Applied Therapeutics

SORD Program Update

October 25, 2021

APPLIED THERAPEUTICS

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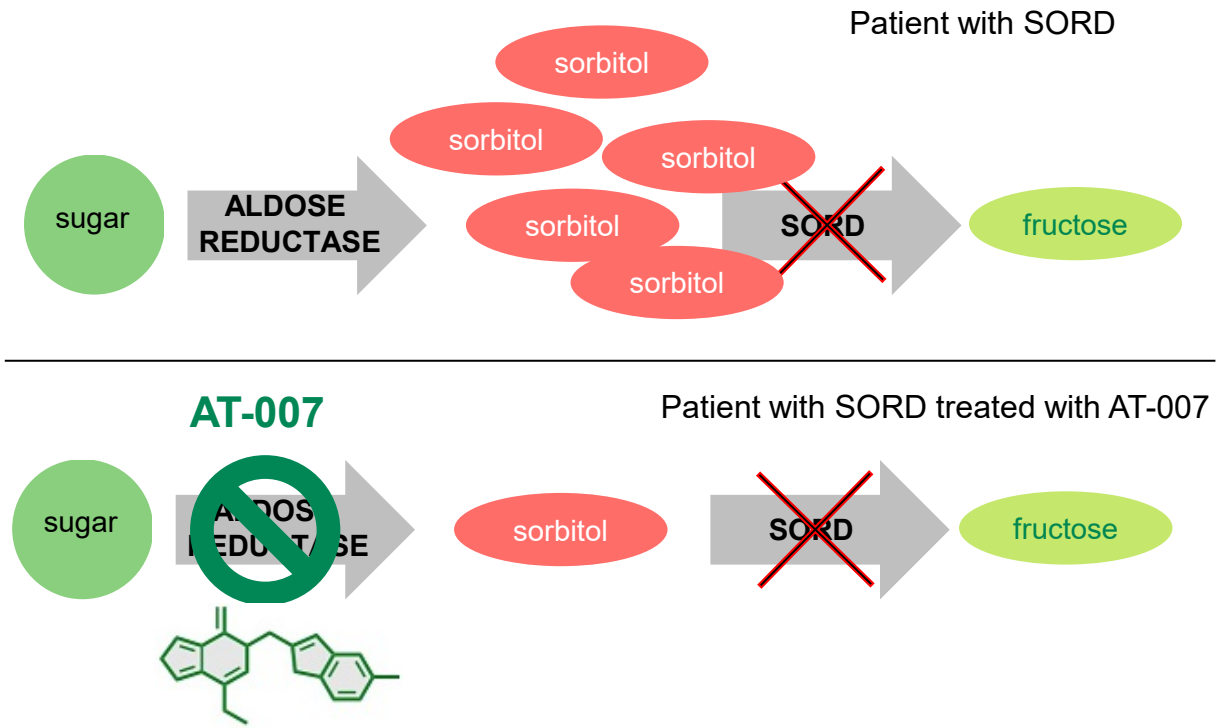
SORD Deficiency is One of the Most Common Recessive Causes of Hereditary Neuropathy, Impacting ~3,000 US Patients

- **Sorbitol Dehydrogenase Deficiency** (SORD Deficiency) is a progressive, debilitating hereditary neuropathy that affects peripheral nerves and motor neurons, resulting in significant disability, loss of sensory function and decreased mobility
- Recently identified mutations in the SORD gene resulting in **loss of enzyme Sorbitol Dehydrogenase (SORD) function** and consequent **intracellular sorbitol accumulation**
- Previously, these patients were diagnosed as a subset of patients with Charcot-Marie-Tooth disease Type 2 (CMT2) or Distal Hereditary Motor Neuropathy (dHMN)
- **~3,300 individuals in the US with SORD Deficiency** (~7-9% CMT2/dHMN patients)
- SORD's **role in metabolism is well defined**, and an understanding of this genetic and biochemical basis of disease offers **new opportunities for treatment** of patients with neuropathy caused by SORD deficiency

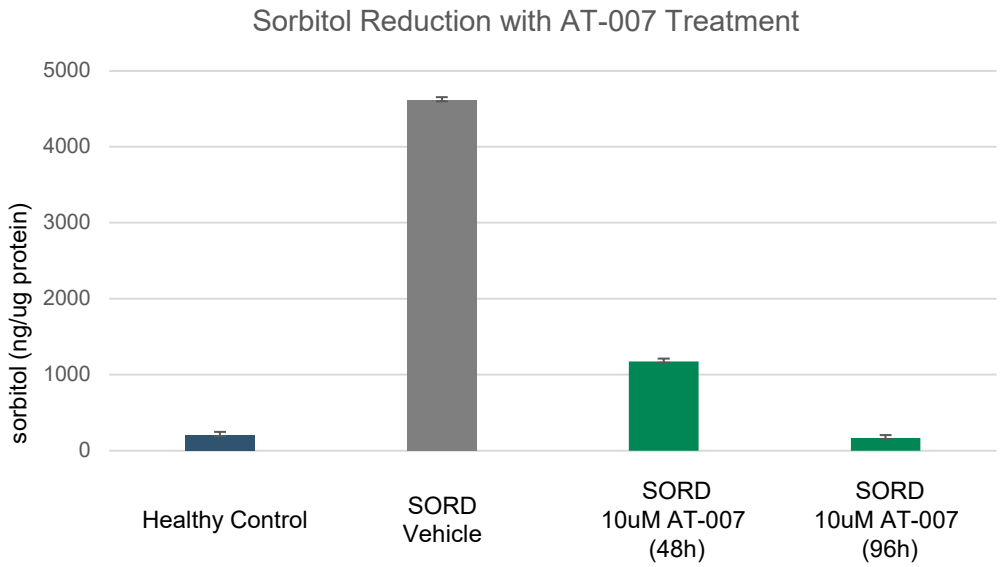
Aldose Reductase Inhibition Addresses the Underlying Cause of SORD by Preventing Conversion of Glucose to Sorbitol



- Patients have very high levels of sorbitol in their cells and tissues as a result of SORD enzyme deficiency
- High toxic sorbitol levels results in cell death and tissue degeneration, such as neuropathy.[1-2]
- AT-007 blocks conversion of glucose to sorbitol, reducing sorbitol levels (substrate reduction)

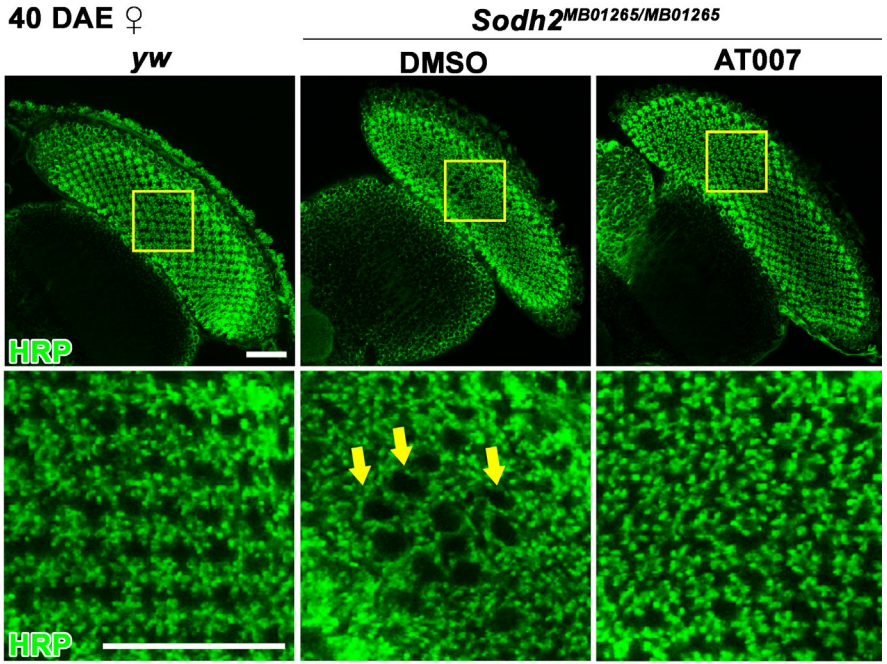
1. Cortese A, et al. *Nat Genet* 2020;52:473–481. 2. Morava E. *Nat Genet* 2020;52:469–470;

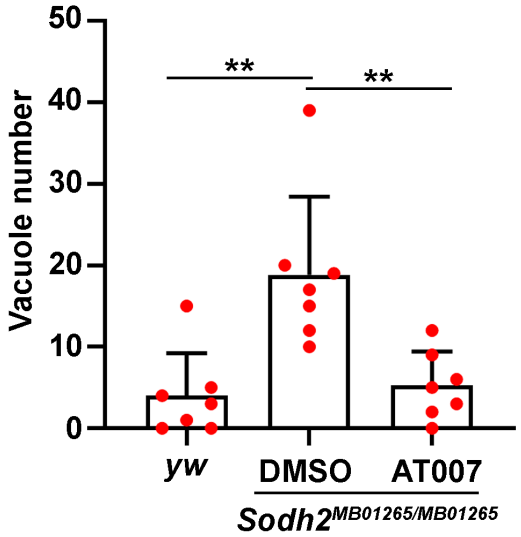
AT-007 Treatment Significantly Reduced Sorbitol Levels in SORD Fibroblasts



Applied Therapeutics, data on file; pilot study

AT-007 Treatment Ameliorated the Disease Phenotype in Drosophila

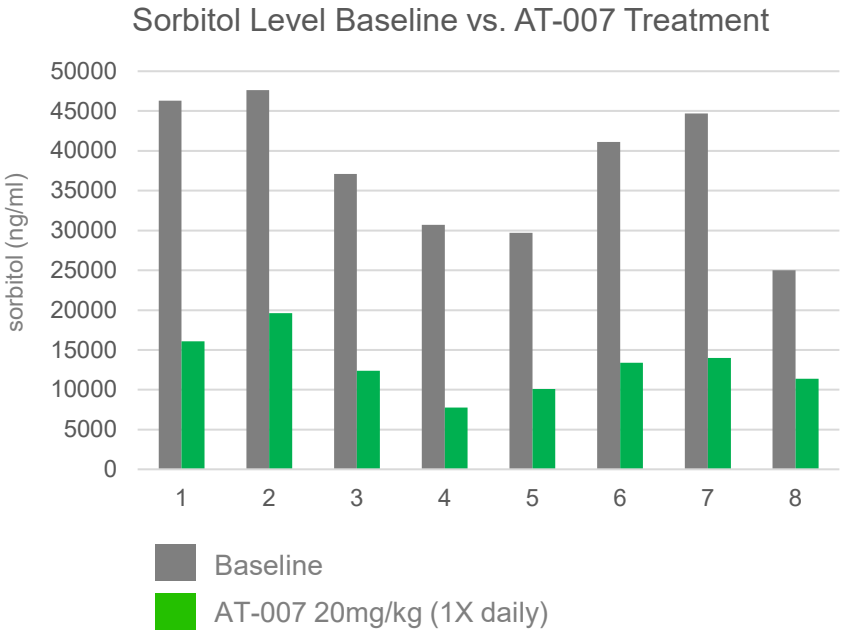


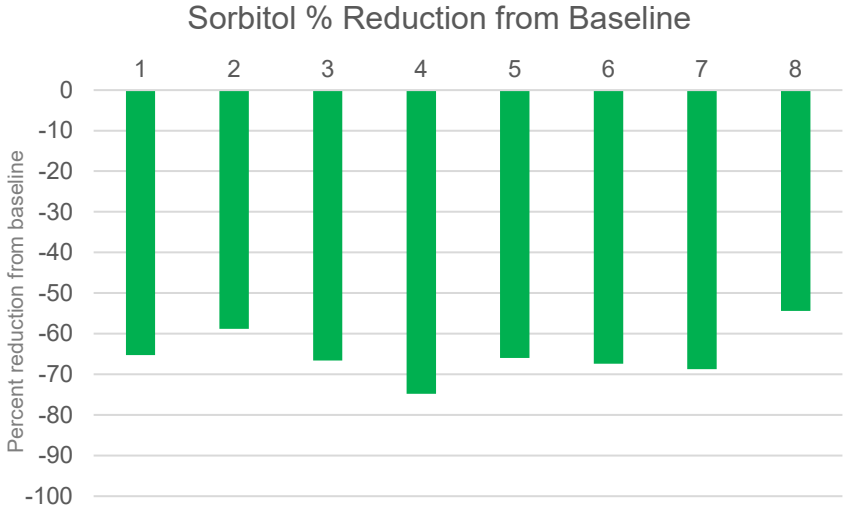


SORD mutant flies were treated with vehicle (DMSO) or 20ug/ml AT-007 in food for 40 days after eclosion (DAE). AT-007 treatment completely prevented neuronal degeneration in SORD mutant flies, as visualized by presence/absence of vacuolar structures.

AT-007 Substantially Reduced Sorbitol in Patients with SORD Deficiency in 30-Day Open-Label Pilot Trial

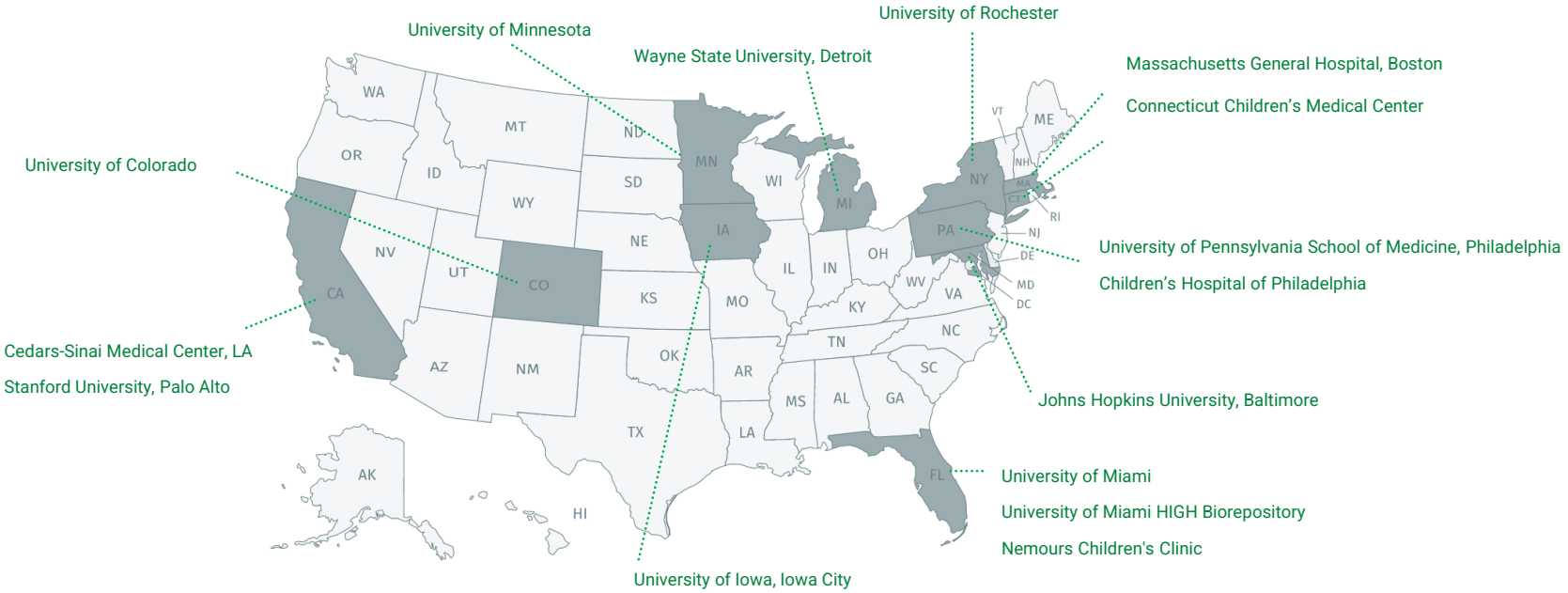
Pilot open-label study data in 8 SORD patients demonstrated mean reduction from baseline of 66% (range 54%-75%)





Mean baseline sorbitol level was ~38,000ng/ml

Inherited Neuropathy Consortium Centers of Excellence and Global CMT Registries Exist to Support Trial Enrollment & SORD Patient Treatment



Available from: https://www.rarediseasesnetwork.org/cms/inc/centers#CSMC. Last accessed August 25, 2020

AT-007: Potential First Therapy for SORD Deficiency

High Unmet Need in SORD

- No approved therapies; limited pipeline for generalized CMT2
- Causes substantial decrease in patient QoL
- Diagnosed in early stage, where treatment may prevent disability progression and positively impact prognosis and QoL

AT-007 Opportunity

- Validated mechanism of action, penetrates CNS
- Favorable safety & tolerability profile
- Convenient oral dosing to optimize adherence and minimize patient burden
- Sorbitol reduction biomarker based clinical development for Accelerated Approval
- Registrational study start expected Q4 2021

AT-007 is expected to be the first disease-modifying therapy for SORD, targeting the underlying cause of disease