

AT-007 Significantly Lowers Blood Sorbitol Levels in Patients with Hereditary Neuropathy Resulting from Sorbitol Dehydrogenase (SORD) Deficiency

Poster 53; E-Poster 1203

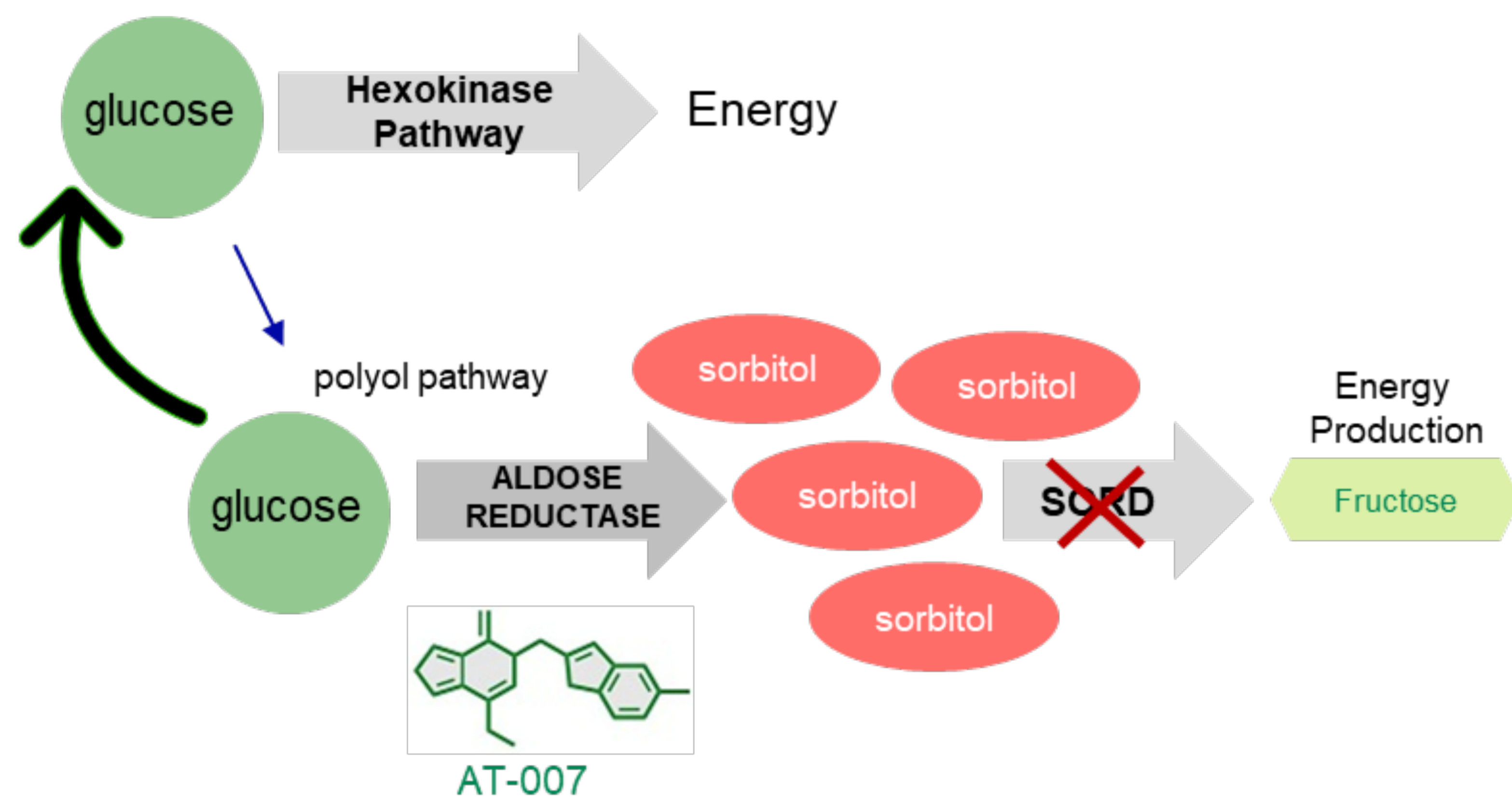
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Introduction

- Sorbitol Dehydrogenase Deficiency (SORD Deficiency) is a rare, progressive, debilitating, hereditary neuropathy^{1,2}.
- SORD Deficiency affects approximately 3,300 patients in the US and 4,000 patients in Europe.
- Prior to the identification of the specific gene defect, patients with SORD Deficiency were classified symptomatically into the broader neurological diseases Charcot-Marie-Tooth Type 2 (CMT2) or distal Hereditary Motor Neuropathy (dHMN).¹

SORD DEFICIENCY PATHOGENESIS

- SORD is the second enzyme in the two-step polyol pathway, an alternative glucose metabolism pathway.¹
- Patients with SORD Deficiency are unable to process sorbitol, which leads to the accumulation of this toxic metabolite in the blood and tissues.¹



- In vitro* and *in vivo* studies have recently demonstrated that treatment with AT-007 prevents accumulation of sorbitol in a SORD-deficient animal model of disease and in cultured human fibroblasts from SORD Deficiency patients.³

Objectives

This open-label pilot study was designed to evaluate the effect of AT-007 treatment on blood sorbitol levels in a cohort of patients with SORD Deficiency.

Methods

- Nine patients were referred to the study as potentially having SORD Deficiency. Whole blood sorbitol and genetic testing confirmed that 8 out of the 9 patients had SORD Deficiency; 1 unconfirmed patient with a non-pathogenic SORD polymorphism was removed from the study.
- Pharmacokinetic and pharmacodynamic parameters were evaluated during the study following exposure to AT-007 at 20mg/kg once daily liquid suspension for up to 30 days.
- Circulating whole blood sorbitol levels were measured by a validated LC-MS-MS assay.
- Genetic testing was performed via GeneDx whole exome sequencing
- 2 out of 8 patients opted to complete the study after 7 days of treatment instead of 30 days due to personal reasons (time commitments, frequent blood draws), not due to safety or tolerability concerns

Results

BASELINE DEMOGRAPHICS

- 4 female and 4 male patients age 19-54 with SORD Deficiency were included in the study
- All patients displayed the most common SORD genetic mutation c753delG, which results in a frameshift leading to absence of detectable SORD enzyme

Patient	Age	Gender	Genetics
1	23	Male	Homozygous c.753delG; p.Ala253GlnfsTer27
2*	32	Male	Homozygous c.753delG; p.Ala253GlnfsTer27
3*	20	Male	Homozygous c.753delG; p.Ala253GlnfsTer27
4	42	Female	Homozygous c.753delG; p.Ala253GlnfsTer27
5	19	Female	Homozygous c.753delG; p.Ala253GlnfsTer27
6	41	Male	Homozygous c.753delG; p.Ala253GlnfsTer27
7	54	Female	Homozygous c.753delG; p.Ala253GlnfsTer27
8	28	Female	Homozygous c.753delG; p.Ala253GlnfsTer27

*Patients 2 & 3 opted to complete the study after 7 days of treatment instead of 30 days due to personal reasons (time commitments, frequent blood draws), not due to safety or tolerability concerns

Results (cont'd)

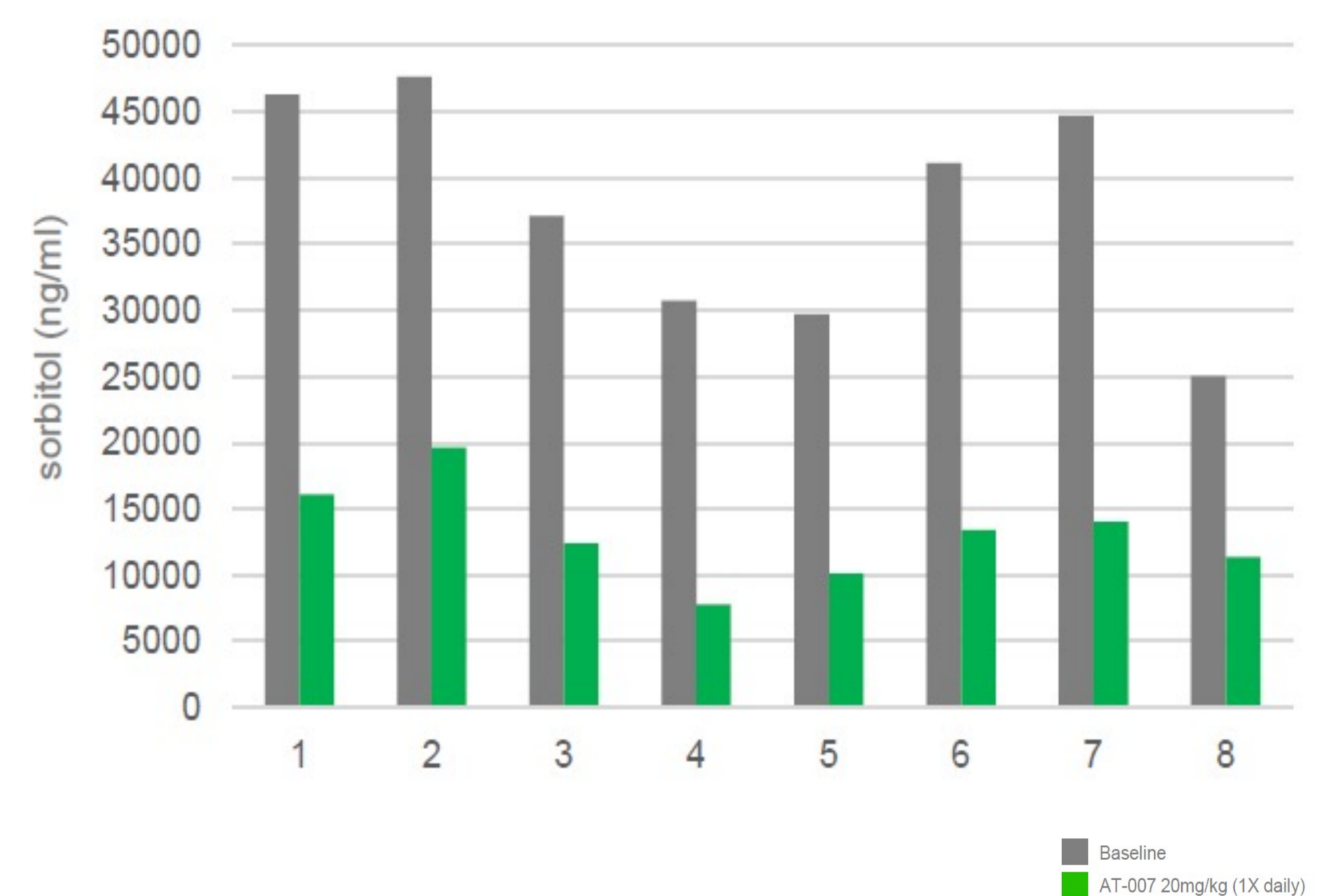
SAFETY, TOLERABILITY, PHARMACOKINETICS

- AT-007 (20mg/kg/day) was generally safe and tolerated.
- AT-007 pharmacokinetic characteristics in patients with SORD Deficiency were similar to those previously demonstrated in healthy volunteers and supported a once daily dosing regimen.

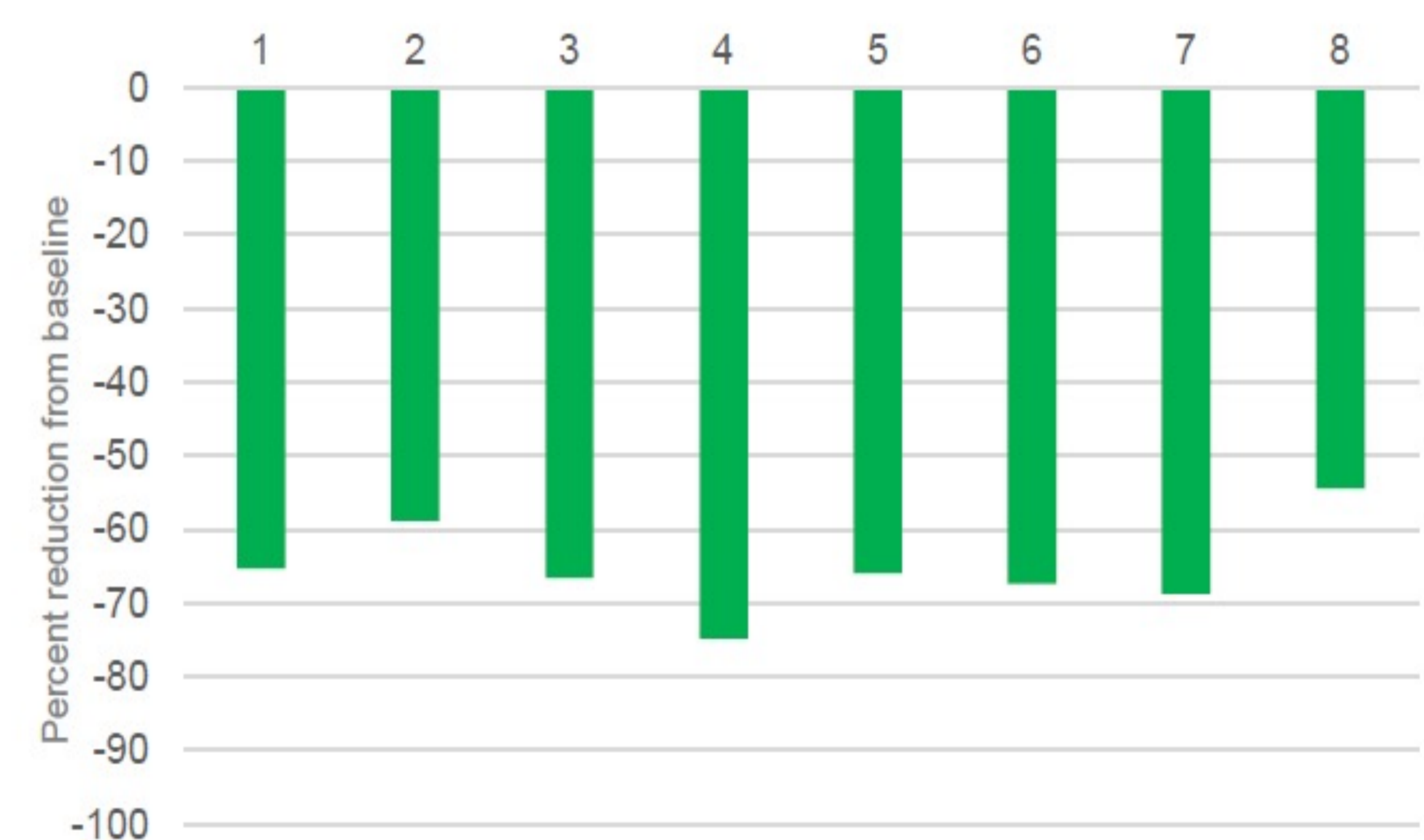
AT-007 REDUCED BLOOD SORBITOL LEVELS

- The mean circulating sorbitol level at baseline was approximately 38,000 ng/ml, which corresponds to a ~100-fold increase when compared with healthy individuals without SORD Deficiency.
- AT-007 reduced whole blood sorbitol levels by a mean of 66% (range 54–75%) from baseline.

Sorbitol Level Baseline vs. AT-007 Treatment



Sorbitol % Reduction from Baseline



Conclusions and future directions

- AT-007 was generally safe and well tolerated.
- AT-007 treatment reduced sorbitol levels substantially from baseline.
- The ongoing placebo-controlled Phase 2/3 INSPIRE study is evaluating the impact of AT-007 treatment on sorbitol reduction and clinical outcomes in patients with SORD Deficiency

Acknowledgements

Thank you to all the patients who participated in this pilot study and their families, the study investigators and staff, as well our colleagues at Applied Therapeutics who have enabled this research to take place.

References

- Cortese A, et al. Nat Genet 2020;52:473–481; 2. Lassuthova P et al. Sc Reports 2021; 11:8443; 3. Oral presentation Peripheral Nerve Society Annual meeting 2021: Pre-Clinical Treatment Studies of SORD Neuropathy with Novel Aldose Reductase Inhibitor (Rebello et al).

Disclosures

This research was funded by Applied Therapeutics Inc.