Exon Skipping Drug Prevents Muscle Wasting and Maintains Muscle Function in Severely Affected, Dystrophin Deficient Mice

October 20, 2009 7:28 PM ET

New Publication in Molecular Therapy Outlines Dramatic Effects in Animals Treated with Splice Switching PPMO, Demonstrates Promise for Treatment of Duchenne Muscular Dystrophy

Publication Videos Show Remarkable Physical Improvement

For Immediate Release

Oxford, United Kingdom & Bothell, WA, USA — October 20, 2009 — An exon skipping PPMO has demonstrated dramatic effects in the prevention and treatment of severely affected, dystrophin and utrophin-deficient mice, preventing severe deterioration of the treated animals and extending their lifespan. These findings were published online today in the journal *Molecular Therapy* and support the promise of this therapeutic approach for the treatment of Duchenne muscular dystrophy (DMD). These results were published by researchers at University of Oxford, AVI BioPharma, Inc. (Nasdaq: AVII) and the University of Western Australia, Perth.

DMD is an incurable muscle–wasting disease associated with errors in the gene that makes dystrophin. Studies and research have shown that the ability to skip certain exons in dystrophin pre-mRNA could circumvent these dystrophin gene errors and provide a potential treatment for DMD patients. The paper "Prevention of Dystrophic Pathology in Severely Affected Dystrophin/Utrophin-deficient Mice by Morpholino-oligomer-mediated Exon-skipping" details the successful exon skipping and treatment of utrophin/dystrophin double knockout (dKO) mice with a cell-penetrating peptide-conjugated phosphorodiamidate morpholino oligomers (PPMO) targeting exon 23 in dystrophin pre-mRNA.

Videos accompanying the online publication show visual evidence of pronounced curving of the spine and dramatically reduced mobility as a result of deficiency of both dystrophin and utrophin proteins (dKO Mouse No Treatment/Supplementary Video S1). Treatment of affected mice from 10 days of age for six week with the mouse-specific PPMO at a dosage of 25 mg/kg/week resulted in a nearly complete skipping of exon 23 in all of the muscles examined except the heart. Skipping of exon 23 restored the reading frame of dystrophin mRNA and led to widespread continued translation of dystrophin protein. Treated dKO mice showed near normal measures for most of the examined parameters, including striking prevention of kyphosis and maintaining of near normal mobility. The publication also featured a video illustrating the impact of the treatment on the dKO mice (dKO Mouse Post-Treatment with PPMO/Supplementary Video S2).

"This research demonstrates remarkable prevention of dystrophic pathology and retained near normal muscle function in severely affected dKO mice following treatment with a PPMO," said Dame Kay Davies, Ph.D, Director of the MRC Functional Genomics Unit and Head of the Department of Physiology, Anatomy and Genetics at University of Oxford and senior author on the paper. "Notably, this study demonstrates for the first time the efficiency of such an exon-skipping approach in the dKO mouse, which is a much more severe and progressive mouse model of DMD. These findings, should they prove to be replicated in human studies, suggest great potential for the treatment of DMD patients with a PPMO."

"Antisense-mediated exon-skipping represents one of the most promising approaches for the treatment of DMD because of its capacity to correct the reading frame and restore dystrophin expression," said Steve Wilton, Ph.D. Professor at the Center for

Neuromuscular and Neurological Disorders, University of Western Australia, Perth, Western Australia, Australia and co-author of the study.

The dystrophin-deficient *mdx* mouse has historically been used as the primary model of DMD, although this mouse does not experience the severe, body-wide dystrophy that considerably shortens lifespan in humans. Therefore, double-knockout (dKO) mice, which present a much more severe and progressive dystrophic phenotype than *mdx* mice, could represent a more appropriate model to test the therapeutic potential of the antisense approach.

"In a very challenging model of severe DMD, this study confirms our belief that PPMO, a next generation of AVI drug candidates under development, holds great promise as a treatment for incurable muscle wasting in DMD patients," said Ryszard Kole, PhD, Senior Vice President of Discovery Research at AVI BioPharma and co-author of the study.

AVI BioPharma is developing AVI-4658 for the treatment of DMD. This first generation PMO drug candidate is designed to skip exon 51 of the dystrophin gene, allowing for restoration of the reading frame in the dystrophin mRNA sequence. Results from a Phase 1 proof-of-concept trial showed that injection of the drug into the muscles of a series of boys with DMD successfully induced dystrophin production in a dose-responsive manner. Further, the drug was well tolerated, with no significant drug–related adverse events detected. AVI is currently conducting an ongoing Phase 1b/2 dose-finding clinical trial evaluating the systemic delivery of AVI-4658 for treatment of DMD. This is an open label, 12-week safety trial, which includes measures of drug efficacy and pharmacokinetics and is being conducted in London, UK at the UCL Institute of Child Health / Great Ormond Street Hospital NHS Trust facilities and at the Royal Victoria Infirmary, Newcastle-Upon-Tyne, UK which is the coordinating center for the European Treat Neuromuscular Diseases (Treat-NMD) initiative.

AVI BioPharma is also developing a second generation chemistry exon skipping drugs, with a PPMO, AVI-5038, nearing IND submission for the treatment of DMD by skipping exon 50.

About Duchenne Muscular Dystrophy (DMD)

DMD is one of the most common fatal genetic disorders to affect children around the world. Approximately one in every 3,500 boys worldwide is afflicted with Duchenne Muscular Dystrophy with 20,000 new cases reported each year. It is a devastating and incurable muscle-wasting disease associated with specific inborn errors in the gene that codes for dystrophin, a protein that plays a key structural role in muscle fiber function. Symptoms usually appear in male children by age three. Progressive muscle weakness of the legs and pelvis eventually spreads to the arms, neck, and other areas. By age 10, braces may be required for walking, and most patients are confined to a wheelchair by age 12. Eventually, this progresses to complete paralysis and increasing difficulty in breathing, requiring ventilatory support. The condition is terminal and death usually occurs before the age of 30. The outpatient cost of care for a non-ambulatory DMD boy is among the highest of any disease. There is currently no cure for DMD, but for the first time ever, there are promising therapies in or moving into clinical development.

About University of Oxford

Oxford University's Medical Sciences Division is one of the largest biomedical research centres in Europe. It represents almost one-third of Oxford University's income and expenditure, and two-thirds of its external research income. Oxford's world-renowned global health programme is a leader in the fight against infectious diseases (such as malaria, HIV/AIDS, tuberculosis and avian flu) and other prevalent diseases (such as cancer, stroke, heart disease and diabetes). Key to its success is a long-standing network of dedicated Wellcome Trust-funded research units in Asia (Thailand, Laos and Vietnam) and Kenya, and work at the MRC Unit in The Gambia. Long-term studies of patients around the world are supported by basic science at Oxford and have led to many exciting developments, including potential vaccines for tuberculosis, malaria and HIV, which are in clinical trials.

About AVI BioPharma

AVI BioPharma is focused on the discovery and development of RNA–based drugs utilizing proprietary derivatives of its antisense chemistry (morpholino-modified phosphorodiamidate oligomers or PMOs) that can be applied to a wide range of diseases and genetic disorders through several distinct mechanisms of action. Unlike other RNA therapeutic approaches, AVI's antisense technology has been used to directly target both messenger RNA (mRNA) and its precursor (pre-mRNA), allowing for both up- and down-regulation of targeted genes and proteins. AVI's RNA–based drug programs are being evaluated for the treatment of Duchenne muscular dystrophy as well as for the treatment of cardiovascular restenosis through our partner Global Therapeutics, a Cook Group Company. AVI's antiviral programs have demonstrated promising outcomes in Ebola Zaire and Marburg Musoke virus infections and may prove applicable to other viral targets such as HCV or Dengue viruses. For more information, visit www.avibio.com.