

Press Release

Astellas Announces Data from ASPIRO Study in X-linked Myotubular Myopathy Published in *The Lancet Neurology*

Preliminary data analysis on ventilator dependence and motor improvement are reported alongside overall safety findings

TOKYO, November 15, 2023 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Naoki Okamura, "Astellas") today announced that *The Lancet Neurology* published a preliminary data analysis from the ASPIRO trial, evaluating the safety and efficacy of investigational AT132 (resamirigene bilparvovec), an adeno-associated viral vector (AAV) gene replacement therapy designed to deliver a functional human *MTM1* gene for the treatment of pediatric patients with X-linked myotubular myopathy (XLMTM). The AT132 IND and ASPIRO trial are currently on clinical hold. The manuscript was first published online on November 15th and will be available in the December 2023 print issue of *The Lancet Neurology*.

Perry B. Shieh, M.D., Ph.D., Professor of Neurology and Pediatrics, University of California Los Angeles, and Principal Investigator for ASPIRO

“There is a real need for treatments for these patients. These preliminary data document for the first time that there is potential for gene therapy to provide clinical improvements in patients with XLMTM, including improvement in ventilator dependence and achievement of major motor milestones. Additionally, important issues related to liver health in participants with XLMTM receiving gene therapy have been identified and will continue to require careful evaluation.”

Richard Wilson, Senior Vice President, Primary Focus Lead, Genetic Regulation, Astellas

“We are grateful for the opportunity to share this important analysis. We are focused on patients and the potential impact of gene therapy and are driven to deliver transformational benefits for people living with rare genetic diseases. While we continue our efforts to address the ongoing clinical hold for ASPIRO, this publication serves to provide information that may guide efforts aimed at advancing promising therapies for XLMTM.”

The manuscript reports data as of February 28, 2022. At the time of this data cut, the study included 24 boys with XLMTM dosed with AT132. An exploratory analysis was conducted of two dosing cohorts (lower-dose at 1.3×10^{14} vg/kg and higher-dose at 3.5×10^{14} vg/kg) who received a single infusion of AT132, compared with a control group comprised of two subjects who were enrolled but not dosed and 12 children from a natural history study.

At baseline, all participants were ventilator dependent, three were able to sit independently for 30 seconds, and none had achieved more advanced milestones. By 24 weeks post-dosing,

the lower-dose cohort demonstrated an estimated 77.7% (95% CI: 40.22, 115.24) greater reduction in mean hours of ventilator support from baseline compared with controls (p=0.0002). The higher-dose cohort demonstrated an estimated 22.8% (95% CI 6.15, 39.37) greater reduction from baseline compared with controls (p=0.0077). Of the 24 boys dosed in the study, 16 participants, including six at the lower-dose and 10 at the higher-dose, achieved ventilator independence as of the data cut. Five participants at the lower-dose and three participants in the higher-dose cohort were able to walk independently; several other major motor milestones were achieved after gene therapy.

There were three deaths in the higher-dose cohort (18%), followed by one death in the lower-dose cohort (14%). All four participants had ongoing hepatic and hepatobiliary serious adverse events (SAEs), which had progressed to cholestatic liver failure at the time of death. Treatment-emergent SAEs were observed in two of the seven participants at the lower-dose, and nine of 17 at the higher-dose. Five of the 20 surviving dosed participants had hepatobiliary SAEs.

Of the 14 participants in the non-treated cohort (two in the control group and 12 from a natural history study), none achieved ventilator independence while five were able to sit unassisted for 30 seconds by the end of the 48-week period. No other motor milestones were achieved.

These data demonstrate the potential of a therapeutic approach for myotubularin replacement using recombinant AAV gene therapy.

About X-linked Myotubular Myopathy

XLMTM is a serious, life-threatening, rare neuromuscular disease that is characterized by extreme muscle weakness, respiratory failure and early death. Mortality rates are estimated to be 50 percent in the first 18 months of life. For those patients who survive past infancy, there is an estimated additional 25 percent mortality by the age of 10. XLMTM is caused by mutations in the MTM1 gene that lead to a lack or dysfunction of myotubularin, a protein that is needed for normal development, maturation and function of skeletal muscle cells. The disease affects approximately 1 in 40,000 to 50,000 newborn males.

XLMTM places a substantial burden of care on patients, families and the healthcare system, including high rates of healthcare utilization, hospitalization and surgical intervention. More than 80 percent of XLMTM patients require ventilator support, and the majority of patients require a gastrostomy tube for nutritional support. In most patients, normal developmental motor milestones are delayed or never achieved. Currently, only supportive treatment options, such as ventilator use or a feeding tube, are available.

About AT132 for the treatment of X-linked Myotubular Myopathy

Astellas is developing AT132, an AAV8 vector containing a functional copy of the MTM1 gene, for the treatment of XLMTM. AT132 may provide patients with improved outcomes based on the ability of AAV8 to target skeletal muscle and increase myotubularin expression in targeted tissues following a single intravenous administration. The preclinical development of AT132 was conducted in collaboration with Genethon (www.genethon.fr).

AT132 has been granted Regenerative Medicine and Advanced Therapy (RMAT), Rare Pediatric Disease, Fast Track, and Orphan Drug designations by the U.S. Food and Drug Administration (FDA), and Priority Medicines (PRIME) and Orphan Drug designations by the European Medicines Agency (EMA).

About ASPIRO

ASPIRO is a two-part, multinational, randomized, open-label ascending dose trial to evaluate the safety and preliminary efficacy of AT132 in XLMTM patients less than five years of age. Primary endpoints include safety (adverse events and certain laboratory measures) and efficacy (assessments of neuromuscular and respiratory function). Secondary endpoints include the burden of disease and health-related quality-of-life, and muscle tissue histology and biomarkers.

About Astellas

Astellas Pharma Inc. is a pharmaceutical company conducting business in more than 70 countries around the world. We are promoting the Focus Area Approach that is designed to identify opportunities for the continuous creation of new drugs to address diseases with high unmet medical needs by focusing on Biology and Modality. Furthermore, we are also looking beyond our foundational Rx focus to create Rx+® healthcare solutions that combine our expertise and knowledge with cutting-edge technology in different fields of external partners. Through these efforts, Astellas stands on the forefront of healthcare change to turn innovative science into VALUE for patients. For more information, please visit our website at <https://www.astellas.com/en>.

About Astellas Gene Therapies

Astellas Gene Therapies is an Astellas Center of Excellence developing genetic medicines with the potential to deliver transformative value for patients. Our gene therapy drug discovery engine is built around innovative science, a validated AAV platform, and industry leading internal manufacturing capability with a particular focus on rare diseases of the eye, CNS and neuromuscular system. Astellas Gene Therapies will also be advancing additional Astellas gene therapy programs toward clinical investigation. Astellas Gene Therapies is based in San Francisco, with manufacturing and laboratory facilities in South San Francisco, Calif., Sanford, N.C. and Tsukuba, Japan.

Astellas Cautionary Notes

In this press release, statements made with respect to current plans, estimates, strategies and beliefs and other statements that are not historical facts are forward-looking statements about the future performance of Astellas. These statements are based on management's current assumptions and beliefs in light of the information currently available to it and involve known and unknown risks and uncertainties. A number of factors could cause actual results to differ materially from those discussed in the forward-looking statements. Such factors include, but are not limited to: (i) changes in general economic conditions and in laws and regulations, relating to pharmaceutical markets, (ii) currency exchange rate fluctuations, (iii) delays in new product launches, (iv) the inability of Astellas to market existing and new products effectively, (v) the inability of Astellas to continue to effectively research and develop products accepted by customers in highly competitive markets, and (vi) infringements of Astellas' intellectual property rights by third parties. Information about pharmaceutical products (including products currently in development) which is included in this press release is not intended to constitute an advertisement or medical advice. AT132 is an investigational gene therapy: there is no guarantee that AT132 will receive regulatory approval or become commercially available for XLMTM.

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