ENANTA PHARMACEUTICALS INC
Form 10-K
December 18, 2013
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 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 September 30, 2013

OR

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

Commission File Number 001-35839

ENANTA PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

DELAWARE	2834	04-3205099
(State or other jurisdiction of incorporation or organization)	(Primary Standard Industrial Classification Code Number)	(I.R.S. Employer Identification Number)

500 Arsenal Street

Watertown, Massachusetts 02472

(617) 607-0800

(Address, including zip code, and telephone number, including area code, of registrant s principal executive offices)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class:	Name of each exchange on which registered:
Common Stock, $0.01 Par Value	The NASDAQ Stock Market LLC (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 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 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 x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T 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 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. x

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

Large accelerated filer ¨	Accelerated filer ¨
Non-accelerated filer x (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 the last business day of the registrant s most recently completed second fiscal quarter, March 28, 2013, based on the last reported sale price of the registrant s common stock of $18.20 per share was $221,157,646. The number of shares of the registrant s Common Stock, $0.01 par value, outstanding as of December 16, 2013, was 17,961,713 shares.

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DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant s Definitive Proxy Statement for its 2014 Annual Meeting of Stockholders scheduled to be held on February 6, 2014, which Definitive Proxy will be filed with the Securities and Exchange Commission not later than 120 days after the registrant s fiscal year end of September 30, 2013, are incorporated by reference into Part III of this Form 10-K.

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As used in this Form 10-K, Enanta, the Company, we, our, and us refer to Enanta Pharmaceuticals, Inc., except w
the context otherwise requires or as otherwise indicated.

NOTE REGARDING FORWARD LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements concerning our business, operations and financial performance and condition, as well as our plans, objectives and expectations for our business operations and financial performance and condition. Any statements contained herein that are not statements of historical facts may be deemed to be forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as aim, anticipate, assume, believe, contemplate, continue, could, due, estimate, may, objective, plan, predict, potential, positioned, seek, should, target, will, would, and other are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- the continued commitment of our collaborators, AbbVie and Novartis, with respect to the development of product candidates incorporating ABT-450, ABT-493 and EDP-239, respectively;
- the completion, success and timing of preclinical studies and clinical trials conducted by AbbVie, Novartis or us;
- our and our collaborators abilities to obtain and maintain regulatory approval of therapies involving our product candidates;
- the receipt and timing of any milestone payments or royalties from AbbVie, Novartis or any other collaborator;
- our ability to obtain and maintain collaborators for our development programs or to obtain additional funding;
- the success of competing HCV or MRSA drugs that are now or later become available or other developments or projections relating to our competitors and our industry;
- changes in our or our collaborators plans to develop and commercialize our product candidates;
- the rate and degree of market acceptance of any of our product candidates and any combination therapies developed by AbbVie, Novartis or us;

the size and growth of the potential markets for our product candidates and our collaborators and our abilities to serve those markets, including our belief that substantial opportunities exist for improved treatments in HCV and bacterial infections;

our ability to obtain and maintain intellectual property protection for our product candidates and operate our business without infringing on the intellectual property rights of others;

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

regulatory developments in the United States and foreign countries affecting disease indications for our product candidates or anti-infective drugs generally;

the performance of third-party manufacturers of our product candidates, including our collaborators;

the accuracy of our estimates regarding our expenses, future revenue, capital requirements and needs for additional financing;

our expectations regarding the time during which we will be an emerging growth company under the JOBS Act; and

our financial performance.

These forward-looking statements are based on our management s current expectations, estimates, forecasts and projections about our business and the industry in which we operate and our management s beliefs and assumptions. These forward-looking statements are not guarantees of future performance or development and involve known and unknown risks, uncertainties and other factors that are in some cases beyond our control. As a result, any or all of our forward-looking statements in this Annual Report on Form 10-K may turn out to be

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inaccurate. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under Risk Factors and discussed elsewhere in this Annual Report on Form 10-K. These forward-looking statements speak only as of the date of this Annual Report on Form 10-K. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future. You should, however, review the factors and risks we describe in the reports we will file from time to time with the SEC after the date of this Annual Report on Form 10-K.

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ENANTA PHARMACEUTICALS, INC.

ANNUAL REPORT ON FORM 10-K

For the year ended September 30, 2013

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PART I

ITEM 1. BUSINESS

BUSINESS

Overview

We are a research and development-focused biotechnology company that uses its robust chemistry-driven approach and drug discovery capabilities to create small molecule drugs in the infectious disease field. We are discovering and developing inhibitors designed for use against the hepatitis C virus, referred to as HCV. We believe that a successful approach to a complete cure for HCV in most patients will likely require treatment with a combination of drugs that attack different mechanisms necessary for replication and survival of HCV. Further, as there are many variants of HCV, we are developing inhibitors that may be used in multiple combination therapies, each designed and tested for effectiveness against one or more of those variants. Our development of inhibitors for validated HCV target mechanisms, as well as our collaborations with AbbVie (which name refers to Abbott Laboratories for all periods before January 1, 2013) and Novartis, should allow us to participate in multiple drug combinations as we and our collaborators seek the best combination therapies for HCV in its various forms. We estimate that total worldwide sales of HCV therapies were over $4 billion in 2012, and we expect that sales will continue to grow with the anticipated introduction of new therapies. In addition to our HCV programs, we have used our internal research capabilities to discover a new class of antibiotics, which we are developing for the treatment of multi-drug resistant bacteria, including MRSA. We have utilized our internal chemistry and drug discovery capabilities and our collaborations to generate all of our development-stage programs, and we have active research efforts to broaden our infectious disease drug pipeline.

Our HCV portfolio includes inhibitors of four fundamental, validated HCV targets:

NS3 Protease Inhibitors: ABT-450 and ABT-493. Our lead product candidate, ABT-450, is an inhibitor of NS3 protease, which is a key protein in HCV viral replication. ABT-450 is being developed as part of our AbbVie collaboration that has yielded ABT-450 and our next-generation protease inhibitor, ABT-493. ABT-450 co-administered with ritonavir, which we refer to together as ABT-450/r, is being tested in seven all-oral, interferon-free Phase 3 studies in combination with one of AbbVie s non-nucleoside polymerase and one of its NS5A inhibitors, plus ribavirin, for the treatment of HCV in genotype 1-infected patients. Six of these trials are expected to be part of the initial registration package designed for a total of at least 2,200 patients using a combination of these three directing-acting antivirals, or DAAs, plus ribavirin. Three of these Phase 3 trials are using the three-DAA combination with and without ribavirin.

In November and December 2013 AbbVie released preliminary results from the first two of these clinical trials, SAPPHIRE-I and SAPPHIRE-II, which were the first announced Phase 3 trial results of any company for an all-oral, interferon-free therapy in genotype 1 HCV patients. SAPPHIRE-I was a 631-patient trial of previously untreated, or naïve, adult patients and SAPPHIRE-II was a 394-patient trial of treatment-experienced adult patients who had previously failed pegylated interferon and ribavirin treatment. Both of these trials demonstrated after 12 weeks of treatment that 96% of patients treated with the new regimen had no quantifiable virus in their blood 12 weeks after treatment, also known as SVR_{12}. AbbVie has guided that preliminary results from the remaining four phase 3 trials will be released during 2013 and into early 2014. AbbVie has publicly projected that its development plan would support a target commercial launch of a combination HCV therapy in early 2015. We believe that we, together with

AbbVie, will obtain exclusivity in ABT-450 in the United States and other major market jurisdictions based on pending composition and use patent claims for ABT-450, which we expect will continue at least into 2029, assuming all such patents issue.

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Our Enanta-AbbVie collaboration has also produced ABT-493, a next-generation protease inhibitor for HCV. In 2013 AbbVie initiated combination studies of ABT-493 with ABT-530 (AbbVie s next-generation NS5A inhibitor) in healthy volunteers, and we expect ABT-493 to begin dosing in HCV patients in late 2013.

NS5A Inhibitor: EDP-239. We have had a robust drug discovery effort directed at the NS5A protein, which plays a key role in HCV viral replication. In February 2012, we entered into a collaboration with Novartis for the worldwide development, manufacture and commercialization of NS5A inhibitors, including our lead NS5A product candidate, EDP-239. In November 2012, Novartis initiated a Phase 1 clinical trial for EDP-239, and in 2013 initiated a trial testing EDP-239 in HCV patients. We believe that we, together with Novartis, have exclusivity to EDP-239 in the United States based on issued patent composition and use claims, which we expect will continue at least into 2030.

Cyclophilin Inhibitors. Our research activities have also focused on a more recently validated target against HCV, cyclophilin, which is a protein in the human body that has been shown to be involved in HCV replication. By focusing on this human, or host, target rather than a viral target, we have selected a mechanism shown to be less susceptible to the HCV resistance that can occur due to viral mutation in response to therapy. Using our extensive chemistry expertise with small molecules, we have identified a series of active cyclophilin binders designed to disrupt the interactions of HCV with cyclophilin. We expect to advance a lead cyclophilin inhibitor into preclinical drug metabolism, pharmacokinetic, and safety studies in 2014.

Nucleotide Polymerase Inhibitor. We have a small-molecule drug discovery effort underway for inhibitors of nucleotide polymerase in a clinically validated mechanism that is less susceptible to HCV resistance. Our researchers have identified a promising lead series with significant antiviral potency *in vitro*. We expect to select a candidate to advance into preclinical studies on our own in 2014.

In addition to our HCV programs, we have used our internal research capabilities to discover a new class of antibiotics, called Bicyclolides, which we are developing for the treatment of multi-drug resistant bacteria, including MRSA. These new antibiotic candidates include intravenous and oral forms for treatment of hospital and community infections arising from MRSA. EDP-788 is our lead candidate for the treatment of MRSA. Our preclinical and early clinical development of EDP-788 is funded under a contract with NIAID. We are conducting IND-enabling studies and plan to initiate a clinical trial in the first quarter of 2014.

In connection with our collaboration efforts, AbbVie has funded all research and development of our protease inhibitors since we entered into the collaboration in November 2006, and is responsible for obtaining regulatory approvals and commercializing ABT-450 and any next-generation products worldwide. In 2006, we received $57.2 million from AbbVie in connection with our entry into the collaboration agreement and AbbVie s simultaneous purchase of preferred stock from us. We also received a $40.0 million milestone payment in December 2010 following AbbVie s successful completion of a Phase 2a clinical trial and a $15.0 million milestone payment in December 2012 based on AbbVie s initiation of dosing in a Phase 3 clinical trial that includes ABT-450. Assuming AbbVie s successful development of the first protease inhibitor product, we will also be eligible to receive $195 million of additional pre-commercialization milestone payments, as well as $80 million of additional milestone payments for each follow-on protease inhibitor product, if any, developed by AbbVie and tiered royalties per product ranging from the low double digits up to twenty percent, or up to the high teens on a blended basis, on AbbVie s net sales, if any, allocable to our collaboration s protease inhibitors.

Under our collaboration with Novartis, we received a $34.4 million upfront payment in March 2012, and an $11.0 million milestone payment in January 2013 based on Novartis initiation of dosing in a Phase 1 clinical trial that includes EDP-239. In addition, we are eligible to receive up to $395 million of additional milestone payments for the first NS5A inhibitor product for which the specified milestones are achieved. We are also eligible to receive tiered royalties ranging on a blended basis from the low double digits up to the high teens on

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Novartis net sales, if any, allocable to each of our collaboration s NS5A inhibitors. Novartis will fund all costs associated with further development, regulatory approvals and commercialization of any NS5A inhibitor product candidates in this collaboration and we retain co-detail rights in the United States.

Our Strategy

Our primary objective is to become a leader in the infectious disease field, with a focus on HCV and multi-drug resistant bacterial infections. Our strategy includes the following key elements:

Develop compounds against four fundamental, validated HCV targets to give us multiple opportunities to participate in one or more of the potentially successful combination therapies for HCV. We believe that a successful approach to a complete cure for HCV in most patients will likely require treatment with a combination of drugs that attack different mechanisms necessary for replication and survival of HCV. As there are many variants of HCV, we are developing inhibitors that may be used in multiple combination therapies, each to be designed and tested for effectiveness against one or more of those variants, or genotypes. Our HCV portfolio includes inhibitors of four fundamental, validated HCV targets that we believe will provide the necessary therapeutic compounds for combination therapy, with the goal of placing one or more of our compounds into the combination or combinations that will ultimately be approved and accepted as preferred treatments for one or more genotypes of HCV.

Collaborate with large pharmaceutical partners to accelerate the development and commercialization of our lead HCV compounds. Our strategic partnerships allow us to join forces with collaborators with substantially greater resources and late-stage development and commercialization expertise as we seek the right combination for a cure for one or more genotypes of HCV. After testing ABT-450 in various combinations in clinical trials, AbbVie is combining ABT-450 with one of AbbVie s own non-nucleoside inhibitors and one of its NS5A inhibitors. In addition, AbbVie is conducting combination studies of our collaboration s next-generation protease inhibitor, ABT-493, with AbbVie s next-generation NS5A inhibitor, ABT-530. At the same time, our own lead NS5A product candidate, EDP-239, can become part of combination therapies developed by Novartis. The result is that our product candidates are being tested in multiple regimens using different combinations of mechanisms, increasing our chances of participating in more than one commercially successful combination therapy for HCV in its various forms.

Develop independently our own next generation HCV compounds and combination therapies with lower susceptibility to viral resistance. We are independently developing a lead cyclophilin inhibitor and will be selecting a nucleotide polymerase inhibitor for development, both of which we are seeking to design with lower susceptibility to the viral resistance that is being generated by first-generation (currently marketed) and second-generation HCV products. We are considering potential development of a combination of these two types of inhibitors.

Continue to leverage and fortify our intellectual property portfolio. We believe we have a strong intellectual property position relating to the development and commercialization of HCV-targeted therapeutics and antibiotics for the treatment of resistant pathogens.

Invest in research and early-stage development of product candidates. We intend to continue to invest significant resources in research programs and early-stage development of product candidates in an effort to identify and advance additional compounds that have the potential to address significant unmet medical needs in the infectious disease field. We will continue to seek further innovations for the treatment of HCV and other viral infections, as well as antibiotics for the treatment of resistant bacteria, such as MRSA.

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Our Research and Development Pipeline

The following table summarizes our product development pipeline in HCV antivirals as well as MRSA antibiotics:

As detailed above, our only product candidate that has advanced beyond Phase 2 clinical trials is ABT-450. Phase 3 trials of ABT-450 in combination therapy started in October 2012, and the full registration program of six trials involving approximately 2,200 patients has been fully enrolled and the preliminary results of the first two trials have been reported. We estimate that it may be early 2015 before a New Drug Application, or NDA, for one of our collaborator s combination therapies that includes ABT-450 could be approved by the FDA.

Our HCV Programs

Background and Overview of HCV Market

HCV is a virus that is a common cause of viral hepatitis, an inflammation of the liver. HCV is typically contracted by contact with the blood or other body fluids of another individual infected with HCV. HCV is a leading cause of chronic liver disease, including cirrhosis, organ failure and cancer, and the leading cause of death from liver disease in the United States. HCV disease progression occurs over a period of 20 to 30 years, with the majority of HCV-infected individuals generally exhibiting no major symptoms in the early stages of the disease. Therefore, until a major symptom is diagnosed, many individuals are unaware they are infected and live

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undiagnosed without seeking treatment. For that reason, new guidelines proposed by the United States Centers for Disease Control and Prevention, or CDC, and currently under review would recommend screening for all Americans born between the years 1945 and 1965 so that HCV-infected individuals would be aware of their condition and could consider treatment options.

An estimated 150 million people worldwide are chronically infected with HCV and have an increased risk of eventually developing liver cirrhosis or liver cancer. More than 350,000 people die every year from HCV-related liver diseases. As of July 2008, the CDC estimated that approximately 3.2 million people in the United States are chronically infected with HCV, with an estimated 17,000 new infections each year. We believe that the chronically infected population remains largely untreated, even with the introduction of new regimens containing a protease inhibitor in 2011. Currently approved therapies for HCV, which include interferon, ribavirin and the new protease inhibitors, had aggregate worldwide sales of over $4 billion in 2012. We believe that annual worldwide sales of these therapies and future approved therapies could increase sales in this market to $10 to $20 billion within the next ten years.

HCV is a small, single-stranded RNA virus. The specific genetic makeup, or genotype, of the virus can vary and at least six genotypes have been characterized in HCV-infected patients, with over 50 sub-types identified. Genotypes are designated with numbers (genotypes 1-6) and subtypes with letters (*e.g.* genotype 1a). HCV genotypes 1, 2, 3, and 4 are found worldwide, but their prevalence varies among geographic regions. Genotype 1, including its subtypes 1a and 1b, is the most common genotype globally, accounting for approximately 74% of all HCV infections. It is estimated that patients with genotype 2 or 3 represent approximately 12% of the worldwide chronically infected HCV population, with approximately 6% comprised of genotypes 4 through 6 and the remaining 8% of patients in other undesignated categories. The specific genotype and subtype of HCV in a patient appears to play a significant role in the degree of efficacy of standard of care therapy. Genotype 1 is the most difficult genotype to treat and the most common in North America and Europe.

Since the discovery of the virus in the late 1980s, considerable progress has been made in the treatment of HCV-infected individuals. However, a protective vaccine is not yet available and current treatments remain ineffective in a large percentage of the HCV-treated population. The standard of care for HCV traditionally has consisted of weekly injections of interferon, a protein that interferes with viral replication, with twice-daily dosing of ribavirin for 24 to 48 weeks. Ribavirin is a broad-spectrum drug that prevents the replication of a number of DNA and RNA-based viruses. This regimen has been moderately effective in many patients, resulting in a cure in only about 50% of genotype 1-infected patients. Medical practice defines a cure as the point at which there is no quantifiable virus in a patient s blood for a sustained period of time after cessation of therapy, which is often referred to as a sustained virologic response, or SVR.

Recently introduced treatment regimens contain direct acting antivirals, or DAAs, with initial approval coming for protease inhibitors. The first two protease inhibitors approved, telaprevir (Incivek , Vertex Pharmaceuticals) and boceprevir (Victrelis , Merck), have shown cure rates of approximately 70% in genotype 1-infected patients. Telaprevir and boceprevir were approved for use in combination with interferon and ribavirin in patients infected with genotype 1 virus in 2011, and combination therapy incorporating a protease inhibitor has emerged as a new standard of care for HCV patients. In November 2013 the FDA approved a new protease inhibitor from Janssen Therapeutics, simeprevir (Olysio), for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease. Simeprevir has shown cure rates of up to 80% in genotype 1-infected patients. However, the once-daily treatment must still be combined with pegylated interferon and ribavirin. In December 2013, the FDA approved sofosbuvir (Sovaldi), a nucleotide analogue inhibitor of the HCV NS5B polymerase enzyme from Gilead. Sofosbuvir is a once-a-day treatment given in combination with ribavirin for the treatment of chronic hepatitis C in adult patients with genotype 2 or 3 infection. Sofosbuvir may also be given in combination with pegylated interferon and ribavirin

for the treatment of chronic hepatitis C in treatment-naïve adult patients with genotype 1 (the predominant genotype in the major world markets) and genotype 4 infection.

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These new treatment regimens have several limitations that highlight the need for improved HCV therapies, particularly for genotype 1 HCV, including:

Sub-Optimal Cure Rates. Current approved regimens containing a protease inhibitor lead to a cure rate of approximately 70%- 80% in previously untreated, genotype 1 patients. Clinical trial participants taking Sovaldi-based therapy (Sofosbuvir) achieved SVR_{12} rates of 50-90 percent. The cure rate is on average lower among patients who did not fully respond to prior treatments with interferon and ribavirin therapy. There is a need for a cure for the patients who have failed therapy, many of whom may have developed HCV variants that are resistant to the specific protease inhibitors used in the protease-based therapies.

Dependence on Interferon. Current HCV therapy for genotype 1 (the predominant genotype in the major world markets) still includes injected interferon as part of the treatment regimens, which produces adverse events in over 50% of patients. Interferon often causes flu-like symptoms, fatigue, headaches and nausea during treatment, which affects patients quality of life and can lead to abandonment of therapy over the standard 24 to 48 weeks of therapy. We believe this has led to many patients waiting for the availability of new, interferon-free therapies before undergoing treatment.

Side Effects Associated With Currently Approved Protease Inhibitors. Other serious side effects of the new regimens containing a protease inhibitor include rash, anemia, itching (known as pruritus), and gastrointestinal effects. Rash is observed in more than a quarter of the patients taking simeprevir and in approximately half of patients treated with telaprevir and telaprevir-containing therapy and requires strict adherence to a rash management plan in close collaboration with an experienced dermatologist. Boceprevir administration can worsen the anemia that is observed with interferon and ribavirin therapy alone.

Inconvenient Treatment Regimen. Though simeprevir and Sovaldi are once-a-day medicines, the pharmaceutical properties of telaprevir and boceprevir require that they be dosed approximately every 8 hours, thus resulting in a complex treatment regimen that also includes weekly injections of interferon. All currently approved protease inhibitors require co-administration with interferon for treatment of genotype 1 HCV. We believe that demanding dosing requirements such as these can often lead to poor compliance with the treatment regimen and can accelerate the development of HCV resistance.

While providing a step forward, we believe these new treatment regimens may only provide sub-optimal cure rates, will still require treatment with interferon for many patients, including genotype 1 patients, may carry other undesirable side effect profiles, may require inconvenient dosing regimens, may be ineffective in many patient populations and may often result in HCV resistance. Accordingly, we believe there remains a significant unmet medical need in the HCV field, with an urgent need for improved treatments for HCV.

Scientific Background

Many of the new approaches under development targeting HCV focus directly on the viral life cycle and proteins that are critical to HCV replication. Replication of the HCV genome occurs on intracellular membranes and requires the participation of multiple viral proteins, some of which have enzymatic activities. Agents, often referred to as inhibitors, that target viral proteins directly are generally referred to as direct acting antivirals, or DAAs. Current DAA development efforts typically focus on the NS3 protease, the NS5A protein, and the NS5B polymerase. In addition to

targets in HCV itself, there are human host proteins that are critical to viral replication. Inhibitors that interfere with host targets resulting in antiviral activity are referred to as host-targeted antivirals, or HTAs. One of the most promising HTA approaches to HCV treatment focuses on the human host protein known as cyclophilin A, or cyclophilin.

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Key Proteins in the HCV Replication Complex

NS3 Protease. As HCV replicates, it generates long strands of protein that must be processed into many individual active functional proteins that are referred to as non-structural proteins with the designated abbreviation NS, including NS3 and NS5A. The NS3 protease is responsible for most of this protein processing of the newly translated HCV protein, and plays an essential role in the viral life cycle. Inhibition of the protease prevents these new critical proteins from forming and therefore prevents replication and survival of the virus. NS3 protease inhibition is the mechanism of action for the two most recently approved HCV drugs, telaprevir and boceprevir, both of which are DAAs.

NS5A. The NS5A protein has key roles in both the RNA replication of HCV and modulation of the physiology of its host cell in the body. Research has shown that targeting NS5A gives rise to profound antiviral activity, and as a result, this protein has emerged as an additional important DAA target for anti-HCV drug development.

NS5B Polymerase. HCV is a single-stranded RNA virus, and NS5B is an HCV RNA polymerase responsible for synthesis of new HCV RNA, allowing the HCV genome to be copied and the virus to survive and replicate. Two separate classes of DAA inhibitors of NS5B polymerase are in development as treatments for HCV. Nucleoside/nucleotide inhibitors of NS5B directly inhibit the active site of that enzyme and prevent further elongation of the RNA, and thus are equally active against all HCV genotypes. A second class, known as non-nucleoside inhibitors, affects replication of the RNA by altering the shape of the enzyme at remote sites on the enzyme surface so that any given inhibitor is usually only active against certain HCV genotypes.

Cyclophilin. Viral function requires an interaction of the viral protein NS5A with the human host protein known as cyclophilin. Inhibitors that interfere with this NS5A-cyclophilin interaction would essentially provide a treatment that protects the human host cells from infection by the virus. Several studies using the immunosuppressive drug cyclosporine A, a known cyclophilin inhibitor, support the clinical validation of cyclophilin as an HTA for treatment of HCV infection. However, the immunosuppressive activity of cyclosporine A and associated side effects limit its clinical use and thus efforts are now focused on new agents devoid of immunosuppressive activity. Alisporivir, a nonimmunosuppressive cyclosporine A derivative under development by Novartis, has demonstrated effectiveness against many HCV genotypes, a high barrier to HCV resistance and no cross-resistance with several DAAs.

The ultimate goal in HCV treatment is complete cure with total eradication of the virus, measured by SVR. We believe that combination therapy will improve overall cure rates and will reduce the probability of resistance arising to any single antiviral agent. In particular, a combination of target mechanisms that includes those with a

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high barrier to resistance (cyclophilin, polymerase) may prove to be the most effective combination against multiple genotypes of HCV. Unlike treatment for certain viruses, such as HIV, complete clearance of the HCV virus is possible with effective therapy. This exciting prospect suggests that the ultimate goal of a complete cure with total eradication of the virus is within reach.

Our Approach to the Treatment of HCV

We are pursuing four fundamental, validated targets within the HCV field that represent a broad approach to the disease and specifically address the urgent unmet medical needs in current HCV therapies. Our approach incorporates the main targets for future HCV therapy. Our DAA approach directly targets three critical proteins of HCV, incorporating inhibitors of NS3 protease, NS5A protein, and NS5B polymerase. Inhibitors in our HTA approach protect the human host protein cyclophilin from being co-opted into the viral replication machinery of HCV. We believe a combination of inhibitors from our programs may provide a truly effective all-oral interferon-free or interferon/ribavirin-free therapeutic approach to HCV, with complete eradication of virus, low resistance rates, convenient dosing and acceptable side effect profiles.

ABT-450, a Protease Inhibitor for HCV Infection

Our protease inhibitor, ABT-450, discovered through our collaboration with AbbVie and currently in Phase 3 clinical trials, is a potent DAA that has demonstrated *in vitro* potency against known resistant HCV mutants. In Phase 1 studies, ABT-450 co-administered with ritonavir, a commonly used boosting agent to increase the blood concentrations of many protease inhibitors, was shown to be safe and well tolerated. Co-administration of ABT-450 with ritonavir, which we refer to together as ABT-450/r, has enabled once-daily dosing of ABT-450. Phase 2 studies have demonstrated the efficacy of ABT-450/r in patients with chronic HCV, and other interferon-free Phase 2 studies of ABT-450-containing regimens continue. In addition, AbbVie is conducting Phase 3 trials of ABT-450/r in combination with AbbVie s non-nucleoside polymerase and NS5A inhibitors, with and without ribavirin. While AbbVie and other companies are developing interferon-free and interferon/ribavirin-free HCV therapies in clinical trials, the efficacy of this approach has not yet been proven conclusively, nor has it resulted yet in any product approved by the FDA.

We believe that a treatment regimen containing ABT-450/r may have significant advantages over currently approved genotype 1 HCV treatment regimens containing protease inhibitors because of the following key attributes:

Improved Antiviral Activity. Compared to the current leading protease inhibitor, telaprevir, ABT-450 has demonstrated superior antiviral activity against HCV in patients, including genotype1.

No Interferon. Current genotype 1 HCV therapy still includes injected interferon. Interferon is often associated with flu-like symptoms, fatigue, headaches and nausea during treatment. ABT-450/r is being developed for use in one or more interferon-free regimens.

Tolerability. As noted above, serious side effects of current regimens for genotype 1 HCV that contain protease inhibitors include rash, anemia, pruritus, or itchy skin, and gastrointestinal effects. In contrast, most side effects in clinical trials including ABT-450/r to date were mild to moderate.

Shorter Treatment Regimen. ABT-450/r is being tested in various treatment combinations that are only 12 weeks in duration, as compared to the 24 to 48 weeks of treatment required with some of the current interferon-containing regimens.

More Convenient Treatment Regimen. ABT-450/r is being developed for oral, once-daily dosing. All of the combinations including ABT-450/r that AbbVie is testing include only orally administered drugs dosed either once or twice daily without the use of interferon. By comparison, current treatment regimens containing a protease inhibitor require weekly interferon injections.

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Under the AbbVie collaboration, we have granted AbbVie an exclusive worldwide royalty-bearing license, including a right to grant sublicenses, to our intellectual property position for NS3 protease inhibitors. We also granted AbbVie access to our drug discovery capabilities in the NS3 protease inhibitor field. AbbVie is responsible for and funds all costs associated with the development, manufacturing and commercialization of ABT-450 and other compounds under this collaboration agreement. We will be eligible to receive milestone payments and royalties with respect to these compounds if such products are successfully commercialized by AbbVie.

In November 2013, AbbVie announced preliminary results of its SAPPHIRE-I trial, and in December 2013 it announced preliminary results of its SAPPHIRE-II trial. These are the first of six Phase 3 trials for an ABT-450-containing regimen for treating genotype 1 infected patients. Results of the other four trials are expected to continue to be reported through the end of 2013 and into the first calendar quarter of 2014. These six trials are expected to be part of the initial registration package designed for a total of 2,200 patients using a combination of three DAAs, including ABT-450/r, one of AbbVie s non-nucleoside polymerase inhibitors and one of AbbVie s NS5A inhibitors, plus ribavirin. Three of these Phase 3 trials are using the same three-DAA (3D) combination, with and without ribavirin. In addition, in November 2013 AbbVie announced topline results of a Phase 2 clinical study, known as PEARL-I, in genotype 1a- and 1b-infected patients using a two-DAA (2D) dosing regimen containing a combination of ABT-450/r and ABT-267 dosed once daily. In PEARL-I, 95% of treatment-naïve patients with genotype 1b and 90% of treatment-experienced patients who had been null responders had sustained viral response 12 weeks after treatment. AbbVie is also conducting a Phase 2 study of the 2D regimen in Japan in genotype 1b and genotype 2-infected patients.

AbbVie has announced that it expects regulatory filings in the second calendar quarter of 2014 for an ABT-450-containing treatment regimen for genotype 1 HCV patients. In addition, in May 2013 AbbVie announced that its investigational direct-acting antiviral (DAA) combination with and without ribavirin for the treatment of genotype 1 hepatitis C virus (HCV) infection was designated as a breakthrough therapy by the U.S. Food and Drug Administration, or FDA. According to the FDA, breakthrough therapy designation is intended to expedite the development and review of drugs for serious or life-threatening conditions. For a breakthrough therapy, once a New Drug Application, or NDA, is accepted by the FDA, the agency in its discretion can grant it priority review status, which would set a date for regulatory action within six months of the NDA filing.

AbbVie has also announced that its development plan would support a target commercial launch of such a combination therapy in early 2015. AbbVie projects that there will be a potential worldwide market opportunity of $12-14 billion for HCV therapies by 2016 based upon an assumed treatment rate of 300,000 to 350,000 patients per year across all genotypes of HCV in the U.S., Japan, Canada and four major European countries, or the G7 countries. In addition, AbbVie had previously projected that peak sales for the combination therapies AbbVie is developing could reach $2 billion or more worldwide. AbbVie s projections are subject to risks and uncertainties. The actual market opportunity may vary and there is no guarantee what portion, if any, of the resulting market opportunity will be captured by an ABT-450-containing regimen, assuming that AbbVie obtains approval of such a regimen. One or more Phase 3 trials containing ABT-450/r could take longer than anticipated to complete or could have unexpected results, the FDA could find that the results of these trials are not adequate to support marketing approval, the FDA could require additional clinical trials as a condition for approval, or other HCV products could come to market sooner or achieve greater market acceptance than any for which AbbVie ultimately obtains approval.

Clinical Development

Phase 1. An Investigational New Drug Application, or IND, was filed for ABT-450 in December 2008 and clinical testing began in early 2009. ABT-450 was evaluated in a Phase 1a single ascending dose trial in doses ranging from 25 mg to 900 mg, with and without ritonavir. Data from this trial showed that ritonavir co-administration significantly

boosted the ABT-450 plasma concentrations. ABT-450 is being developed with low

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dose ritonavir to enhance exposure and allow once-daily dosing of ABT-450. A 14-day multiple dose study showed that ABT-450/r was well tolerated and demonstrated pharmacokinetics consistent with once-daily dosing.

Phase 2. In the first quarter of 2010, we and AbbVie announced the advancement of ABT-450/r into Phase 2 clinical trials. The objective of the initial Phase 2 study was to assess the safety, tolerability, pharmacokinetics and antiviral activity of multiple dose strengths of ABT-450/r in treatment-naïve adults (*i.e.*, those who have not previously received treatment for HCV) infected with HCV genotype 1. These initial studies with ABT-450/r paved the way for additional Phase 2a and 2b combination studies that use interferon-free regimens. The Pilot and Co-Pilot trials, which were initiated in late 2010 and early 2011, respectively, included combination trials of ABT-450/r with one or the other of two of AbbVie s non-nucleoside polymerase inhibitors. The Aviator study, which was initiated in 2011, was a trial of ABT-450/r and various combinations of two or three of the following: one of AbbVie s non-nucleoside polymerase inhibitors, one of its NS5A inhibitors and ribavirin.

All of the Phase 2 combination regimens tested by AbbVie were interferon-free, with a significantly shorter treatment duration (12 weeks) and a simpler treatment paradigm compared to the currently approved protease inhibitor regimens for genotype 1, all of which include weekly injections of interferon, and some of which require daily oral doses of ribavirin for 24 to 48 weeks.

AbbVie Aviator Study. The Aviator study consisted of HCV genotype 1 non-cirrhotic patients enrolled in an open-label trial of a 12-week interferon-free regimen consisting of three DAAs, with and without ribavirin. One combination in the study consisted of ABT-450/r once daily, plus ABT-267 (AbbVie s NS5A inhibitor), plus ABT-333 (AbbVie s non-nucleoside polymerase inhibitor) twice daily, plus weight-based ribavirin twice daily, which is the same combination now being tested in Phase 3 trials. As reported in an initial data abstract from the ongoing study, ABT-450/r was evaluated in treatment-naïve patients and treatment-experienced patients who had little or no decrease in HCV during prior treatment with the standard of care, known as null responders. Results from this ongoing trial demonstrated SVR_{12} in 99% of treatment-naïve HCV genotype 1-infected patients and in 93% of previous null responders (as compared with 47% SVR_{12} seen in the Co-Pilot study). The most common AEs were fatigue (28% and 27%) and headache (28% and 31%) for treatment-naïve and previous null responders, respectively. Initial results from the Aviator Phase 2 studies provided compelling support for the potential development of an interferon-free combination containing ABT-450 for treatment of HCV.

Other Studies: AbbVie has announced that it is conducting additional exploratory clinical studies to determine if a combination of ABT-450/r and ABT-267 dosed once daily can provide high cure rates in specific HCV populations, including a Phase 2 study, known as PEARL-I, in genotype 4-, 1a- and 1b-infected patients and a study in Japan in genotype 1b- and 2-infected patients. Preliminary results announced in November 2013 from the PEARL-I study demonstrated SVR_{12} rates of 95% (40/42) in HCV genotype1b, treatment-naïve patients and 90% (36/40) among prior null responders.

Phase 3. In November 2013, AbbVie announced preliminary results of its SAPPHIRE-I trial, the first of six Phase 3 trials for an all-oral, interferon-free, ABT-450-containing regimen for treating genotype 1-infected patients. Results of SAPPHIRE-I, SAPPHIRE-II and of the other four Phase 3 trials are expected to be part of the initial registration package designed for a total of at least 2,200 patients using a combination of the same three DAAs, including ABT-450/r, one of AbbVie s non-nucleoside polymerase inhibitors and one of AbbVie s NS5A inhibitors, plus ribavirin. The trials are designed to produce placebo-controlled results for treatment-naïve patients (SAPPHIRE-I) and treatment-experienced patients (SAPPHIRE-II), as well as separate results for genotype 1a (PEARL-IV) and 1b (PEARL-II and PEARL-III) patients, and patients with compensated cirrhosis (TURQUOISE-II). Three of these Phase 3 trials (PEARL-II, PEARL-III and PEARL-IV) are using the three-DAA combination, with and without ribavirin.

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Study Name	Genotype/(Number of) Patients	Treatment Regimen	Treatment Duration	SVR_{12}[d]
SAPPHIRE-I	GT1, treatment-naïve (631)	ABT-450/r[b] +ABT-267[c]	12 weeks	GT1a = 95% GT1b = 98%
		ABT-333 Ribavirin Placebo	12 weeks, then active treatment for 12 weeks	
SAPPHIRE-II	GT1, treatment-experienced (394)	ABT-450/r +ABT-267 ABT-333 Ribavirin	12 weeks	GT1a = 96% GT1b = 97%
		Placebo	12 weeks, then active treatment for 12 weeks	
PEARL-II	GT1b, treatment-experienced (210 [a])	ABT-450/r +ABT-267 ABT-333 Ribavirin	12 weeks	
		ABT-450/r +ABT-267 ABT-333	12 weeks	
PEARL-III	GT1b, treatment-naïve (400 [a])	ABT-450/r +ABT-267 ABT-333 Ribavirin	12 weeks	
		ABT-450/r +ABT-267 ABT-333	12 weeks	

		Placebo	
PEARL-IV	GT1a, treatment-naïve (300 [a])	ABT-450/r +ABT-267	12 weeks
		ABT-333	
		Ribavirin	
		ABT-450/r +ABT-267	12 weeks
		ABT-333	
		Placebo	
TURQUOISE-II	GT1, treatment-naïve and treatment-experienced (with compensated cirrhosis) (380 [a])	ABT-450/r +ABT-267	12 weeks
		ABT-333	
		Ribavirin	
		ABT-450/r +ABT-267	24 weeks
		ABT-333	
		Ribavirin	

[a] projected study population

[b] ABT-450/ritonavir

[c] ABT-267 is co-formulated with ABT-450/r, administered as two pills once daily

[d] SVR_{12} (Sustained Virological Response at 12 weeks after treatment completion): Continued HCV virus RNA below lower limit of measurable quantitation (LLOQ) 12 weeks after end of treatment (EOT)

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AbbVie SAPPHIRE-I Trial. The SAPPHIRE-I Phase 3 trial used a three-DAA, or 3D, regimen, consisting of boosted protease inhibitor ABT-450/ritonavir, NS5A inhibitor ABT-267, and non-nucleoside polymerase inhibitor ABT-333. The SAPPHIRE-I study used this 3D regimen plus ribavirin. Results from the 631-patient SAPPHIRE-I trial demonstrated a sustained virologic response at 12 weeks post-treatment (SVR_{12}) of 96% in treatment-naïve adult patients chronically infected with genotype 1 HCV. The majority of patients were genotype 1a, which is considered the more difficult-to-treat subtype. The SVR_{12} rates of genotype 1a and genotype 1b were 95% and 98%, respectively. These results were based on an intent-to-treat analysis and were achieved after 12 weeks of treatment. The rate of virologic relapse or breakthrough was low, occurring in 1.7 percent of patients receiving the 3D regimen. The treatment regimen was well tolerated, with an equal percentage of patients in the active and placebo arms (0.6 percent) discontinuing treatment due to adverse events.

AbbVie SAPPHIRE-II Trial. The SAPPHIRE-II Phase 3 trial used the same 3D regimen as in SAPPHIRE-I, including ribavirin. Results from the 394-patient SAPPHIRE-II trial demonstrated a sustained virologic response at 12 weeks post-treatment (SVR_{12}) in 96% of the treatment-experienced adult patients in the trial, all of whom were chronically infected with genotype 1 HCV and had previously failed pegylated interferon and ribavirin treatment. The majority of patients were genotype 1a, which is considered the more difficult-to-treat subtype and approximately 49% of the patients were prior null responders, namely patients defined as not achieving a significant reduction in the HCV virus during their prior treatment. The SVR_{12} rates of genotype 1a and genotype 1b were 96% and 97%, respectively. These results were based on an intent-to-treat analysis and were achieved after 12 weeks of treatment. The rate of virologic relapse or breakthrough was low, occurring in 2 percent of patients receiving the 3D regimen plus ribavirin. The treatment regimen was well tolerated, with 1 percent of patients in the active arm and no patients in the placebo arm discontinuing treatment due to adverse events.

Additional information about AbbVie s Phase 3 studies can be found on www.clinicaltrials.gov.

Next-Generation HCV Protease Inhibitor

AbbVie is also developing a next-generation protease inhibitor, ABT-493, discovered within the Enanta-AbbVie collaboration. AbbVie has announced that this protease inhibitor has demonstrated activity in preclinical *in vitro* testing against a broad range of HCV genotypes, including variants that have shown strong resistance to first generation protease inhibitors. AbbVie has also announced that this next-generation protease inhibitor was designed to enable once-daily dosing without ritonavir and to be co-formulated with AbbVie s next-generation NS5A inhibitor, ABT-530. AbbVie initiated a Phase 1 clinical trial of this next-generation protease inhibitor in November 2012, and is expected to begin dosing ABT-493 in HCV patients late in 2013.

EDP-239, an NS5A Inhibitor for HCV Infection

EDP-239, another DAA, is our lead NS5A inhibitor. The EDP-239 compound has demonstrated potent activity against major genotypes in the replicon assay, which is a common *in vitro* test for determining potency of an active compound in reducing HCV replication.

In addition, EDP-239 has additive to synergistic antiviral activity when used in combination with other anti-HCV therapeutics (DAA and HTA) in reducing HCV replication. Preclinical studies support excellent permeability and absorption potentials in humans. The compound has preferential penetration to the liver, which is the target site of infection, across all preclinical models tested. Human pharmacokinetic and pharmacodynamic modeling suggests a low, once-daily clinical dose for future testing. Novartis has completed Phase 1 trials with EDP-239 and has initiated proof-of-concept studies in HCV patients.

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We discovered EDP-239 internally at Enanta and entered into a collaboration with Novartis in February 2012, granting Novartis exclusive, worldwide rights to develop, manufacture and commercialize EDP-239. Novartis will fund all costs associated with the development, manufacture and commercialization of EDP-239 and related NS5A products. In addition, through August 2013, Novartis was responsible for funding our drug discovery efforts on additional selected compounds targeting NS5A. Under the agreement, we received an upfront payment of $34.4 million, and in January 2013 we received an $11.0 million milestone payment based on Novartis initiation of dosing in a Phase 1 clinical trial that includes EDP-239. We are eligible to receive up to $395 million of additional payments if Novartis achieves specified clinical, regulatory, and commercial milestones. We are also eligible to receive tiered royalties ranging on a blended basis from the low double digits up to the high teens on worldwide net sales of products, and retain co-detail rights, which would allow us to staff up to a specified percentage of the sales force for a designated product in the United States.

In addition to EDP-239, we have developed other NS5A inhibitors in the discovery stage under our Novartis collaboration, which may become candidates to be follow-on NS5A inhibitors.

Cyclophilin (Cyp) Inhibitors for HCV Infection

In anticipation of resistance arising to DAA HCV therapy that targets viral proteins, we have been developing an alternative HTA approach that targets the human host protein, cyclophilin, which is essential for replication of HCV.

Interruption of Viral Replication of HCV RNA by Cyclophilin Inhibitor

Abbreviation: CypA refers to cyclophilin A

We have demonstrated in replicon assays that multiple lead cyclophilin targeting inhibitors are potent inhibitors of HCV replication and are more potent than the clinical stage cyclophilin inhibitor alisporivir. Typically, cyclophilin inhibitors are based on the structures of cyclosporine A, which is known to be immunosuppressant with associated side effects that limit its clinical use. Based on our understanding of the structural elements of cyclosporine A that contribute to immunosuppressive activity, we have designed those elements out of our cyclophilin inhibitors and have confirmed a lack of *in vitro* immunosuppressive activity. We are advancing our lead candidates in preclinical studies and are continuing to generate and characterize a number of additional cyclophilin inhibitors in the discovery phase. We plan to select the most promising candidate and conduct IND-enabling studies in 2014.

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Nucleotide Polymerase Inhibitor Program for HCV Infection

We also have a program to develop inhibitors to HCV polymerase, which is another DAA mechanism considered to have a high barrier to resistance. Our researchers have identified a promising nucleotide lead series with significant antiviral potency *in vitro*. One of our lead compounds has demonstrated better *in vitro* potency than a reference clinical stage nucleotide inhibitor, GS-7977 (Sofosbuvir), under development by Gilead Sciences. We have an ongoing discovery effort in this inhibitor class and are considering a number of compounds for further development. We plan to select a candidate in 2014 that is suitable for advancement into preclinical studies.

Our MRSA Antibacterial Program

Background of MRSA Antibiotics

The past three decades have witnessed a dramatic change in the epidemiology of resistant Gram-positive bacterial infections all over the world. Families of common Gram-positive organisms include *Streptococcus*, or *Strep*, *Staphylococcus*, or *Staph*, and *Enterococcus*. Among the conditions associated with these pathogens are skin infections, bacteremia and endocarditis. One of these pathogens, known as methicillin-resistant *Staph aureus,* or MRSA, was principally identified when resistance was observed to methicillin, an early antibiotic used for *Staph aureus* and other bacterial infections. Increasingly, strains of MRSA have been identified that are also resistant to many other antibiotics.

The recognition and spread of MRSA, as well as *Enterococci* resistant to the antibiotic vancomycin, referred to as VRE, in the community and in healthcare facilities represents a major healthcare challenge. Widespread reports of emerging bacterial resistance to existing antibiotics emphasize the need for continued research and development of novel antimicrobials to address possible life-threatening infections caused by Gram-positive resistant pathogens. MRSA was responsible for approximately 94,000 reported infections that resulted in over 19,000 deaths in the United States in 2005, compared to approximately 16,000 deaths from AIDS.

In addition to the high potential for large hospital outbreaks, MRSA and Gram-positive resistance are moving out from hospitals into the community. During the past decade, rates of MRSA in the community have increased rapidly. Thus, an urgent need exists for the development of new antibiotics that will be effective against Gram-positive organisms that are resistant to current antibiotics in the macrolide class, such as clarithromycin (BiaxinTM), azithromycin (ZithromaxTM) and telithromycin (KetekTM), as well as VRE and *Enterococci* that are resistant to the oxazolidinone class of antibiotics, such as linezolid (Zyvox). In addition, there exists a significant need for agents that would allow step-down dosing, wherein MRSA patients being treated in a hospital setting with intravenous treatment could be sent home on the same drug to be taken orally.