Govorestat (AT-007) Receives Orphan Medicinal Product Designation from the EMA for Treatment of SORD Deficiency

May 25, 2023

- *EMA Orphan Designation reflects high unmet need in SORD Deficiency and benefit of govorestat treatment in reducing toxic sorbitol levels*
- *New data published in Journal of Clinical Investigation further elucidates the molecular pathophysiology of SORD neuropathy and the role of sorbitol in neuronal toxicity*

NEW YORK, May 25, 2023 (GLOBE NEWSWIRE) -- Applied Therapeutics, Inc. (Nasdaq: APLT), a clinical-stage biopharmaceutical company developing a pipeline of novel drug candidates against validated molecular targets in indications of high unmet medical need, today announced that AT-007 (govorestat) has been granted orphan medicinal product designation by the European Medicines Agency (EMA) for treatment of Sorbitol Dehydrogenase (SORD) Deficiency. Additionally, the Company announced that new data has been published in the Journal of Clinical Investigation on govorestat treatment in models of SORD Deficiency.

EMA Orphan Medicinal Product Designation of AT-007 (govorestat) in SORD Deficiency

“We are pleased that the EMA has recognized the high unmet medical need in SORD Deficiency, and the benefit of govorestat treatment in reducing toxic sorbitol levels in patients with SORD Deficiency as well as preventing disease progression in the animal model of disease,” said Shoshana Shendelman, PhD, Founder and CEO of Applied Therapeutics. “Orphan designation for govorestat marks an important step towards advancing our regulatory initiatives in Europe.”

Orphan medicinal product designation provides certain benefits and incentives in the EU, including protocol assistance, fee reductions, and ten years of market exclusivity once the medicine is on the market. Applied Therapeutics has partnered govorestat for treatment of SORD Deficiency as well as Galactosemia in Europe with ADVANZ Pharma.

Sorbitol reduction via govorestat ameliorates synaptic dysfunction and neurodegeneration in sorbitol dehydrogenase deficiency
Yi Zhu, Amanda G. Lobato, Adriana P. Rebelo, Tijana Canic, Natalie Ortiz-Vega, Xianzun Tao, Sheyum Syed, Christopher Yanick, Mario Saporta, Michael Shy, Riccardo Perfetti, Shoshana Shendelman, Stephan Züchner, R. Grace Zhai
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The new data on govorestat treatment in models of SORD Deficiency was recently published in the Journal of Clinical Investigation. The article can be accessed here.

https://insight.jci.org/articles/view/164954/pdf

The molecular and cellular pathophysiology of SORD neuropathy was investigated through use of patient-derived cells and a drosophila model of disease, finding reduced adenosine triphosphate (ATP) production and reactive oxygen species (ROS) accumulation in the central nervous system (CNS) and muscle, indicating mitochondrial dysfunction as a result of increased sorbitol accumulation. Govorestat treatment significantly reduced sorbitol levels in patient-derived fibroblasts, patient iPSC-derived motor neurons, and SORD-deficient drosophila. Govorestat treatment in the SORD drosophila model mitigated synaptic degeneration and significantly improved synaptic transduction, locomotor activity, and mitochondrial function. Moreover, govorestat treatment significantly reduced ROS accumulation in patient derived cells and drosophila CNS and muscle. These findings uncover the molecular and cellular pathophysiology of sorbitol toxicity in SORD neuropathy, and govorestat provides a potential treatment strategy for patients with SORD Deficiency.

About Sorbitol Dehydrogenase (SORD) Deficiency

Sorbitol Dehydrogenase Deficiency (SORD Deficiency) is a rare, progressive, debilitating hereditary neuropathy that affects peripheral nerves and motor neurons. SORD Deficiency is one of the most common forms of recessive hereditary neuropathy and affects approximately 3,300 patients in the U.S. and 4,000 patients in Europe. The disease is caused by a lack of the enzyme sorbitol dehydrogenase, responsible for the metabolism of sorbitol, which causes sorbitol to accumulate at high levels and become toxic to the body. Intracellular sorbitol accumulation results in significant disability, loss of sensory function, neuromuscular dysfunction, and decreased mobility.

About Govorestat (AT-007)

Govorestat is a central nervous system (CNS) penetrant Aldose Reductase inhibitor (ARI) in development for the treatment of several rare neurological diseases, including Galactosemia, SORD Deficiency, and PMM2-CDG.

In a study in children with Galactosemia aged 2-17, treatment with AT-007 demonstrated clinical benefit on activities of daily living, behavioral symptoms, cognition, fine motor skills and tremor. Govorestat also significantly reduced plasma galactitol levels in both adults and children with Galactosemia. Galactitol is a toxic metabolite responsible for tissue damage and long-term complications in Galactosemia.

Govorestat is also being studied in the ongoing Phase 3 INSPIRE trial, which is evaluating the effect of AT-007 vs. placebo in patients with SORD

Deficiency on sorbitol reduction as well as clinical outcomes in approximately 50 patients aged 16-55 in the US and Europe. In an interim analysis, AT-007 reduced sorbitol by a mean of 52%, or approximately 16,000 ng/ml, over a 90-day period, which was highly statistically significant vs. placebo ($p<0.001$).

Govorestat has received Orphan Medicinal Product Designation from the European Medicines Agency (EMA) for both Galactosemia and SORD Deficiency. Govorestat has also received Orphan Drug Designation from the U.S. Food and Drug Administration (FDA) for the treatment of Galactosemia, PMM2-CDG, and SORD Deficiency; Pediatric Rare Disease designation for Galactosemia and PMM2-CDG; and Fast Track designation for Galactosemia.

About Applied Therapeutics

Applied Therapeutics is a clinical-stage biopharmaceutical company developing a pipeline of novel drug candidates against validated molecular targets in indications of high unmet medical need. The Company's lead drug candidate, govorestat, is a novel central nervous system penetrant Aldose Reductase Inhibitor (ARI) for the treatment of CNS rare metabolic diseases, including Galactosemia, SORD Deficiency, and PMM2-CDG. The Company is also developing AT-001, a novel potent ARI, for the treatment of Diabetic Cardiomyopathy, or DbCM, a fatal fibrosis of the heart. The preclinical pipeline also includes AT-003, an ARI designed to cross through the back of the eye when dosed orally, for the treatment of Diabetic retinopathy.

To learn more, please visit www.appliedtherapeutics.com and follow the company on Twitter @Applied_Tx.

Forward-Looking Statements

This press release contains "forward-looking statements" that involve substantial risks and uncertainties for purposes of the safe harbor provided by the Private Securities Litigation Reform Act of 1995. Any statements, other than statements of historical fact, included in this press release regarding strategy, future operations, prospects, plans and objectives of management, including words such as "may," "will," "expect," "anticipate," "plan," "intend," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are forward-looking statements. Forward-looking statements in this release involve substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by the forward-looking statements, and we, therefore cannot assure you that our plans, intentions, expectations, or strategies will be attained or achieved.

Such risks and uncertainties include, without limitation, factors that may cause actual results to differ from those expressed or implied in the forward-looking statements in this press release are discussed in our filings with the U.S. Securities and Exchange Commission, including the "Risk Factors" contained therein. Except as otherwise required by law, we disclaim any intention or obligation to update or revise any forward-looking statements, which speak only as of the date they were made, whether as a result of new information, future events or circumstances or otherwise.

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