Applied Therapeutics Rare Disease Forum

March 23, 2021

APPLIED THERAPEUTICS

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Rare Disease Forum Agenda

Topic	Speaker
Welcome & Introduction	Shoshana Shendelman, PhD, CEO & Founder, Applied Therapeutics
ACTION-Galactosemia Kids Program Update	Francesca Lawson, MD, FAHA, Head of Development, Applied Therapeutics
SORD Neuropathy Disease Overview	Stephan Züchner, MD, PhD, University of Miami School of Medicine, Chair, Dept of Genetics
SORD Neuropathy Clinical Program	Shoshana Shendelman, PhD, CEO & Founder, Applied Therapeutics
SORD Patient Video	Jill, Constantino (Parents) & Vittorio Ricci (Young Adult with SORD)
PMM2-CDG Disease Overview	Joseph Muenzer, MD, PhD, University of North Carolia School of Medicine, Prof. Dept of Pediatric Metabolism & Genetics
PMM2-CDG Clinical Program	Shoshana Shendelman, PhD, CEO & Founder, Applied Therapeutics
PMM2-CDG Patient Video	Kara & Carl Berasi Parents of a Child with PMM2-CDG)
Q&A	Applied Therapeutics Management Team Dr. Stephan Züchner, MD, PhD Dr. Joseph Muenzer, MD, PhD

Applying Science to Transform Lives

Our mission is to create transformative, life-changing treatments for patients who desperately need them

SCIENCE

Targeting pathways with known roles in pathogenesis

Novel compounds with improved potency/selectivity

DEVELOPMENT

Clinical efficacy confirmed via biomarkers

Pursuing expedited regulatory pathways

MARKET

Fatal or debilitating diseases with no approved therapies

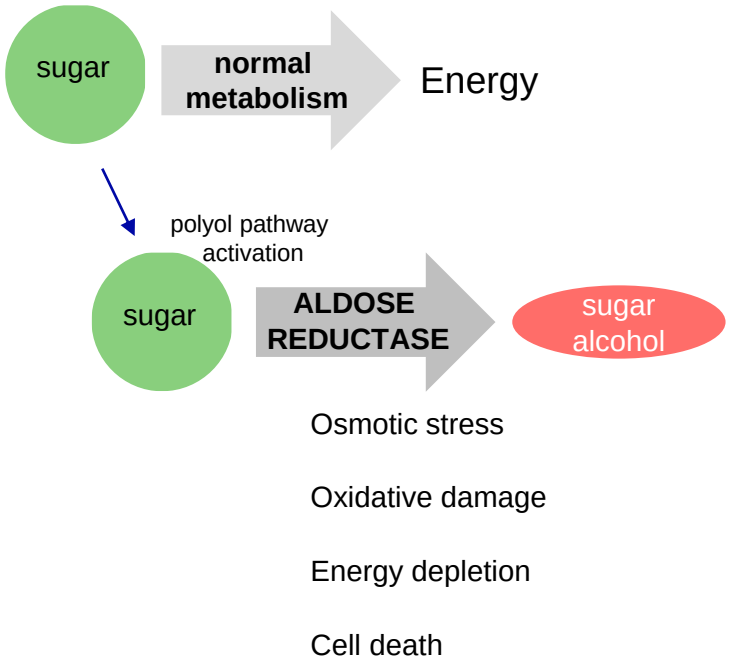
Limited / no competition

Innovative Pipeline with Near-Term Milestones

Compound	Preclinical	Phase 1	Phase 2	Phase 3	Dosing	Target Tissue	Milestones	WW Rights
ALDOSE REDUCTASE FRANCHISE								
AT-007	Galactosemia – Pivotal Phase 2 Study				QD Oral	CNS	Adult study completed; pediatric study ongoing NDA expected 2021	
AT-007	SORD Deficiency				Oral	CNS	Phase 2 ready; clinical study start 2021	
AT-007	PMM2-CDG				Oral	CNS	Phase 2 ready; clinical study start in 2021	
AT-001	Diabetic Cardiomyopathy – Pivotal Phase 3 Study				BID Oral	Systemic	Ph 3 trial initiated in Q3 2019; data in 2022	
AT-001	Diabetic Peripheral Neuropathy				Oral	Peripheral Nerve	Sub-study embedded in DbCM Ph 3 trial	
AT-003	Diabetic Retinopathy				Oral	Retina	Initiate Ph 1 2021	
PI3 KINASE FRANCHISE								
AT-104	PTCL, CTCL, TALL†				SC / Oral	Selective δ/γ inhibitor	Initiate Ph 1 2021	

†Peripheral T-cell lymphoma, cutaneous T-cell lymphoma and T-cell acute lymphoblastic leukemia

Aldose Reductase Inhibitor Overview [1]



Aldose Reductase is an enzyme implicated in multiple metabolic diseases

First and rate limiting enzyme in the polyol pathway – an alternative metabolic pathway activated under stress

Converts sugar to reduced sugar alcohols, which are toxic

Leads to cell death through osmotic dysregulation, reactive oxygen species formation, and energy deficiencies

Prior attempts to inhibit Aldose Reductase were hindered by lack of selectivity and off-target tox issues

1. Brownlee M. Diabetes Care. 2005;54(6):1615-1625.

ACTION-Galactosemia Kids Program Update

Francesca Lawson, MD FAHA

Head of Clinical Development, Applied Therapeutics

Positive adult biomarker data; LTE ongoing

Pediatric trial ongoing

NDA expected ~Q3 2021

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Galactosemia: a Rare Metabolic Disease With No Approved Therapies

- Galactosemia is a **rare, slowly progressing metabolic disease** caused by a **genetic inability to break down the sugar galactose**. Galactose is found in foods, but the human body also naturally produces galactose on its own
- **~3,000 patients in the US** with Galactosemia; ~80 new births per year; Mandatory newborn screening in US and most EU countries
- **Aldose Reductase (AR) enzyme** converts galactose into **galactitol, an aberrant toxic metabolite that builds up in tissues and organs** and causes long-term disease complications
- **AT-007**, a novel CNS penetrant Aldose Reductase inhibitor, **prevents galactitol formation and accumulation** in adult Galactosemia patients; pediatric study ongoing
- **Plan to submit biomarker-based NDA for Accelerated Approval in Q3 2021**

Galactosemia: Disease Progression is Slow But Debilitating

Newborn

- Liver failure
- Kidney problems
- Sepsis
- Brain edema
- Pseudotumor cerebri
- Feeding difficulties
- Growth problems
- Cataracts

Infants/Toddlers

- Speech/language delays
- Coordination problems (fine and gross motor skills)
- Developmental delays
- Attention issues
- Growth problems
- Cataracts

Young Children

- Learning delays
- Issues with fine and gross motor skills (e.g., handwriting)
- Growth problems
- Speech/language problems
- Behavioral and emotional issues
- Tremor

Teen

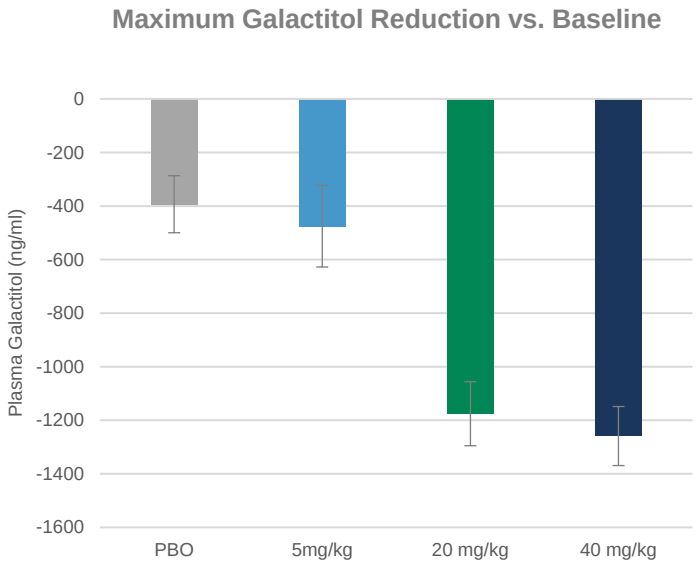
- Puberty and fertility problems (females)
- Growth delays
- Anxiety
- Social problems
- Learning difficulties
- Tremor

Adult

- Tremor
- Seizures
- Anxiety
- Depression
- Attention Deficit Hyperactivity Disorder (ADHD)
- Cataracts

Hawk Partners caregiver research conducted 2020, consistent with International Galactosemia treatment guidelines (Welling et al., 2017)

ACTION-Galactosemia: AT-007 Significantly Decreased Galactitol Levels Safe and Well Tolerated



P<0.01 for 20mg/kg vs. placebo and 40mg/kg vs. placebo
Placebo group updated to include 2 additional patients who participated in 40mg/kg cohort
Maximal reduction on Day 32

Safety

- Favorable safety and tolerability in core study and 3-month extension

Pharmacokinetics/ Pharmacodynamics

- PK supports once-daily dosing
- Rapid and sustained reduction in plasma galactitol
- Galactitol reduction in the brain demonstrated by MR Spectroscopy

All biomarker assays were developed, validated, and performed by Icon Labs Whitesboro, NY (independent 3rd party lab)

ACTION-Galactosemia Kids Pediatric Registrational Clinical Study Design

Part A: PK/PD Dose Range Finding & Biomarker

Part B: Long-Term Safety/ Clinical Outcomes

Part A

- Dose range finding PK/PD study to determine optimal dose in children and biomarker-based assessment of galactitol reduction for NDA submission under Accelerated Approval
- 6 patients per age group; 4 active; 2 placebo
- 18 patients total

Part B

- Long-term clinical outcomes to assess impact on how patients feel and function and to provide long-term safety data
- Up to 18 patients per age group; 12 active; 6 placebo
- Up to 54 patients total (inclusive of Part A patients)

Outcomes Assessed by Composite Endpoint Consisting of 4 Quadrants: Speech, Cognition, Behavior, Motor Skills

Speech

- Expressive Language
- Receptive Language

OWLS-2 (Oral & Written Language Skills 2); Picture Vocabulary Test; Oral Reading Recognition Test

Cognition & Learning

- Cognitive and Intellectual Development
- Attention
- Executive Function
- Memory (episodic and working memory)
- Processing speed

NIH Toolbox Cognition Battey: Flanker Inhibitory Control & Attention Test; Dimensional Change Card Sort; Picture Sequence Memory; List Sorting; Pattern Comparison Processing Speed

Behavioral / Psychosocial

- Atypical Behavior
- Mental Health (Anxiety/Depression)
- Adaptive/Behavior Social Skills
- Communication

Behavior Assessment System for Children (BASC) Vineland Adaptive Behavior Scales

Motor Skills

- Dexterity
- Balance
- Gait Coordination
- Tremor

9-Hole Pegboard; Standing Balance; Scale for Assessment & Rating of Ataxia (SARA); Spiral Drawing Test

Galactosemia Outcomes Worsen Over Time

- **The Galactosemia population has not yet been studied prospectively in a longitudinal study** (same children progressing over time)
  - However, individual patients have been tracked over time, demonstrating progressively worsening symptoms
- **In the ACTION-GALACTOSEMIA Kids trial, a cross-sectional analysis of the first 19 pediatric patients at baseline** was performed to evaluate the effect of age on disease outcomes
  - This analysis provided baseline outcomes assessments on children age 3-15 across all 4 quadrants – speech, cognition, behavior motor skills
- **Disease severity increased with age, demonstrating that Galactosemia progressively worsens over time, impacting speech, cognition, behavior, motor skills**

Baseline Characteristics & Results Overview

Age & Gender

- 19 participants age 3 - 15
- 11 female and 8 male
- 7 patients 2-6yrs, 9 patients 7-12yrs, 3 patients 13-17yrs

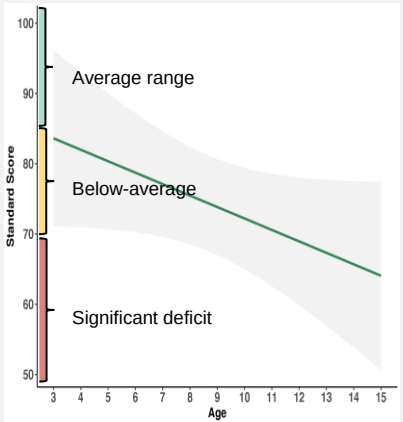
Galactosemia characteristics

- 9 patients homozygous Q188R
- 1 patient homozygous K285N
- 9 patients compound heterozygous

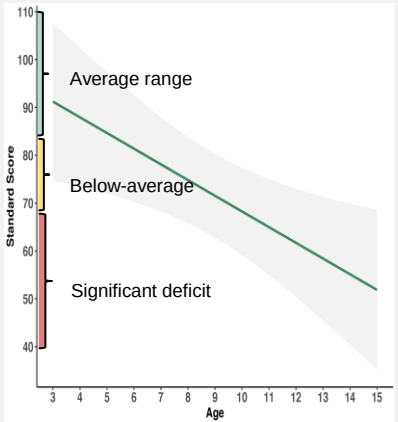
Domain	% Patients with severe impairment (Standard Scores below 2 SD)		
	2-6 yr	7-12 yr	13-17 yr
Speech	0	33.3	66.7
Cognition	0	75.0	100.0
Adaptive Behavior	0	0	33.3
Motor	0	50.0	66.7

Cross Sectional Analysis of Outcomes on 19 Children Age 3-15 Demonstrates Significant Progressive Worsening of Disease Over Time

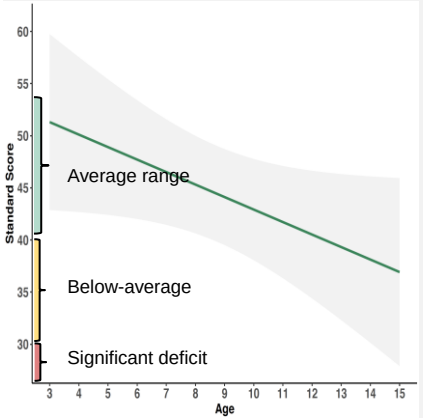
Speech



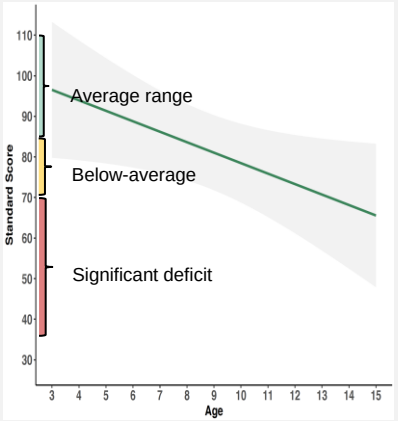
Cognition



Adaptive Behavior



Motor Skills



Data to be presented at ACMG virtual conference, April 2021

Summary & Conclusions

- Galactosemia is a slowly progressive rare disease, which worsens over time with age
- Complications are caused by accumulation of the toxic aberrant metabolite, galactitol
  - Naturally produced by the human body despite galactose-free diet
- Galactitol reduction with AT-007 in a rat model of disease prevented CNS symptoms
- AT-007 treatment in adults with Galactosemia significantly reduced galactitol levels by ~50%
  - Similar degree of reduction shown to be effective in preclinical model
- A pediatric biomarker study is ongoing; patients seamlessly transition to the long-term part of the study, which will study clinical outcomes
- NDA filing expected in Q3 2021 for Accelerated Approval based on galactitol reduction in adults and children

SORD Neuropathy Disease Overview

Biallelic mutations in SORD cause a common and potentially treatable hereditary neuropathy

Stephan Züchner, MD, PhD, FAAN
Professor and Chair, Department for Human Genetics at University of Miami, Miller School of Medicine. University of Miami

Summary: SORD Deficiency as a Newly Identified Pathogenic Cause of CMT2 & Distal Hereditary Motor Neuropathy

- Charcot-Marie-Tooth Disease Type 2 (CMT2) and distal Hereditary Motor Neuropathy (dHMN) are progressive neuropathies affecting both peripheral nerves and motor neurons
- The majority of CMT2 and dHMN patients never receive a genetic diagnosis, and the biochemical cause of their disease is unknown
- Recently, mutations in the SORD gene resulting in deficiencies in the enzyme Sorbitol Dehydrogenase (SORD) were shown to be responsible for disease in a subset of CMT2 patients and dHMN patients
- The role of SORD in metabolism is well defined, and understanding this genetic and biochemical basis of disease offers new opportunities for treatment of patients with neuropathy caused by SORD deficiency

Genetic and Biochemical Basis for SORD Neuropathy

UHealth UNIVERSITY OF MIAMI HEALTH SYSTEM | UNIVERSITY OF MIAMI MILLER SCHOOL of MEDICINE

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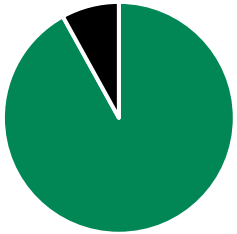
US SORD Population is ~3,300; 7-9% of CMT2 Patients

Estimated frequency of biallelic carriers 1/100,000

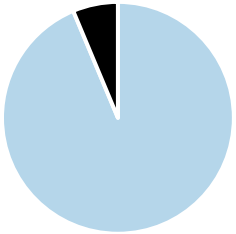
Whole Exome Sequencing from CMT2/dHMN

9/103
(9%)



Sanger sequencing CMT2/dHMN

20/297
(7%)



Gene ID	Chromosome position (CRHg38)	HGVS variant	mutation type	Allele count	Allele number	Allele frequency
SORD	**Chr15:45069018**	**NM_003104.6:c.757delG;(p.Ala253GlnfsTer27)**	**frameshift**	**623**	**142588**	**0.00437**
SH3TC2	Chr5:149026872	NM_024577.4:c.2860C>T;(p.Arg954Ter)	stop gained	94	143270	0.000656
GDAP1	Chr5:74361886	NM_018972.4:c.487C>T;(p.Gln163Ter)	stop gained	21	143188	0.000147
IGHMBP2	Chr11:68939657	NM_002180.2:c.2911_2912delAG;(p.Arg971GlufsTer4)	frameshift	25	143316	0.000174
FDG4	Chr12:32602314	NM_139241.3:c.991delC;(p.Gln443ArgfsTer9)	frameshift	5	143280	0.0000349

Sorbitol Dehydrogenase (SORD) Function

- Enzyme responsible for metabolism of sorbitol to fructose in an alternative metabolic pathway called the polyol pathway[1,2]

Homotetramer (four 38kDa subunits)[3]

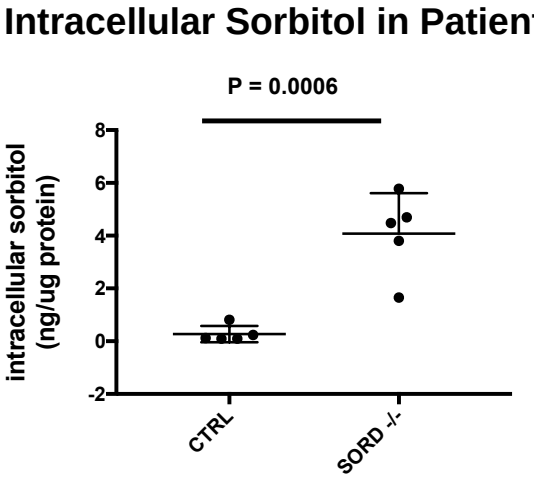
Source: Pauly *et al. Structure* 2003.[3]

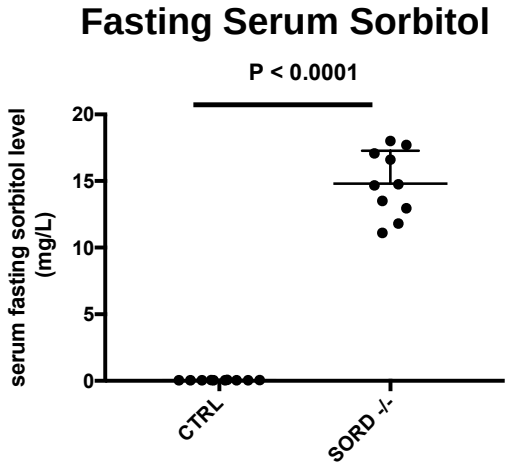
- Second enzyme in the pathway[1,2]
- Ubiquitously expressed in mammalian tissues[4]
- Lack of SORD activity leads to toxic accumulation of sorbitol[1,2]

1. Cortese A, *et al. Nat Genet* 2020;52:473–481. 2. Morava E. *Nat Genet* 2020;52:469–470;
3. Pauly TA, *et al. Structure* 2003;11:1071–1085; El-Kabbani O, et al. Curr Med Chem 2004;11:465-76.

Loss of SORD Enzymatic Activity Results in Increased Intracellular Sorbitol Level and Increased Serum Fasting Sorbitol Level

- Patients with genetic SORD deficiencies demonstrated no detectable SORD levels in cells or plasma[1]
- Increased cellular sorbitol levels in patient fibroblasts[1]
- Fasting serum sorbitol significantly higher in SORD patients vs controls[1]





1. Cortese A, *et al. Nat Genet* 2020;52:473–481.

Clinical Diagnosis & Treatment of SORD Neuropathy

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MILLER SCHOOL
of MEDICINE

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Clinical Presentation

- Slowly progressive neuropathy
  - Results in significant disability and mobility/motility issues

- 100% have limb weakness
  - Lower limb weakness ranging from mild to severe (near paralysis)
  - Upper limb weakness less severe

- ~50% have sensory impairment

Symptoms have a significant impact on patients' quality of life

1. Cortese A, *et al. Nat Genet* 2020;52:473–481.

Standard of Care

No therapies approved to treat SORD deficiency

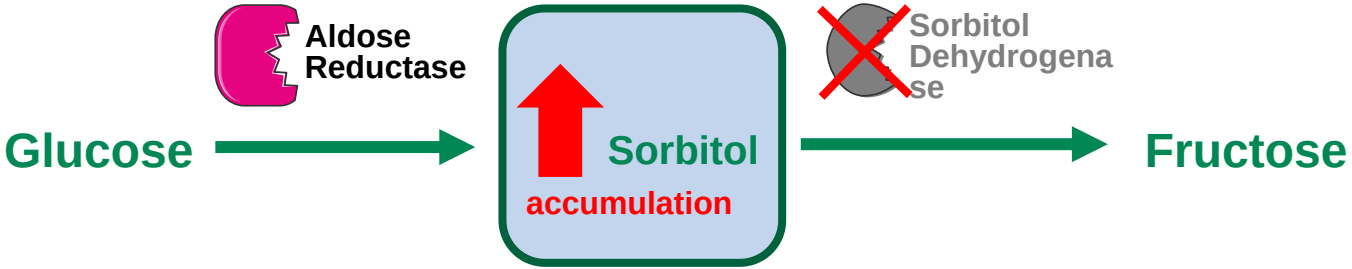
No disease modifying treatments approved for CMT2 or dHMN

Symptomatic treatment for peripheral neuropathic pain

Orthotic or corrective surgery for foot deformities

SORD Neuropathy Pathogenesis of Disease

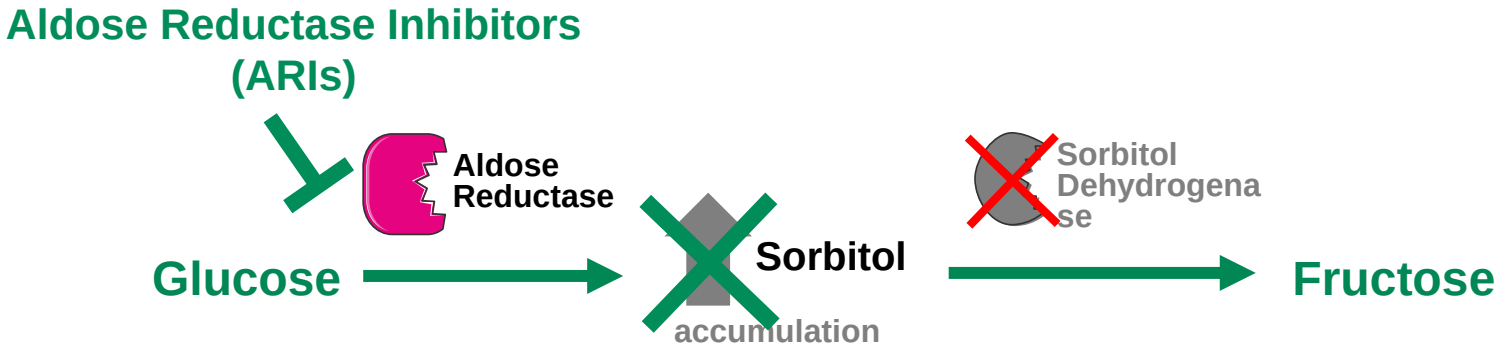
Pathogenesis of Disease



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

Treatment Upstream via Aldose Reductase Inhibition Blocks Sorbitol Generation

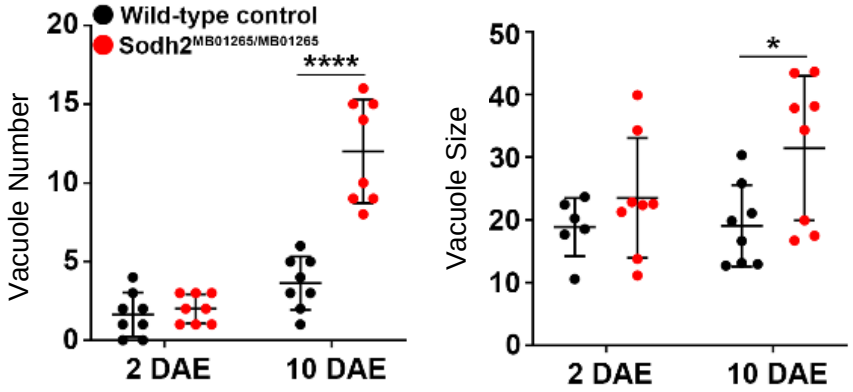
Aldose Reductase Inhibition Reduces Substrate; Leads to Decreased Conversion of Glucose to Sorbitol



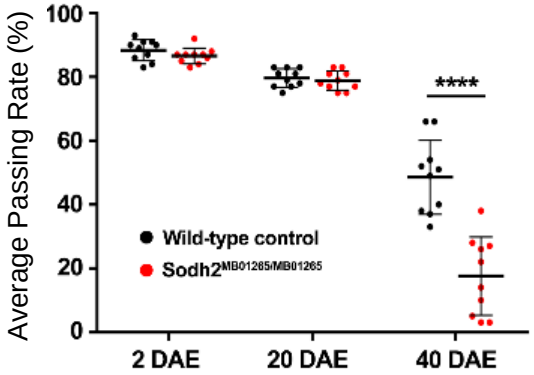
1. Cortese A, *et al. Nat Genet* 2020;52:473–481. 2. Morava E. *Nat Genet* 2020;52:469–470.

Loss of SORD Activity Leads to Neuronal Damage and Loss of Motility in a Drosophila Model

SORD Deficiency Leads to Neuronal Synaptic Damage, as Demonstrated by Increase in Vacuole Number and Size



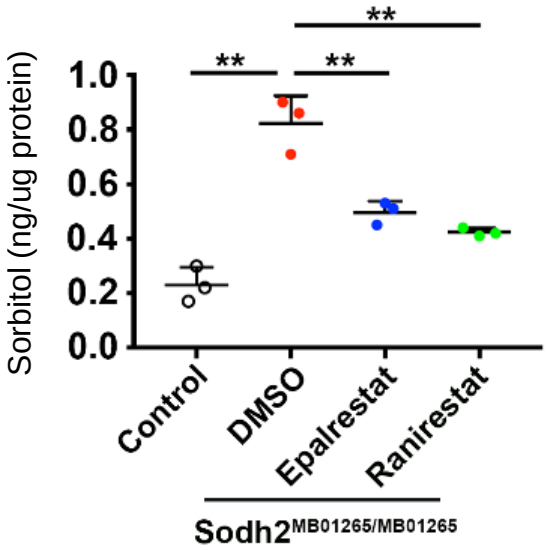
SORD Deficiency Decreases Locomotor Activity (Demonstrated by Passing Rate)



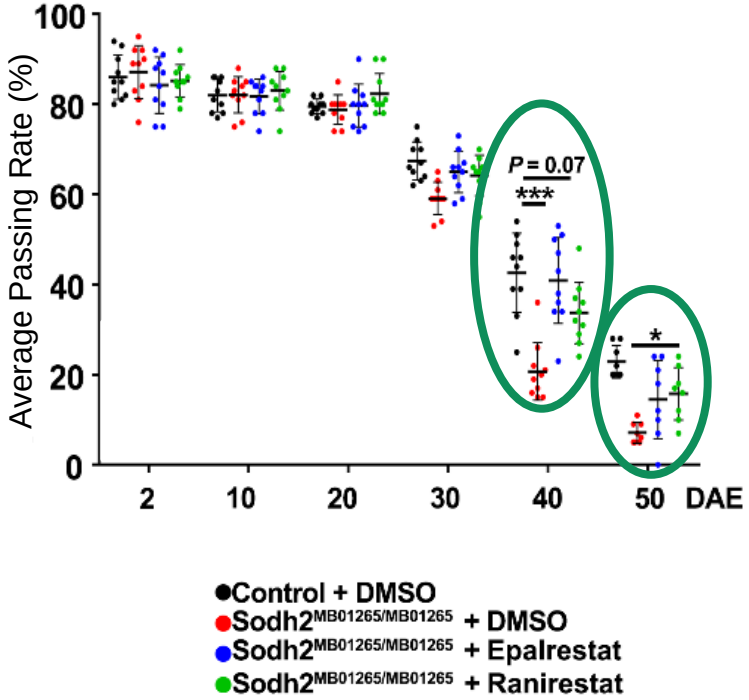
1. Cortese A, *et al. Nat Genet* 2020;52:473–481.
DAE, days after eclosion.

Treatment with Aldose Reductase Inhibitors (ARIs) Epalrestat* and Ranirestat* Normalizes Brain Sorbitol Levels and Rescues the Phenotype in Drosophila Melanogaster

Sorbitol Levels in Brain Homogenate



Mobility & Motility



*Epalrestat and ranirestat are not approved in the US or EU.

1. Cortese A, *et al. Nat Genet* 2020;52:473–481.

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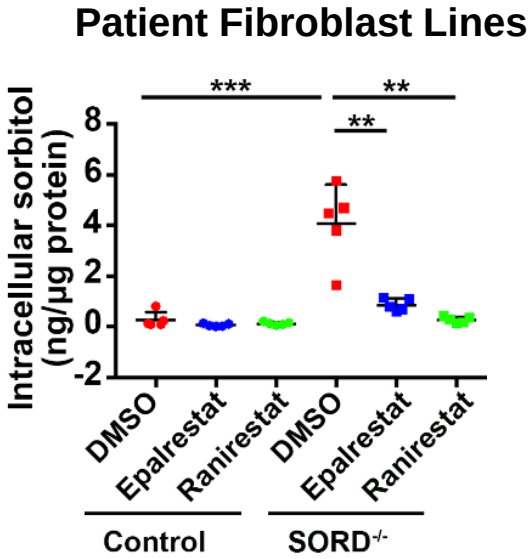
Treatment with First Generation Aldose Reductase Inhibitors (ARIs) Epalrestat* and Ranirestat* Reduce Intracellular Sorbitol in Patient Fibroblasts[1]

Proof of concept: AR inhibition reduces sorbitol in SORD deficiency patient fibroblasts[1]



*Epalrestat and ranirestat are not approved in the US or EU.

1. Cortese A, *et al. Nat Genet* 2020;52:473–481.

Conclusions

- SORD deficiency is a novel genetic cause of CMT2 and dHMN
  - Accounts for ~7-9% of CMT2 and dHMN cases (~3,000 patients in the US)
- Caused by loss of SORD protein activity and consequent intracellular sorbitol accumulation
- Debilitating disease with high unmet medical need
  - Progressive neuropathy; results in disability, loss of sensory function and mobility
  - No drugs approved
- Potentially treatable: beneficial effects of substrate reduction via the application of aldose reductase inhibitors in human-derived cells and Drosophila

1. Cortese A, *et al. Nat Genet* 2020;52:473–481.

Acknowledgments

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Ruxu Zhang (China)
Rebecca Schuele (Tubingen)

AT-007

SORD Neuropathy Clinical Program

Shoshana Shendelman, PhD

CEO & Founder, Applied Therapeutics

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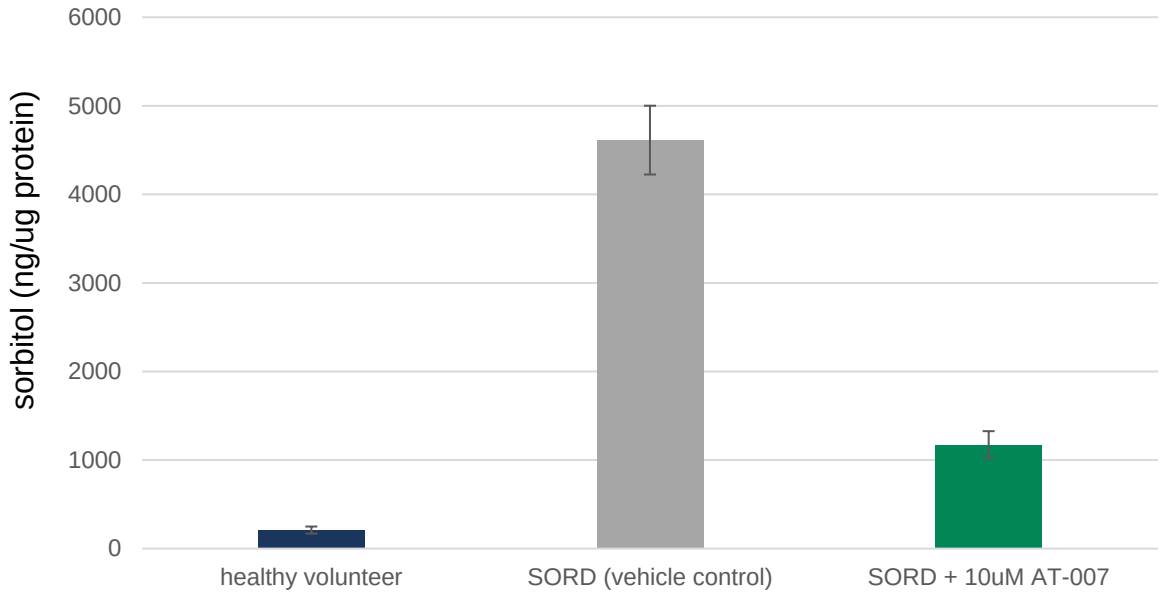
AT-007 Treatment Significantly Reduces Sorbitol Levels in SORD Fibroblasts



Applied Therapeutics, data on file; pilot study

SORD Clinical Development Program

- Pilot study underway (Ph 2a)
  - Pilot study in 6-8 SORD patients initiated
  - Patients will establish baseline control through lead-in period followed by AT-007 treatment
  - Reduction in blood sorbitol level will establish proof of concept, confirm dosing in patient population, and determine appropriate pharmacodynamic timeline for normalization of sorbitol levels
- Registrational study (Ph 2b/3) to be initiated following completion of Ph 2a
  - Under discussion with FDA
  - Sorbitol reduction vs. placebo in a larger cohort to support Accelerated Approval

  or
  - Functional outcomes (such as MNCV or QoL scale)

AT-007: Potential First Treatment for SORD Deficiency

- Potent and selective Aldose Reductase inhibitor
- Favorable safety and tolerability profile
- CNS penetrant: although some degeneration in SORD is due to peripheral nerves, motor neurons are rooted in the CNS
- Significantly reduces sorbitol levels in SORD patient fibroblasts
- Phase 2 clinical trial initiated in SORD patients; blood-based biomarker - reduction in sorbitol level from baseline

SORD Commercial Opportunity

- **Significant market opportunity**: rare disease, approximately 3,300 patients in the US treated at a small number of Centers of Excellence
- **High unmet medical need**: debilitating disease with no approved therapies
- **Well understood biology of disease and disease pathogenesis:** role of Aldose Reductase in metabolism and SORD Neuropathy is well understood; toxic role of sorbitol in disease pathogenesis well established
- **Favorable commercial value proposition:** potential to be the first disease-modifying therapy for SORD Neuropathy; convenient oral dosing; expected pricing in-line with other rare diseases

PMM2-CDG

Disease Overview

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APPLIED THERAPEUTICS

Overview of PMM2-CDG

- Phosphomannomutase 2 deficiency (PMM2-CDG) is the **most common congenital disorder of glycosylation**, a group of ultra-rare genetic metabolic disorders[1,2]
- Approximately **1,000 patients are affected globally**[1,3]
- Onset and severity of **clinical features are highly variable**[4]
- Patients with the infantile form have a **mortality rate of up to 20%** in first year of life[1]
- Patients who survive infancy or present later in life face **lifelong chronic challenges**[4]

The prognosis for PMM2-CDG patients is poor and there are currently no FDA-approved treatments

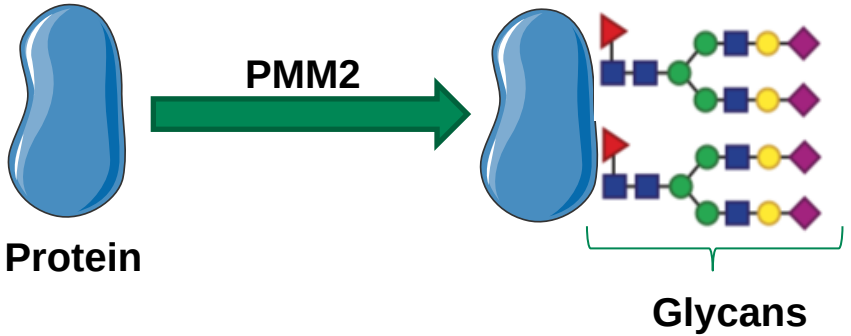
FDA, Food and Drug Administration; PMM2-CDG, Phosphomannomutase 2 congenital disorder of glycosylation.

1. Chang IJ, *et al. Ann Transl Med* 2018;6:doi: 10.21037/atm.2018.10.45; 2. Rare Disease Database. Available at: https://rarediseases.org/rare-diseases/pmm2-cdg/ (Last accessed July 2020); 3. Iyer S, *et al. Dis Model Mech* 2019;12:doi:10.1242/dmm.040584:10.1242/dmm.040584; 4. Monin M-L, *et al. Orphanet Journal of Rare Diseases* 2014;9:207.

Genetic Cause of Disease is Loss of PMM2 Function

- **N-linked protein glycosylation is a type of post-translational modification in eukaryotic cells[1]**
- Different cell types and organs are differentially sensitive to the complex sequelae of hypoglycosylation[2]
- **Complete loss of N-linked protein glycosylation is lethal[2]**

PMM2 (chromosome 16p13.3-p13.2) is an enzyme that catalyzes an essential step in the N-linked glycosylation of proteins, essential for correct protein function[3]



A minimal level of glycosylation is required at all times, in all cells of the body; PMM2-CDG is a multisystem, multi-organ disease[4]

1. Wang Y-C, et al. Cell res 2014;24:143–160; 2. Feeeze HH, et al. Essentials of Glycobiology 3rd edition,): Cold Spring Harbor Laboratory Press; 2015–017. Ch 45; 3. Rare Disease Database. Available at https://rarediseases.org/rare-diseases/pmm2-cdg/ (Last accessed July 2020); 4. Iyer S, et al Disease Models & Mechanisms 2019;11:12(11):dmm040584. doi: 10.1242/dmm.040584

PMM2-CDG Patients Carry a Range of Mutations Affecting Dimerization, Protein Stability, and Catalytic Activity

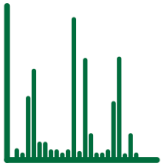
- **Mutations in PMM2 disrupt or destabilize** the protein dimerization necessary for proper function[1]
- Over 80% of disease-causing PMM2 alleles result in amino acid substitutions that destabilize the protein, and **reduce its activity[2]**
- **Symptoms of PMM2-CDG arise** when the catalytic activity of PMM2 falls **below 50%[2]**

The level of PMM2 activity correlates with the number and severity of organ systems that are affected by the disease[2]

1. Yuste-Checa P, *et al. Hum Mutat* 2015;36:851–860; 2. Iyer S, et al Disease Models & Mechanisms 2019;11:12(11):dmm040584. doi: 10.1242/dmm.040584.

Biochemical and Genetic Diagnosis

Analysis of the serum transferrin glycosylation status is used to diagnose patients with congenital disorders of glycosylation (CDG)



Isoelectric focusing or mass spectrometry of serum transferrin specifically diagnoses PMM2-CDG (N-linked glycosylation)

Targeted CDG gene panels or exome/genome sequencing to identify pathogenic variants in CDG genes

MRI, CT and EEG can detect the hallmark cerebellar hypoplasia and abnormal brain function

CDG, congenital disorder of glycosylation; CNS, central nervous system; CT, computerized tomography; MRI, magnetic resonance scanner.

Rare Disease Database. Available at https://rarediseases.org/rare-diseases/pmm2-cdg/ (Last accessed July 2020).

Organ Systems Affected by Congenital Disorders of Glycosylation

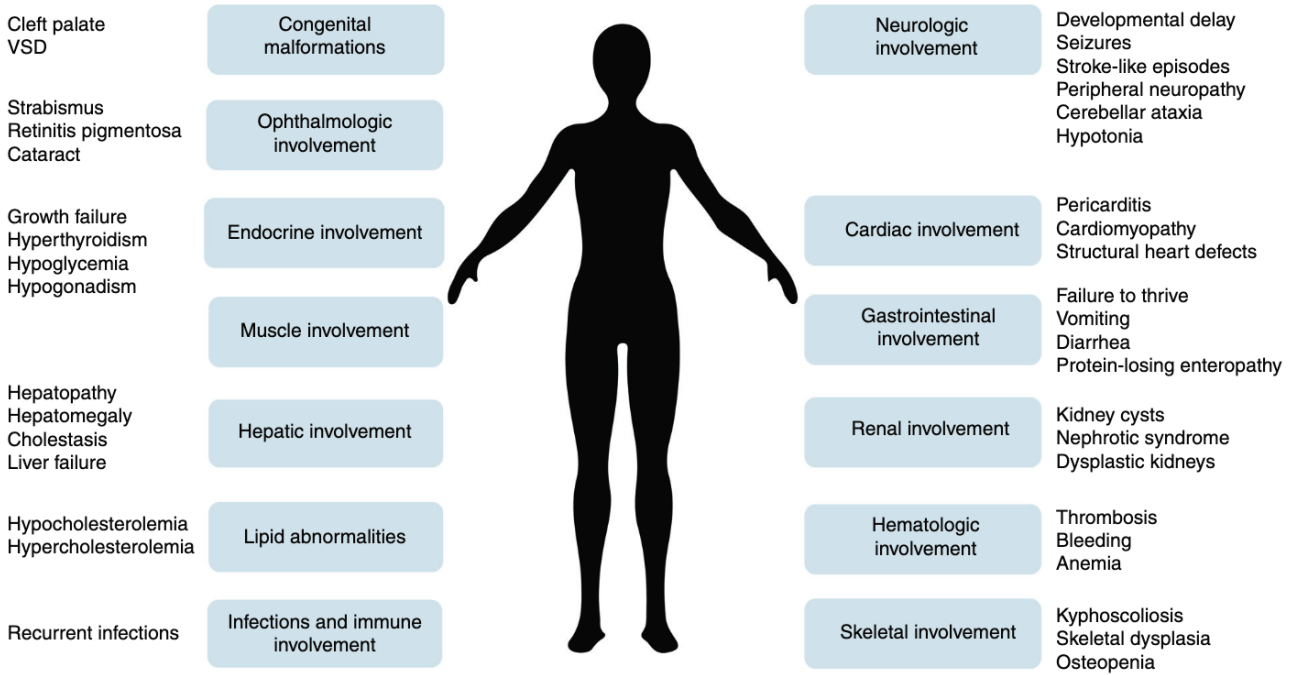


Figure from Verheihen *et al. Genet Med* 2020;22:268–279.

PMM2-CDG Clinical Features

Infancy

- Physical abnormalities
- Abnormal feeding/ failure to thrive
- Developmental delays
- Organ system failures (potentially life threatening) including hepatic, renal and cardiac failure

Childhood

- Cognitive and intellectual deficiency
- Speech delay
- Motor dysfunction; mobility impairment
- Cerebellar ataxia
- Coagulation deficiencies; stroke
- Seizures
- Peripheral neuropathy
- Muscle weakness
- Ophthalmic issues

Adulthood

- Worsening of peripheral neuropathy
- Increased muscle weakness; mobility impairment
- Skeletal malformations (short stature, fixed joints etc.)
- Infertility; hormonal insufficiency

Rare Disease Database. Available at: https://rarediseases.org/rare-diseases/pmm2-cdg/ (Last accessed July 2020).

Aldose Reductase Inhibition in PMM2-CDG

- PMM2 pathway relies on **availability and proper balance of precursor sugars** for production of mannose-1-phosphate
- Imbalance in other metabolic pathways that feed into glycosylation (e.g polyol pathway) can **adversely affect PMM2 activity by deranging sugar balance**
- Generalized cell stress caused by abnormal glycosylation in PMM2-CDG may cause **over-activity of the polyol pathway**, further deranging metabolic pathways
- It is hypothesized that **abnormal AR activity adversely affects PMM2 activity**, which then further stimulates AR activity in a feedback loop

Inhibiting AR activity improves PMM2 activity in patient fibroblasts

AR, aldose reductase

1. Cortese A, et al Nature Genetics 2020;52(5):473-481. doi: 10.1038/s41588-020-0615-4. 2. Morava editorial Nature Genetics 2020;52(5):469-470. doi: 10.1038/s41588-020-0619-0
3. Iyer S, et al Disease Models & Mechanisms 2019;11:12(11):dmm040584. doi: 10.1242/dmm.040584.

AT-007

PMM2-CDG Clinical Program

Shoshana Shendelman, PhD

CEO & Founder, Applied Therapeutics

Pre-clinical proof of concept

Phase 2 expected 2021

APPLIED THERAPEUTICS

PMM2-CDG is Associated with Significant Morbidity / Mortality with No Treatment Options

Poor prognosis, with **20% mortality in first 4 years of life**[1]

Almost all organs can be affected, leading to **multi-system organ failure**[2]

Results in **disorders/disabilities** of CNS, cardiovascular, skeletal, and metabolic systems[2]

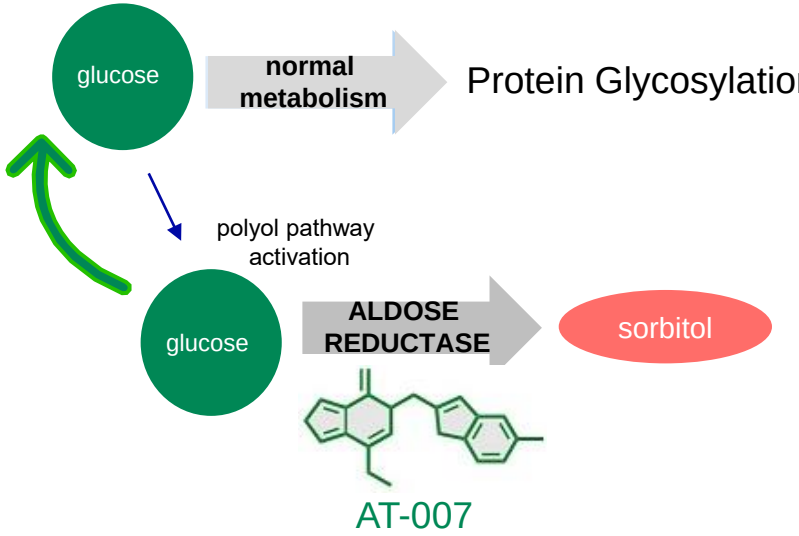
Those who survive infancy **struggle with independent living**, placing a burden on patients & caregivers[2]

Symptom progression requires **close frequent monitoring and management** by supportive multidisciplinary care team

No approved treatments; standard of care is close monitoring and symptomatic or surgical management[3]

1. NORD Rare Disease Database: https://rarediseases.org/rare-diseases/pmm2-cdg/#references. 2. Grünewald, *Biochimica et Biophysica Acta 1792* 2009; 827–834. 3. Monin M-L, et al. *Orphanet Journal of Rare Diseases* 2014; 9:207.

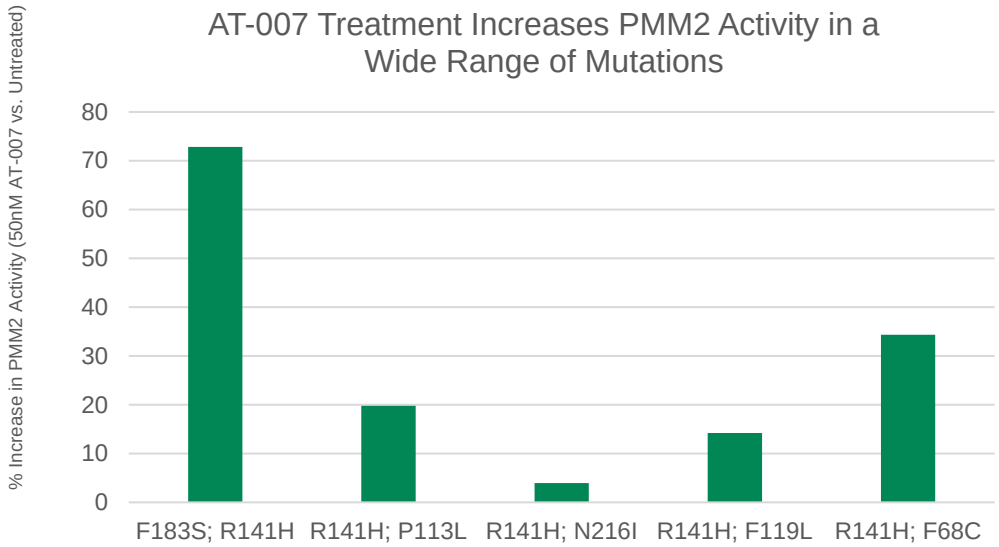
Aldose Reductase Inhibition Improves PMM2 Activity, Addressing the Underlying Cause of PMM2-CDG[1-3]



- AR inhibition blocks the polyol pathway, restoring glucose flow through normal metabolic pathways
- Promotes proper balance of precursor sugars necessary for protein glycosylation
- Results in increased PMM2 activity and protein glycosylation[3]

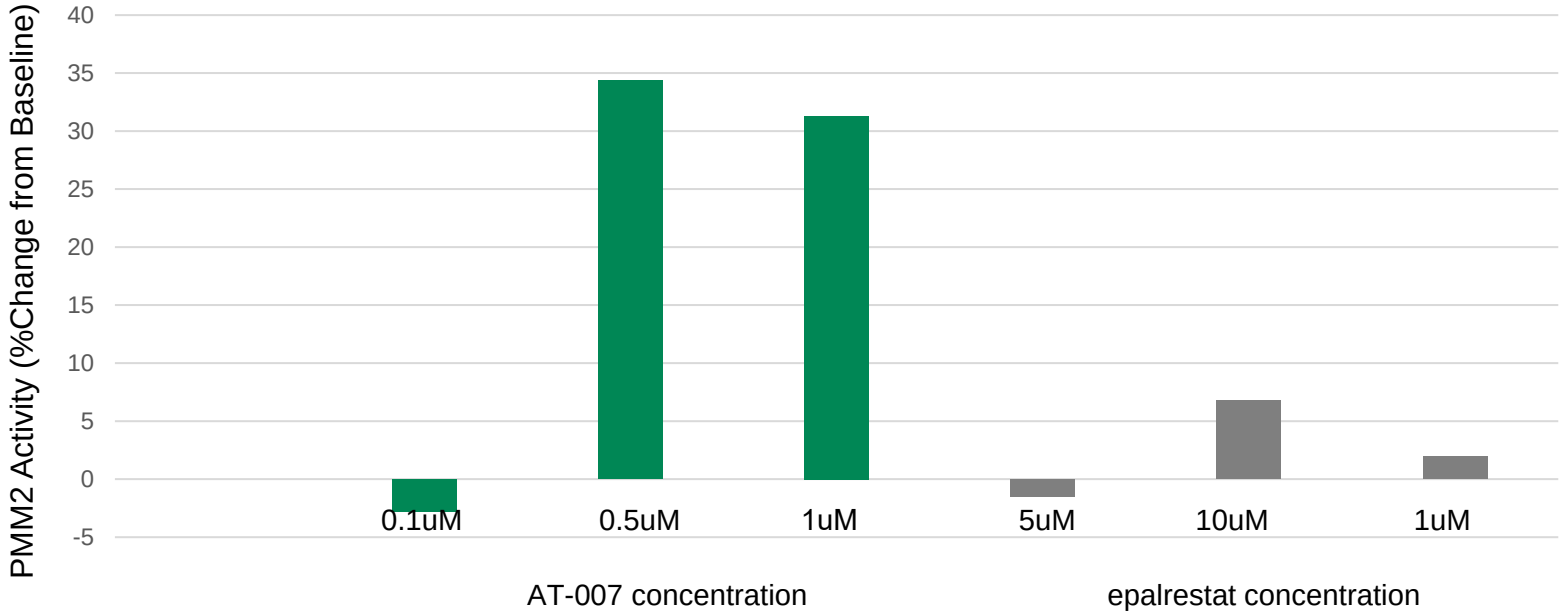
1. Cortese A, et al. *Nat Genet* 2020;52:473–481. 2. Morava *Nat Genet* 2020;52(5):469-470. 3. Iyer S, et al. *Dis Model Mech* 2019;12:doi:10.1242/dmm.040584:10.1242/dmm.040584

AT-007 Increases PMM2 Activity in Patient Fibroblasts



Data on file, Applied Therapeutics, Inc, New York, NY

AT-007 Impact on PMM2 Activity is Greater than Epalrestat
(Single Patient Fibroblast Data R141H/ F68C Genotype)



PMM2-CDG Clinical Development Program

- Pediatric study under design close collaboration with FDA
- Opportunity for biomarker outcome/ Accelerated Approval based on link between PMM2 activity and disease severity
  - Glycosylated transferrin; PMM2 activity
- Expected study start 2021

AT-007: Potential First Treatment Option for PMM2-CDG

- **High unmet medical need**: severe disease with significant morbidity/mortality and high impact on quality of life
- Treatment at a **small number of Centers of Excellence**; limited number of specialists
- Proof of concept preclinical study and single patient compassionate use with epalrestat **support rationale for clinical development**
- **Selective, potent, once-daily therapy with favorable safety/ tolerability profile**
- AT-007 has received **Pediatric Rare Disease Designation and Orphan Designation** for PMM2-CDG
- **Favorable commercial value proposition**: potential to be the first disease-modifying therapy for PMM2-CDG; expected pricing in-line with other rare diseases

Q&A