical study;
- continue the clinical development of SER-287 for the treatment of UC in adults and children and potential other studies of IBD;
- continue the clinical development of SER-401 in a Phase 1b clinical trial in patients with metastatic melanoma;
- conduct research and continue preclinical development of additional Ecobiotic microbiome therapeutic candidates, including SER-301;

- make strategic investments in manufacturing capabilities;
- maintain and augment our intellectual property portfolio and opportunistically acquire complementary intellectual property;
- scale-up manufacturing capabilities to commercialize any products for which we may obtain regulatory approval;
- perform our obligations under the collaboration agreement with NHS;