Sarepta Therapeutics Announces Eteplirsen Meets Primary Endpoint of Increased Novel Dystrophin and Achieves Significant Clinical Benefit on 6-Minute Walk Test After 48 Weeks of Treatment in Phase IIb Study in Duchenne Muscular Dystrophy

October 3, 2012 7:03 AM ET

Oct 03, 2012 (Marketwire via COMTEX) --Sarepta Therapeutics (NASDAQ: SRPT), a developer of innovative RNA-based therapeutics, today announced that treatment with its lead exon-skipping compound, eteplirsen, met the primary efficacy endpoint, increase in novel dystrophin, and achieved a significant clinical benefit on the primary clinical outcome, the 6-minute walk test (6MWT) over the placebo/delayed treatment cohort in a Phase IIb extension trial in Duchenne muscular dystrophy (DMD) patients.

Eteplirsen administered once weekly at either 30 mg/kg or 50 mg/kg for 48 weeks (n=8) resulted in a statistically significant increase ($p \leq 0.001$) 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 ($p \leq 0.009$).

"These data represent a significant milestone and a defining moment of progress and hope for patients with DMD and their families, as well as for those of us in the scientific community who have been pursuing potential treatments for this devastating and deadly disease for decades," said Jerry Mendell, M.D., Director of the Centers for Gene Therapy and Muscular Dystrophy at Nationwide Children's Hospital and principal investigator of the Phase IIb study. Dr. Mendell added, "By addressing the underlying cause of DMD, eteplirsen has demonstrated unparalleled effects on enabling dystrophin production and slowing the progression of the disease as measured by the 6-minute walk test, with no treatment associated adverse events. While eteplirsen is targeted to DMD patients with a specific genetic mutation, I think the implications for all DMD patients with related genetic mutations are clearly evident."

Eteplirsen administered once weekly at 50 mg/kg over 48 weeks resulted in an 89.4 meter benefit compared to patients who received placebo for 24 weeks followed by 24 weeks of treatment with eteplirsen in the open-label extension. In the predefined prospective analysis of the study's intent-to-treat (ITT) population on the primary clinical outcome measure, the change in 6MWT distance from baseline, 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 ANCOVA for ranked data). 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.

"We are extremely excited about these data, as they demonstrate that longer-term treatment with eteplirsen is translating to continued and unprecedented increases in both dystrophin production and clinical benefit across various subgroups of DMD patients involved in this study," said Chris Garabedian, President and CEO of Sarepta Therapeutics. "On a broader scale, these results signify the promise and tremendous potential of our RNA-based technology to impact and modulate disease at the genetic level, which may lead to first-ever opportunities to target serious and life-threatening rare conditions at the origin of disease."

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.

Summary of Dystrophin: Eteplirsen-Treated Patients in All Dose Groups through Week 48*

Treatment Arm	Mean Change from Baseline in % Dystrophin-Positive Fibers	p-value
Eterplirsen (both doses): 48 wks of Tx (n=8)	47.0	≤0.001
Eteplirsen 50 mg/kg (n=4)	41.7	≤0.008
Eteplirsen 30 mg/kg (n=4)	52.1	≤0.001

Placebo/Delayed Tx: 24 wks of Tx (n=4)	38.3	≤0.009
Placebo/50 mg/kg Delayed-Tx (n=2)	42.9	ns
Placebo/30 mg/kg Delayed-Tx (n=2)	34.2	ns

** Values based on Immunofluorescence using anti-dystrophin antibody MANDYS106*

Modified Intent-to-Treat (mITT)

The 6MWT results were further 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).

Summary of 6MWT: Eteplirsen versus Placebo/Delayed-Treatment to Week 48*

Treatment Arm	Mean Change from Baseline in 6MWT (meters)	Estimated Treatment Effect (Eteplirsen minus Placebo/Delayed-Tx)	p-value
Placebo/Delayed-Tx (n=4)	-60.3		
Eteplirsen 50 mg/kg (n=4)	+27.1	87.4 m	≤0.001
Eteplirsen Both Doses (n=6)	+7.3	67.3 m	≤0.001
Eteplirsen 30 mg/kg (n=2)	-31.5	28.8 m	ns

**Note: Analysis based on Mixed Model Repeated Measures test*

Summary of Additional Sub-Group Analyses at Week 48*

Subset	Mean 6MWT Change from Baseline (meters)	Estimated Treatment Benefit (Eteplirsen minus Placebo/delayed-Tx)	p-value
Placebo/delayed Tx: < 9.5 yrs at baseline (n=2; mean=7.6 yrs)	-42.3	58.9 m	≤0.038
Eteplirsen: < 9.5 yrs at baseline (n=3; mean=8.4 yrs)	+16.5		
Placebo/delayed Tx: ≥9.5 yrs at baseline (n=2; mean=10.1 yrs)	-63.5	52.1 m	ns
Eteplirsen: ≥9.5 yrs at baseline (n=3; mean=10.4 yrs)	-11.3		
Placebo/delayed Tx: Higher 6MWT baseline	-53.5	93.8 m	≤0.001

(n=2; mean=422m)			
Eteplirsen: Higher 6MWT baseline (n=3; mean=424m)	+40.3		
Placebo/delayed Tx: Lower 6MWT baseline (n=2; mean=367m)	-65.8	39.6 m	ns
Eteplirsen: Lower 6MWT baseline (n=3; mean=375m)	-26.2		
Placebo/delayed Tx: Genotype 49-50 deletion (n=3; age mean=9.2 yrs, 6MWT BL mean=397m)	-69.0	83.4 m	≤0.001
Eteplirsen: Genotype 49-50 deletion (n=2; age mean=9.1 yrs, 6MWT BL mean=383m)	+14.4		

** Note: Analysis based on Mixed Model Repeated Measures test*

An abstract describing the results from this Phase IIb extension study has been accepted as part of the World Muscle Society (WMS) Congress's Late-Breaking Science program in Perth, Australia during October 9 to October 13, 2012. Principal investigator, Jerry R. Mendell, M.D. of Nationwide Children's Hospital, will present the data via an oral presentation of the abstract titled, "Results at 48 Weeks of a Phase IIb Extension Study of the Exon-Skipping Drug Eteplirsen in Patients with Duchenne muscular dystrophy (DMD)." Dr. Mendell will present on October 13 at 4:00 p.m. WST UTC +8 hours/4:00 a.m. EDT. Dr. Mendell's presentation will be posted on the Sarepta website in the "Events & Presentations" section after the session is completed. In addition, Sarepta is sponsoring an educational symposium at WMS chaired by Professor Steve Wilton, PhD, Head of the Molecular Genetic Therapy Group and Director of Translational Research and Development, Australian Neuromuscular Research Institute at the University of Western Australia. Professor Wilton is a long-time collaborator of Sarepta's whose groundbreaking research has extended the use of antisense oligomers to DMD.

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.

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. The inclusion of the two patients with extreme scores due to rapid progression in the ITT population (n=12) resulted in a violation of the normality assumptions of the Change from Baseline in 6MWT data, and thus required the use of ANCOVA for ranked data. The exclusion of these two patients from the mITT population (n=10) resulted in the 6MWT data becoming normally distributed and the MMRM statistics exhibiting much improved residuals and fit statistics as compared to the ITT population. As such, the estimated mean values and their associated p-values for the mITT population were slightly different from those for the ITT population.

Conference Call and Slide Show

The Company will hold a conference call and broadcast a slide show today at 8:00 a.m. EDT (5:00 a.m. PDT) to discuss these results. The audio conference call may be accessed by dialing 866.356.3093 for domestic callers and 617.597.5381 for international callers. The passcode for the call is 93880948. Please specify to the operator that you would like to join the "Sarepta Therapeutics 48-Week Results Call." To view the slide show while using the audio dial-in please go to the events section of Sarepta's website at www.sareptatherapeutics.com. The call and slide show will also be webcast live under the events section and will be archived there following the call for 90 days. Please connect to Sarepta's website several minutes prior to the start of the broadcast to ensure adequate time for any software download that may be necessary. An audio replay will be available through October 10, 2012 by calling 888.286.8010 or 617.801.6888 and entering access code 67898748.

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

In order to provide Sarepta's investors with an understanding of its current results and future prospects, this press release contains statements that are forward-looking. Any statements contained in this press release that are not statements of historical fact may be deemed to be forward-looking statements. Words such as "believes," "anticipates," "plans," "expects," "will," "intends," "potential," "possible" and similar expressions are intended to identify forward-looking statements. 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.

These forward-looking statements involve risks and uncertainties, many of which are beyond Sarepta's control. Known risk factors include, among others: clinical trials may not demonstrate the safety and efficacy of eteplirsen and/or Sarepta's antisense-based technology platform; treatment of patients with DMD using eteplirsen over a longer duration may not lead to significant clinical benefit; and 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.

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. 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