Sarepta Therapeutics, Inc.
Form 10-K
March 03, 2014
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

x **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2013

Or

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 Or 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period from to

Commission file number: 001-14895

Sarepta Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**93-0797222**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification Number)**

215 First Street

Suite 415

Cambridge, MA **02142**
(Address of principal executive offices) **(Zip Code)**
Registrant s telephone number, including area code: (857) 242-3700

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

Tile of Each Class	**Name of Exchange on Which Registered**
Common Stock, $0.0001 par value	**The NASDAQ Stock Market LLC**

(The NASDAQ Global Select Market)
Securities registered pursuant to Section 12(g) of the Act:

None

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

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ¨ No 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 Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes x No ¨

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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	x	Accelerated filer	¨
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 Act). Yes ¨ No x

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of June 30, 2013 was approximately $1,225,412,000.

The number of outstanding shares of the registrant s common stock as of the close of business on February 24, 2014 was 37,775,169.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant has incorporated by reference into Part III of this Annual Report on Form 10-K, portions of its definitive Proxy Statement for its 2014 annual meeting to be filed with the Commission no later than 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

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Forward-Looking Information

This Annual Report on Form 10-K, including the Management s Discussion and Analysis of Financial Condition and Results of Operations section in Item 7, and other materials accompanying this Annual Report on Form 10-K contain forward-looking statements or incorporate by reference forward-looking statements. The statements contained in this Annual Report on Form 10-K that are not purely historical are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements are identified by words such as believe, anticipate, expect, intend, plan, will, may, seek and other similar expressions. You should read these statements carefully because they discuss future expectations, contain projections of future results of operations or financial condition, or state other forward-looking information. These statements relate to our future plans, objectives, expectations, intentions and financial performance and the assumptions that underlie these statements. These forward-looking statements include, but are not limited to:

our expectations regarding the development and clinical benefits of our product candidates;

the results of our research and development efforts and the efficacy of our PMO-based chemistries and other RNA-based technology;

our expectations regarding our ability to become a leading developer and marketer of RNA-based therapeutics;

the efficacy, potency and utility of our product candidates in the treatment of rare and infectious diseases, and their potential to treat a broad number of human diseases;

our expectations regarding the results of preclinical and clinical testing of our product candidates;

our expectations regarding the timing for initiating a pivotal clinical study, the design of a pivotal study and for filing a new drug application (NDA) for eteplirsen with the approval of the U.S. Food and Drug Administration (FDA);

our expectations regarding the timing, completion and receipt of results from our ongoing development programs;

the timing of and requirements the Company must comply with to receive any required approvals from the FDA or other regulatory approvals for our products outside of the United States;

the impact of regulations as well as regulatory decisions by the FDA and other regulatory agencies on the Company, the development of our product candidates and the Company s financial and contractual obligations;

our expectations regarding the markets for our products;

acceptance of our products, if introduced, in the marketplace;

the possible impact of competitive products, product development, manufacturing, commercialization and technological difficulties;

our expectations regarding partnering opportunities and other strategic transactions;

the extent of protection that our patents provide and our pending patent applications may provide, if patents issue from such applications, to our technologies and programs;

our plans to file additional patent applications to enhance and protect our existing intellectual property portfolio;

our ability to invalidate some or all of the claims covered by patents issued to competitors;

our estimates regarding our future revenues, research and development expenses, other expenses, payments to third parties and changes in staffing levels;

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our estimates regarding how long our currently available cash and cash equivalents will be sufficient to finance our operations and statements about our future capital needs;

our ability to increase the scale of our manufacturing to provide our product to patients in larger scale clinical trials or in potential commercial quantities and meet regulatory and company quality control requirements;

our ability to operate our business without infringing the intellectual property rights of others;

our expectations about funding from government and other sources; and

other factors set forth below under the heading Risk Factors .

All forward-looking statements are based on information available to us on the date of this Annual Report on Form 10-K and we will not update any of the forward-looking statements after the date of this Annual Report on Form 10-K, except as required by law. Our actual results could differ materially from those discussed in this Annual Report on Form 10-K. The forward-looking statements contained in this Annual Report on Form 10-K, and other written and oral forward-looking statements made by us from time to time, are subject to certain risks and uncertainties that could cause actual results to differ materially from those anticipated in the forward-looking statements. Factors that might cause such a difference include, but are not limited to, those discussed in Part I, Item 1 Business and Item 1A Risk Factors of this Annual Report on Form 10-K.

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PART I

Item 1. Business.

Overview

We are a biopharmaceutical company focused on the discovery and development of unique RNA-based therapeutics for the treatment of rare and infectious diseases. Applying our proprietary, highly-differentiated and innovative platform technologies, we are able to target a broad range of diseases and disorders through distinct RNA-based mechanisms of action. We are primarily focused on rapidly advancing the development of our potentially disease-modifying Duchenne muscular dystrophy (DMD) drug candidates, including our lead product candidate, eteplirsen. We are also focused on developing therapeutics for the treatment of infectious diseases, including our lead infectious disease program aimed at the development of a drug candidate for the Marburg hemorrhagic fever virus. By building our infectious disease programs which are primarily funded and supported by the U.S. Department of Defense (DoD), and leveraging our highly-differentiated, proprietary technology platforms, we are seeking to further develop our research and development competencies and identify additional product candidates.

Our highly-differentiated RNA-based technologies work at the most fundamental level of biology and potentially could have a meaningful impact across a broad range of human diseases and disorders. Our lead program focuses on the development of disease-modifying therapeutic candidates for DMD, a rare genetic muscle-wasting disease caused by the absence of dystrophin, a protein necessary for muscle function. Currently, there are no approved disease-modifying therapies for DMD. Eteplirsen is our lead therapeutic candidate for DMD. If we are successful in our development efforts, eteplirsen will address a severe unmet medical need. Last year, we completed a U.S.-based Phase IIb clinical trial for eteplirsen that was initiated in August 2011. Following completion of this study in early 2012, we initiated an open label extension study with the same participants from the original Phase IIb placebo-controlled trial. We are working with the FDA to initiate a pivotal clinical study in 2014 and to determine the possibilities under expedited regulatory programs for eteplirsen.

We are also leveraging the capabilities of our RNA-based technology platforms to develop therapeutics for the treatment of infectious diseases. The DoD has provided significant financial support in the past for the development of therapeutics against Ebola, Marburg, Dengue and influenza viruses. We have attracted DoD s support based in part on our ability to rapidly respond to pathogenic threats by quickly identifying, manufacturing and evaluating novel therapeutic candidates.

The basis for our novel RNA-based therapeutics is our phosphorodiamidate-linked morpholino oligomer, or PMO, chemistries. Unlike other RNA-based therapeutics, which are often used to down-regulate gene expression, our technologies can be used to selectively up-regulate or down-regulate the production of a target protein, or direct the expression of novel proteins involved in human diseases and disorders. Further, we believe the charge-neutral nature of our PMO-based molecules may have the potential to reduce off-target effects, such as immune stimulatory effects often seen in alternative RNA-based technologies. We believe that our highly-differentiated, novel, proprietary and innovative RNA-based technology platforms, based on charge neutral morpholino oligomers, may represent a significant improvement over traditional RNA-based technologies.

On July 12, 2012, our common stock began trading on The NASDAQ Global Market on a split-adjusted basis following a one-for-six reverse stock split that was effective on July 11, 2012. As of January 2, 2014, our Common Stock is quoted on The NASDAQ Global Select Market. Unless otherwise noted, all share amounts, share prices and exercise prices included throughout this report give effect to the July 2012 one-for-six reverse stock split.

Since our inception in 1980, we have incurred losses of $543.2 million, substantially all of which resulted from expenditures related to research and development, general and administrative charges and losses on changes in warrant valuation partially offset by revenue generated from research contracts with and grants primarily from

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the DoD. As of December 31, 2013, we have completed all of our contracts with the DoD except for the July 2010 contract for the development of therapeutics against the Marburg virus. The period of performance for our August 2012 contract with the DoD concluded in the third quarter of 2013. In November 2012 we also entered into a consortium agreement with various parties that received an E.U. Health Innovation-1 2012 Collaborative research grant to support development of an exon 53-skipping therapeutic, based on our PMO chemistry, for which minimal revenues have been earned to date. We have not generated any material revenue from product sales to date, and there can be no assurance that revenues from product sales will be achieved. Moreover, even if we do achieve revenue from product sales, we are likely to continue to incur operating losses in the near term.

As of December 31, 2013, we had $264.9 million of cash, cash equivalents and invested cash, comprised of $257.0 million of cash and cash equivalents and $7.9 million of restricted investments, which we believe, taking into consideration our outstanding warrants, is sufficient to fund our current operational plan for the next twelve months. Should our funding from the DoD cease or be delayed, we would likely curtail certain infectious disease research and development efforts unless additional funding was obtained. We are also likely to pursue additional cash resources through public or private financings, seeking additional government contracts, and by establishing collaborations or licensing our technologies to other companies.

We were originally incorporated in the State of Oregon on July 22, 1980 and on June 6, 2013, we reincorporated in the State of Delaware. Our principal executive offices are located at 215 First Street, Suite 415, Cambridge, MA 02142 and our telephone number is (857) 242-3700. Our common stock trades on The NASDAQ Global Select Market under the symbol SRPT.

Where You Can Find Additional Information

We make available free of charge through our corporate website, www.sarepta.com, our annual reports, quarterly reports, current reports, proxy statements and all amendments to those reports as soon as reasonably practicable after such material is electronically filed or furnished with the SEC. These reports may also be obtained without charge by submitting a written request via mail to Investor Relations, Sarepta Therapeutics, Inc., 215 First Street, Suite 415, Cambridge, MA 02142 or by e-mail to investorrelations@sarepta.com. Our Internet website and the information contained therein or incorporated therein are not intended to be incorporated into this Annual Report on Form 10-K. In addition, the public may read and copy any materials we file or furnish with the Securities and Exchange Commission, or the SEC, at the SEC s Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549 or may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. Moreover, the SEC maintains an Internet site that contains reports, proxy and information statements, and other information regarding reports that we file or furnish electronically with the SEC at www.sec.gov.

Objectives and Business Strategy

We believe that our highly-differentiated, proprietary RNA-based technology platforms can be used to develop novel pharmaceutical products to treat a broad range of diseases and address key unmet medical needs. We intend to leverage our RNA-based technology platforms, organizational capabilities and resources to become a leading developer and marketer of RNA-based therapeutics, including for the treatment of rare and infectious diseases, with a diversified portfolio of product candidates and approved products. In pursuit of this objective, we intend to engage in the following activities:

- advancing the development of eteplirsen and our other drug candidates for the treatment of DMD to realize the product opportunities of such candidates and provide significant clinical benefits;

- successfully executing our government funded infectious disease therapeutic programs and building on and leveraging our experience with such programs to further develop our research and development capabilities and garner additional external funding; and

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leveraging our highly-differentiated, proprietary RNA-based technology platforms to identify product candidates in additional therapeutic areas and explore various strategic opportunities, including potential partnering, licensing or collaboration arrangements with industry partners.

Development Programs

Our currently active RNA-based drug programs are being clinically evaluated for the treatment of DMD and have also demonstrated promising antiviral activity in infectious diseases such as Marburg and H1N1 influenza in certain animal models. Our active lead product candidates are at various stages of development summarized below.

Program	Indication	Mechanism	Chemistry	Development Stage	Developer / Collaborator
Eteplirsen	DMD (exon 51)	Exon Skipping	PMO	Phase IIb*	Proprietary
AVI-7288	Marburg virus	Translation Suppression	PMO*plus*®	Phase I	Proprietary/U.S. Government
AVI-7100	H1N1 influenza virus	Translation Suppression	PMO*plus*®	Phase I	Proprietary/U.S. Government

* We announced results from our Phase IIb clinical study in eteplirsen in April 2012 and are currently conducting a long-term open label extension phase to this clinical trial.

For purposes of the table above, Development Stage indicates the most advanced stage of development that has been completed or is ongoing. In the table above, under the heading Development Stage, Phase IIb indicates clinical safety and efficacy testing in a small patient population, and Phase I indicates initial clinical safety testing in healthy volunteers or a limited patient population, or trials directed toward understanding the mechanisms or metabolism of the drug.

Duchenne Muscular Dystrophy Program

Duchenne muscular dystrophy, or DMD, is one of the most common fatal genetic disorders affecting children (primarily boys) around the world. DMD is a devastating and incurable muscle-wasting disease associated with specific mutations in the gene that codes for dystrophin, a protein that plays a key structural role in muscle fiber function. The absence of dystrophin in muscle cells leads to significant cell damage and ultimately causes muscle cell death and fibrotic replacement. The disease occurs in approximately one in every 3,500 male births worldwide. Females are rarely affected by the disorder. Initial symptoms, which usually appear between the ages of three and five, include progressive muscle weakness of the legs and pelvis, manifested as difficulty walking, running or climbing stairs, which eventually spreads to the arms, neck, and other areas. By age ten, braces may be required for walking, and many individuals require full-time use of a wheelchair before age 12. Eventually muscular degeneration progresses to the point of complete paralysis. Disease progression is also typically associated with respiratory muscle dysfunction and a corresponding difficulty in breathing, which may require ventilatory support, and cardiac muscle dysfunction which may lead to heart failure. DMD is ultimately fatal and death usually occurs before the age of 30. There is currently no approved disease modifying treatment or cure for DMD.

The yearly cost of care for individuals with DMD is high and increases with disease progression. Although DMD is a rare disease, we believe it represents a substantial product opportunity due to the severity and inexorable progression of the symptoms.

Our lead program is designed to address specific gene mutations that result in DMD by forcing the genetic machinery to skip over an adjacent contiguous piece (*i.e*, one or more exons) of RNA and, thus, restore the ability of the cell to express a new, truncated but functional, dystrophin protein. We believe that the expression of

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this truncated dystrophin protein may restore, prevent or slow deterioration of muscle function, as exemplified by the less severe muscular dystrophy phenotype, called Becker muscular dystrophy.

Eteplirsen. Eteplirsen is an antisense PMO-based therapeutic in clinical development for the treatment of individuals with DMD who have an error in the gene coding for dystrophin that can be treated by skipping exon 51. Eteplirsen targets the most frequent series of mutations that cause DMD. Eteplirsen has been granted orphan drug designation in the United States and European Union. In 2007, the FDA granted eteplirsen fast track status and we are continuing to discuss with FDA the possibility of expedited regulatory programs for eteplirsen based on the Phase IIb data. See Government Regulation for additional information.

In October 2010, we announced results from a clinical trial of eteplirsen, AVI Study 28. Data from this study were published in *The Lancet* in July 2011. AVI Study 28 was a Phase Ib/IIa open label, dose-ranging, clinical trial assessing the safety, tolerability, pharmacokinetics and exploratory efficacy of eteplirsen in ambulatory individuals with DMD. Participants in AVI Study 28 were between the ages of five and 15 with errors in the gene coding for dystrophin, which were amenable to treatment by skipping exon 51. Participants were dosed once per week for 12 weeks. A total of 19 participants were enrolled and these individuals were assigned to one of six dose cohorts of 0.5, 1.0, 2.0, 4.0, 10.0 or 20.0 mg/kg. Of the 19 participants enrolled, 18 received at least ten of the 12 doses planned in this trial. After completion of dosing, participants were followed for an additional 14 weeks. Muscle biopsies were taken before treatment and 17 participants had a second biopsy at week 14, two weeks after administration of the final dose. The primary objective of the trial was to assess the safety of eteplirsen at these doses over the 26-week duration of the trial. Secondary trial objectives included assessment of plasma pharmacokinetics, urinary elimination and exploratory endpoints evaluating biological activity and clinical performance. This trial was conducted by investigators in the United Kingdom at the University College London Institute of Child Health / Great Ormond Street Hospital in London and at the Royal Victoria Infirmary in Newcastle-Upon-Tyne. In AVI Study 28, (i) eteplirsen induced exon 51 skipping in all cohorts and new dystrophin protein expression in cohort 3; (ii) eteplirsen was well-tolerated in all participants with no drug-related serious adverse events or severe adverse events, except that one participant exhibited deteriorating cardiac function, which was considered probably disease related; (iii) adverse events were mostly mild or moderate in intensity, not dose-related, and none were considered probably or definitely related to eteplirsen; and (iv) there was no detectable immune response to newly made dystrophin.

Based on the AVI 28 study results, we initiated a Phase IIb trial for eteplirsen in August 2011, AVI 4658-us-201, or Study 201, at Nationwide Children s Hospital in Columbus, Ohio and we announced the results from this study in April 2012. This was a randomized, double-blind, placebo-controlled study to assess the efficacy, safety, tolerability and pharmacokinetics of eteplirsen administered intravenously in two different doses over 24 weeks for the treatment of ambulant boys with DMD. Exploratory clinical measures of ambulation, muscle function and strength were also captured and evaluated during the course of the trial. Study 201 included 12 participants and muscle biopsies of all participants were performed prior to initiation of treatment. The 12 participants with a genotypically-confirmed appropriate genetic mutation were randomized into one of three treatment groups with four participants in each group. The first treatment group received a weekly intravenous administration of eteplirsen at a dose of 50.0 mg/kg. The second treatment group received a weekly intravenous administration of eteplirsen at a dose of 30.0 mg/kg. The third and final treatment group received a weekly administration of placebo. Participants receiving the 50.0 mg/kg dose received a second biopsy at 12 weeks after initiation of treatment, and participants receiving the 30.0 mg/kg dose received a second biopsy at 24 weeks after initiation of treatment. The results from Study 201 determined that treatment with eteplirsen met the primary efficacy endpoint in the study. Eteplirsen administered once weekly at 30mg/kg over 24 weeks resulted in a statistically significant ($p \leq 0.002$) increase in novel dystrophin (22.5% dystrophin-positive fibers as a percentage of normal) compared to no increase in the placebo group. In the study, a shorter duration of eteplirsen treatment, 12 weeks, did not show a significant increase in novel dystrophin (0.79% dystrophin-positive fibers as a percentage of normal; p-value NS), despite administration of the drug at a higher dose (50mg/kg once weekly). No significant improvements in clinical outcomes in the treated groups were observed compared to placebo.

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All participants in Study 201 were enrolled in an open-label extension study 4658-us-202, or Study 202, following the completion of Study 201 and all participants, including those from the placebo group in Study 201, are receiving either 30.0 mg/kg or 50.0 mg/kg for the duration of Study 202. The purpose of Study 202 is to evaluate the ongoing safety, efficacy and tolerability of eteplirsen. The primary efficacy endpoint was the change from baseline at week 48 in the percentage of dystrophin-positive fibers in muscle biopsy tissue as measured by immunohistochemistry. The primary clinical outcome measure was the change from baseline to week 48 on the six minute walk test, or the 6MWT. Study 202 is now in a long-term extension phase in which patients continue to be followed for safety and clinical outcomes approximately every 12 weeks through week 108 (which includes the original 28 weeks of Study 201).

On July 24, 2012, we announced interim results from Study 202 which indicated that treatment with eteplirsen over 36 weeks achieved a significant clinical benefit on the primary clinical outcome measure, the 6MWT, over a placebo/delayed treatment cohort. Eteplirsen administered once weekly at 50mg/kg over 36 weeks resulted in a 69.4 meter benefit compared to patients who received placebo for 24 weeks followed by 12 weeks of treatment with eteplirsen. In the predefined prospective analysis of the study s intent-to-treat population on the primary clinical outcome measure, the change in 6MWT distance from baseline, eteplirsen-treated patients who received 50mg/kg of the drug weekly demonstrated a decline of 8.7 meters in distance walked from baseline (mean=396.0 meters), while patients who received placebo/delayed-eteplirsen treatment for 36 weeks showed a decline of 78.0 meters from baseline (mean=394.5 meters), for a statistically significant treatment benefit of 69.4 meters over 36 weeks ($p \leq 0.019$). There was no statistically significant difference in the 6MWT between the cohort of patients who received 30mg/kg weekly of eteplirsen and the placebo/delayed treatment cohort. The safety profile of eteplirsen was evaluated across all subjects through the 36 weeks eteplirsen was administered and there were no treatment-related adverse events, no serious adverse events and no discontinuations. Furthermore, no treatment-related changes were detected on any safety laboratory parameters, including several biomarkers for renal function.

On October 3, 2012, we announced 48-week results from Study 202 which indicated that treatment with eteplirsen met the predefined primary efficacy endpoint, increase in novel dystrophin, and achieved a significant clinical benefit on the predefined primary clinical outcome measure, the 6MWT, over the placebo/delayed treatment cohort. Eteplirsen administered once weekly at either 30 mg/kg or 50 mg/kg for 48 weeks (n=8) resulted in a statistically significant increase ($p<0.001$) in dystrophin-positive fibers to 47.0% of normal. The placebo/delayed treatment cohort, which had received 24 weeks of eteplirsen at either 30 mg/kg or 50 mg/kg following 24 weeks of placebo (n=4), also showed a statistically significant increase in dystrophin-positive fibers to 38.3% of normal ($p<0.009$).

In the predefined analysis of the study s intent-to-treat population on the primary clinical outcome measure, the change in 6MWT distance from baseline at week 48, eteplirsen-treated patients who received 50 mg/kg of the drug weekly (n=4) demonstrated an increase of 21.0 meters in distance walked from baseline (mean=396.0 meters), while patients who received placebo/delayed-eteplirsen treatment (n=4) showed a decline of 68.4 meters from baseline (mean=394.5 meters), for a statistically significant treatment benefit of 89.4 meters over 48 weeks ($p=0.016$, using analysis of covariance for ranked data using mixed model repeated measures). There was no statistically significant difference between the cohort of patients who received 30 mg/kg weekly of eteplirsen and the placebo/delayed treatment cohort. The safety profile of eteplirsen was evaluated across all subjects through 48 weeks and there were no treatment-related adverse events, no serious adverse events, and no discontinuations. Furthermore, no clinically significant treatment-related changes were detected on any safety laboratory parameters, including several biomarkers for renal function.

On December 7, 2012, we announced updated data from Study 202 which showed patients treated with eteplirsen and evaluable on ambulatory measures (modified Intent to Treat population, or the mITT population) for 62 weeks maintained a statistically significant clinical benefit on the primary clinical outcome measure, the 6MWT, compared to patients who received placebo for 24 weeks followed by 38 weeks of eteplirsen treatment. In the mITT population, which includes evaluable patients from both the 30mg/kg and 50mg/kg dose cohorts,

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patients treated with eteplirsen for 62 weeks demonstrated a statistically significant benefit ($p \leq 0.007$) of 62 meters over the placebo/delayed-treatment cohort using a mixed-model repeated measure statistical test. The mITT population utilized for the 62 week analysis consisted of 10 of the enrolled 12 patients (4 eteplirsen-treated patients receiving 50 mg/kg weekly, 2 eteplirsen-treated patients receiving 30 mg/kg weekly, and 4 placebo/delayed-treatment patients), and excluded two patients who showed signs of rapid disease progression and lost ambulation by week 24. The eteplirsen treatment cohort (n=6) continued to show disease stabilization with less than a 5% decline in walking distance on the 6MWT from baseline. The placebo/delayed-treatment cohort (n=4) also demonstrated stability in walking distance from week 36 through week 62 with a less than 10 meter change over this timeframe, the period in which dystrophin was likely produced, with confirmation of significant dystrophin levels at week 48 through analysis of muscle biopsies in these patients.

The safety profile of eteplirsen was evaluated across all patients through week 62 and there were no clinically significant treatment-related adverse events, no serious adverse events, and no discontinuations. One patient had a laboratory treatment-related adverse event, a transient elevation of urine protein on a urine dipstick test, however this elevation was not observed on a 24-hour urine protein measurement and resulted in no clinical symptoms or interruption of treatment. This patient did not show elevations of the specific renal markers of cystatin C or KIM-1. Across both the treatment and placebo/delayed treatment cohorts there is evidence of continued stabilization on pulmonary function tests, echocardiogram, muscle strength and clinical laboratory tests over the 62 weeks.

Results from the mITT population, which combines the evaluable eteplirsen-treated patients across the 30mg/kg and 50mg/kg cohorts, have been previously reported and will be used as the primary assessment of ambulatory clinical measures for the remainder of Study 202. Given there was no significant difference between the 30 mg/kg and 50 mg/kg arms on the production of dystrophin through 48 weeks, we believe this mITT population is the most appropriate to assess dystrophin production and its potential predictive benefits on ambulatory clinical outcomes, such as the 6MWT.

On April 5, 2013, we announced that, after 74 weeks, patients in the 30 mg/kg and 50 mg/kg dose cohorts in the mITT population (n=6) showed a statistically significant treatment benefit of 65.2 meters ($p \leq 0.004$) when compared to the placebo/delayed-treatment cohort (n=4). The eteplirsen-treated patients in the mITT population demonstrated less than a 5 percent decline (13.4 meters) from baseline in walking ability. After experiencing a substantial decline earlier in the study, the placebo/delayed-treatment cohort also demonstrated stabilization in walking ability from week 36 through 74, the period in which meaningful levels of dystrophin were likely produced, with a less than 10 meter decline over this timeframe. Through 74 weeks, eteplirsen was well tolerated and there were no clinically significant treatment-related adverse events, serious adverse events, hospitalizations or discontinuations. As previously reported at 62 weeks, one patient had a transient elevation of urine protein on a laboratory urine dipstick test, which resolved and resulted in no clinical symptoms. The patient continued treatment without interruption and remained free of proteinuria through week 74. Across both the eteplirsen (mITT) and placebo/delayed-treatment cohorts, there was evidence of continued stabilization on clinical laboratory tests, echocardiogram, pulmonary function tests and muscle strength through 74 weeks of participating in Study 202.

On June 19, 2013, we announced that after 84 weeks, patients in the 30 mg/kg and 50 mg/kg dose cohorts in the mITT population (n=6) showed a statistically significant treatment benefit of 46.4 meters ($p \leq 0.045$) when compared to the placebo/delayed-treatment cohort (n=4). The eteplirsen-treated patients in the mITT population demonstrated less than a 6 percent decline (20.5 meters) from baseline in walking ability. The placebo/delayed-treatment cohort also demonstrated stabilization in walking ability from Week 36 through 84, the period from which meaningful levels of dystrophin were likely produced, with an increase of 3.3 meters over this timeframe. These analyses were based on the maximum 6MWT score when the test was performed on two consecutive days. Through 84 weeks, eteplirsen was well tolerated and there were no clinically significant treatment-related adverse events, no serious adverse events, hospitalizations or discontinuations. One boy in the placebo/delayed-treatment cohort was not able to perform the 6MWT at the Week 84 clinic visit due to a physical injury unrelated

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to treatment, and therefore had no 6MWT data captured at the Week 84 time point. The boy has recovered from the injury, continues to be ambulatory and is expected to be evaluated on the 6MWT at future clinic visits. Across all patients in the eteplirsen and placebo/delayed-treatment cohorts, there was evidence of continued stabilization on clinical laboratory tests, echocardiograms, pulmonary function tests and measures of muscle strength through 84 weeks of participating in Study 202.

On September 26, 2013, we announced that after 96 weeks, patients in the 30 mg/kg and 50 mg/kg eteplirsen cohorts in the mITT population (n=6) experienced less than a 5 percent decline (17.5 meters) from baseline in walking ability. A statistically significant treatment benefit of 70.8 meters ($p \leq 0.001$) was observed for the mITT population compared with the placebo/delayed-treatment cohort (n=4). The placebo/delayed-treatment cohort also demonstrated stabilization in walking ability from Week 36 through 96, the period from which meaningful levels of dystrophin were likely produced, with a decline of 18.5 meters over this timeframe. These analyses were based on the maximum 6MWT score when the test was performed on two consecutive days. As previously reported, a boy in the placebo/delayed-treatment cohort was not able to perform the 6MWT at the Week 84 clinic visit due to a broken ankle assessed by the investigator as a treatment-unrelated adverse event. Although this boy received rehabilitation and was able to perform the 6MWT, his walking ability at the time of the test had not returned to the level observed prior to the injury, and this lower 6MWT distance contributed to the overall decline in the placebo/delayed-treatment cohort. The decline in walking distance observed in this cohort from Week 36 improves from a decline of 18.5 meters to a decline of 4.7 meters when this patient s 96-week test score is excluded from the analysis. Through 96 weeks, eteplirsen was well tolerated and there were no reported clinically significant treatment-related adverse events, no treatment-related serious adverse events, hospitalizations or discontinuations. Across patients in the eteplirsen and placebo/delayed-treatment cohorts, there is evidence of continued stabilization on clinical laboratory tests, echocardiograms, pulmonary function tests and measures of muscle strength through 84 weeks of participating in Study 202.

On January 15, 2014, we announced that at 120 weeks, patients in the 30 mg/kg and 50 mg/kg eteplirsen cohorts who were able to perform the 6MWT (modified Intent-to-Treat or mITT population; n=6) experienced a decline of 13.9 meters, or less than 5 percent, from baseline in walking ability. A statistically significant treatment benefit of 64.9 meters ($p \leq 0.006$) was observed for the mITT population compared with the placebo/delayed-treatment cohort (n=4). The placebo/delayed-treatment cohort also demonstrated stabilization in walking ability for more than 1.5 years, from Week 36 through 120, the period from which meaningful levels of dystrophin were likely produced, with a decline of 9.5 meters over this timeframe. These analyses were based on the maximum 6MWT score when the test was performed on two consecutive days. In addition, on February 5, 2014, we announced that results through more than two years of treatment showed stable pulmonary function in the Intent-to-Treat (ITT) study population (N=12). Through 120 weeks, eteplirsen was well tolerated and there were no reported clinically significant treatment-related adverse events and no treatment-related serious adverse events. In addition, there were no treatment-related hospitalizations or discontinuations.

We will continue to have discussions with the FDA during the first quarter of 2014 regarding the design of the pivotal study, the clinical results from our Phase IIb study of eteplirsen and the possibility of expedited regulatory programs for eteplirsen based on the Phase IIb data. Based on feedback from these meetings, we will make a determination regarding the most appropriate regulatory path for pursuing regulatory approval of eteplirsen. Any such determination will be further informed by subsequent meetings with the FDA. Regardless of the approval process and path ultimately pursued, we anticipate initiating a pivotal clinical study for eteplirsen and commencing dosing during the second or third quarter of 2014.

Pan-Exon Strategy. In addition to our lead product candidate, eteplirsen, we are pursuing development of additional exon-skipping drugs, to support our broad-based development program for the treatment of DMD. For example, as of December 31, 2013, we have pre-clinical studies under way for exon 45-skipping and exon 53-skipping therapeutics, a lead sequence identified for an exon-50 skipping therapeutic and lead sequence selection under way for exon 44, exon 52, exon 55 and exon 8-skipping therapeutics.

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To support certain activities to enable an Investigational New Drug, or IND, for an exon 45-skipping therapeutic, we are collaborating with Children s National Medical Center in Washington, D.C. and the Carolinas Medical Center (in Charlotte, N.C.). This collaboration is funded primarily through two grants, one from DoD s Congressionally Directed Medical Research Program to Children s National Medical Center and the other from the National Institute of Neurological Disorders and Stroke to the Carolinas Medical Center. This funding is intended to pursue the most promising treatments for DMD. The collaboration will support a series of Good Laboratory Practice, or GLP, toxicology studies for an exon 45-skipping drug candidate based on our PMO chemistry.

To support certain clinical proof of concept studies and IND-enabling activities for an exon 53-skipping therapeutic, we announced in November 2012 that we are collaborating with University College London s scientist, Professor Francesco Muntoni, M.D., the Dubowitz Neuromuscular Centre, the Institute of Child Health and other scientists from the European Union and the United States. In connection with this collaboration, the consortium received an E.U. Health Innovation-1 2012 Collaborative research grant to support development of an exon 53-skipping therapeutic, based on our PMO chemistry. Targeting exon 53 with this technology will potentially address one of the most prevalent sets of mutations in DMD that are amenable to exon-skipping (deletion of exons 42-52, 45-52, 47-52, 48-52, 49-52, 50-52, or 52) by potentially restoring the cellular machinery s ability to produce a functional dystrophin protein.

To support certain IND-enabling activities for an exon 50-skipping therapeutic, we entered into a Cooperative Research and Development Agreement, or CRADA, in August 2012 with the National Institutes of Health, or NIH, which was anticipated to be supported through in-kind research conducted either by the Therapeutics for Rare and Neglected Diseases program or by contract research organizations. We and NIH mutually agreed to terminate the CRADA in February 2013 and we are now developing exon 50 utilizing our own research and development capabilities. We do not anticipate any significant changes in IND filing timelines due to the termination.

These collaborations and our DMD program, which includes eteplirsen, are part of our larger pan-exon strategy for the development of drug candidates to address the most prevalent exon deletions in the DMD population. Because the majority of DMD patients have exon deletions that cluster together, a small number of exon-skipping therapies will potentially be disease-modifying for a relatively large percentage of DMD patients. Approximately 75-80% of the total DMD population is potentially treatable with exon-skipping therapeutics. According to an article by Aartsma-Rus et. al published in 2009 in the Human Genome Variation Society Journal, of the exon skipping amenable population, exon 51 skipping is applicable to the largest sub-group, equal to approximately 13%. Skipping of exons 50, 45, 44, 52, 55 and 8 is applicable to approximately 4%, 8%, 6%, 4%, 2% and 2%, respectively.

Infectious Disease Programs

With the financial support of the U.S. government, we are currently implementing our RNA-based technology platforms in our infectious disease programs for the development of therapeutics to treat infectious diseases, such as Marburg and influenza. In the past, DoD has provided significant financial support for our development of therapeutics designed to treat Ebola, Marburg and influenza viruses. We have also entered into an agreement with the National Institute of Allergy and Infectious Diseases, or NIAID, part of NIH, under which NIAID is providing clinical support for the development of our therapeutic candidate for the treatment of influenza.

Our current arrangement with DoD supports development of our Marburg drug candidate, AVI-7288, including activities necessary to obtain approval of an NDA by the FDA, if DoD exercises all of its options under the arrangement. On August 29, 2012, we entered into an additional agreement with DoD related to the Marburg virus to evaluate the feasibility of an intramuscular route of administration using AVI-7288 and completed the performance of our obligations under this agreement in the third quarter of 2013. Under a separate arrangement,

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DoD similarly provided funding to advance the development of our H1N1 influenza drug candidate, AVI-7100, through an IND application with the FDA and to preclinically evaluate its therapeutic potential against H5N1 (avian flu), Tamiflu® resistant H1N1 (pandemic flu) and H3N2 (seasonal flu) which concluded in 2011. In December 2012, we entered into an agreement with NIAID to support further development of AVI-7100. Under the agreement, NIAID researchers are allowed to proceed with a Phase I, study to assess the safety, tolerability and pharmacokinetics of single and multiple doses of AVI-7100 in healthy volunteers. Per the terms of the agreement, we provided AVI-7100 to NIAID and in return, we will have the right to use the data from this clinical study to support future development of AVI-7100.

Without continued government support of these programs we would likely significantly curtail our development efforts with respect to these programs. Future funding and support is subject to availability of budgeted funds from DoD and the Department of Health and Human Services, or DHHS, as government support for some of our infectious disease programs has previously been discontinued or not renewed due to government budget constraints. For example, our current arrangement with DoD initially provided for support of the development of our Ebola virus drug candidate; however, on October 2, 2012, the Company received notice from DoD that the Ebola portion of the arrangement was terminated for the convenience of the government due to funding constraints. The Company previously received a stop-work order for the Ebola portion of the arrangement with DoD which was in effect from August 2, 2012 through the termination on October 2, 2012. The termination only applies to the Ebola portion of the arrangement with DoD and the Marburg portion remains actively in development under the DoD arrangement. Additionally, the period of performance for our June 2010 H1N1 influenza contract with DoD expired in June 2011. Additional research for this antiviral program is being conducted by NIAID as described elsewhere in this report.

In the periods presented in this report, substantially all of our revenues were derived from research and development contracts with and grants from the U.S. government. As of December 31, 2013, we had completed all of our contracts with the U.S. government except for the Marburg portion of the July 2010 agreement for the development of therapeutics against Marburg and Ebola viruses. For a more detailed description of our contracts with the U.S. government, see Management s Discussion and Analysis of Financial Condition and Results of Operations U.S. Government Contracts and Note 6 Government Contracts of the consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Hemorrhagic Fever Virus Programs. Our infectious disease therapeutic programs use our translation suppression technology and apply our proprietary PMO-*plus*® chemistry backbone, an advanced generation of our base PMO chemistry backbone that selectively introduces positive backbone charges to improve selective interaction between the drug and its target. Our translation suppressing technology is based on Translation Suppressing Oligomers which are PMO-based compounds that stop or suppress the translation of a specific protein by binding to their specific target sequence in mRNA. We are pursuing development and regulatory approval of our Marburg hemorrhagic fever virus product candidate under the FDA s Animal Rule. The Animal Rule provides that under certain circumstances, where it is unethical or not feasible to conduct human efficacy studies, the FDA may grant marketing approval based on adequate and well-controlled animal studies when the results of those studies establish that the drug or biological product is reasonably likely to produce clinical benefit in humans. Demonstration of the product s safety in humans is still required. See Government Regulation Animal Rule for additional information.

Marburg virus. AVI-7288 is designed for post-exposure prophylaxis after documented or suspected exposure to Marburg virus. Marburg hemorrhagic fever is a severe and often fatal disease in humans that was first recognized in 1967. It is caused by an RNA virus of the Filoviridae family and is understood to be endemic to Africa. The Marburg virus is classified as a Category A bioterrorism agent by the Centers for Disease Control and Prevention, or CDC, and was determined to be a material threat to national security by the Secretary of Homeland Security in 2006. Onset of the disease is often sudden and the symptoms include fever, chills, nausea, vomiting, chest pain and diarrhea. Increasingly severe symptoms may also include massive hemorrhaging and multiple organ dysfunction. There are currently no treatments for Marburg virus infection beyond supportive care

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and the mortality rate is very high. For Marburg virus infection, our lead product candidate is currently AVI-7288. Previously, our lead product candidate for Marburg virus infection was AVI-6003 which is a combination of AVI-7287 and AVI-7288; however, in February 2012, we announced that we received agreement from the FDA to remove AVI-7287 and we are now proceeding with a single oligomer approach, AVI-7288, given that efficacy in non-human primates has been demonstrated to be attributable to this single oligomer. During the 2012 fiscal year, we completed Phase I single ascending-dose studies in healthy volunteers with our candidates for the treatment of Ebola virus and Marburg virus and in July 2012, we announced results from a non-human primate study of the efficacy of AVI-7288. In September 2012, we announced that the FDA has granted fast track status for the development of AVI-7288 and our product candidate against Ebola, AVI-7537. In March 2013, with the support of DoD s Joint Project Manager Medical Countermeasure Systems, in non-human primate study, we completed an evaluation of the feasibility of in intramuscular route of administration using AVI-7288, including an evaluation of the tolerability, pharmacokinetics, and efficacy of intramuscular AVI-7288. The data showed that intramuscular administration of AVI-7288 resulted in survival rates up to 100 percent in treated subjects, similar to efficacy observed in previous studies that evaluated the drug when administered by intravenous injection. In May 2013, we initiated dosing of AVI-7288 in a Phase I multiple ascending dose study which we expect to complete in the first quarter of 2014. In February 2014, we announced positive safety results from a Phase I multiple ascending dose study of AVI-7288 in healthy volunteers.

Ebola virus. AVI-7537 is a single agent designed for post-exposure prophylaxis after documented or suspected exposure to the Ebola virus. The hemorrhagic fever caused by the Ebola virus is severe and often fatal in humans and there are currently no treatments for Ebola beyond supportive care. AVI-6002, a combination of AVI-7537 and AVI-7539, was previously our product candidate for the Ebola virus. However, based on our evaluation of the efficacy of AVI-7537 as a single agent versus a combination with AVI-7539 which demonstrated that efficacy could be attributed to the single oligomer AVI-7537, we transitioned our focus to this product candidate in 2012. Although we believe AVI-7537 has the potential to be a therapeutic option for the Ebola virus, we suspended our development efforts with respect to our Ebola program after the August 2012 stop-work order and subsequent termination for convenience by DoD of support for this program in 2012. The termination only applies to the Ebola portion of our arrangement with DoD and the Marburg portion remains in effect.

Development Status of Hemorrhagic Fever Virus Programs. Non-human primates infected with Marburg virus and treated with our precursor product candidate, AVI-6003, achieved 100% survival and primates infected with Ebola virus and treated with, AVI-6002, achieved 80% survival, in each case compared to universal lethality in both control groups. In addition to survival, primates treated with AVI-6002 and AVI-6003 have demonstrated decreases in levels of viremia, in harmful inflammatory indicators and in virus induced liver damage. Additional data have also demonstrated that the surviving animals were resistant to viral infection after subsequent injection with the virus.

During the 2012 fiscal year, we completed Phase I single ascending-dose studies in healthy adult volunteers with its drug candidates for the treatment of Ebola virus and Marburg virus demonstrating positive safety data for each therapeutic candidate. In February 2012, we announced positive safety results from all six cohorts of our Phase I single ascending dose trials of AVI-6002 and AVI-6003. For each group, safety, clinical laboratory and renal biomarker results through five days after treatment were reviewed by an independent Data and Safety Monitoring Board, or DSMB, which issued recommendations for both studies to progress as planned to multiple ascending dose studies after no safety concerns were identified. The Phase I single ascending dose trials were designed to characterize the safety, tolerability and pharmacokinetics of each therapeutic candidate in healthy adult volunteers. In the two studies, a total of 60 healthy human subjects (five per group) were enrolled into six sequential dose groups (0.01, 0.1, 1.0, 3.0, 6.0 or 9.0 mg/kg). Within each group, four subjects received the indicated dose of the therapeutic and one subject received placebo. Final, unblinded safety and pharmacokinetic results for all subjects were completed in 2012.

In July 2012, we announced that AVI-7288 demonstrated up to 100% survival in a non-human primate study exploring the drug s effect when the initiation of treatment is delayed to various time points post-infection.

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This study showed a high degree of survival between 83% and 100% in each of four post-exposure cohorts that received daily treatments with AVI-7288 beginning one-, 24-, 48-, or 96-hours after infection, compared to 0% survival in the placebo-treated control group.

In March 2013, we announced positive results from a non-human primate study of AVI-7288. The data showed that intramuscular administration of AVI-7288 resulted in survival rates up to 100 percent in treated subjects, similar to efficacy observed in previous studies that evaluated the drug when administered by intravenous injection.

We initiated a Phase I multiple ascending dose study in May 2013, designed to characterize the safety, tolerability and pharmacokinetics of multiple doses of AVI-7288 in healthy adult volunteers. The randomized, double-blind placebo-controlled study has been overseen by an independent DSMB, which reviewed the safety and clinical laboratory data after each dose cohort prior to enrolling the next higher dose cohort. The final cohort completed dosing in the first quarter of 2014. In February 2014, we announced positive safety results from a Phase I multiple ascending dose study of AVI-7288 in healthy volunteers. An independent DSMB reviewed the safety profile and recommended proceeding with further development of AVI-7288 at doses up to 16 mg/kg. Subject to approval under the existing contract with the Joint Project Manager Transformational Medical Technologies program (renamed Medical Countermeasure Systems in 2013) of the DoD (the JMP-MCS), further development of AVI-7288 is planned pursuant to FDA s Animal Efficacy Rule.

Influenza Program. Our infectious disease therapeutic programs are also focused on the development of our product candidates designed to treat pandemic influenza viruses. AVI-7100 is our lead product candidate for the treatment of influenza and employs our PMO-*plus*® technology. In December 2012, we entered into an agreement with NIAID which permits NIAID to conduct a Phase I single and multiple ascending dose study with AVI-7100. In June 2010, we were awarded a contract under DoD s Transformational Medical Technologies, or TMT, program (renamed Medical Technologies Systems in 2013), which funded our activities to develop AVI-7100 as a medical countermeasure against the pandemic H1N1 influenza virus. The period of performance for this contract ended in June 2011. See Management s Discussion and Analysis of Financial Condition and Results of Operations U.S. Government Contracts and Note 6 Government Contracts of the consolidated financial statements included elsewhere in this Annual Report on Form 10-K for additional information.

Symptoms of H1N1 influenza include fever, cough, runny nose, headache, chills and fatigue. Many people infected with H1N1 also have respiratory symptoms without a fever. Severe illness and deaths have also occurred. The CDC estimated that between April 2009 and April 2010 there were up to 89 million cases of H1N1 infection in the United States. The CDC also estimated that there were up to 403,000 H1N1-related hospitalizations in the United States during the same time period.

The TMT program established a contract with us to conduct a rapid response exercise against a real-world emerging threat like the pandemic H1N1 virus. The intent of the exercise was to demonstrate our capability to efficiently respond to a real-world emerging viral threat by rapidly designing and producing multiple therapeutic candidates and evaluating preclinical efficacy. Initially the exercise involved identifying target sequences against H1N1, designing several drug candidates utilizing proprietary derivatives of our PMO chemistry, and then manufacturing the candidates in sufficient quantity for limited preclinical testing. We successfully accomplished these steps in approximately one week, demonstrating our ability to rapidly respond to a real-world viral threat utilizing our RNA-based technology platforms.

Subsequently, we evaluated the preclinical activity of AVI-7100 and found that it showed a favorable safety profile in ferrets, rats and monkeys. In separate ferret studies, AVI-7100 demonstrated activity as a potentiator of Tamiflu® and activity towards preventing transmission of Tamiflu®-resistant H1N1.

In June 2011, we initiated dosing of AVI-7100 via intravenous infusion in single-ascending doses in up to 48 healthy adult volunteers. The first dose cohort in this Phase I, randomized, double-blind, placebo-controlled

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study was completed and received a favorable review from the DSMB to proceed to the next dose escalation. The period of performance under this DoD contract subsequently ended and, as a result, continued development was suspended until we entered into the clinical trial agreement with NIAID.

Under the December 2012 agreement with NIAID, NIAID researchers are allowed to proceed with a Phase I, double-blind, placebo-controlled, dose-escalating study to assess the safety, tolerability and pharmacokinetics of single and multiple doses of an intravenous formulation of AVI-7100 in healthy volunteers. Per the terms of the agreement, we provided AVI-7100 to NIAID and in return, we will have the right to use the data from this clinical study to support future development of AVI-7100.

Discovery Stage Program Overview

Our PMO-chemistries are highly-differentiated from other RNA technologies, including antisense, siRNA and RNAi. Unlike these technologies, which are often used for down-regulation of gene expression, ours can be used to selectively up-regulate or down-regulate the expression of proteins involved in human diseases and disorders, or direct the production of novel proteins with clinically relevant properties.

In addition to our pan-exon strategy for DMD, our preclinical research efforts are focused on the creation of product candidates for the treatment of other neuromuscular, infectious and rare diseases.

Chemistry Technology

Our core chemistry is based on phosphorodiamidate-linked morpholino oligomers, or PMOs, and this core chemistry has been safely dosed in over 400 patients. PMOs are synthetic molecules based on a fundamental redesign of the natural nucleic acid structure of DNA and RNA. PMOs bind to complementary sequences of RNA by standard Watson-Crick nucleic acid base-pairing and control gene expression by steric blockade of targeted RNA. Structurally, the key difference between PMOs and naturally occurring DNA and RNA is that while PMOs, like DNA and RNA, have nucleic acid bases, those bases are bound to synthetic morpholine rings instead of deoxyribose (in DNA) or ribose (in RNA) rings, and they are linked through phosphorodiamidate groups instead of phosphate groups. Replacement of anionic phosphates with the charge-neutral phosphorodiamidate groups eliminates ionization in the usual physiological pH range, thus PMOs in organisms or cells are uncharged molecules. Because of these modifications, PMOs are especially resistant to degradation by plasma and intracellular enzymes. Unlike some other RNA-based technologies, including siRNAs and other types of antisense, PMOs rely on steric blocking rather than cellular enzymatic activity for their biological effects. In this way, PMOs operate fundamentally differently from other well-known RNA-based technologies.

We have developed three new PMO-based chemistry platforms in addition to our original PMO-based technology. We believe that the novel, favorable characteristics intrinsic in these new platforms will allow for the development of drug candidates with superior delivery, specificity, therapeutic windows and drug-like properties.

PPMO. The first of these novel chemistries is based on peptide conjugated PMOs, or PPMOs, in which cellular uptake of the PMO component, as well as its potency and specificity of tissue targeting, may be significantly enhanced.

PMO-plus®. The second of these chemistries, PMO*plus*®, includes the addition of selectively introduced positive charges to the PMO backbone. We believe that while PMO-*plus*® has potentially broad therapeutic applications, it has thus far shown to be particularly effective in increasing the potency of PMO-based oligomers.

PMO-X . The third of these chemistries, PMO-X , involves novel, selective, and proprietary backbone chemistry modifications. We believe PMO-X may provide enhanced in vivo potency for our drug candidates, as well as greater flexibility in modulation of their tissue targeting, cellular delivery and uptake.

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We intend to continue to support our internal research and development efforts in order to advance our proprietary chemistries and to develop new analogues that may provide additional benefits in key characteristics of drug performance.

Mechanisms of Action

Humans have far fewer genes than the number of unique proteins expressed in the human proteome. The genetic information stored in human DNA is not contiguous. Short DNA stretches, called exons that code for fragments of the protein are separated by long non-coding pieces of DNA called introns. During processing of precursor or pre-mRNA, which is copied from the DNA template, introns are removed and exons spliced together to create the mature mRNA, from which a functional protein can be made. Pre-mRNA copied from a gene can be spliced through alternative paths, such that different exons are combined, creating multiple mRNAs and, hence, generate multiple proteins from a single gene.

Our PMO-based molecules are designed to sterically block the access of cellular machinery to pre-mRNA and mRNA without degrading the RNA. Through this selective targeting, two distinct biologic mechanisms of action can be initiated: (1) modulation of pre-mRNA splicing (also commonly described as splice switching, exon skipping or directed alternative splicing) and (2) inhibition of mRNA translation (also commonly described as translation suppression). Through these mechanisms, steric-blocking oligonucleotides can repair defective RNA, up or down-regulate the production of selected proteins, or produce novel or remodeled proteins.

Material Agreements

We believe that our RNA-based technology could be broadly applicable for the potential development of pharmaceutical products in many therapeutic areas. To further exploit our core technology, we have and may continue to enter into research, development or commercialization alliances with universities, hospitals, independent research centers, non-profit organizations and pharmaceutical and biotechnology companies for specific molecular targets or selected disease indications. We may also selectively pursue opportunities to access certain intellectual property rights that complement our internal portfolio through license agreements or other arrangements.

U.S. Department of Defense and DHHS Agreements

We currently have contracts with DoD and its agencies and DHHS and its agencies that fund and/or support our programs. For a more detailed description of our contracts with the U.S. government, see Management s Discussion and Analysis of Financial Condition and Results of Operations U.S. Government Contracts below and Note 6 Government Contracts of the consolidated financial statements included elsewhere in this Annual Report on Form 10-K. Our contracts with the government may be subject to renegotiation or termination at the election of the government. For a description of the risks we face relating to such rights of the government see Risk Factors Risks Relating to Our Business .

University of Western Australia

In November 2008, we entered into an exclusive license agreement with the University of Western Australia, or UWA, for certain patents and technical information relating to the use of certain antisense sequences for the treatment of DMD and in April 2013, we entered into an agreement with UWA under which this license agreement was amended and restated, referred to in this report as the Amended and Restated UWA License Agreement. The Amended and Restated UWA License Agreement grants us specific rights to the treatment of DMD by inducing the skipping of certain exons. Our lead clinical candidate, eteplirsen, falls under the scope of the license granted under the Amended and Restated UWA License Agreement. Any future drug candidates developed for the treatment of DMD by exon skipping may or may not fall under the scope of the Amended and Restated UWA License Agreement.

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Under the Amended and Restated UWA License Agreement, we are required to meet certain performance diligence obligations related to development and commercialization of products developed under the license. We believe we are currently in compliance with these obligations. In 2013, we made an initial upfront payment to UWA of $1.1 million upon execution of the Amended and Restated UWA License Agreement. We may be required to make additional payments to UWA of up to $6 million in the aggregate based on successful achievement of certain regulatory and commercialization-related milestones of eteplirsen and up to five additional product candidates and also may be required to pay royalties ranging from a fraction of a percent to the low single-digit percentages on net sales of products covered by issued patents licensed from UWA during the term of the Amended and Restated UWA License Agreement. We are not under any current obligation to make royalty payments to UWA until a product candidate is approved for commercial sale.

The terms of the Amended and Restated UWA License Agreement will expire on a country-by-country basis on the expiration date of the last to expire valid claim or patent within the patents licensed to us under this agreement or upon the earliest to occur of the following:

- failure by us or UWA to cure a breach or default of any material obligation we each have under the agreement after notice from the non-breaching party within the specified time periods;
- a mutual agreement to terminate the agreement;
- by UWA in the event a party passes a resolution to wind-up or if a receiver, administrator, trustee or person performing similar functions is appointed by a court or liquidator over any of our assets; or
- upon our notice to UWA that we no longer desire to commercialize products covered under the agreement.

Currently, the latest date on which an issued patent covered by our agreement with UWA expires is April 2026, however, pending patents could result in a later expiration date.

Strategic Alliances

Isis Ercole Agreement

In May 2003, Ercole Biotechnology, Inc., or Ercole, and Isis Pharmaceuticals, Inc., or Isis, entered into a collaboration and license agreement related to RNA splicing. Research collaboration activity defined in the agreement expired in 2006. In March 2008, we acquired all of the stock of Ercole in exchange for 5,811,721 shares of our common stock, which was valued at approximately $8.4 million, and the assumption of approximately $1.8 million in liabilities of Ercole. We also issued warrants to purchase our common stock (also classified as equity), which were valued at $437,000, in exchange for certain outstanding warrants issued by Ercole. In connection with the March 2008 acquisition, we assumed Ercole s obligations under the Isis agreement. This agreement contains several cross-licenses between the parties granting each party certain exclusive and nonexclusive rights under a selected set of the other parties patents and patent applications for the research, development, and commercialization of antisense therapeutics using RNA splicing with respect to certain gene targets.

Subject to the satisfaction of certain milestones triggering the obligation to make any such payments, we may be obligated to make milestone payments to Isis of up to $23.4 million in the aggregate for each product developed under a licensed patent under this agreement.

As of December 31, 2013, we have not made, and are not under any current obligation to make, any such milestone payments, as the conditions triggering any such milestone payment obligations have not been satisfied. The range of percentage royalty payments required to be made by us under the terms of this agreement is from a fraction of a percent to mid single-digit percentages. We believe that our DMD, Ebola, Marburg and influenza programs will not fall under the scope of this agreement and therefore will not be subject to milestone or royalty obligations under its provisions.

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Subject to the satisfaction of certain milestones triggering the obligation to make any such payments, Isis may be obligated to make milestone payments to us of up to $21.1 million in the aggregate for each product developed under a licensed patent under this agreement. As of December 31, 2013, Isis has not made, and is not under any current obligation to make, any such milestone payments, as the conditions triggering any such milestone payment obligations have not been satisfied. The percentage royalty payments required to be made by Isis under the terms of this agreement is a fraction of a percent. As to any product commercialized under the agreement, the agreement will terminate on the expiration date of the last to expire licensed patent covering such product. The last to expire Sarepta owned patent covered under this agreement expires on September 9, 2014. The last Isis owned patent covered under this agreement expires on March 27, 2028. In addition, either party may terminate this agreement in the event:

- a material breach by the other party is not cured within a specified period of time; or
- the other party commences bankruptcy, reorganization, liquidation or receivership proceedings or upon the assignment of a substantial portion of the assets for the benefit of creditors by the other party with certain exceptions.

Charley s Fund Agreement

In October 2007, Charley s Fund, Inc., or Charley s Fund, a nonprofit organization that funds drug development and discovery initiatives specific to DMD, awarded us a $2.45 million research grant and, in May 2009, the grant authorization was increased to a total of $5.0 million. Pursuant to the related sponsored research agreement, the grant was provided to support the development of product candidates related to exon 50 skipping using our proprietary exon skipping technologies. As of December 31, 2013, Charley s Fund has made payments of approximately $3.4 million to us. Revenue associated with this research and development arrangement is recognized based on the proportional performance method, using the payment received method. To date, we have recognized $60,000 as revenue, but did not recognize any revenue for the years ended December 31, 2013, 2012 and 2011. We do not expect to receive any incremental funding under the grant and have deferred $3.3 million of previous receipts which are anticipated to be recognized as revenue once we complete the remaining milestones.

Under the terms of the sponsored research agreement, as amended, if we and any of our strategic partners elect to discontinue the development and commercialization of any product containing any molecular candidate arising or derived from the research sponsored by Charley s Fund for reasons other than safety or efficacy, we must grant to Charley s Fund an exclusive, royalty-bearing, fully-paid, worldwide license, with right of sublicense, to any such product. Depending on whether and when Charley s Fund obtains a license to any such product, percentage royalty payments on net sales required to be made by Charley s Fund to us under the terms of the sponsored research agreement, as amended, would be in the mid-single-digits. Under the terms of the sponsored research agreement, as amended, if we are able to successfully commercialize any molecular candidate arising or derived from the research sponsored by Charley s Fund either through sales of products or through licensing or partnership arrangements with a third party that include rights for such third party to sell, distribute, promote or market such products or the underlying intellectual property, then we are obligated to repay the research funds paid to us by Charley s Fund, up to an amount equal to the total amount of funds provided by Charley s Fund to us. In connection with this repayment obligation, we agreed that we would pay a mid range single-digit percentage royalty on net sales of products containing any molecular candidate arising or derived from the research sponsored by Charley s Fund and a mid-teens amount of any upfront cash and/or milestone payments received from a licensing or partnership arrangement with a third party with respect to such products (in each case, up to an amount equal to the total amount of funds provided by Charley s Fund to us). This agreement will terminate by its own terms at the completion of the research being sponsored by Charley s Fund. The Sarepta technology upon which the agreement is based is covered by certain patents, the last of which expires following the termination of the agreement.

Previously, we noted unexpected toxicology findings in the kidney as part of our series of preclinical studies for AVI-5038, our PMO-based candidate designed for the treatment of individuals with DMD who have an error

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in the gene coding for dystrophin that can be treated by skipping exon 50. We have conducted additional preclinical studies and have not alleviated the toxicity problem. Pursuant to the terms of our agreement with Charley s Fund, the receipt of additional funds is tied to the satisfaction of certain clinical milestones. Because of the toxicity issues with AVI-5038, satisfaction of the additional milestones under the agreement is unlikely and we do not expect to receive any additional funds from Charley s Fund.

Manufacturing

We believe we have developed proprietary manufacturing techniques that allow synthesis and purification of our product candidates to support clinical development. We have entered into certain manufacturing and supply arrangements with third-party suppliers which will in part utilize these techniques to support production of certain of our product candidates and their components. We do not have, and do not intend to establish in the near term, any of our own internal mid-to-large scale manufacturing capabilities to support our product candidates.

For our current development programs we have entered into supply agreements with certain large pharmaceutical manufacturing firms for the production of the custom raw materials required for PMO production and the active pharmaceutical ingredients, or APIs, for our product candidates.

For our DMD program, we are working with our existing manufacturers to increase our API production capacity from small-scale to mid-scale. During 2014, we will also evaluate whether to increase our API production capacity to a commercial scale. This decision will depend in significant part on our discussions with the FDA in 2014 as well as our expectations regarding clinical trial needs and the potential feasibility and timing of an NDA filing and subsequent commercialization.

There are a limited number of companies that can produce raw materials and APIs in the quantities and with the quality and purity that we require for our DMD development efforts. Due to their technical expertise, experience in manufacturing our product candidates and sophistication of their manufacturing facilities and quality systems, we are considering our existing manufacturers, as well as other manufacturers with relevant expertise, for the further scale-up of the production of raw materials and APIs for our DMD program. Establishing a relationship with alternative suppliers can be a lengthy process and might cause delays in our development efforts. If we are required to seek alternative supply arrangements, the resulting delays and potential inability to find a suitable replacement could materially and adversely impact our business.

Manufacturers and suppliers of product candidates are subject to the FDA s current Good Manufacturing Practices, or cGMP, requirements, and other rules and regulations prescribed by foreign regulatory authorities. We depend on our third-party suppliers and manufacturers for continued compliance with cGMP requirements and applicable foreign standards.

Sales and Marketing Strategy

We have not obtained regulatory approval for any of our product candidates and thus have not yet established a commercial organization or distribution capabilities. Due to the rare nature of DMD and the lack of disease-modifying treatments, patients suffering from DMD, together with their physicians, often have a high degree of organization and are well informed, which may simplify the identification of a target population for eteplirsen, our lead product candidate, if it is approved. We believe that, if approved for commercial sale, it will be possible to commercialize eteplirsen with a relatively small specialty sales force that calls on the physicians, foundations and other patient-advocacy groups focused on DMD. Our current expectation is to commercialize eteplirsen ourselves in the United States and plan to recruit a sales force and take other steps to establish the necessary commercial infrastructure at such time as we believe that eteplirsen is approaching marketing approval. We will continue to evaluate whether to market our DMD product candidates outside of the United States ourselves or enter into arrangements with other pharmaceutical or biotechnology companies for the marketing and sale of our products outside the United States either globally or on a country-by-country basis.

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Patents and Proprietary Rights

Our success depends in part upon our ability to protect our core technology and intellectual property. To accomplish this, we rely on a combination of intellectual property rights, including patents, trade secrets, copyrights and trademarks, as well as regulatory exclusivity and contractual protections.

We seek patent protection for certain of our proprietary technologies by filing patent applications in the United States and other countries. As of February 28, 2014, we owned or controlled approximately 312 U.S. and corresponding foreign patents and 186 U.S. and corresponding foreign patent applications. We intend to protect our proprietary technology with additional filings as appropriate.

Our patents and patent applications are directed to our product candidates as well as to our RNA-based technology platforms. Although we believe our patents and patent applications provide us with a competitive advantage, the ability to fully realize the potential for exclusivity based on our patent positions can be uncertain as they typically involve complex legal and factual questions. Even if patent claims are allowed, the claims may not issue, or in the event of issuance, may not be sufficient to protect the technology owned by or licensed to us or our collaborators. Even if our patents and patent applications do provide our product candidates and platform technology with a basis for exclusivity, we and our collaborators may not be able to develop or commercialize such product candidates or platform technology due to patent positions held by a third party. For example, our competitor Prosensa has rights to European Patent No. EP 1619249. We opposed this patent in the Opposition Division of the European Patent Office, or the Opposition Division, and in November 2011, we announced that, although we succeeded in invalidating some of the patent s claims, the Opposition Division maintained in amended form certain claims of this patent relating to the treatment of DMD by skipping dystrophin exons 51 and 46. We and Prosensa both appealed this decision in June 2013; however, pending final resolution of this matter, the patent at issue may provide the basis for Prosensa or other parties that have rights to such patent to assert that our drug eteplirsen infringes on such patent. The outcome of the appeal cannot be predicted or determined as of the date of this report. If as part of any appeal in the European Union we are unsuccessful in invalidating Prosensa s claims that were maintained by the Opposition Division or if claims previously invalidated by the Opposition Division are restored on appeal, our ability to commercialize both eteplirsen and other therapeutic candidates for our pan-exon strategy could be materially impaired. We are also aware of certain pending and granted claims that have been issued to Prosensa in Japan that may provide the basis for Prosensa or other parties to assert that eteplirsen infringes on such claims. We believe we have a basis to invalidate some or all of these claims and are evaluating the potential initiation of invalidation proceedings. Because we have not yet initiated an invalidation proceeding in Japan, the outcome and timing of any such proceeding cannot be predicted or determined as of the date of this report. We are also aware of certain claims that Prosensa has rights to in the United States that may provide the basis for Prosensa or other parties that have rights to these claims to assert that our drug eteplirsen infringes on such claims. We believe we have valid defenses to any such allegations or a basis to invalidate some or all of these claims and do not believe that Prosensa s granted claims and pending claims should they be granted should be deemed to prevent our ability to commercialize eteplirsen in the United States; however, as noted below, the biotechnology intellectual property landscape continues to evolve and we cannot be certain of this assessment. The DMD patent landscape is continually evolving and multiple parties, both commercial entities and academic institutions, may have rights to claims that could provide these parties a basis to assert that our product candidates infringe on these claims. Similarly, we may be able to assert that certain activities engaged in by these parties infringe on our patent rights. There has been, and we believe that there will continue to be, significant litigation in the biopharmaceutical and pharmaceutical industries regarding patent and other intellectual property rights. We cannot be certain that other third parties will not assert patent infringement in the future with respect to any of our development programs.

Our product candidates and our technology are primarily protected by composition of matter and use patents and patent applications. Currently, our lead clinical product candidates are AVI-7288 (Marburg), AVI-7100 (Influenza) and AVI-4658 (Eteplirsen). We own issued patents covering composition and methods of use for AVI-7288 in the United States. We have exclusively licensed patents covering composition of matter and methods of use for AVI-4658 in the United States and Europe. Additionally, we have pending patent applications

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for composition and methods of use for AVI-7100 and issued and/or pending patent applications for composition and methods of use for other product candidates in the United States, Canada, South America, Europe, Asia, Australia, New Zealand, and/or the Middle East. Patent protection based on currently granted patents and patents granting from currently pending patent applications covering our product candidates and our technology will expire over the following time frames:

Product Candidate / Technology	Expiration of Patent Protection*
Eteplirsen	2025 (patents) 2030 (patents)
Other DMD exons	2025 (patents) 2034 (patent applications)
Exon-skipping	2013 (patents) 2023 (patents)
Antivirals (Ebola, Marburg, Dengue and Influenza)	2022 (patents) 2030 (patents)
Chemistry (PPMO, PMO*plus*® and PMO-X)	2024 (patents) 2032 (patent applications)
Antibacterials	2018 (patents) 2031 (patent applications)
Other rare diseases	2025 (patent applications) 2034 (patent applications)
Other targets and programs	2019 (patents) 2034 (patent applications)

* Stated expiration dates do not account for any patent term extension or pediatric extensions that may be available in the United States and certain foreign jurisdictions.

In addition to patent protection, we also rely on trade secrets and proprietary know-how, especially when we do not believe that patent protection is appropriate or can be obtained. Our policy is to require each of our employees, consultants and advisors to execute a confidentiality and inventions assignment agreement before beginning their employment, consulting or advisory relationship with us. These agreements generally provide that the individual must keep confidential and not disclose to other parties any confidential information developed or learned by the individual during the course of their relationship with us except in limited circumstances. These agreements also generally provide that we shall own all inventions conceived by the individual in the course of rendering services to us.

We are the owner of four federal trademark registrations in the United States: AVI BioPharma®, Cytoporter®, PMO-plus® and NeuGene®. We have pending trademark applications in the United States for the following trademarks: PMO-X ; Sarepta ; Sarepta Therapeutics and the Sarepta Therapeutics logo; Let s Skip Ahead ; The Promise of Science, Realized ; Transformation, Within Reach ; and Turning Discovery Into Recovery . In the European Union, we have trademark registrations for AVI BioPharma® and Sarepta® and pending applications for the following trademarks: the Sarepta Therapeutics logo; The Promise of Science, Realized ; Transformation, Within Reach ; and Turning Discovery Into Recovery . We have licensed certain technology to supplement and support certain of our core technologies. We have certain obligations and minimum royalties under those agreements, which costs are not material to our business and can be terminated at our discretion with minimal notice.

Our commercial success will depend in part on obtaining and maintaining patent protection and trade secret protection of the use, formulation and structure of our product candidates, and the methods used to manufacture them, as well as successfully defending these patents against third-party challenges. Our ability to protect our product candidates from unauthorized making, using, selling, offering to sell or importing by third parties is dependent on the extent to which we have rights under valid and enforceable patents that cover these activities.

We do not have patents or patent applications in every jurisdiction where there is a potential commercial market for our product candidates. For each of our programs, our decision to seek patent protection in specific foreign markets, in addition to the United States, is based on many factors, including:

- our available resources;
- the number and types of patents already filed or pending;
- the likelihood of success of the product candidate;

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- the size of the commercial market;
- the presence of a potential competitor in the market; and
- whether the legal authorities in the market effectively enforce patent rights.

We continually evaluate our patent portfolio and patent strategy and believe our owned and licensed patents and patent applications provide us with a competitive advantage; however, if markets where we do not have patents or patent applications become commercially important, our business may be adversely affected.

The patent positions of pharmaceutical, biotechnology and other life sciences companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in biotechnology patents has emerged to date in the United States, and tests used for determining the patentability of patent claims in all technologies are in flux. In addition, there is no assurance as to the degree and range of protections any of our patents, if issued, may afford us or whether patents will be issued. For example, patents which may be issued to us may be subjected to further governmental review that may ultimately result in the reduction of their scope of protection, and pending patent applications may have their requested breadth of protection significantly limited before being issued, if issued at all. The pharmaceutical, biotechnology and other life sciences patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in the patents that we own or have licensed or in third-party patents. Further, since publication of discoveries in scientific or patent literature often lags behind actual discoveries, there is no assurance that we were the first creator of inventions covered by our pending patent applications, or that we were the first to file patent applications for these inventions.

Government Regulation

The testing, manufacturing, labeling, advertising, promotion, distribution, exportion and marketing of our products are subject to extensive regulation by governmental authorities in the United States and in other countries. In the United States, the FDA, under the Federal Food, Drug and Cosmetic Act and its implementing regulations, regulates pharmaceutical products. Failure to comply with applicable U.S. requirements may subject us to administrative or judicial sanctions, such as FDA refusal to approve pending NDAs, withdrawal of approval of approved products, warning letters, untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, civil penalties and/or criminal prosecution.

Drug Approval Process

To obtain FDA approval of a product candidate, we must, among other things, submit data providing substantial evidence of safety and efficacy of the product, as well as detailed information on the manufacture and composition of the product candidate and proposed labeling. The testing and collection of data and the preparation of necessary applications are expensive and time-consuming. The FDA may not act quickly or favorably in reviewing these applications, and we may encounter significant difficulties or costs in our efforts to obtain FDA approvals that could delay or preclude us from marketing our products.

The steps required before a drug may be approved for marketing in the United States generally include the following, with exceptions noted in the section captioned Government Regulation Animal Rule :

- preclinical laboratory tests and animal tests;
- submission to the FDA of an IND for human clinical testing, which must become effective before human clinical trials commence;
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the drug product for each indication;

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the submission to the FDA of an NDA;

satisfactory completion of an FDA inspection of the manufacturing facilities at which the product is made to assess compliance with cGMP;

satisfactory FDA audit of the clinical trial site(s) that generated the data in support of the NDA and also potentially the nonclinical site(s); and

FDA review and approval of the NDA.

Preclinical studies may include laboratory evaluations of the product chemistry, toxicity, and formulation, as well as animal studies to assess the potential safety and efficacy of the product candidate. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements. The results of the preclinical studies, together with manufacturing information and analytical data, are submitted to the FDA as part of the IND, which must become effective before clinical trials may be commenced. The IND will become effective automatically 30 days after receipt by the FDA, unless the FDA raises concerns or questions about the conduct of the clinical trials as described in the protocol submitted as part of the IND prior to that time. In this case, the trials are placed on clinical hold, and the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can proceed.

Clinical trials involve the administration of the product candidate to healthy volunteers or participants under the supervision of a qualified principal investigator. Clinical trials are conducted under protocols detailing the objectives of the study, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND. Clinical trials must be conducted in accordance with the FDA s good clinical practices requirements and state subject rights laws. Further, each clinical trial must be reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which the clinical trial will be conducted. The IRB will consider, among other things, clinical trial design, participant informed consent, ethical factors, the safety of human subjects, and the possible liability of the institution. The FDA may order the partial, temporary or permanent discontinuation of a clinical trial at any time or impose other sanctions if it believes that the clinical trial is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial subjects. The IRB may also require the clinical trial at that site to be halted, either temporarily or permanently, for failure to comply with the IRB s requirements, or may impose other conditions.

Clinical trials typically are conducted in three sequential phases prior to approval, but the phases may overlap. A fourth, or post-approval, phase may include additional clinical studies. These phases generally include the following; however, in the rare disease space, the number of subjects involved in each phase can be significantly less than the general parameters set forth below:

Phase I. Phase I clinical trials involve the initial introduction of the drug into human subjects. These studies are designed to determine the safety of usually single doses of the compound and determine any dose limiting intolerance, as well as evidence of the metabolism and pharmacokinetics of the drug in humans. Phase I studies usually involve less than 100 subjects and are most commonly conducted in healthy adult volunteers.

Phase II. Phase II clinical trials usually involve studies in a limited patient population to evaluate the efficacy of the drug for specific, targeted indications, to determine dosage tolerance and optimal dosage, and to identify possible adverse effects and safety risks. Phase II studies usually involve patients with the disease under investigation and numbers may vary from several dozen to several hundred.

Phase III. If a compound is found to be potentially effective and to have an acceptable safety profile in Phase II (or sometimes Phase I) studies, the clinical trial program will be expanded to further confirm clinical efficacy, optimal dosage and safety within an expanded patient population which may involve

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geographically dispersed clinical trial sites. Phase III studies usually include several hundred to several thousand patients. Generally, two adequate and well-controlled Phase III clinical trials are required by the FDA for approval of an NDA.

Phase IV. Phase IV clinical trials are studies required of or agreed to by a sponsor that are conducted after the FDA has approved a product for marketing. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication and to document a clinical benefit in the case of drugs approved under accelerated approval regulations. If the FDA approves a product while a company has ongoing clinical trials that were not necessary for approval, a company may be able to use the data from these clinical trials to meet all or part of any Phase IV clinical trial requirement. Failure to promptly conduct Phase IV clinical trials could result in withdrawal of approval for products approved under accelerated approval regulations.

A company seeking marketing approval for a new drug in the United States must submit to the FDA the results of the preclinical and clinical trials, together with, among other things, detailed information on the manufacture and composition of the product candidate and proposed labeling, in the form of an NDA, including payment of a user fee. The FDA reviews all NDAs submitted before it accepts them for filing and may request additional information rather than accepting an NDA for filing. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act, or PDUFA, the FDA has ten months in which to complete its initial review of a standard NDA and respond to the applicant, and six months for a priority NDA. The FDA does not always meet its PDUFA goal dates for standard and priority NDAs. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the NDA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date. If the FDA s evaluations of the NDA and the clinical and manufacturing procedures and facilities are favorable, the FDA may issue an approval letter. If the FDA finds deficiencies in the NDA, it may issue a complete response letter, which contains the conditions that must be met in order to secure final approval of the NDA. If and when those conditions have been met to the FDA s satisfaction, the FDA will issue an approval letter, authorizing commercial marketing of the drug for certain indications. If the FDA s evaluation of the NDA submission and the clinical and manufacturing procedures and facilities is not favorable, the FDA may refuse to approve the NDA. Sponsors that receive a complete response letter may submit to the FDA information that represents a complete response to the issues identified by the FDA. Resubmissions by the NDA sponsor in response to a complete response letter trigger new review periods of varying length (typically two to six months) based on the content of the resubmission. The FDA may also refer an application to an appropriate advisory committee, typically a panel of clinicians, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendations of the advisory committee.

A sponsor may also seek approval of its drug candidates under programs designed to accelerate the FDA s review and approval of NDAs. For instance, a sponsor may seek FDA designation of a drug candidate as a fast track product. Fast track products are those products intended for the treatment of a serious or life-threatening disease or condition and which demonstrate the potential to address unmet medical needs for such disease or condition. If fast track designation is obtained, the FDA may initiate early, frequent, communication and begin reviewing sections of an NDA before the application is complete. This rolling review is available if the applicant provides, and the FDA approves, a schedule for the remaining information. We were granted fast track status for eteplirsen in 2007 and we announced in September 2012 that the FDA granted fast track status for the development of both AVI-7288 and AVI-7537.

The Food and Drug Administration Safety and Innovation Act, or FDASIA, enacted and signed into law in 2012 amended the criteria for the fast track and accelerated approval pathways and, as a result, the pathways now share many common eligibility criteria. FDASIA provides both sponsor companies and the FDA greater flexibility with expedited regulatory mechanisms. The statute clarifies that a fast track product may be approved pursuant to an accelerated approval (Subpart H) or under the traditional approval process. In addition, FDASIA codified the accelerated approval pathway as separate and apart from fast track pathway, meaning that for drugs

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to be eligible for accelerated approval, they do not need to be designated under the fast track pathway. FDASIA reinforces the FDA s authority to grant accelerated approval based on surrogate endpoints that are reasonably likely to predict clinical benefit, and provides for a more expansive use of non-surrogate clinical endpoints by authorizing the FDA to grant accelerated approval based on the use of clinical endpoints that can be measured earlier in the development process than irreversible morbidity or mortality, and that are reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. In determining whether to grant accelerated approval, the FDA must consider the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Approvals of this kind typically include requirements for appropriate post-approval Phase IV clinical trials. FDASIA retains this requirement and further requires those studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit. We had various meetings with the FDA in 2013 and will continue to have meetings with the FDA during 2014 to discuss the clinical results from our Phase IIb study of eteplirsen and most appropriate regulatory review pathway based on these data. In addition, we also plan to have discussions with the FDA to finalize the pivotal clinical study design for eteplirsen. Based on feedback from these meetings, we will continue to pursue the most appropriate regulatory path for regulatory review and approval of eteplirsen. Our determination will be further informed by subsequent meetings with the FDA.

Additionally, FDASIA established a new, expedited regulatory mechanism referred to as breakthrough therapy designation. Breakthrough therapy designation, fast track, and accelerated approval are not mutually exclusive and are meant to serve different purposes. The breakthrough therapy designation is focused on expediting the development and review process and by itself does not create an alternate ground for product approval. A sponsor may seek FDA designation of a drug candidate as a breakthrough therapy if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA issued draft guidance entitled Expedited Programs for Serious Conditions Drugs and Biologics in June 2013 and if deemed necessary, is required to amend its regulations by July 2014. We will continue to evaluate, with input from the FDA, which expedited programs are appropriate to incorporate in our regulatory approach for eteplirsen and our other DMD product candidates.

Finally, drug candidates, upon submission of an NDA, may also be eligible for priority review, or review within a six month timeframe from the date a complete NDA is accepted for filing, if a sponsor shows that its drug candidate provides a significant improvement compared to marketed drugs.

While FDASIA provides certain authorities and direction to the FDA, it is unclear how the FDA will interpret and implement FDASIA provisions, in particular, in considering what the appropriate regulatory approval pathway is for eteplirsen. We cannot be sure that any of our drug candidates will qualify for any of these expedited development, review and approval programs, or that, if a drug does qualify, that the product candidates will be approved, will be accepted as part of any such program or that the review time will be shorter than a standard review.

Often, even after a drug has been approved by the FDA for sale, the FDA may require that certain post-approval requirements be satisfied, including the conduct of additional clinical studies. If such post-approval conditions are not satisfied, the FDA may withdraw its approval of the drug. In addition, holders of an approved NDA are required to:

- report certain adverse reactions to the FDA;
- submit annual and periodic reports summarizing product information and safety data;
- comply with certain requirements concerning advertising and promotional labeling for their products; and
- continue to have quality control and manufacturing procedures conform to cGMP after approval.

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The FDA periodically inspects the sponsor s records related to safety reporting and/or manufacturing; this latter effort includes assessment of compliance with cGMP. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved NDA, including withdrawal of the product from the market.

Many other countries and jurisdictions have similar drug development and regulatory review processes. We have conducted clinical trials in the United Kingdom and intend to submit for marketing approval in countries other than the United States. Therefore, we will have to comply with the legal and regulatory requirements in the countries where we conduct trials and submit for marketing approval.

Animal Rule

In the case of product candidates that are intended to treat rare life-threatening diseases, such as infection caused by exposure to various hemorrhagic fever viruses, conducting controlled clinical trials to determine efficacy may be unethical or unfeasible. Under regulations issued by the FDA in 2002, often referred to as the Animal Rule, the approval of such products can be based on clinical data from trials in healthy human subjects that demonstrate adequate safety, and immunogenicity and efficacy data from adequate and well-controlled animal studies. Among other requirements, the animal studies must establish that the drug or biological product is reasonably likely to produce clinical benefits in humans. Because the FDA must agree that data derived from animal studies may be extrapolated to establish safety and effectiveness in humans, seeking approval under the Animal Rule adds significant time, complexity and uncertainty to the testing and approval process. No animal model is established as predicting human outcomes in the prevention or treatment of any filovirus disease. We have yet to demonstrate the predictive value of our animal studies to the FDA s satisfaction. In addition, products approved under the Animal Rule are subject to additional requirements including post-marketing study requirements, restrictions imposed on marketing or distribution or requirements to provide information to patients. The Animal Rule is a rarely-used regulatory pathway and most of the products approved to-date under the Animal Rule have built upon existing indications with human data to support efficacy. Additional clarity on Animal Rule requirements is not anticipated until the FDA releases an updated version of its draft guidance on the Animal Rule that was first published in January 2009.

Emergency Use Authorization

The Commissioner of the FDA, under delegated authority from the Secretary of DHHS may, under certain circumstances, issue an Emergency Use Authorization, or EUA, that would permit the use of an unapproved drug product or unapproved use of an approved drug product. Before an EUA may be issued, the Secretary must declare an emergency based on one of the following grounds:

- a determination by the Secretary of the Department of Homeland Security that there is a domestic emergency, or a significant potential for a domestic emergency, involving a heightened risk of attack with a specified biological, chemical, radiological or nuclear agent or agents;
- a determination by the Secretary of DoD that there is a military emergency, or a significant potential for a military emergency, involving a heightened risk to U.S. military forces of attack with a specified biological, chemical, radiological, or nuclear agent or agents; or
- a determination by the Secretary of DHHS of a public health emergency that effects or has the significant potential to affect, national security, and that involves a specified biological, chemical, radiological, or nuclear agent or agents, or a specified disease or condition that may be attributable to such agent or agents.

In order to be the subject of an EUA, the FDA Commissioner must conclude that, based on the totality of scientific evidence available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a disease attributable to the agents described above; that the product s potential benefits outweigh its potential risks; and that there is no adequate, approved alternative to the product.

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The Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) enhanced existing EUA requirements, including by:

- Providing clearer authority for the FDA to issue EUAs before a chemical, biological, radiological or nuclear emergency occurs to enable stakeholders to prepare for use of unapproved medical products, or unapproved uses of approved products, if certain criteria are met (referred to as pre-event EUAs)
- Allowing the FDA to issue an EUA based on the HHS Secretary s determination that there is a potential for a public health emergency involving a chemical, biological, radiological or nuclear threat agent (not only based on an actual emergency)
- Expanding the time period for collection and analysis of information about a medical countermeasure s safety and effectiveness for a reasonable period beyond the effective period of the EUA
- Expressly permitting FDA, as part of issuance of an EUA, to categorize the complexity of an in vitro diagnostic device to indicate whether the test can be performed at a point-of-care setting or only in a more sophisticated laboratory

The FDA strongly encourages an entity with a possible candidate product, particularly one at an advanced stage of development, to contact the FDA Center responsible for the candidate product before a determination of actual or potential emergency. Such an entity may submit a request for consideration that includes data to demonstrate that, based on the totality of scientific evidence available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition. This is called a pre-EUA submission and its purpose is to allow FDA review considering that during an emergency, the time available for the submission and review of an EUA request may be severely limited. We intend to work with DoD in the future on a pre-EUA submission with respect to our product candidate intended to treat Marburg in order to inform and expedite the FDA s issuance of an EUA, should one become necessary in the event of an emergency or potential emergency.

Orphan Drug Designation and Exclusivity

In the United States, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for this type of disease or condition will be recovered from sales in the United States for that drug. In the United States, orphan drug designation must be requested before submitting an application for marketing approval. An orphan drug designation does not shorten the duration of the regulatory review and approval process. The approval of an orphan designation request does not alter the standard regulatory requirements and process for obtaining marketing approval. Safety and efficacy of a compound must be established through adequate and well-controlled studies. If a product which has an orphan drug designation subsequently receives FDA approval for the indication for which it has such designation, the product is entitled to an orphan drug exclusivity period, which means the FDA may not grant approval to any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as where an alternative product demonstrates clinical superiority to the product with orphan exclusivity. In addition, holders of exclusivity for orphan drugs are expected to assure the availability of sufficient quantities of their orphan drugs to meet the needs of patients. Failure to do so could result in the withdrawal of marketing exclusivity for the drug. Distinct from orphan drug exclusivity, the FDA may provide six months of pediatric exclusivity to a sponsor of an NDA, if the sponsor conducted a pediatric study or studies of such product. This process is initiated by the FDA as a written request for pediatric studies that applies to sponsor s product. If the sponsor conducts qualifying studies and the studies are accepted by the FDA, then an additional six months of pediatric exclusivity will attach to any periods of regulatory exclusivity such as orphan drug exclusivity and new chemical entity exclusivity, and any Orange Book listed patents for the listed product. Competitors may receive approval of different drugs or biologics for the indications for which a prior approved orphan drug has exclusivity. We have been granted orphan drug designation for eteplirsen, AVI-7288, AVI-7537 and AVI-5038 in the United States.

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The European Orphan Drug Regulation as applied by the European Medicines Agency (EMA) is considered for drugs intended to diagnose, prevent or treat a life-threatening or very serious condition afflicting five or fewer out of 10,000 people in the European Union, including compounds that for serious and chronic conditions would likely not be marketed without incentives due to low market return on the sponsor s development investment. The medicinal product considered should be of significant benefit to those affected by the condition as compared to previously approved products for the same indication. Benefits of being granted orphan drug designation are significant, including ten years of market exclusivity. During this ten-year period, the EMA may not accept a new marketing application for a similar drug for the same therapeutic indication as the orphan drug. Distinct from orphan drug exclusivity, the EMA may provide a sponsor having an approved Pediatric Investigation Plan (PIP) or pediatric exclusivity waiver, which may lead to a two-year period of market exclusivity beyond the original ten-year period of orphan drug exclusivity. We have been granted orphan drug designation for eteplirsen and AVI-5038 in the European Union.

Other Regulatory Requirements

In addition to regulation by the FDA and certain state regulatory agencies, we are also subject to a variety of foreign regulations governing clinical trials and the marketing of other products. Outside of the United States, our ability to market a product depends upon receiving a marketing authorization from the appropriate regulatory authorities. The requirements governing the conduct of clinical trials, marketing authorization, pricing and reimbursement vary widely from country to country. In any country, however, we will only be permitted to commercialize our products if the appropriate regulatory authority is satisfied that we have presented adequate evidence of safety, quality and efficacy. Whether or not FDA approval has been obtained, approval of a product by the comparable regulatory authorities of foreign countries must be obtained prior to the commencement of marketing of the product in those countries. The time needed to secure approval may be longer or shorter than that required for FDA approval. The regulatory approval and oversight process in other countries includes all of the risks associated with regulation by the FDA and certain state regulatory agencies as described above.

Pharmaceutical Pricing and Reimbursement

In both U.S. and foreign markets, our ability to commercialize our products successfully, and to attract commercialization partners for our products, depends in significant part on the availability of adequate financial coverage and reimbursement from third-party payers, including, in the United States, governmental payers such as the Medicare and Medicaid programs, managed care organizations, and private health insurers. Third-party payers are increasingly challenging the prices charged for medicines and examining their cost effectiveness, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the cost effectiveness of our products. Even with the availability of such studies, our products may be considered less safe, less effective or less cost-effective than alternative products, and third-party payers may not provide coverage and reimbursement for our product candidates, in whole or in part.

Political, economic and regulatory influences are subjecting the healthcare industry in the United States to fundamental changes. There have been, and we expect there will continue to be, legislative and regulatory proposals to change the healthcare system in ways that could significantly affect our business, including the Patient Protection and Affordable Care Act of 2010. We anticipate that the U.S. Congress, state legislatures and the private sector will continue to consider and may adopt healthcare policies intended to curb rising healthcare costs. These cost containment measures include:

- controls on government funded reimbursement for drugs;
- mandatory discounts under certain government sponsored programs;
- controls on healthcare providers;
- challenges to the pricing of drugs or limits or prohibitions on reimbursement for specific products through other means;

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reform of drug importation laws; and

expansion of use of managed care systems in which healthcare providers contract to provide comprehensive healthcare for a fixed cost per person.

We are unable to predict what additional legislation, regulations or policies, if any, relating to the healthcare industry or third party coverage and reimbursement may be enacted in the future or what effect such legislation, regulations or policies would have on our business. Any cost containment measures, including those listed above, or other healthcare system reforms that are adopted could have a material adverse effect on our business prospects.

Competition

The pharmaceutical and biotechnology industries are intensely competitive, and any product candidate developed by us would likely compete with existing drugs and therapies. There are many pharmaceutical companies, biotechnology companies, public and private universities, government agencies and research organizations that compete with us in developing various approaches to the treatment of rare and infectious diseases. Many of these organizations have substantially greater financial, technical, manufacturing and marketing resources than we have. Several of them have developed or are developing therapies that could be used for treatment of the same diseases that we are targeting. In addition, many of these competitors have significantly greater commercial infrastructures than we have. Our ability to compete successfully will depend largely on:

our ability to complete clinical development and obtain regulatory approvals for our product candidates;

the efficacy, safety and reliability of our product candidates;

the timing and scope of regulatory approvals;

product acceptance by physicians and other health-care providers;

protection of our proprietary rights and the level of generic competition;

the speed at which we develop product candidates;

our ability to supply commercial quantities of a product to the market;

obtaining reimbursement for product use in approved indications;

our ability to recruit and retain skilled employees; and

the availability of substantial capital resources to fund development and commercialization activities, including the availability of funding from the U.S. government.

DMD Program Competition. Currently, no product has been approved for the treatment of DMD. Companies including, but not limited to, Prosensa (which announced it regained rights to Drisaparsen and all other programs for the treatment of DMD from GlaxoSmithKline plc, or

GSK, in January 2014), and PTC Therapeutics, Inc., or PTC, have product candidates in development for the treatment of DMD. PTC has an exon 51 skipping product candidate in early development while Prosensa is reviewing its Phase III data to determine whether it can seek approval of its exon 51 skipping product candidate drisaparsen. Several companies have recently entered into collaborations or other agreements for the development of product candidates, including messenger RNA, gene or small molecule therapies that are potential competitors for therapies being developed in the muscular dystrophy, neuromuscular and rare disease space, including Biogen Idec, Inc., Isis Pharmaceuticals, Inc., Alexion Pharmaceuticals, Inc., PTC, Sanofi, Alnylam Pharmaceuticals, Inc., or Alnylam, Moderna Therapeutics, Inc., Summit plc and Oxford University.

The Prosensa / GSK program commenced treatment in December 2010 in a Phase III clinical study in ambulant individuals with DMD who have a dystrophin gene mutation amenable to treatment by skipping

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exon 51. Prosensa s candidate for skipping exon 51, GSK2402968, utilizes a different chemistry, 2 O-methyl-phosphorothioate, which has the potential for different performance, safety and tolerability characteristics than eteplirsen. This randomized, placebo-controlled study was fully enrolled, with approximately 180 participants who were being dosed for 48 weeks. The primary efficacy endpoint for Prosensa s study was a measure of muscle function using the 6-MWT. In September 2013, GlaxoSmithKline plc and Prosensa announced that the Phase III clinical study of drisaparsen did not meet the primary endpoint of a statistical significant improvement in the 6 MWT compared to placebo. In September 2010, the Prosensa / GSK program commenced a Phase II double-blind, placebo-controlled study. This study is designed to assess the efficacy of two different dosing regimens of GSK2402968 administered over 24 weeks in DMD patients, and then to continue observing the patients over a second 24-week interval for a total study time frame of 48 weeks. This study completed enrollment with 54 DMD patients in October 2011 and has since concluded. Another study using GSK2402968 in non-ambulatory DMD patients has been initiated using a 6 mg/kg dose and is anticipated to enroll 20 patients. Like Prosensa, other companies continue to pursue approval of products for the treatment of DMD and their products may or may not prove to be safer and/or more efficacious than, or obtain marketing approval before, eteplirsen.

Hemorrhagic Fever Virus Programs. No specific treatment has been proven effective, and no approved vaccine currently exists for either Ebola or Marburg. Investigational compounds cannot be tested for efficacy on humans except in outbreak environments so these agents must be tested extensively in animals and meet strict government regulations. Vaccine development is in the early stages in both the biotechnology industry and by U.S. government agencies (*e.g.*, the National Institute of Allergy and Infectious Diseases and the DoD). The government is also supporting early stage research on therapeutics against hemorrhagic fever viruses, including broad-spectrum therapeutics. With respect to therapeutics in advanced development, on January 2014, Tekmira Pharmaceuticals Corp. announced it has dosed the first subject in aPhase I human clinical trial for TKM-Ebola, a systemically delivered RNAi therapeutic for the treatment of Ebola virus infection under a contract with the DoD. We commenced initial human safety studies of our therapeutic candidates against Marburg and Ebola viruses in May 2011, however, the DoD terminated further funding of our Ebola program in October 2012 and further development of our Marburg therapeutic candidate will depend on receiving additional funding from the DoD.

Influenza Program. Currently, there are two therapeutic products for influenza that have received market approval from the FDA and are recommended for use in the United States. These are: (1) oseltamivir (Tamiflu), a Roche Holding and Gilead product; and (2) zanamivir (Relenza), a GSK product. In addition to these products, Biota Pharmaceuticals and Daiichi Sankyo s laninamivir and BioCryst s peramivir were launched in 2010 in Japan. Currently, funding from the DHHS Biomedical Advanced Research and Development Authority is helping support clinical trials of Biota and Daiichi Sankyo s laninamivir, BioCryst s peramivir, Ansun Biopharma s Fludase, and Romark Laboratories nitazoxanide. In addition, other companies have influenza therapeutic compounds against viral and host targets in various stages of development, including Toyama Chemical s favipiravir which is in a Phase II clinical trial in the United States, under a DoD contract with MediVector, Inc., and has completed a Phase III trial in Japan. DHHS is currently seeking additional antiviral therapeutics for the treatment of influenza infections.

In addition to therapeutic products, other companies are focusing development efforts on universal influenza vaccines, including BiondVax Pharmaceuticals Ltd. and Immune Targeting Systems which are in Phase II and Dynavax in Phase I. Successful development of a universal influenza vaccine could lead to a reduction in the number of influenza cases and, therefore, the market size.

Platform Technology. We believe that other biotechnology and pharmaceutical companies share a focus on RNA-based drug discovery and development. Competitors with respect to our RNA-based technologies include, but are not limited to, Alnylam, Tekmira Pharmaceuticals Corp., Isis, Prosensa, Sanofi Aventis, and Santaris Pharma A/S. We are unaware of any other commercial organization that is developing therapeutics based on a PMO chemistry platform.

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Research and Development

Since our inception, we have focused on the discovery and development of unique RNA-based therapeutics for the treatment of rare and infectious diseases. We are primarily focused on rapidly advancing the development of our potentially disease-modifying DMD drug candidates, including our lead product candidate, eteplirsen. We are also focused on developing therapeutics for the treatment of infectious diseases, including our lead infectious disease program aimed at the development of a drug candidate for the Marburg hemorrhagic fever virus. By building our infectious disease programs, which are primarily funded and supported by the DoD, and leveraging our highly-differentiated, proprietary technology platforms including our next-generation PMO chemistries (PMO-X , PMO-*plus*®, and PPMO) which we have designed to enhance delivery, target selectivity and drug potency, we are seeking to further develop our research and development competencies and identify additional product candidates.

During 2012, we completed a U.S.-based Phase IIb clinical trial for eteplirsen that was initiated in August 2011. Following completion of this study in early 2012, we initiated an open label extension study with the same participants from the original Phase IIb placebo-controlled trial. We are working with the FDA to initiate a pivotal clinical study and determine the feasibility of expedited regulatory programs for eteplirsen. The lengthy process of securing FDA approvals for new drugs requires the expenditure of substantial resources. Accordingly, we cannot currently estimate, with any degree of certainty, the amount of time or money that we will be required to expend in the future on our product candidates prior to their regulatory approval, if such approval is ever granted.

Research and development expenses represent a substantial percentage of our total operating expenses, which primarily consist of costs associated with research activities as well as costs associated with our product development efforts, conducting preclinical studies, and clinical trial and manufacturing costs. The Company does not maintain or evaluate, and therefore does not allocate, internal research and development costs on a project-by-project basis. As a result, a significant portion of our research and development expenses are not tracked on a project-by-project basis, as the costs may benefit multiple projects.

The following table summarizes the primary components of our research and development external expenditures for our principal research and development programs, and our internal research and development expenditures in the aggregate for each of the years ended December 31, 2013, 2012 and 2011. Prior to January 1, 2011, the Company did not track research and development expenditures on a project level, as such, the inception-to-date expenses represent the period from January 1, 2011 to December 31, 2013.

	Year Ended December 31,			January 1, 2011 to December 31,
	2013	2012	2011	2013
Research and Development Expense (in thousands)				
Development programs				
DMD	$ 43,511	$ 12,181	$ 10,420	$ 66,112
Infectious Diseases	5,701	22,956	28,016	56,673
Internal research and development costs	23,697	17,265	28,426	
Total research and development expense	$ 72,909	$ 52,402	$ 66,862	

Employees

As of December 31, 2013, we had 146 employees, 54 of which hold advanced degrees. Of these employees, 98 are engaged directly in research and development activities and 48 are in administration. None of our employees are covered by collective bargaining agreements and we consider relations with our employees to be good.

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Item 1A. Risk Factors.

Factors That Could Affect Future Results

Set forth below and elsewhere in this Annual Report on Form 10-K and in other documents we file with the SEC are descriptions of risks and uncertainties that could cause actual results to differ materially from the results contemplated by the forward-looking statements contained in this Annual Report on Form 10-K. Please review our legend titled Forward-Looking Information at the beginning of this Annual Report on Form 10-K which is incorporated herein by reference. Because of the following factors, as well as other variables affecting our operating results, past financial performance should not be considered a reliable indicator of future performance and investors should not use historical trends to anticipate results or trends in future periods. The risks and uncertainties described below are not the only ones facing us. Other events that we do not currently anticipate or that we currently deem immaterial also affect our results of operations and financial condition.

Risks Relating to Our Business

Our product candidates are at an early stage of development, and it is possible that none of our product candidates will ever become commercial products.

Our product candidates are in relatively early stages of development. These product candidates will require significant further development, financial resources and personnel to obtain regulatory approval and develop into commercially viable products, if at all. Currently, eteplirsen in DMD, AVI-7288 in Marburg and AVI-7100 in influenza are in active clinical development. AVI -7537 in Ebola is no longer in clinical development as a result of the October 2012 notice we received from the DoD, terminating the program for the development of AVI-7537 for the convenience of the government due to funding constraints. The rest of our product candidates are in preclinical development. We expect that much of our effort and many of our expenditures over the next several years will be devoted to development activities associated with eteplirsen and other exon-skipping candidates as part of our larger pan-exon strategy in DMD, our infectious disease candidates, our proprietary chemistry, and other potential therapeutic areas that provide long-term market opportunities. With current resources, we may be restricted or delayed in our ability to develop these and other clinical and preclinical product candidates.

Our ability to commercialize any of our product candidates, including eteplirsen, depends on first receiving required regulatory approvals. It is possible that our product candidates, including eteplirsen, may never receive regulatory approval, including any designations that would expedite the review or approval process for various reasons, including: any failure to meet the applicable regulatory requirements to obtain regulatory approval for any of our product candidates including any failure to conduct a pivotal study with an FDA approved design, file an NDA prior to or in the time-frame suggested by the FDA, demonstrate the safety and effectiveness for any of our product candidates, lack of funding, changes in the regulatory landscape, new scientific developments, including the results for clinical trials of competitor drugs, and the FDA s interpretation and analysis of such developments in connection with our product candidates, manufacturing or other reasons. If we are unable to obtain regulatory approval for any of our current product candidates, it could delay or eliminate any potential product commercialization and product revenue for our Company.

Even if a product candidate receives regulatory approval, the resulting product may not gain market acceptance among physicians, patients, healthcare payers and t