Sarepta Therapeutics Announces a Continued Benefit on Walking Test Through 62 Weeks in Phase IIb Open-Label Extension Study of Eteplirsen in Duchenne Muscular Dystrophy

December 7, 2012 8:32 AM ET

Data to Be Presented at European Neuromuscular Centre Workshop

Dec 07, 2012 (Marketwire via COMTEX) --Sarepta Therapeutics (NASDAQ: SRPT), a developer of innovative RNA-based therapeutics, today announced updated data from Study 202, its open-label, Phase IIb extension study of eteplirsen for the treatment of Duchenne muscular dystrophy (DMD). Patients treated with eteplirsen for 62 weeks and evaluable on ambulatory measures (modified Intent-to-Treat population) maintained a statistically significant clinical benefit on the primary clinical outcome measure, the 6-minute walk test (6MWT), compared to patients who received placebo for 24 weeks followed by 38 weeks of eteplirsen treatment. As reported previously, Study 202 met its primary endpoint of increased novel dystrophin as assessed in muscle biopsies at week 48 and is now in the long-term extension phase in which patients continue to be followed for safety and clinical outcomes.

In the modified Intent-to-Treat (mITT) population, which includes evaluable patients from both the 30mg/kg and 50mg/kg dose cohorts, patients treated with eteplirsen for 62 weeks demonstrated a statistically significant benefit of 62 meters over the placebo/delayed-treatment cohort using a mixed-model repeated measure statistical test. The mITT 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 excludes 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 and the cohort has shown less than a 5% decline in walking distance on the 6-minute walk test 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.

"We are excited to see continued stability on the 6-minute walk test with more than a year of follow-up where we would otherwise predict a significant decline," said Chris Garabedian, President and CEO of Sarepta Therapeutics. "Furthermore, the placebo / delayed treatment group has shown stability over the last 26 weeks of treatment, the period in which we would expect to see dystrophin levels translate to clinical benefit. These clinical data support our belief that the dystrophin levels we observed at 48 weeks are potentially an important surrogate marker in assessing disease progression in Duchenne and renews our commitment to advance this program forward as we prepare our primary 48 week dataset for discussion with the FDA."

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 previously been 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, this mITT population is the most appropriate to assess dystrophin production and its potential predictive benefits on ambulatory clinical outcomes, such as the 6MWT.

Summary of Additional 6MWT Analyses

As pre-specified in both the Study 201 and Study 202 protocols and statistical analysis plans, the 6MWT was evaluated on two consecutive days at time-points that coincided with a muscle biopsy procedure, namely the baseline visit, and weeks 12, 24, and 48. The maximum distance walked of the two measures on any such visits representing the "best effort" score was prospectively defined for inclusion in the statistical analysis. These data were used to represent the primary clinical endpoint in these studies, however only a single measure of the 6MWT will be captured for each timepoint beyond week 48 in which this test is taken.

The 6MWT data were also evaluated through week 62 using the various methods of using the repeated test results including assessments of minimum values, average values, and the day 1 (first measure) values in assessing changes in 6MWT distance from baseline. Given the inherent variability in an effort-dependent outcome, such as a single-measure 6MWT, the robustness of the treatment effect seen with the prospectively specified analysis was confirmed with these additional analyses.

Summary of 6MWT: Eteplirsen versus Placebo/Delayed-Treatment to Week 62*

Results by Type of Analysis on Repeated 6MWT values	Baseline 6MWT Value (meters)	Adjusted Mean 6MWT Change from Baseline (meters)	Estimated Treatment Benefit (Eteplirsen minus Placebo/delayed-Tx)	p-value
Maximum Score Eteplirsen (n=6)	399.7	-15.6	61.9 m	≤0.007
Maximum Score Placebo/delayed Tx (n=4)	394.5	-77.6		
Mean Score Eteplirsen (n=6)	388.6	-4.2	59.5 m	≤0.012
Mean Score Placebo/delayed Tx (n=4)	380.3	-63.8		
Minimum Score Eteplirsen (n=6)	377.5	+7.1	57.1 m	≤0.021
Minimum Score Placebo/delayed Tx (n=4)	366.0	-50.0		
Day 1 Score Eteplirsen (n=6)	379.7	+4.7	59.6 m	≤0.018
Day 1 Score Placebo/delayed Tx (n=4)	371.5	-55.0		

** Note: All analyses are based on Mixed Model Repeated Measures test*

Principal investigator, Jerry R. Mendell, M.D. of Nationwide Children's Hospital, will present this data via an oral presentation at the European Neuromuscular Centre (ENMC) Workshop today, December 7, 2012 at 4:20 p.m. UTC/GMT +1 hours/10:20 a.m. EDT. Dr. Mendell's presentation will be posted on the Sarepta website in the "Events & Presentations" section after the session is completed.

About Study 201 and Study 202 (Phase IIb Eteplirsen Study)

Study 4658-US-201 was conducted at Nationwide Children's Hospital in Columbus, Ohio. Twelve boys meeting the inclusion criteria being between 7 and 13 years of age with appropriate deletions of the dystrophin gene that confirm eligibility for treatment with an exon-51 skipping drug, received double-blind IV infusions of placebo (n=4), 30 mg/kg of eteplirsen (n=4), or 50 mg/kg of eteplirsen once weekly for 24 weeks (n=4). Muscle biopsies for evaluation of dystrophin were obtained at baseline for all subjects, and after 12 weeks for patients in the 50 mg/kg cohort and after 24 weeks for patients in the 30 mg/kg cohort. Two placebo patients were randomized to the 30 mg/kg cohort and two placebo patients were randomized to the 50 mg/kg cohort. This study design allowed Sarepta to investigate the relationship of dose and duration of eteplirsen treatment on the production of dystrophin over the course of the 24-week study.

Study 4658-US-202 is the extension study to 201 and continues to assess the long-term safety and efficacy of open-label eteplirsen. The four placebo patients were rolled over to open-label eteplirsen at week 24, with six patients on 30 mgs/kg, and six patients on 50 mgs/kg. Third biopsies occurred at 48 weeks in the original Study 201-treated patients, and at 24 weeks, the same time point, in the original placebo patients. 6MWT was performed at 32 weeks, 36 weeks, 48 weeks and will continue to be performed every 12 weeks going forward.

About Dystrophin

Dystrophin, a large structural protein, is critical to the stability of myofiber membranes in skeletal, diaphragmatic and cardiac muscle, protecting muscle fibers from contraction-induced damage. Loss of functional dystrophin destabilizes the dystroglycan protein complex, impairing its localization to the muscle membrane, and compromising the integrity of the membrane structure. The absence of functional dystrophin results in muscle membrane breakdown with muscle fibers being replaced by adipose and fibrotic tissue.

About the 6-Minute Walk Test

The 6-minute walk test (6MWT) was developed as an integrated assessment of cardiac, respiratory, circulatory, and muscular capacity (American Thoracic Society 2002) for use in clinical trials of various cardiac and pulmonary conditions. In recent years the 6MWT has been adapted to evaluate functional capacity in neuromuscular diseases and has served as the basis for regulatory approval of a number of drugs for rare diseases, with mean changes in the 6MWT ranging from 28 to 44 meters (Rubin 2002, Wraith 2004, Muenzer 2006). Additionally, published data from longitudinal natural history studies assessing dystrophinopathy, a disease continuum comprised of DMD and Becker muscular dystrophy, support the utility of the 6MWT as a clinically meaningful endpoint (McDonald C, et al, Muscle & Nerve, December 2010) in DMD. These data show that boys with DMD experience a significant decline in walking ability compared to healthy boys over one year, suggesting that slowing the loss of walking ability is a major treatment goal.

Modified Intent-to-Treat (mITT)

The 6MWT results were analyzed using the mITT population which excluded two patients who were randomized to the 30 mg/kg weekly eteplirsen cohort who showed signs of rapid disease progression within weeks after enrollment and were unable to perform measures of ambulation beyond 24 weeks. This mITT population consisted of 10 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).

About the Statistical Methodology

The Mixed Model Repeated Measures (MMRM) test was used for all statistical analyses of the 6MWT results, including for all subgroups. Analysis of Covariance (ANCOVA) for ranked data was used when the assumptions of normality of the dependent variable (the change in 6MWT distance from baseline) were violated. Baseline 6MWT scores and duration since diagnosis were included as covariates.

About Duchenne Muscular Dystrophy and Eteplirsen

Duchenne muscular dystrophy (DMD) is an X-linked rare, degenerative neuromuscular disorder causing severe, progressive muscle loss and a premature death. One of the most common fatal genetic disorders, DMD affects approximately one in every 3,500 boys worldwide. A devastating and incurable muscle-wasting disease, DMD is associated with specific errors in the gene that codes for dystrophin, a protein that plays a key structural role in muscle fiber function. Progressive muscle weakness eventually spreads to the arms, neck and other areas. Eventually, this progresses to complete paralysis and increasing difficulty in breathing due to respiratory muscle dysfunction requiring ventilatory support, as well as cardiac muscle dysfunction leading to heart failure. The condition is terminal, and death usually occurs before the age of 30.

Eteplirsen is Sarepta's lead drug candidate that is designed to address the underlying cause of DMD by enabling the production of a functional dystrophin protein. Data from clinical studies of eteplirsen in DMD patients have demonstrated a broadly favorable safety and tolerability profile and restoration of dystrophin protein expression. Eteplirsen uses Sarepta's novel phosphorodiamidate morpholino oligomer (PMO)-based chemistry and proprietary exon-skipping technology to skip exon 51 of the dystrophin gene enabling the repair of specific genetic mutations that affect approximately 13 percent of the total DMD population. By skipping exon 51, eteplirsen may restore the gene's ability to make a shorter, but still functional, form of dystrophin from messenger RNA, or mRNA. Promoting the synthesis of a truncated dystrophin protein is intended to improve, stabilize or significantly slow the disease process and prolong and improve the quality of life for patients with DMD.

Sarepta is also developing other PMO-based exon-skipping drug candidates intended to treat additional patients with DMD.

About Sarepta Therapeutics

Sarepta Therapeutics is focused on developing first-in-class RNA-based therapeutics to improve and save the lives of people affected by serious and life-threatening rare and infectious diseases. The Company's diverse pipeline includes its lead program eteplirsen, for Duchenne muscular dystrophy, as well as potential treatments for some of the world's most lethal infectious diseases. Sarepta aims to build a leading, independent biotech company dedicated to translating its RNA-based science into transformational therapeutics for patients who face significant unmet medical needs. For more information, please visit us at www.sareptatherapeutics.com.

Forward-Looking Statements and Information

This press release contains forward-looking statements. These forward-looking statements generally can be identified by use of words such as "believes or belief," "anticipates," "plans," "expects," "will," "intends," "potential," "possible," "advance" and similar expressions. These forward-looking statements include statements about the development of eteplirsen and its efficacy, potency and utility in the treatment of DMD and the potential for the creation of novel dystrophin to lead to significant clinical benefit over a longer course of treatment.

Each forward-looking statement contained in this press release is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statement. Applicable risks and uncertainties include, among others: subsequent clinical trials may fail to demonstrate the safety and efficacy of eteplirsen or replicate results; treatment of patients with DMD using eteplirsen over a longer duration may not lead to significant clinical benefit; any of Sarepta's drug candidates, including eteplirsen, may fail in development, may not receive required regulatory approvals, or be delayed to a point where they do not become commercially viable; and those identified under the heading "Risk Factors" in Sarepta's Quarterly Report on Form 10-Q for the three months ended September 30, 2012, and filed with the Securities and Exchange Commission.

Any of the foregoing risks could materially and adversely affect Sarepta's business, results of operations and the trading price of Sarepta's common stock. For a detailed description of risks and uncertainties Sarepta faces, you are encouraged to review the Company's filings with the Securities and Exchange Commission. We caution investors not to place considerable reliance on the forward-looking statements contained in this press release. Sarepta does not undertake any obligation to publicly update its forward-looking statements based on events or circumstances after the date hereof.

Sarepta Investor and Media Contact:
Erin Cox
425.354.5140
Email Contact