Synthetic Biologics, Inc.
Form 10-K
March 02, 2017

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

FORM 10-K

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2016

OR

¨TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES ACT OF 1934

For the transition period from to

Commission File Number: 1-12584

SYNTHETIC BIOLOGICS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Nevada	**13-3808303**
(State or Other Jurisdiction of Incorporation or Organization)	*(I.R.S. Employer Identification Number)*

9605 Medical Center Drive, Ste. 270 **Rockville, MD**	**20850**
(Address of Principal Executive Offices)	*(Zip Code)*

Registrant's telephone number, including area code:
(301) 417-4364

Securities registered pursuant to Section 12(b) of the Act:	**Name of each exchange on which registered:**
Common Stock, $0.001 par value per share	**NYSE MKT, LLC**

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

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act.

Yes ¨ No x

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 x

Indicate by check mark whether the issuer: (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 x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (section 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files).

Yes x No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of issuer'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. x

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated file, a non-accelerated file, or a smaller reporting company. See the definitions of “large accelerated filer, “accelerated filer” and “smaller reporting company” in Rule 12b-2 of the Exchange Act. (Check one):

Large Accelerated Filer ¨		Accelerated Filer	x
Non-accelerated Filer	¨ (Do not check if a smaller reporting company)	Smaller Reporting Company	¨

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act).

Yes ¨ No x

The aggregate market value of the registrant’s common stock held by non-affiliates of the registrant as of June 30, 2016, the last business day of the registrant’s recently completed second quarter, was approximately $141 million based on $1.80, the closing price of the registrant’s common stock as reported by the NYSE MKT on that date.

As of February 28, 2017, the registrant had 117,541,978 shares of common stock outstanding.

Documents incorporated by reference: **None**

SYNTHETIC BIOLOGICS, INC.

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PART I

Special Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K (this "Annual Report") contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), that involve substantial risks and uncertainties. The forward-looking statements are contained principally in Part I, Item 1. "Business," Part I, Item 1A. "Risk Factors," and Part II, Item 7. "Management's Discussion and Analysis of Financial Condition and Results of Operations," but are also contained elsewhere in this Annual Report. In some cases you can identify forward-looking statements by terminology such as "may," "should," "potential," "continue," "expects," "anticipates," "intends," "plans," "believes," "estimates," and simila These statements are based on our current beliefs, expectations, and assumptions and are subject to a number of risks and uncertainties, many of which are difficult to predict and generally beyond our control, that could cause actual results to differ materially from those expressed, projected or implied in or by the forward-looking statements.

You should refer to Item 1A. "Risk Factors" section of this Annual Report for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this Annual Report will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. We do not undertake any obligation to update any forward-looking statements.

Unless the context requires otherwise, references to "we," "us," "our," and "Synthetic Biologics," refer to Synthetic Biologic Inc. and its subsidiaries.

Item 1. ***Business***

Overview

We are a late-stage clinical company focused on developing therapeutics designed to preserve the microbiome to protect and restore the health of patients. Our lead candidates poised for Phase 3 development are: (1) SYN-010 which is intended to reduce the impact of methane-producing organisms in the gut microbiome to treat an underlying cause of irritable bowel syndrome with constipation (IBS-C), and (2) SYN-004 (ribaxamase) which is designed to protect

the gut microbiome from the effects of certain commonly used intravenous (IV) beta-lactam antibiotics for the prevention of *C. difficile* infection (CDI), antibiotic-associated diarrhea (AAD) and the emergence of antimicrobial resistance (AMR). We are also developing preclinical stage monoclonal antibody therapies for the prevention and treatment of pertussis, and novel discovery stage biotherapeutics for the treatment of phenylketonuria (PKU).

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Our Product Pipeline

* Two Phase 2 studies completed. Planning a Phase 2b/3 pivotal trial

C- Cedars-Sinai Medical Center Collaboration

I-Intrexon Collaboration

T- The University of Texas at Austin Collaboration

Summary of Clinical and Preclinical Programs

Therapeutic Area	Product Candidate	Status
Treatment of IBS-C	SYN-010 (oral modified-release lovastatin lactone)	· Reported supportive topline data from two Phase 2 clinical trials (4Q 2015 & 1Q 2016) · Received Type C meeting responses from U.S. Food and Drug Administration (FDA) regarding late-stage aspects of clinical pathway (2Q 2016) · Presented detailed data supporting previously reported positive topline data from two Phase 2 clinical trials at Digestive Disease Week Conference 2016 (DDW) (May 2016) · Held End of Phase 2 meeting with FDA (July 2016) · Confirmed key elements of Pivotal Phase 2b/3 clinical trial design pursuant to consultations with the FDA (1Q 2017) · Plan to initiate first Phase 2b/3 adaptive pivotal clinical trial (2017) · Collaboration with Cedars-Sinai Medical Center

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Prevention of CDI and AAD (Degrade IV beta-lactam antibiotics)	SYN-004 (ribaxamase) (oral enzyme)	· Reported supportive Phase 1a/1b data (1Q 2015) · Initiated Phase 2b proof-of-concept clinical trial (3Q 2015) · Reported supportive topline data from first Phase 2a clinical trial (4Q 2015) · Reported supportive topline data from second Phase 2a clinical trial (2Q 2016) · Received USAN approval of the generic name “ribaxamase” for SYN -004 (July 2016) · Completed Enrollment of Phase 2b proof-of concept clinical trial (3Q 2016) · Awarded contract by the Centers for Disease Control and Prevention (CDC) (4Q 2016) · Announced positive topline data from Phase 2b proof-of-concept clinical trial, including achievement of primary endpoint of significantly reducing CDI (1Q 2017) · Plan to initiate Phase 3 clinical trial(s) (1H 2018)
Prevention of CDI and AAD (Degrade oral beta-lactam antibiotics)	SYN-007 (oral enzyme)	· Preclinical work ongoing to determine ability of SYN-007 to protect the gut microbiome and degrade oral beta-lactam antibiotics
Prevention and Treatment of pertussis	SYN-005 (monoclonal antibody therapies)	· Reported supportive preclinical research findings (2014) · The University of Texas at Austin (“UT Austin”) received a grant from the Bill and Melinda Gates Foundation to support a preclinical study to evaluate the prophylactic capability of SYN-005 (4Q 2015) · Collaborations with Intrexon and UT Austin

All of our programs are supported by our growing intellectual property portfolio. We are maintaining and building our patent portfolio through: filing new patent applications; prosecuting existing applications; and licensing and acquiring new patents and patent applications. In total, we hold approximately 140 U.S. and foreign patents and have over 55 U.S. and foreign patents pending.

Our Microbiome-Focused Pipeline

Our IBS-C and CDI/AAD programs are focused on protecting the healthy function of the gut microbiome, or gut flora, which is home to billions of microbial species and composed of a natural balance of both “good” beneficial species and potentially “bad” pathogenic species. When the natural balance or normal function of these microbial species is disrupted, a person’s health can be compromised.

SYN-010 — Treatment of Irritable Bowel Syndrome with Constipation (IBS-C)

SYN-010 is our proprietary, modified-release formulation of lovastatin lactone that is intended to reduce methane production by certain microorganisms (*M. smithii*) in the gut while minimizing disruption to the microbiome. Methane produced by *M. smithii* is an underlying cause of pain, bloating and constipation associated with IBS-C, and published reports have associated higher intestinal methane production with increased constipation severity in IBS-C patients. SYN-010 is intended to act primarily in the intestinal lumen while avoiding systemic absorption, thereby targeting the major cause of IBS-C, not just the patient’s symptoms.

In December 2013, through our subsidiary Synthetic Biomics, Inc. (SYN Biomics), we entered into a worldwide exclusive license agreement with Cedars-Sinai Medical Center (CSMC) and acquired the rights to develop products for therapeutic and prophylactic treatments of acute and chronic diseases, including the development of SYN-010 to target IBS-C. We licensed from CSMC a portfolio of intellectual property comprised of several U.S. and foreign patents and pending patent applications for various fields of use, including IBS-C, obesity and diabetes. An investigational team led by Mark Pimentel, M.D. at CSMC discovered that these products may reduce the production of methane gas by certain GI microorganisms.

We believe SYN-010 may reduce the impact of methane producing organisms on IBS-C.

Irritable Bowel Syndrome

IBS is a functional GI disorder characterized by gas, abdominal pain, bloating and diarrhea or constipation, or alternating episodes of both. The illness affects both men and women; however, two-thirds of diagnosed sufferers are women. The onset of IBS can begin anytime from adolescence to adulthood. Four bowel patterns may be seen with IBS including: IBS-C (constipation predominant), IBS-D (diarrhea predominant), IBS-M (mixed diarrhea and constipation) and IBS-U (unsubtyped). According to GlobalData's IBS — Global Drug Forecast and Market Analysis to 2023 (December 2014) stringent disease diagnosis criteria to ensure market relevance and a population most likely to receive a diagnosis and prescription drug treatment, the prevalence of IBS in adults in the United States, Europe and Japan was expected to be 41.1 million in 2016, and it has been reported that up to 20 percent of all IBS patients have IBS-C Extensive studies conducted by Dr. Pimentel and collaborators have shown that overproduction of methane gas is directly associated with bloating, pain and constipation in IBS-C patients. Investigators at CSMC have discovered that inhibiting intestinal methane production may reverse constipation associated with IBS-C, and may be beneficial in treating other major diseases such as obesity, insulin resistance and type 2 diabetes.

Limitations of Current Treatments and Market Opportunity

Currently, the FDA approved therapies for the treatment of IBS-C and other treatments include prescription and over-the-counter laxatives, which provide patients with temporary symptomatic relief and often cause diarrhea, but do not treat the underlying cause of pain, bloating and constipation associated with IBS-C. According to GlobalData, IBS — Global Drug Forecast and Market Analysis to 2023 (December 2014), the estimated global sales for IBS therapeutics for 2016 was $669.3 million, and global sales are expected to be greater than $1.5 billion in 2023.

Overview of our 2 Phase 2 Clinical Trials

In 2015 and 2016, we reported supportive data from our two SYN-010 Phase 2 trials, the first study was comprised of a randomized, double-blind, placebo-controlled, 4-week study comparing SYN-010 21 mg and 42 mg dose strengths to placebo (Study 1), followed by an open-label study in which eligible patients who completed Study 1 received SYN-010 42 mg for an additional 8 weeks (Study 2). The two Phase 2 SYN-010 clinical trials evaluated the change from baseline (Day 1 of Study 1) in breath methane, stool frequency and abdominal pain and bloating at the end of weeks 1, 4, 8 and 12 (Study 2 – Day 84) in patients diagnosed with IBS-C and with breath methane levels greater than 10 parts per million (ppm) at screening.

First Phase 2 Clinical Trial Results (4 Week Placebo-Controlled Acute Study)

In December 2015, we reported supportive topline results from our first Phase 2 placebo-controlled, randomized clinical trial of SYN-010, including lowered breath methane and improved stool frequency in patients with IBS-C. This first Phase 2 clinical trial was initiated in June 2015 and enrolled 63 patients who were randomized using a 1:1:1 ratio to one of three groups, including two different SYN-010 dose groups (21 mg and 42 mg) and a placebo group. Patients received single oral doses of SYN-010 or a placebo each day for 28 days. The primary objective of this clinical trial was to evaluate the change from baseline in the area under the curve (AUC) of breath methane, as determined by a lactulose breath test, in methane-positive patients with IBS-C after seven days of treatment with one of two dose levels of SYN-010 as compared with a placebo. The trial's secondary endpoints included improvement in the number of complete spontaneous bowel movements (CSBM) per week, and improvement in abdominal pain and bloating per standard scales required per FDA guidance. There were no serious adverse events observed.

In the first Phase 2 clinical trial of SYN-010, plasma trough levels of lovastatin species were low and variable, such that ≥50% of patients had undetectable plasma levels of each lovastatin analyte at days 7 and 28. In the few patients with detectable trough levels at day 28, concentrations of both lovastatin lactone and lovastatin beta-hydroxyacid were significantly lower than those reported in published studies of commercial lovastatin formulations. Modest reductions from baseline in mean cholesterol, LDL-C and triglycerides were observed after 7 days of SYN-010 treatment; however, changes were not different between SYN-010 and Placebo at Day 28 and were not evident after 12 weeks (Day 84). No significant changes in mean ALT or creatine kinase were observed in these patients. Changes in cholesterol, LDL-C, and triglycerides did not correlate with SYN-010 dose, or with changes in body weight, changes in breath methane, or plasma trough levels of either lovastatin lactone or lovastatin -hydroxyacid.

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Second Phase 2 Clinical Trial Results (8 Week Open-Label Extension Study)

In January 2016, we reported supportive topline data from our second Phase 2 clinical trial of SYN-010, which was initiated in October 2015. As the patients completed the first Phase 2 clinical trial, they were eligible to immediately rollover into the second Phase 2 clinical trial (multi-center, open-label) of SYN-010 that evaluated the sustainability of the effect of one dose strength of SYN-010 (42 mg) on breath methane production in 54 breath methane-positive patients with IBS-C, as well as key clinical outcomes, including frequency of CSBM, abdominal pain and bloating.

Patients in the second Phase 2 clinical trial reported compliance with the daily SYN-010 dosing regimen such that all patients in the second Phase 2 clinical trial received a minimum of 8 weeks treatment with SYN-010 42 mg. Patients who completed the second Phase 2 clinical trial demonstrated a statistically significant decrease in methane production ($p=0.002$) from the beginning of the first Phase 2 clinical trial (Baseline, Day 1, prior to any drug administration in the randomized study) to the end of the second Phase 2 clinical trial (12 weeks, Day 84), thus meeting the clinical trial's primary endpoint. Topline data from the second Phase 2 clinical trial also showed improvements in secondary efficacy endpoints, including: (1) a statistically significant reduction in the mean IBS Symptom Severity Score (IBS-SSS; $p<0.0001$), which includes abdominal pain, bloating, stool frequency and quality of life scores, for all patients from the first Phase 2 clinical trial baseline to the end of the second Phase 2 clinical trial, and (2) an increase in the percentage of patients identified as Monthly Responders, an FDA-defined composite measure incorporating improvements in CSBMs and abdominal pain.

Daily doses of SYN-010 were well-tolerated by IBS-C patients over the combined 12 weeks of the Phase 2a clinical trials (at least 8 weeks of SYN-010 42 mg). No serious adverse events were observed and there were no incidences of drug-related diarrhea.

DDW 2016 Presentation

In May 2016, we presented detailed data from two Phase 2 clinical trials of two dose strengths of SYN-010 at DDW2016.

Clinical data from the 57 patients who completed Study 1 and the 54 patients who completed Study 2 showed clinically meaningful improvements in measurable endpoints, including:

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Data from Study 1 demonstrating that three times as many patients in the placebo group took rescue medication compared to patients on either the 21 mg or 42 mg dose strength of SYN-010.

- Data from all patients who participated in both Study 1 and Study 2 and who were administered the 42 mg dose strength of SYN-010 for at least eight weeks demonstrated an inverse correlation (p=0.0259) between breath methane AUC and complete spontaneous bowel movements (CSBM). A similar inverse correlation (p=0.0028) was observed between breath methane AUC and spontaneous bowel movements (SBM).

- Data demonstrating the 42 mg dose strength of SYN-010 had a similar overall drug response rate to comparable FDA approved and clinical stage therapies for the treatment of IBS-C with a significantly lower rate of diarrhea in study participants.

- Data demonstrating clear improvements in abdominal pain, bloating and quality of life measures (IBS-SSS) in participants who were administered SYN-010.

Clinical Pharmacokinetic Study

In May 2016, we reported results from a separate completed randomized, open-label clinical study of healthy volunteers which evaluated the pharmacokinetic (PK) profile of the active ingredient of SYN-010. The PK data in healthy volunteers supported the modified-release profile of SYN-010, which is designed to avoid drug release in the stomach and deliver the antimethanogenic drug form, lovastatin lactone, into the lower small intestine and colon while reducing systemic exposure to the cholesterol-lowering lovastatin beta-hydroxyacid metabolite. Lovastatin lactone concentrations in stool samples from these healthy volunteers were equivalent to concentrations that caused 90% inhibition of methane production by stool samples from IBS-C patients in vitro. Consistent with the Phase 2a studies in IBS-C patients, data reported from this study demonstrated that the administration of SYN-010 21 mg and 42 mg did not result in adverse changes to the lipid profiles of study participants.

Phase 3 Planning

On July 20, 2016, we participated in an End of Phase 2 meeting with the FDA. Following a review of data from the two Phase 2 clinical trials of SYN-010 conducted by us, a collaborative and positive discussion ensued with the FDA to determine the optimal pathway to advance SYN-010 into Phase 3 development. On January 18, 2017, and in accordance with guidance from the FDA, we confirmed our plan to conduct a Phase 2b/3 adaptive design study for our first pivotal trial of SYN-010 which we plan to initiate during 2017.

In accordance with collaborative discussions with the FDA, key components of the SYN-010 Phase 2b/3 adaptive pivotal trial will include:

- A 12-week, multi-center, double-blind, placebo-controlled, adaptive design clinical trial
- A study population of approximately 840 adult subjects diagnosed with IBS-C
- Evaluation of efficacy and safety of two dose strengths of SYN-010 (21 mg and 42 mg) compared to placebo
- Conducted in approximately 150 clinical sites in North America
- Study subjects will be randomized in a 1:1:1 ratio, receiving either 21 mg of SYN-010, 42 mg of SYN-010, or placebo
- Enrollment will be open to all IBS-C patients; breath-methane will be measured at baseline to ensure a comparable ratio of high-to-low breath methane IBS-C patients in each treatment arm
- An interim futility analysis may be conducted when approximately 50% of patients in each dosing arm have completed treatment

Consistent with FDA written guidance, the primary objective for this study is to determine the efficacy of SYN-010, measured as an improvement from baseline in the percentage of overall weekly responders[1] during the 12-week treatment period for SYN-010 21 mg and 42 mg daily doses compared to placebo. Secondary efficacy endpoints for both dose strengths of SYN-010 will measure changes from baseline in abdominal pain, bloating, bowel movement frequency and stool consistency. Exploratory outcomes include adequate relief and quality of life measures using the well-validated EQ-5D-5L and PAC-SYM patient questionnaires.

Anticipated Regulatory Strategy

We believe that we will be able to utilize the regulatory approval pathway provided in Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the "FDCA") for SYN-010. A New Drug Application (NDA) submitted under Section 505(b)(2), referred to as a 505(b)(2) NDA, contains full safety and efficacy reports but allows at least some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. We believe we can rely in part on the FDA's previous findings of safety for Mevacor (lovastatin) in published clinical data. We expect to rely on published clinical trials using Mevacor to provide support of efficacy.

Intellectual Property

The SYN-010 intellectual property portfolio includes approximately 70 issued U.S. and foreign patents, and approximately 20 U.S. and foreign patents pending.

SYN-004 (ribaxamase) — Prevention of C. difficile infections (CDI) and antibiotic-associated diarrhea (AAD)

SYN-004 (ribaxamase) is an oral prophylactic therapy designed to degrade certain IV beta-lactam antibiotics within the GI tract and maintain the natural balance of the gut microbiome for the prevention of CDI, AAD and emergence of antibiotic-resistant organisms. Beta-lactam antibiotics are a mainstay in hospital infection management and include the commonly used penicillin and cephalosporin classes of antibiotics.

[1] An overall 12-week responder is defined as a subject with a weekly response in at least 50% of the weeks of treatment (6 of 12 weeks). Weekly Responder is defined as a patient who experiences a decrease in weekly average score for worst abdominal pain in the past 24 hours of at least 30% compared with Study 1 Baseline and a stool frequency increase of 1 or more CSBM per week compared with Study 1 Baseline.

In November 2012, we acquired a series of oral beta-lactamase enzymes (P1A, P2A and P3A) and related assets targeting the prevention of CDI, the leading healthcare-associated infection that generally occurs secondary to treatment with IV antibiotics from Prev ABR LLC. The acquired assets include a pre-Investigation New Drug (IND) package for P3A (which we now refer to as ribaxamase, formerly SYN-004), Phase 1 and Phase 2 clinical data for P1A, manufacturing processes and data, and a portfolio of issued and pending U.S. and foreign patents intended to support an IND and Biologics License Application (BLA) with the FDA. Utilizing this portfolio of assets, we developed a proprietary, second generation oral beta-lactamase enzyme product candidate that we call ribaxamase.

Compared to the first generation oral enzyme candidate of P1A, we believe that the second generation candidate, SYN-004 (ribaxamase), will have activity against a broader spectrum of beta-lactam antibiotics, including both penicillins and certain cephalosporins. Due to the structural similarities between P1A and SYN-004 (ribaxamase), and based on previous discussions with the FDA, certain preclinical data collected on P1A was used in support of an IND application for our new product candidate, SYN-004 (ribaxamase). P1A was evaluated in four Phase 1 and one Phase 2 clinical trials conducted in Europe. In total, 112 patients and 143 healthy normal subjects participated in these studies.

Beta-lactamase enzymes have the ability to degrade beta-lactam antibiotics that may be excreted into the Gastro Intestinal tract (GI tract). P1A (the first generation candidate) showed acceptable safety and tolerability in a Phase 1 clinical trial. In addition, data from two Phase 2 clinical trials demonstrated that P1A had the ability to preserve GI microflora in hospitalized patients treated with IV ampicillin or the combination of piperacillin and tazobactam.

C. difficile

C. *difficile* is the leading type of hospital acquired infection and is frequently associated with IV beta-lactam antibiotic treatment. According to an article published in the New England Journal of Medicine (Leffler DA et al. N Engl J Med 2015; 372: 1539-1548), CDIs more than quadruple the cost of hospitalizations, increasing annual expenditures by approximately $1.5 billion in the U.S. CDI is a rising global hospital acquired infection (HAI) problem in which the toxins produced by *C. difficile* bacteria result in AAD, and in the most serious cases, pseudomembranous colitis (severe inflammation of the lower GI tract) that can lead to death. The CDC identified *C. difficile* as an “urgent public health threat,” particularly given its resistance to many drugs used to treat other infections. CDI is a major unintended risk associated with the prophylactic or therapeutic use of IV antibiotics, which may alter the natural balance of microflora that normally protect the GI tract, leading to *C. difficile* overgrowth and infection. Other risk factors for CDI include hospitalization, prolonged length of stay (estimated at 4-7 days), underlying illness, and immune-compromising conditions including the administration of chemotherapy and advanced age. In addition, approximately 25% of patients who have been diagnosed with CDI experience a recurrence of CDI within one to three months.

Limitations of Current Treatments and Market Opportunity

CDI is a widespread and often drug resistant infectious disease. According to an article published in the New England Journal of Medicine (Leffler DA et al. N Engl J Med 2015; 372:1539-1548), it is estimated that 453,000 patients are infected with *C. difficile* annually in the U.S., and it has been reported that approximately 29,000 patients die due to a CDI each year. CDI has surpassed methicillin-resistant staphylococcus aureus (MRSA) as the most frequent hospital acquired infection. Controlling the spread of CDI has proven challenging, as the *C. difficile* spores are easily transferred to patients via normal contact with healthcare personnel and with inanimate objects. There is currently no vaccine or approved product for the prevention of CDI.

According to IMS Health Incorporated, each year 24 million unique patients are administered some form of IV antibiotic in the U.S. which may contribute to the onset of CDI*. Additional data that we requisitioned suggests SYN-004's (ribaxamase's) significant target market is represented by the 117 million average days SYN-004 (ribaxamase) could be administered with target IV beta-lactam antibiotics to the 16.7 million hospitalized patients each year, which at a price point of $100 per day indicates a potential market size of approximately $12.0 billion. This estimate is based upon data that we requisitioned and derived from the following report: Arlington Medical Resources (AMR), a Decision Resources Group Company, 2014 Audits of Acute Care Hospital Antibiotic Utilization. Currently there are no approved treatments designed to protect the gut microbiome from the damaging effects of IV antibiotics. We believe SYN-004's ability to degrade certain beta-lactam antibiotics will be consistent with, or more effective than results previously demonstrated by PIA, SYN-004's predecessor, in Phase 1 and Phase 2 studies conducted by IPSAT. In previously reported clinical studies, SYN-004 (ribaxamase) demonstrated greater efficacy in degrading certain cephalosporins (ceftriaxone) compared to its predecessor, PIA. The worldwide market for SYN-004 (ribaxamase) could represent a multi-billion dollar opportunity for us.

* This information is an estimate derived from the use of information under license from the following IMS Health Incorporated information service: CDM Hospital database for full year 2012. IMS expressly reserves all rights, including rights of copying, distribution, and republication.

Phase 1a and 1b Clinical Trial Pharmacokinetic Data

In March 2015, we reported supportive pharmacokinetic data from our Phase 1a and 1b clinical trials, which suggests that SYN-004 (ribaxamase) may have no effect on the IV antibiotic in the bloodstream, allowing the antibiotic to fight the primary infection. In February 2015, we reported supportive topline results from our Phase 1b clinical trial of escalating doses of oral SYN-004 (ribaxamase), with no safety or tolerability issues reported at dose levels and dose regimens both meeting and exceeding those expected to be studied in upcoming clinical trials. The Phase 1a (40 participants) and 1b (24 participants) clinical trials of SYN-004 (ribaxamase) were initiated in December 2014.

First Phase 2a Clinical Trial Topline Results

In December 2015, we reported supportive topline results from our Phase 2a clinical trial of SYN-004 (ribaxamase), including data from ten ileostomized participants that demonstrated SYN-004 (ribaxamase) successfully degraded residual IV ceftriaxone in the chyme (digestive fluid in the small intestine) without affecting the intended level of ceftriaxone in the bloodstream. This Phase 2a clinical trial was initiated in March 2015 to evaluate the GI antibiotic-degrading effects and the safety of SYN-004 (ribaxamase).

Second Phase 2a Clinical Trial Topline Results

In June 2015, we initiated a second Phase 2a clinical trial of SYN-004 (ribaxamase) to evaluate the GI antibiotic-degrading ability and the safety of SYN-004 (ribaxamase), in the presence of the proton pump inhibitor (PPI), esomeprazole, in healthy participants with functioning ileostomies.

In May 2016, we reported supportive topline results from our second Phase 2a clinical trial of SYN-004 (ribaxamase), including data demonstrating the 150 mg dose of SYN-004 (ribaxamase), both alone and in the presence of the proton pump inhibiter (PPI), esomeprazole, degraded residual IV ceftriaxone to levels that were low or not detectable in the intestinal chyme (digestive fluid in the small intestine) of 14 healthy participants with functioning ileostomies. In addition, ceftriaxone plasma concentrations in study participants were very similar in the presence or absence of an oral PPI, suggesting limited drug-drug interactions with esomeprazole. The 150 mg dose strength of SYN-004 (ribaxamase) was well tolerated by all participants in this clinical trial.

Additional Studies

Data from an additional study conducted in humanized pigs demonstrated that when administered with ceftriaxone, SYN-004 (ribaxamase) prevented ceftriaxone-remediated changes in the pig fecal microflora, protecting the microbiome from antibiotic-mediated damage when compared to pigs who only received ceftriaxone.

CDC's Broad Agency Announcement

On October 6, 2016, we announced the award of a government contract by the CDC's Broad Agency Announcement (BAA) 2016-N-17812. The contract amount is up to $521,014. The award will support research conducted during our ongoing, randomized, placebo-controlled Phase 2b proof-of-concept clinical study of SYN-004 (ribaxamase) and the CDCs' efforts to assess how selective pressure from IV antibiotics may lead to the emergence of antibiotic resistance in the gut microbiome. The funding will also support research to evaluate SYN-004's (ribaxamase's) ability to reduce selective pressure associated with the emergence of antibiotic-resistant organisms in the gut microbiomes of patients enrolled in our Phase 2b clinical trial. We will examine DNA isolated from longitudinal samples obtained during the clinical trial and look for changes to the patient's gut resistome, specifically examining for alterations in the presence and/or abundance of antibiotic resistance genes.

Phase 2b Clinical Trial Design & Topline Results / Phase 3 Planning

In September 2015, we initiated a randomized placebo-controlled Phase 2b proof-of-concept clinical trial intended to evaluate the ability of SYN-004 (ribaxamase) to prevent CDI, *C. difficile* associated diarrhea (CDAD) and AAD in patients hospitalized for a lower respiratory tract infection and receiving IV ceftriaxone. A planned interim analysis was triggered and conducted following the enrollment of approximately 80% of the planned patients who also completed the follow-up period outlined in the study protocol. In September 2016, and following a closed session with the independent Interim Analysis Committee (IAC) in which we remained blinded to the study data, a recommendation was given by the IAC to continue the study per protocol without modification, indicating that the study was adequately powered and should continue as planned. No safety issues were identified by the IAC during the interim analysis. Based upon the recommendation by the IAC, we completed enrollment in this trial in September 2016 with 413 patients exceeding the desired sample size of 372 patients. Analysis of an exploratory endpoint from this trial designed to evaluate the ability of SYN-004 (ribaxamase) to limit disruption of the gut microbiome diversity, also known as dysbiosis, is ongoing.

On January 5, 2017, we announced positive topline data from our Phase 2b clinical trial demonstrating SYN-004 (ribaxamase) achieved its primary endpoint of significantly reducing CDI. Preliminary analysis of the data indicated seven confirmed cases of CDI in the placebo group compared to two cases in the ribaxamase treatment group. Patients receiving ribaxamase achieved a 71.4% relative risk reduction (p-value=0.045) in CDI rates compared to patients receiving placebo. Adverse events reported during this trial were comparable between treatment and placebo arms.

Preliminary analysis of the data demonstrated a significant reduction in new colonization by vancomycin-resistant enterococci (VRE) for patients receiving ribaxamase compared to placebo (p-value=0.0002). With agreement from the FDA, the study included a secondary endpoint to assess ribaxamase's capacity to decrease the incidence of antibiotic-associated diarrhea from all causes. Preliminary analysis of the data suggested a trend towards such a reduction (p-value=0.13), which was due, for the most part, to the reduction of CDI.

We are in the process of further analyzing data from this clinical trial and expect to share additional results from additional exploratory endpoints as they become available later this year, including results focused on ribaxamase's ability to prevent the emergence of antimicrobial resistance in the gut microbiome.

In 2017, we also plan to enter into strategic discussions with the CDC, hold an end of Phase 2 meeting with the FDA, and expect to initiate Phase 3 trial(s) towards the first half of 2018 or later.

SYN-007 — Prevention of CDI and AAD

Preclinical work is ongoing to determine the ability of SYN-007 to degrade oral beta-lactam antibiotics and protect the gut microbiome. SYN-007 comprises a reformulated version of SYN-004 for use with oral beta-lactam antibiotics versus IV beta-lactam antibiotics.

SYN-006 — Prevention of CDI and AAD

The development of SYN-006 is in the discovery stage. SYN-006 is intended to be an oral prophylactic therapy designed to degrade IV carbapenem antibiotics (a third class of beta-lactam antibiotics) within the GI tract and maintain the natural balance of the gut microbiome for the prevention of CDI and AAD. While SYN-004 (ribaxamase) is intended to degrade penicillin and certain cephalosporins in the GI tract, the SYN-006 discovery program has the potential to expand the activity to a broader spectrum of IV beta-lactam antibiotics in the GI tract to include carbapenem antibiotics.

C. difficile: Intellectual Property

The SYN-004 (ribaxamase) intellectual property portfolio includes approximately 60 issued U.S. and foreign patents, and approximately 35 U.S. and foreign patents pending.

Research Programs

Infectious disease outbreaks are increasing while intervention options are declining due to widespread multidrug-resistant bacteria, increasing numbers of immuno-compromised patients (e.g., the elderly and cancer patients) and the isolation of new pathogens.

SYN-005 — Pertussis (Whooping Cough)

Bordetella pertussis (B. pertussis) is a gram-negative bacterium that infects the upper respiratory tract, causing uncontrollable and violent coughing. Antibiotic treatment does not have a major effect on the course of pertussis. While such treatment can eliminate the *B. pertussis* bacteria from the respiratory tract, it does not neutralize the pertussis toxin. Infants with pertussis often require hospitalization in pediatric intensive care units, frequently requiring mechanical ventilation. The incidence of pertussis is increasing due to the declining effectiveness of the acellular vaccine introduced in the 1990s, exposure of unvaccinated and under-vaccinated individuals including infants who are not yet fully vaccinated and exposure of individuals whose immunity has diminished over time.

According to the World Health Organization (WHO), there are 50 million cases of whooping cough, and it is estimated that *B. pertussis* infection causes up to 300,000 deaths each year worldwide, primarily among unvaccinated infants.

Intrexon Collaboration and The University of Texas at Austin Agreement

In August 2012, we entered into a worldwide exclusive channel collaboration with Intrexon through which we intend to develop monoclonal antibody (mAb) therapies for the treatment of certain infectious diseases not adequately addressed by existing therapies. In December 2012, we initiated mAb development for the prevention and treatment of pertussis focusing on toxin neutralization. Unlike antibiotics, we are developing a mAb therapy to target and neutralize the pertussis toxin as a prophylaxis for high-risk newborns and in order to reduce the mortality rate in infected infants.

To further the development of this potential therapy for pertussis, we entered into an agreement with UT Austin to license the rights to certain research and pending patents related to pertussis antibodies. These research efforts are being conducted at the Cockrell School of Engineering in the laboratory of Associate Professor, Jennifer A. Maynard, Ph.D., the Laurence E. McMakin, Jr. Centennial Faculty Fellow in the McKetta Department of Chemical Engineering. Dr. Maynard brings to the project her expertise in defining the key neutralizing epitopes of pertussis toxin to optimize the potential efficacy of antibody therapeutics.

Preclinical Development

Working with our collaborator, Intrexon, and our academic collaborator, UT Austin, we have established a humanized mAb product candidate, SYN-005, designed to neutralize pertussis toxin, a major cause of pertussis-mediated infant morbidity and mortality. The two humanized mAbs, hu1B7 and hu11E6, bound tightly to the toxin and potently neutralized the toxin. In addition, the antibodies, individually or in combination, were highly efficacious in a murine model of pertussis in which they completely mitigated elevations of the white blood cell count that is characteristic of the illness.

In April 2014, and again in September 2014, we received positive preclinical research findings of SYN-005 for the treatment of pertussis in three non-human primate studies (n = 19). In the latter two pertussis studies in particular, SYN-005 rapidly stopped the rise in white blood cell count that is characteristic of the disease and accelerated its return to baseline.

In September 2014, we received U.S. Orphan Drug Designation from the FDA for SYN-005 for the treatment of pertussis.

In April 2015, preclinical efficacy data that support advancing SYN-005 toward clinical trials were presented in two poster presentations at the European Congress of Clinical Microbiology and Infectious Diseases meeting (ECCMID) 2015 in Copenhagen, Denmark. The data suggest that SYN-005 has therapeutic potential to diminish morbidity, long-term complications and mortality from pertussis in critically ill infants. In addition, the data support a prophylactic approach for use in newborns that has the potential to save thousands of lives annually, particula