Applied Therapeutics

February 2023

APPLIED THERAPEUTICS

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

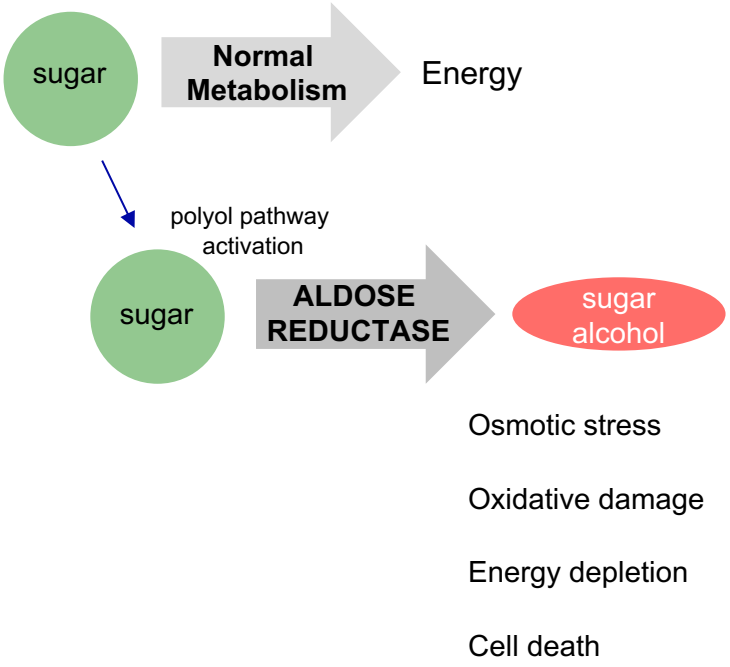
Fatal or debilitating diseases with no approved therapies

Limited / no competition

Innovative Pipeline with Near-Term Milestones

Compound	Preclinical	Phase 1	Phase 2	Phase 3	Dosing	Target Tissue	Milestones	Rights
ALDOSE REDUCTASE FRANCHISE								
AT-007	Galactosemia (ACTION)				QD Oral	CNS	Positive adult and pediatric biomarker data; pediatric Phase 3 outcomes trial ongoing	ROW; ADVANZ PHARMA EU
	SORD Deficiency (INSPIRE)				Oral	CNS	Positive pilot study data; Phase 3 registrational trial ongoing	ROW; ADVANZ PHARMA EU
	PMM2-CDG				Oral	CNS	Phase 2 ready; Expanded Access open	WW
AT-001	Diabetic Cardiomyopathy (ARISE-HF)				BID Oral	Systemic	Ph 3 registrational trial data read-out YE 2023	WW
	Diabetic Peripheral Neuropathy				Oral	Peripheral Nerve	Sub-study embedded in DbCM Ph 3 trial	WW
AT-003	Diabetic Retinopathy				Oral	Retina	Phase 1 ready	WW

Aldose Reductase: 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

Applied Therapeutics' compounds are 1,000 X more potent than "old" ARIs and highly selective; no off-target inhibition of aldehyde reductase

AT-007
GALACTOSEMIA

- Orphan Drug Designation
- Pediatric Rare Disease Designation (PRV)
- Fast-Track Designation

Positive adult & pediatric biomarker data

Pediatric Ph 3 clinical outcomes study ongoing

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Galactosemia is a Rare Metabolic Disease With No Approved Therapies and Significant Unmet Need

Disease Overview

- Rare autosomal recessive metabolic disease caused by deficiencies in the GALT or GALK enzymes
- Patients are unable to metabolize the simple sugar galactose, which is found in foods but also synthesized endogenously by the body
- Results in long-term CNS complications including speech, cognition, behavior and motor skills deficiencies; ovarian insufficiency in females
- Progressively worsens with age

Standard of Care/ Diagnosis

- No approved therapies to treat Galactosemia
- Mandatory newborn screening in US and most EU countries
- Galactose-restricted diet implemented immediately after birth and adhered to for life
- Dietary restriction prevents newborn fatalities but does not prevent long-term CNS complications due to endogenous galactose production by the body
- Patients are primarily seen by metabolic geneticists

Mechanism of Disease

- People with Galactosemia are unable to metabolize galactose, which accumulates in cells and tissues
- At abnormally high levels, galactose becomes a substrate for Aldose Reductase, which converts galactose to a toxic and aberrant metabolite, galactitol
- Galactitol is highly toxic (especially to neurons) and causes redox derangement, cell death
- Plasma galactitol level correlates with severity of disease

Market Size / Opportunity

- Known prevalent and addressable population (~3K US, ~7K WW)
- Small commercial footprint focused on KOLs at Centers of Excellence
- Strong patient community engagement
- Payer feedback supports access/pricing
- Composition of matter IP through 2037 (not including extensions)

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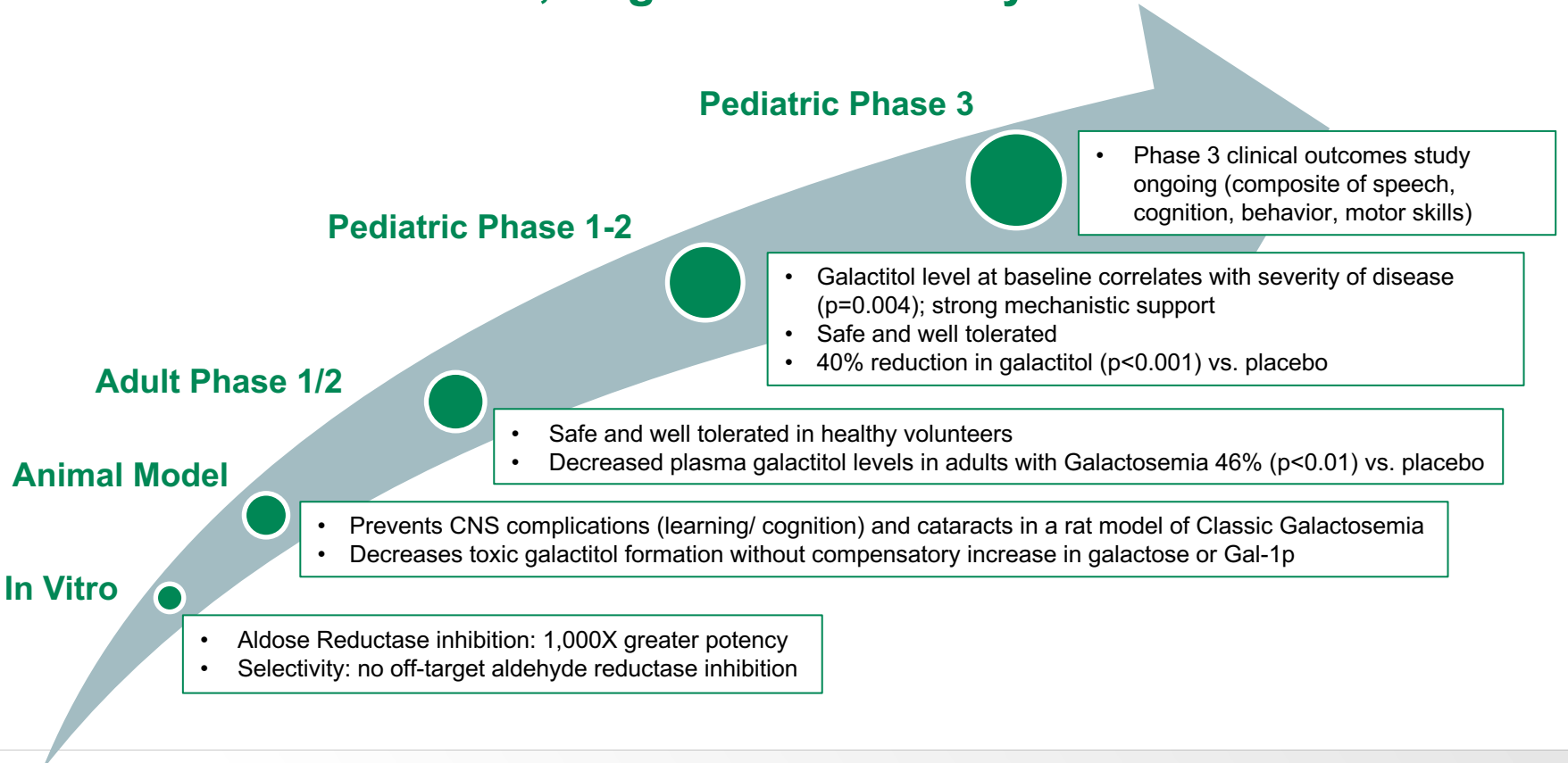
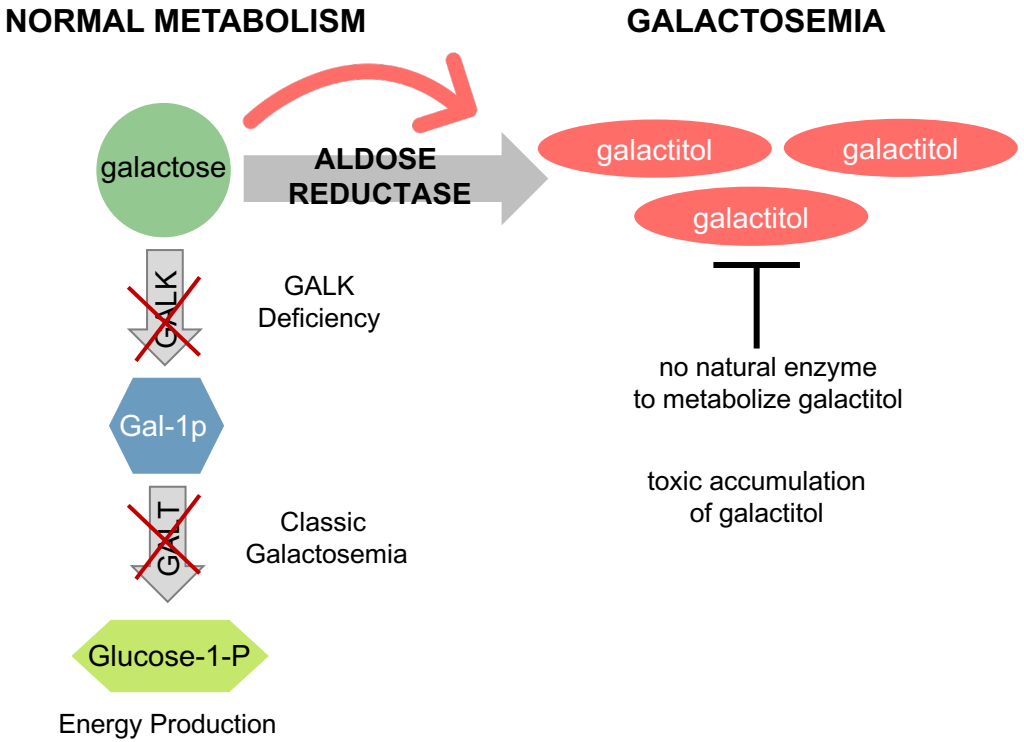
Data on file: Symphony Claims Data, Feb. 2017-Jan. 2021. Phytila et al. *JIMD Rep*. 2015; 15: 79–93. Burgard et al. *Report on the practices of newborn screening for rare disorders*. 2011. Swaiman et al. *Pediatric Neurology*. 2018.

AT-007 Has Demonstrated Effectiveness In Vitro, In Vivo, and in Phase 1/2 Clinical Trials; Registrational Study Readout 2023



Deficiency in GALT or GALK Leads to Inability to Metabolize Galactose; AR Converts Excess Galactose to Toxic Galactitol

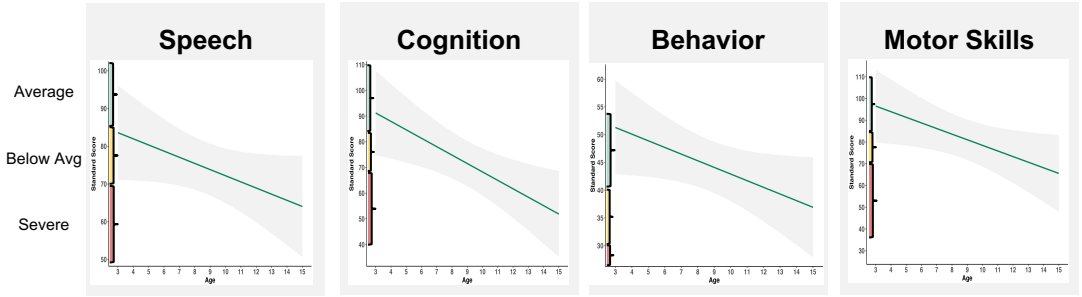


- **CNS Complications:**
  - Speech Deficiencies
  - Cognition/ Learning/ IQ/ Memory
  - Behavior/ Psychiatric
  - Motor Skills (Tremor, Ataxia)
  - Seizures
- **Other Complications:**
  - Ovarian Insufficiency
  - Cataracts

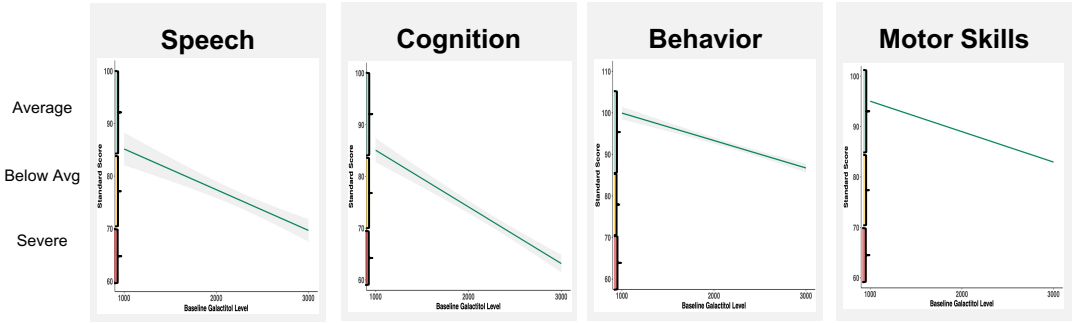
AR = Aldose Reductase

Natural History: Galactosemia is a Progressive Disease that Worsens with Age; Disease Severity Correlates with Plasma Galactitol Level

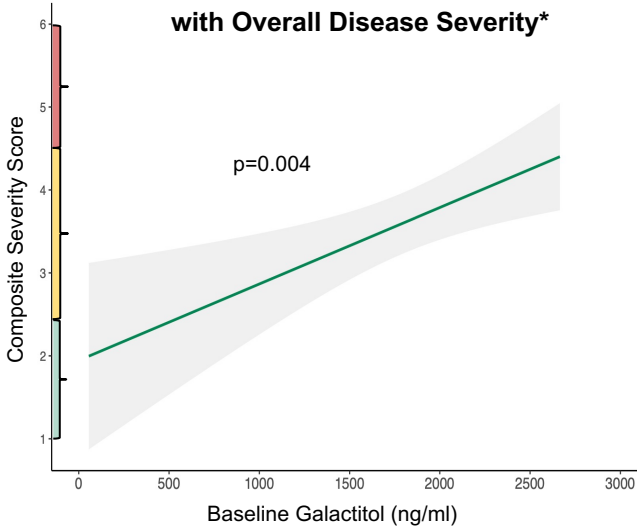
Natural history of disease demonstrates progressive worsening with age



Baseline galactitol level correlates with severity of clinical functional outcomes



Plasma Galactitol Level Correlates with Overall Disease Severity*



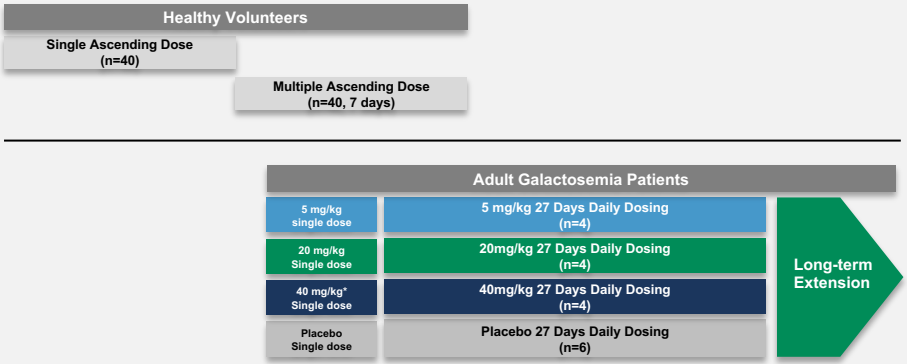
*Overall severity based on composite score comprised of 4 CNS quadrants

No correlation observed between Gal-1p and disease severity

Abstract eP011: Progressive Worsening of Central Nervous System Phenotype in Children with Classic Galactosemia: a Cross-Sectional Analysis; ACMG 2021 conference; Perfetti R et al. Galactitol Level is a Predictor of Disease Severity in Children with Classic Galactosemia on Galactose Restricted Diet. Poster presented at: International Congress Inborn Errors of Metabolism Annual Meeting; November 21-23, 2021; Sydney, Australia.

AT-007 Significantly Reduced Galactitol Levels in the Galactosemia Adult Phase 1/2 Study (ACTION-Galactosemia); Safe and Well-Tolerated

Adult Phase 1/2 Study Design



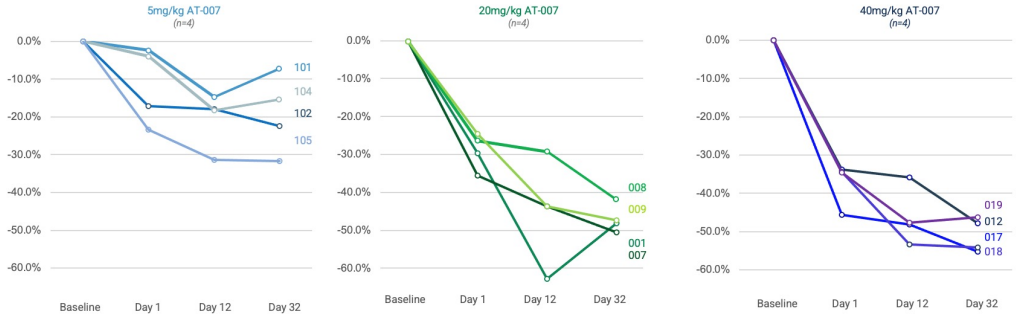
Safety

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

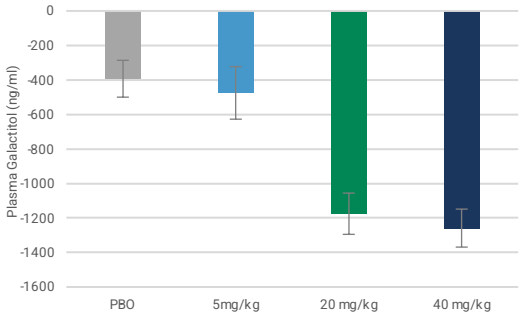
Pharmacokinetics/ Pharmacodynamics

- 20mg/kg dose selected as optimal dose
- PK supports once-daily dosing
- Rapid, sustained and significant reduction in plasma galactitol
- Galactitol reduction in the brain demonstrated by MR Spectroscopy
- No compensatory increase in galactose or Gal-1p

Galactitol Reduction vs. Baseline (Individual Patient Values)



Maximum Galactitol Reduction vs. Baseline

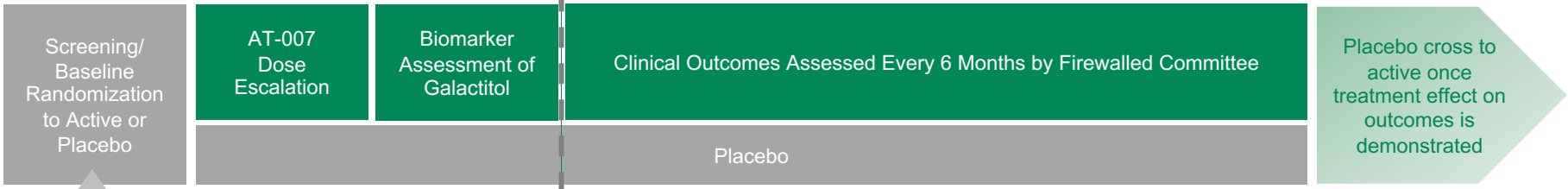


p<0.01 (20 mg/kg and 40 mg/kg vs. placebo)

AT-007 ACTION-Galactosemia Kids Pediatric Registrational Clinical Study - Ongoing in 47 Children Age 2-17

PK/PD Dose Range Finding & Biomarker Data

Long-Term Clinical Outcomes

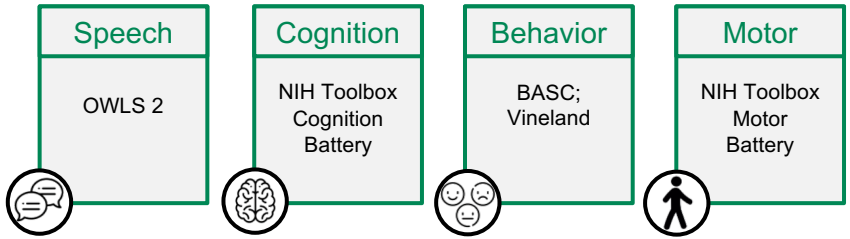


Significant Reduction in Galactitol in Children Aged 2-17 with Weight-Based Dosing

Weight Group	AT-007 Dose (QD)	% Reduction From Baseline
>40kg	15mg/kg	38.29%
20-40kg	20mg/kg	41.43%
<20kg	30mg/kg	39.83%
All groups	**15-30mg/kg**	**40.19% (p<0.001)**

- Safe and well tolerated
- No compensatory increase in galactose or Gal-1p

Primary Endpoint:
Global Assessment of Change (Global Statistical Test) - Composite of CNS function



12 month results: Safe and well tolerated; trend in clinical benefit favoring AT-007 vs. placebo
Next analysis: 18 months

Strong Demand for Galactosemia Education and Treatment from Caregivers and HCPs

GALACTOSEMIA TOGETHER

Engaging the Galactosemia Community through Social

537 Facebook followers // **35,000+** post views

Support and Education at Galactosemia.com

100,000+ website visitors // **80,000+** high valued engagements

Sharing the Galactosemia Story via 2D & 3D MOD Videos

48,000+ complete video views

Awards

W3 AWARDS

WEBAWARDS 2021

DTC NATIONAL

AT-007

SORD DEFICIENCY

- Orphan Drug Designation

Preclinical proof of concept demonstrated

Positive pilot study completed

Registrational Phase 3 study ongoing

SORD Deficiency is a Rare Neurological Disease with No Approved Therapies and High Unmet Need

Disease Overview

- 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
- Autosomal recessive genetic disease, caused by mutations in the SORD gene resulting in loss of SORD enzyme function
- Average age of onset is 17 years old

Standard of Care/ Diagnosis

- No approved therapies to treat SORD Deficiency
- Genetic testing commercially available (GeneDx)
- Prior to 2020, patients were diagnosed symptomatically as CMT2 or dHMN; new screening efforts are quickly re-categorizing CMT2/dHMN patients with SORD
- Primarily treated by neurologists/ neuromuscular specialists at Inherited Neuropathy Consortium (INC) Centers of Excellence

Mechanism of Disease

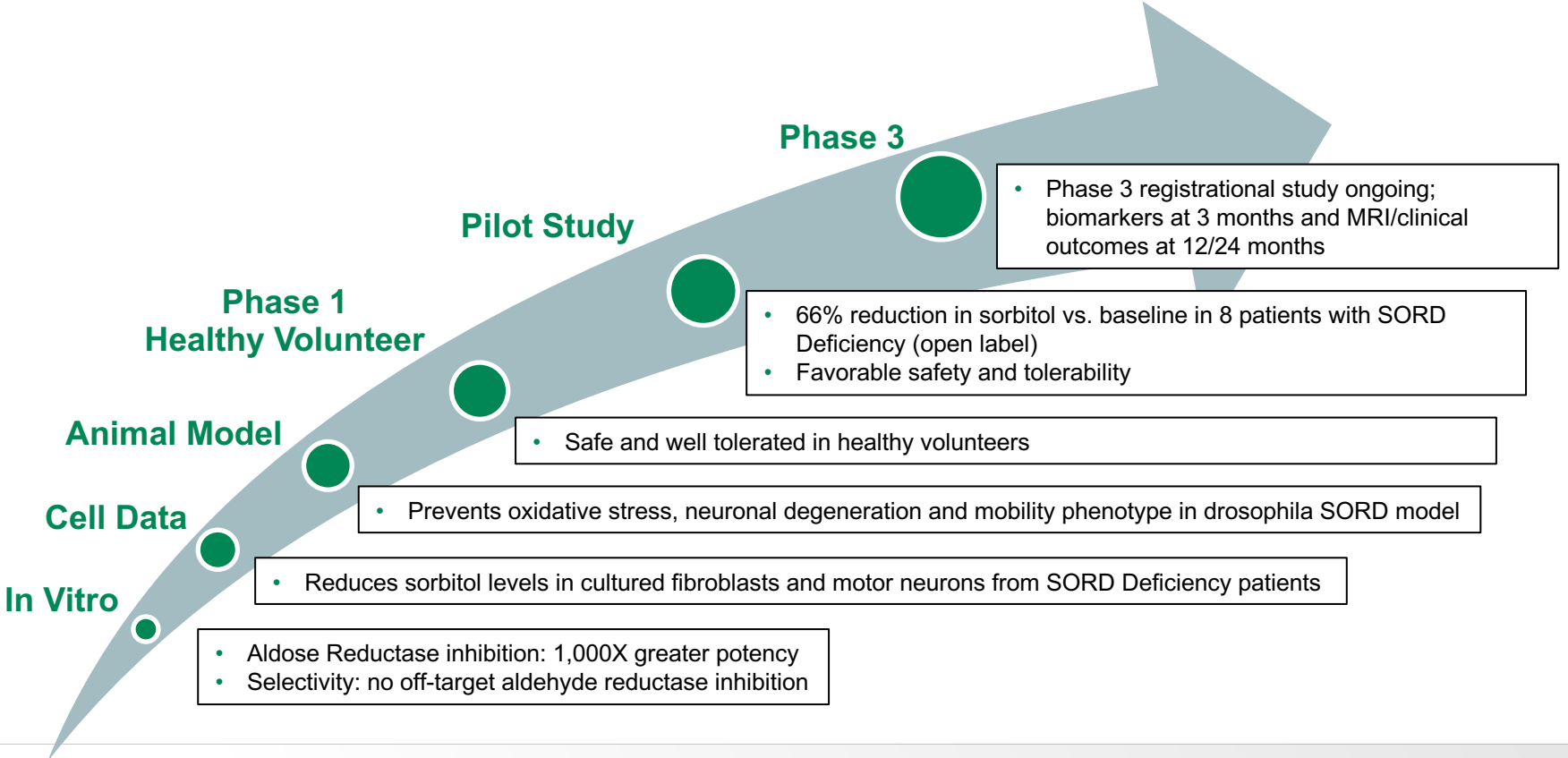
- Patients with SORD Deficiency are unable to metabolize sorbitol
- Aldose Reductase converts glucose to sorbitol, which then accumulates at up to 100X normal levels in patients with SORD Deficiency
- Sorbitol is toxic to cells (especially neurons), resulting in osmotic stress, redox derangement and energetic destabilization

Market Size/ Opportunity

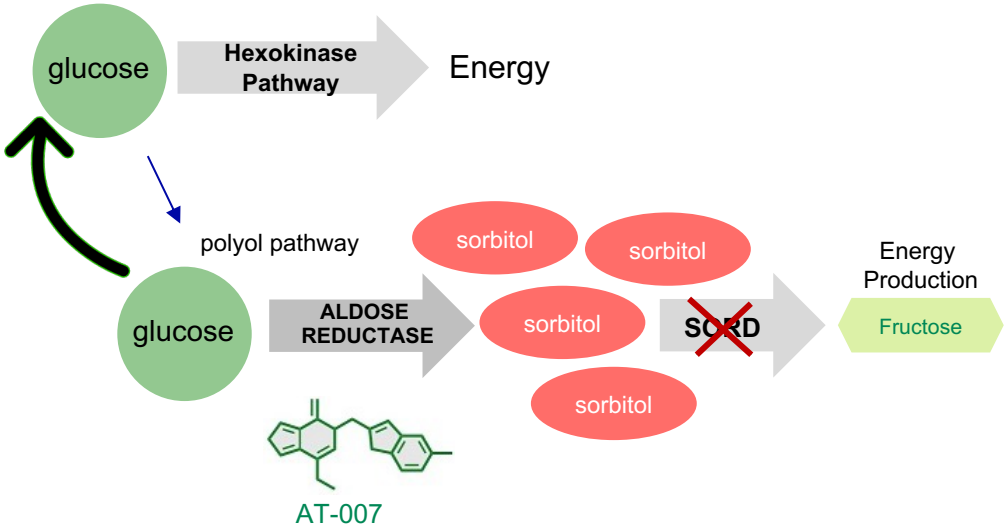
- ~3,300 individuals in the US with SORD Deficiency; 7,000 US+EU combined
- Small commercial footprint focused on KOLs at COEs
- Strong patient community engagement
- Payer feedback supports access/pricing
- Composition of matter IP through 2037; IP covering ARI treatment of SORD Deficiency through 2040

CMT2 = Charcot-Marie-Tooth Type 2; dHMN = distal Hereditary Motor Neuropathy; COE = Centers of Excellence; ARI = Aldose Reductase Inhibitor

AT-007 Has Demonstrated Effectiveness In Vitro, In Vivo, and in a SORD Pilot Study; Phase 3 Biomarker Data Expected in 2022; Outcomes 2023



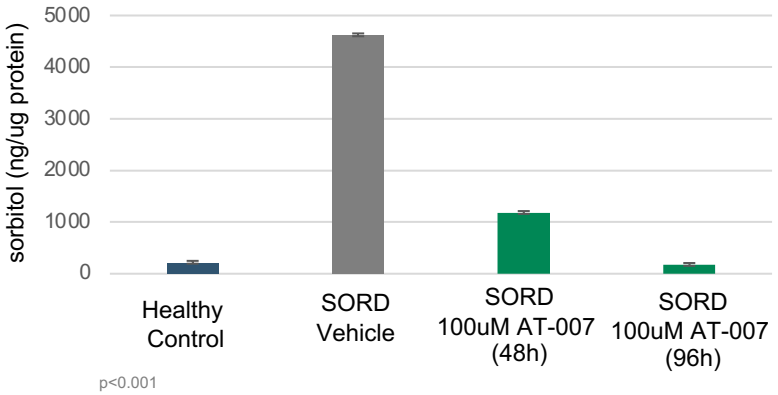
Aldose Reductase Inhibition Addresses the Underlying Cause of SORD Neuropathy by Preventing Conversion of Glucose to Sorbitol



- People with SORD Deficiency are missing the SORD enzyme, which follows Aldose Reductase in the polyol pathway
  - As a result, people with SORD Deficiency are unable to metabolize sorbitol
  - Sorbitol accumulates in blood, cells and tissues at very high levels
  - High toxic sorbitol levels result in cell death and tissue degeneration, leading to neuropathy

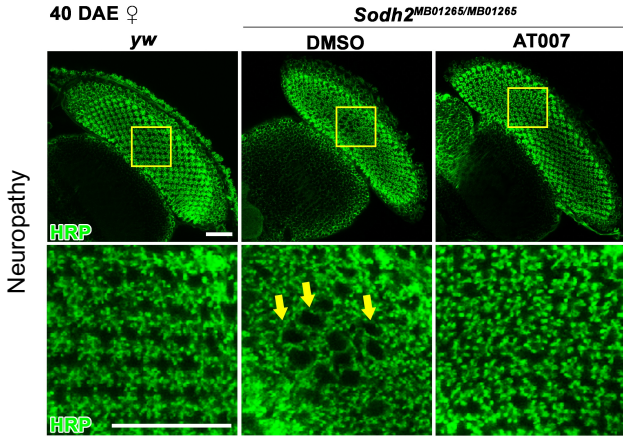
AT-007 Treatment Reduces Sorbitol Levels in SORD Patient Cells; Prevents CNS Phenotype in a Drosophila SORD Deficiency Model

Sorbitol Reduction in Patient Fibroblasts with AT-007 Treatment

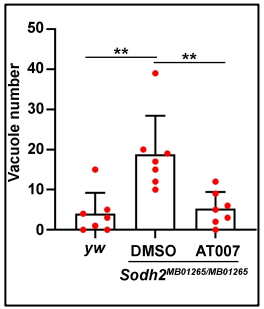


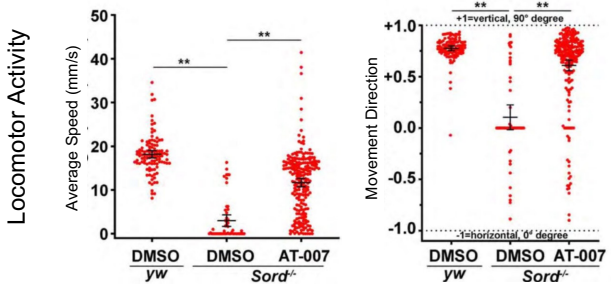
- Sorbitol accumulation causes mitochondrial dysfunction and reactive oxygen species formation, resulting in axonal neuropathy
- Treatment with AT-007 reduces sorbitol and prevents downstream neuronal damage
- AT-007 treatment normalizes lower limb function in drosophila

AT-007 Prevents the SORD Disease Phenotype in Drosophila



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

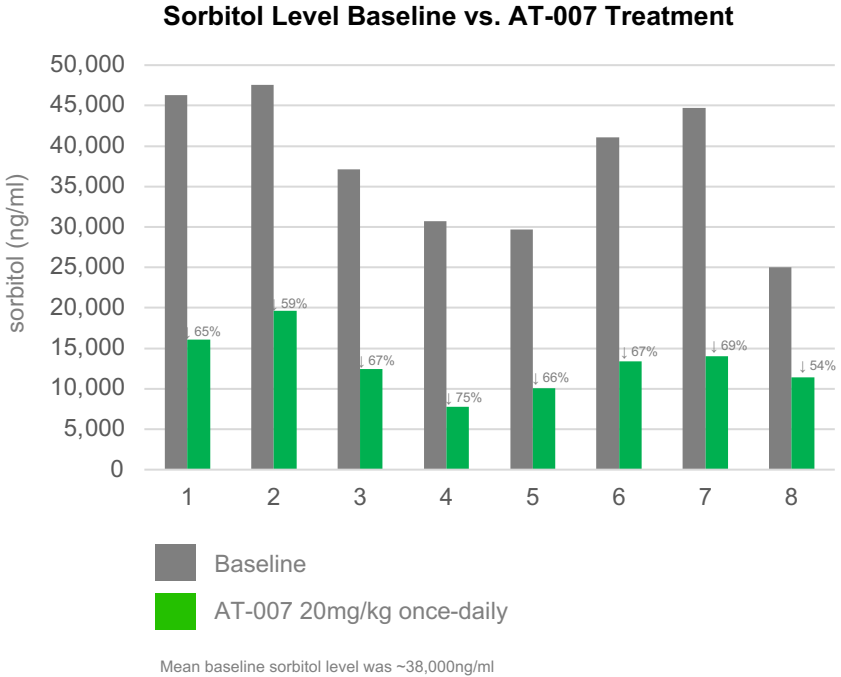




Fly geotactic activity was recorded using an automated monitoring system. *yw* flies (control) treated with DMSO and SORD deficient flies treated with DMSO or 10 µg/ml AT- 007 at 10 DAE. Data are presented as mean ± SE, $^{**}p < 0.01$ from trial-by-trial comparisons.

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

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



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

Safety

- AT-007 safe and well tolerated; no SAEs

Pharmacokinetics/ Pharmacodynamics

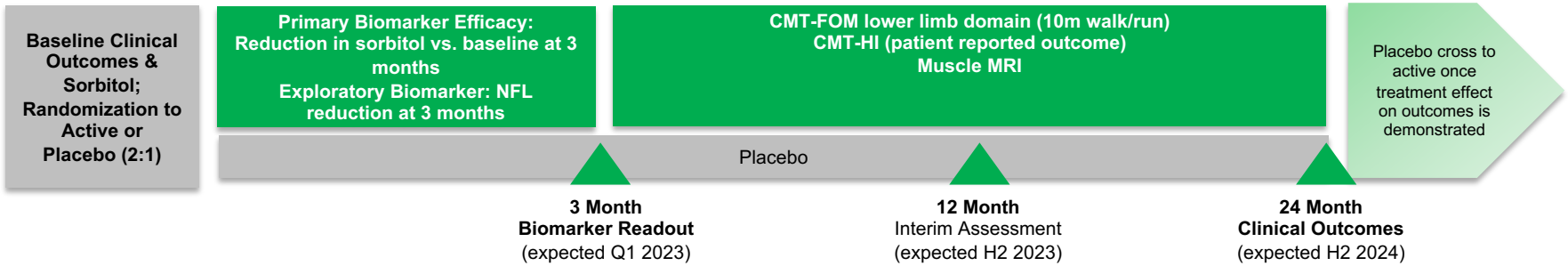
- Rapid and sustained reduction in sorbitol
- No compensatory increase in glucose level

Sorbitol Correlation with Severity

- Baseline sorbitol correlated with disease severity
- Higher sorbitol level was associated with greater disability, need for leg braces, and upper limb involvement (tremor/ weakness)

SORD Neuropathy Phase 3 Registrational Study (INSPIRE)

Double-Blind, Randomized, Placebo-Controlled Multi-Center Study in ~50 SORD Patients ≥16 years old



Cross-sectional analysis of the first cohort in the INSPIRE trial confirms that sorbitol level statistically correlates with clinical outcomes

CMT-FOM Domains and Tests

Domain	Test item
Strength	Handgrip,[a] n Foot plantar flexion,[a] n Foot dorsiflexion,[a] n
Upper limb function	Functional dexterity test,[a] s 9-hole peg test,[a] s
Lower limb function	10-m walk/run, s Stair climb, s Sit to Stand, 30 s
Balance	Stance with eyes open,[a] s Stance with eyes closed,[a] s Single leg stance,[a] s
Mobility	Timed up and go, s 6-min walk test,[a] m

outcome	variable	constant	p value
10MWR	sorbitol	age	p<0.05
4-stair-climb	sorbitol	age	p<0.05
sit-to-stand	sorbitol	age	p<0.05

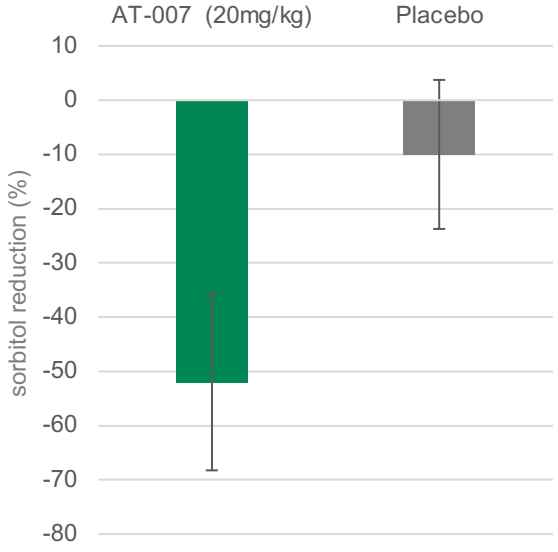
- Statistically significant correlation of sorbitol with lower limb clinical outcome measures
- Confirms sorbitol as a key driver of disease severity and disease progression over time
- Supports lower limb metrics evaluated in INSPIRE Phase 3 trial

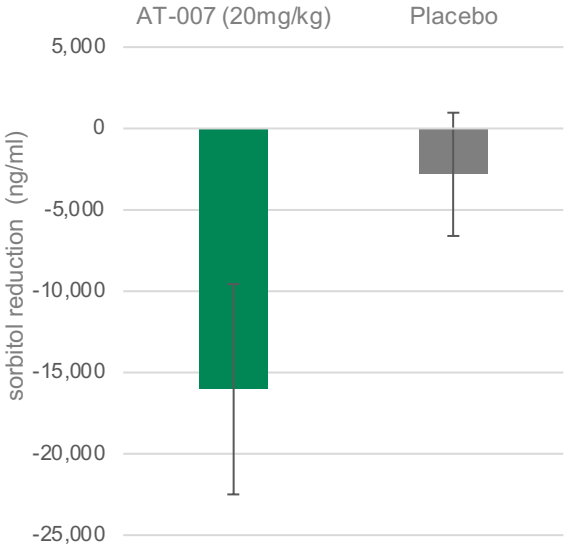
CMT = Charcot-Marie-Tooth, FOM = Functional Outcomes Measure, HI = Health Index, MRI = Magnetic Resonance Imaging, 10MWR = 10-Meter Walk/Run

AT-007 Significantly Reduced Sorbitol Levels in the Phase 3 INSPIRE Trial

3 Month Sorbitol Reduction Interim Analysis

AT-007: 52% Reduction in Sorbitol from Baseline (~16,000ng/ml) p<0.001 vs. placebo





Mean baseline sorbitol level was ~29,000ng/ml

Placebo

AT-007 20mg/kg once-daily

Safety

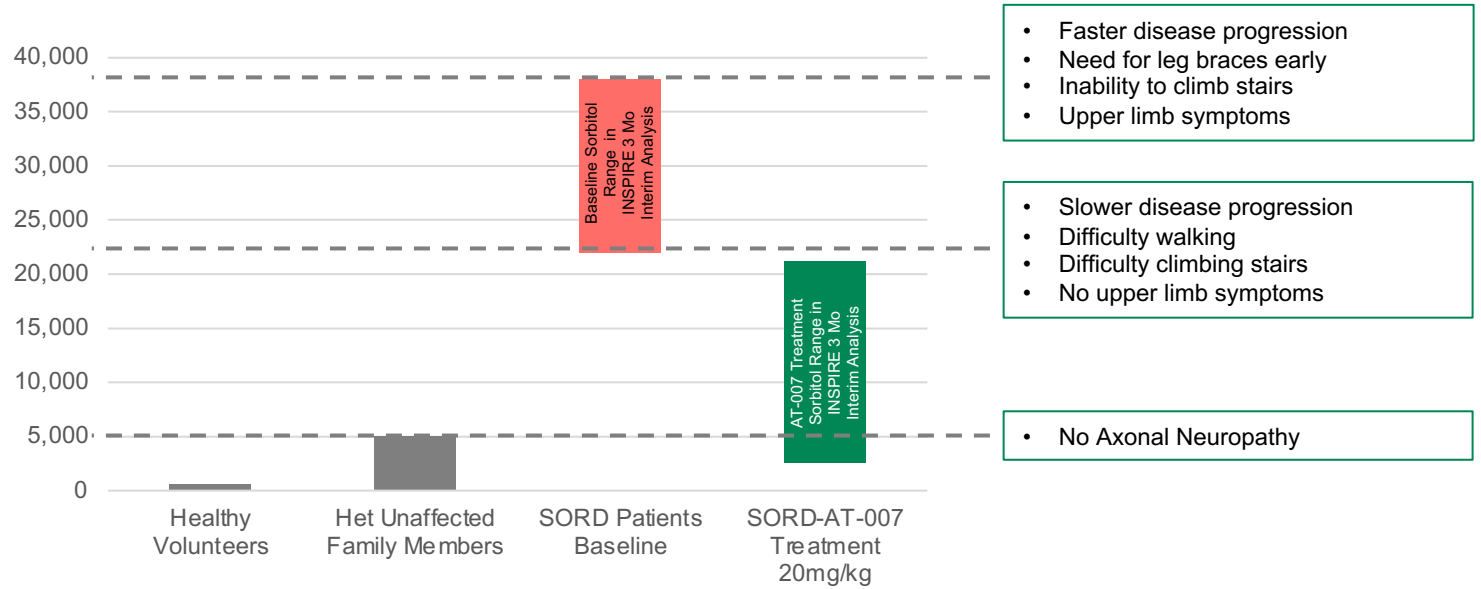
- AT-007 safe and well tolerated

Clinical Impact of Sorbitol Reduction

- Sorbitol reduction expected to impact clinical outcomes, including primary clinical outcome measure, 10m walk/run test

Sorbitol Reduction with AT-007 in the INSPIRE Study is Expected to Translate into Clinically Meaningful Impact on Symptoms of Disease

AT-007 Treatment Substantially Reduces Sorbitol Levels - Expected to Translate Clinically into Slowing or Halting Progression of Disease

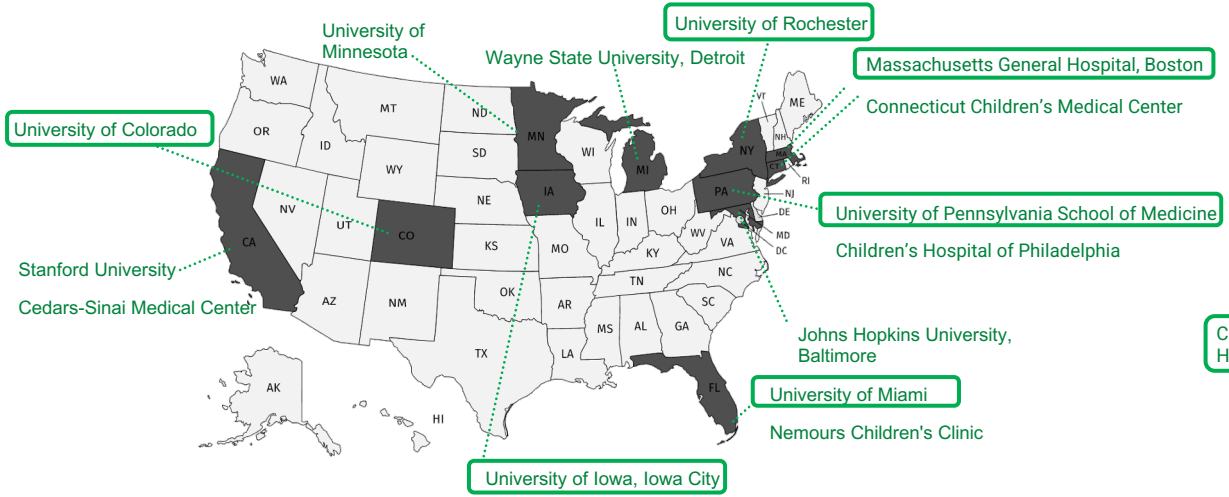


"Het" = heterozygous for SORD mutation (1 mutated allele, 1 normal allele)

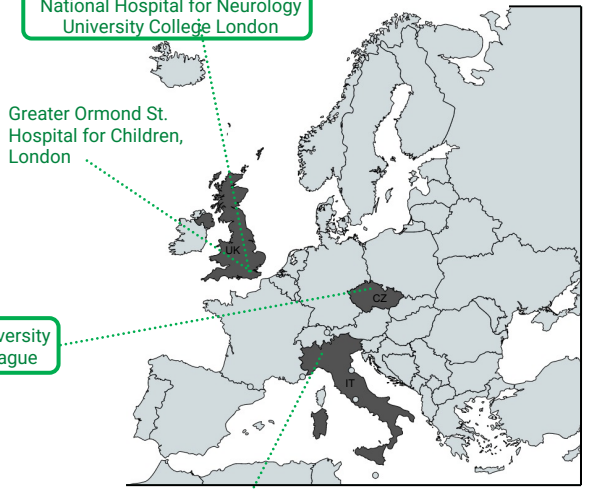
Disease progression data from Perfetti R, Dastgir J, Shendelman S. Circulating Sorbitol Levels and Severity of Disease in Patients with Sorbitol Dehydrogenase (SORD) Deficiency 2022 Annual Meeting of the Peripheral Nerve Society, Poster 162; E-Poster 1383

Inherited Neuropathy Consortium Centers of Excellence and Global CMT Registries Exist to Support Diagnosis and Treatment

US



UK & EU



Centers participating in INSPIRE Phase 2/3 trial

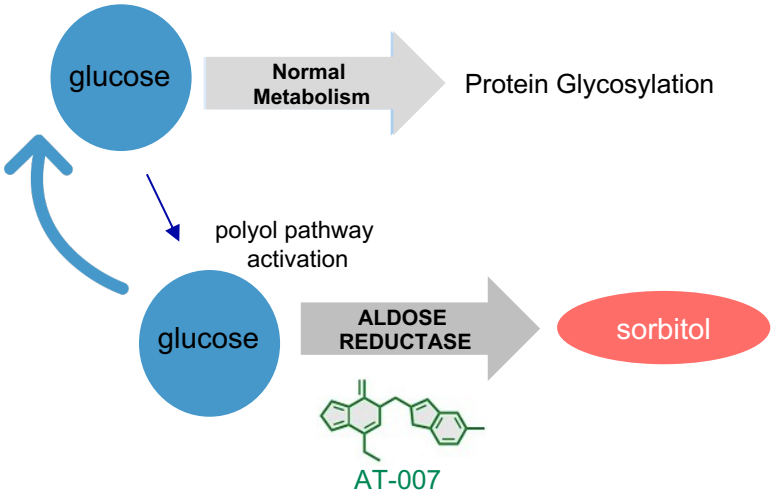
www.rarediseasesnetwork.org/cms/inc/centers#CSMC.

PMM2-CDG

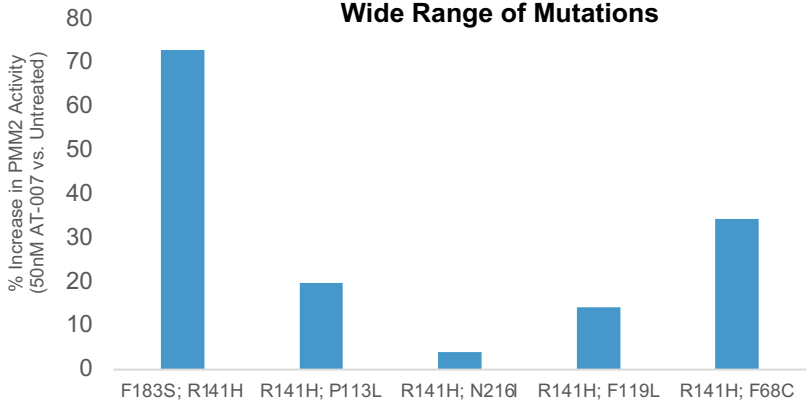
Aldose Reductase Inhibition Improves PMM2 Activity
AT-007 Granted Orphan & Pediatric Rare Disease Designation for PMM2-CDG; Single-Patient IND Open – Phase 2 Ready

PMM2-CDG†, is an ultra-rare mutation of the PMM2 gene (phosphomannomutase) which **results in loss of PMM2 protein function and systemic deficient glycosylation of proteins, disrupting the function of critical tissues and organs**

Sorbitol is a biomarker of PMM2-CDG severity



AT-007 Treatment Increases PMM2 Activity in a Wide Range of Mutations



- 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

High unmet need with no approved therapies; ~1K cases WW, 20% infant mortality

Program has received Orphan Designation and Pediatric Rare Disease Designation from FDA

AT-001

DIABETIC CARDIOMYOPATHY

Phase 1/2 pilot study completed

Registrational Phase 3 study ongoing

Diabetic Cardiomyopathy is a Form of Heart Failure Affecting ~20% of Diabetics; Significant Unmet Need with No Approved Treatments

Disease Overview

- Form of Heart Failure (Stage B) causing structural cardiac damage and resulting in decreased cardiac functional capacity
- Affects ~20% of diabetics
- Diagnosed by echocardiogram or elevated cardiac biomarkers (NTproBNP or troponin)

Standard of Care

- No approved therapies to treat DbCM or prevent progression to overt heart failure/ death
- Once DbCM patients have developed overt HF, they are eligible for standard HF therapies in addition to standard diabetes treatments

Mechanism of Disease

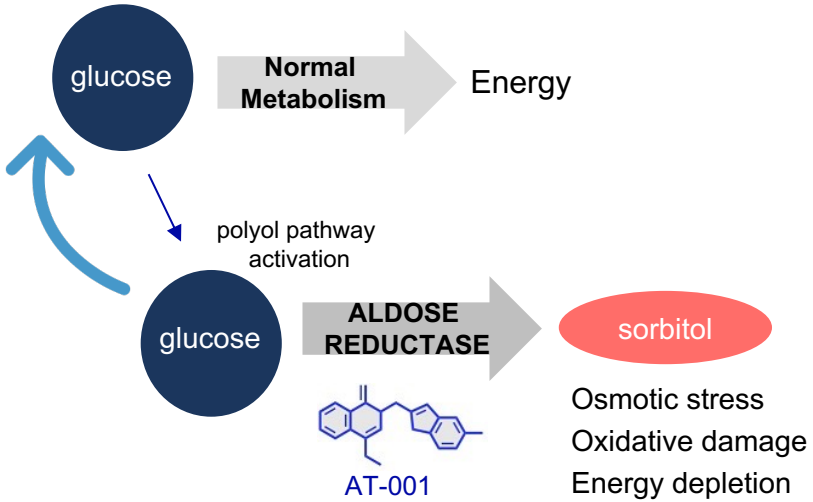
- Hyperactivation of the polyol pathway is a key underlying mechanism in DbCM
- Aldose Reductase activation causes intracellular sorbitol accumulation, osmotic stress, cell death, generation of ROS and impaired cardiac energetics
- Previous AR inhibitors demonstrated clinical efficacy, but were associated with off-target safety signals due to lack of selectivity

Market Size/ Opportunity

- Blockbuster potential
- Addressable population of ~6M patients US, 5M in EU5
- Anticipated pricing in line with Entresto & SGLT2s
- Composition of matter IP through 2031 (not including extensions)

Brownlee M. Diabetes Care. 2005;54(6):1615-1625; Miki T, et al. Heart Fail Rev. 2013;18(2):149-166.

DbCM: Mechanism of Disease



Both Type 1 and Type 2 diabetes results in hyperglycemia; the polyol pathway is then hyperactivated to rid the body of the excess glucose

Aldose Reductase, the first and rate limiting enzyme in the polyol pathway, converts this glucose into sorbitol and eventually fructose

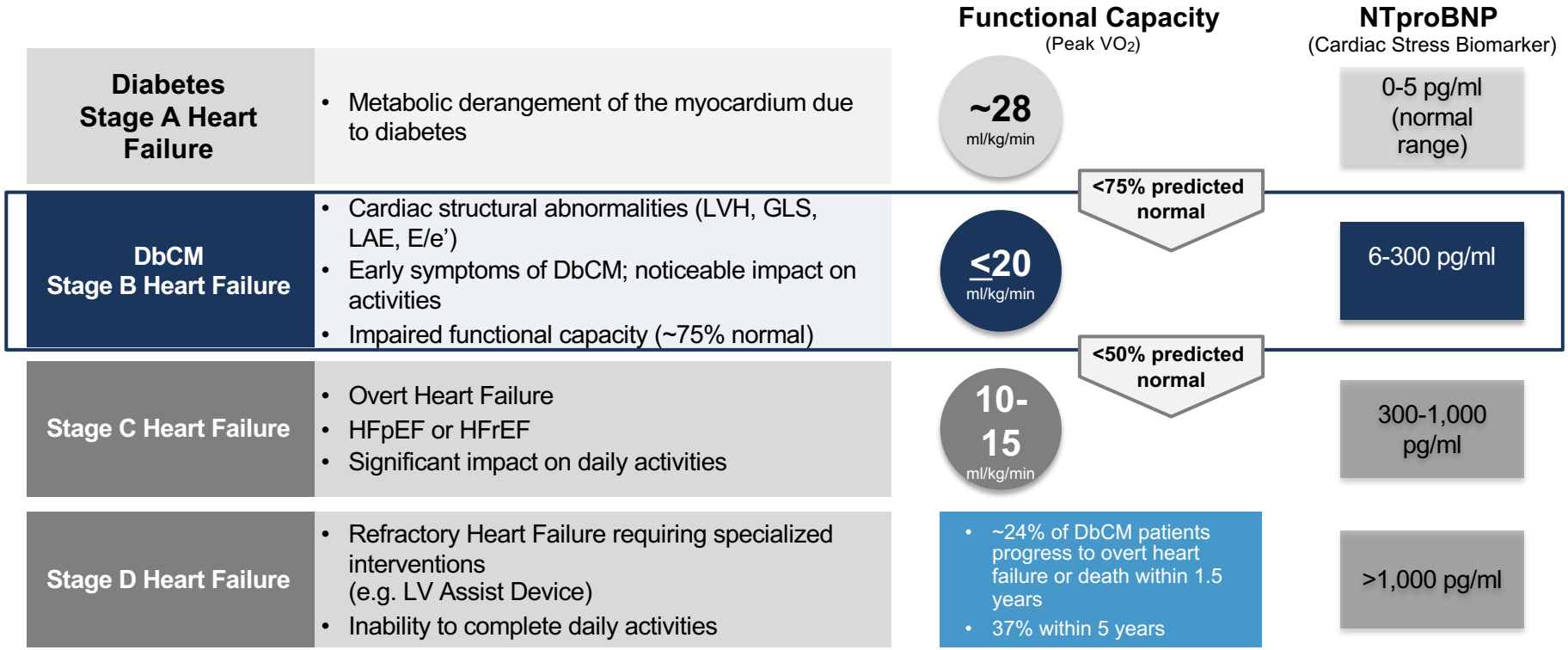
Excess sorbitol and fructose cause several downstream processes that result in cell death, including osmotic dysregulation and ROS formation

AR activation also detracts glucose from the energy efficient hexokinase/glycolytic pathway, resulting in less energy production for cardiomyocytes

This results in heart fibrosis, a “hardening” of the heart muscle, which means it cannot effectively pump blood to the rest of the body

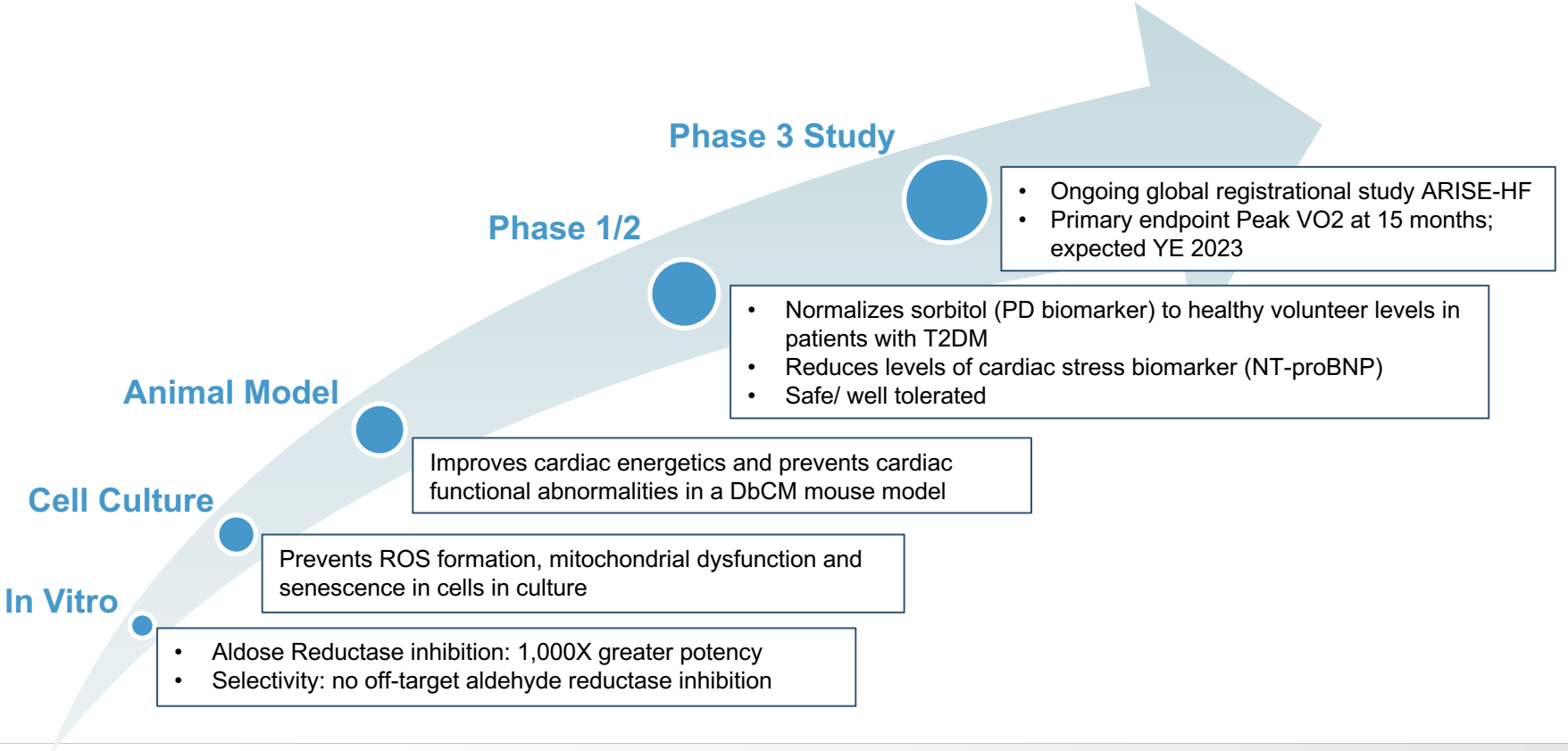
Brownlee M. Diabetes Care. 2005;54(6):1615-1625; Miki T, et al. Heart Fail Rev. 2013;18(2):149-166.

Diabetic Cardiomyopathy is a Form of Stage B Heart Failure



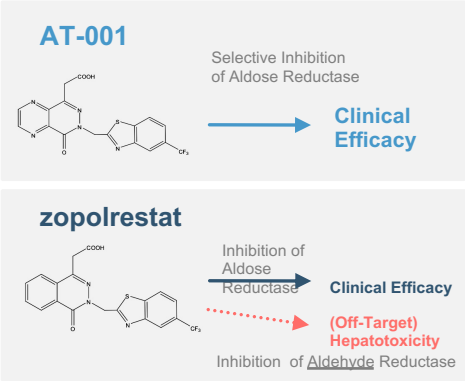
Kosmala et al, JACC VOL. 65, NO.3, 2015; Swank et al. Circ HF 2012; Wang et al. JACC: Cardiovasc Imaging 2018; From et al. JACC 2010

AT-001 Has Demonstrated Effectiveness In Vitro, In Vivo, and in Phase 1/2 Clinical Trials; Registrational Study Readout Expected 2023



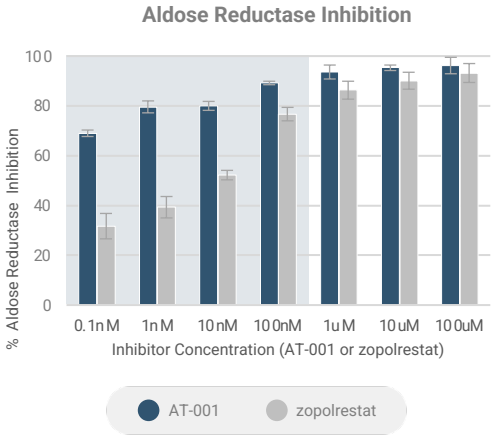
In Vitro: AT-001 Provides Greater Potency and Improved Target Selectivity vs. "Old" Aldose Reductase Inhibitors

Applied Therapeutics' **AT-001 was developed to selectively inhibit Aldose Reductase with 1,000X greater potency and *without* off-target inhibition** of Aldehyde Reductase[2]



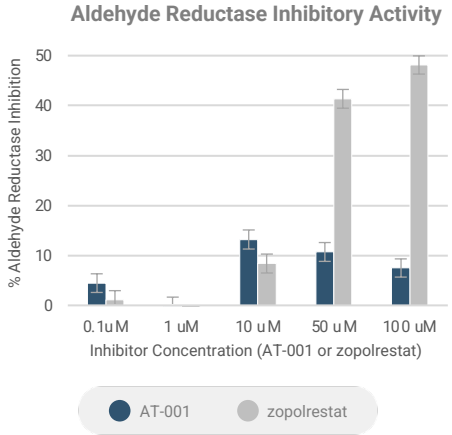
Compound	IC_{50}	MTD in animals	Tissue Penetration (in rats) Systemic/ Heart	Nerve	Retina	CNS
AT-001	30pM	>2,000mg/kg	✓	✓	✓	X
zopolrestat	10nM	100mg/kg	✓	✓	X	X

AT-001 demonstrated improved IC_{50} and IC_{90} vs. zopolrestat



Data based on In Vitro Enzyme Inhibition & Cultured Hepatocytes

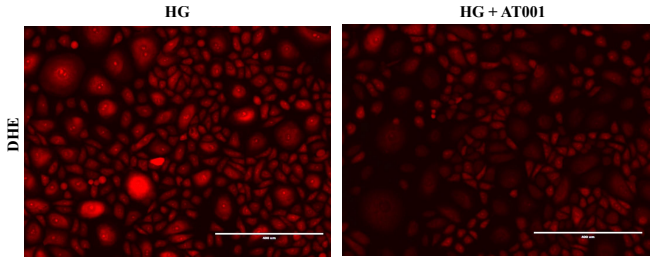
Unlike zopolrestrat, AT-001 does not inhibit Aldehyde Reductase



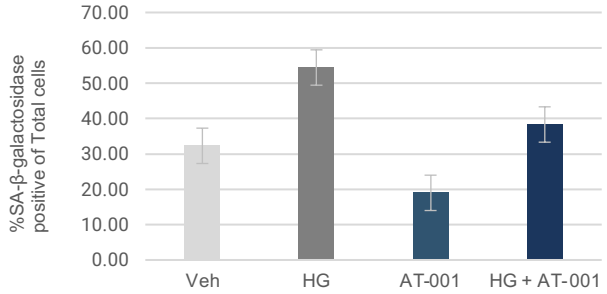
Poster # 632: "Addressing safety and specificity with aldose reductase inhibition: development of AT-001 for diabetic cardiomyopathy" 56th Annual Meeting of the European Association for the Study of Diabetes (EASD) Sept 2020

AT-001 Treatment Prevents Reactive Oxygen Species Generation & Mitochondrial Stress Caused by High Glucose Exposure

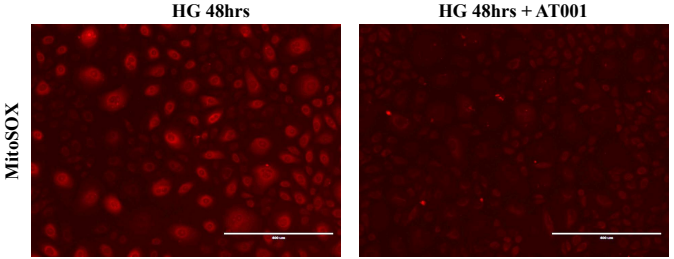
Dihydroethidium (DHE) Staining for Cytosolic ROS



Quantitation of Cell Senescence Via SA-β-gal Staining



MitoSOX™ Staining for Mitochondrial ROS



HG- NHK cells exposed to 25mM glucose (high glucose) for 48hrs
HG + AT-001 - cells treated with 0.18nM AT-001 along with above mentioned HG exposure

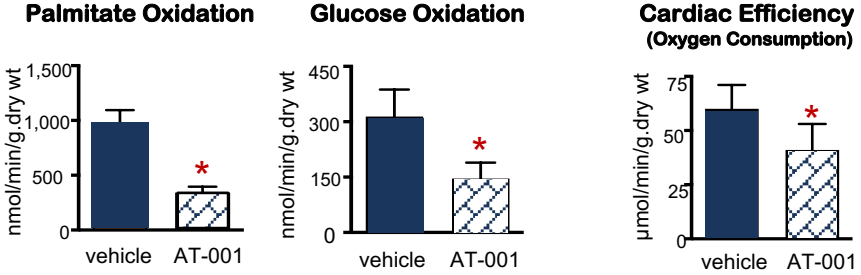
- In patients with diabetes, metabolism of glucose through the polyol pathway results in generation of Reactive Oxygen Species (ROS), which has been identified as a key mediator of tissue damage and causal in diabetic complications. Selective inhibition of AR reduces oxidative stress and mitigates these complications.
- AT-001 prevents the production and accumulation of ROS as assessed by both DHE quantitation and MitoSOX™ staining, demonstrating effective reduction of oxidative damage in the cytosol and mitochondria of cells.
- Evaluation via SA-β-gal staining showed less senescence in cells exposed to high glucose in the presence of AT-001

Poster #629: "AT-001 a new aldose reductase inhibitor with improved selectivity and specificity protects from cellular damage" 56th Annual Meeting of the European Association for the Study of Diabetes (EASD) Sept 2020

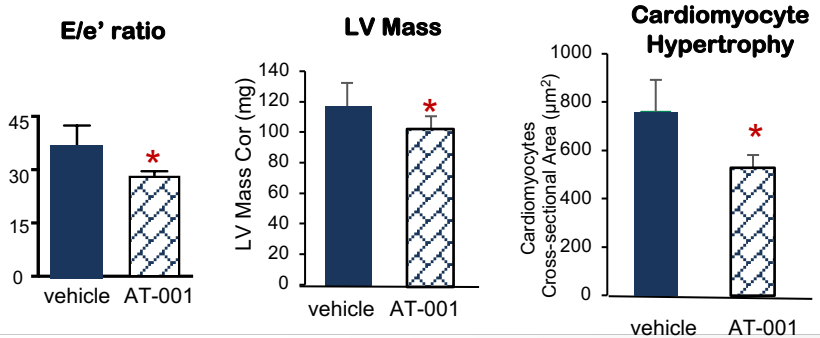
AT-001 Improves Cardiac Energetics, Prevents Cardiac Dysfunction and Prevents Fibrosis in an Animal Model of DbCM

AT-001 Treatment in a DbCM Mouse Model (Design)

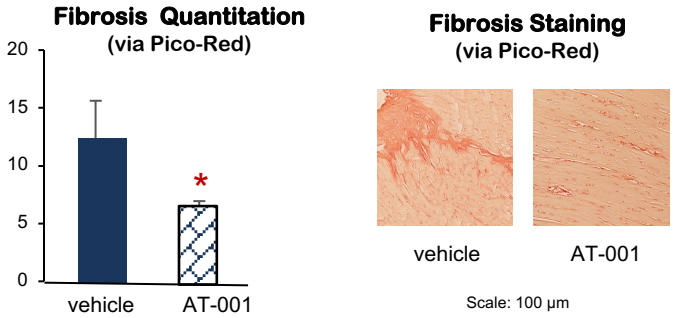
AT-001 Improves Cardiac Energetics



AT-001 Improves Cardiac Function and Prevents LVH



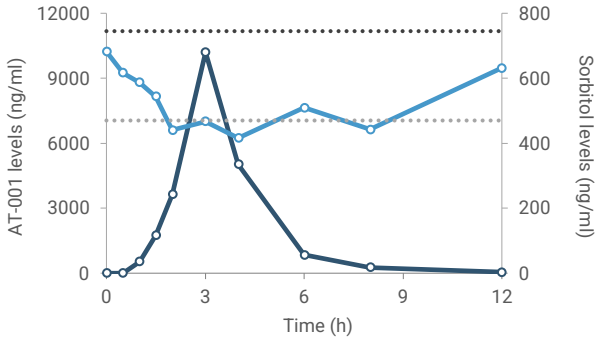
AT-001 Prevents Fibrosis and Adverse Remodeling



Keshav et al Pharmacological Inhibition of Aldose Reductase by AT-001 Prevents Abnormal Cardiac Energy Metabolism and Improves Heart Function in an Animal Model of Diabetic Cardiomyopathy, AHA 2020;
Keshav et Al Aldose Reductase Inhibition By At-001 Alleviates Fibrosis and Adverse Remodeling In Diabetic Cardiomyopathy By Reducing Myocardial Fatty Acid Oxidation, AHA 2022

Phase 1: AT-001 Normalizes Sorbitol, a Biomarker of AR Activity, in Diabetic Patients

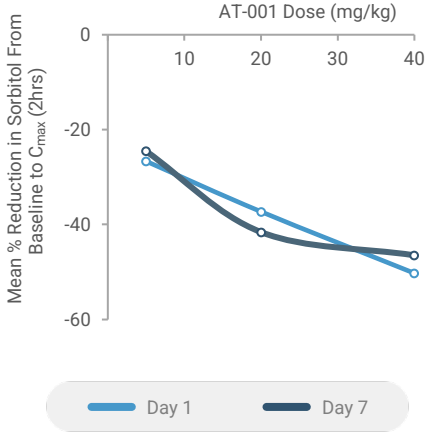
Proof of Biological Activity



AT-001 normalized sorbitol in diabetics to healthy volunteer levels

No compensatory increase in glucose level

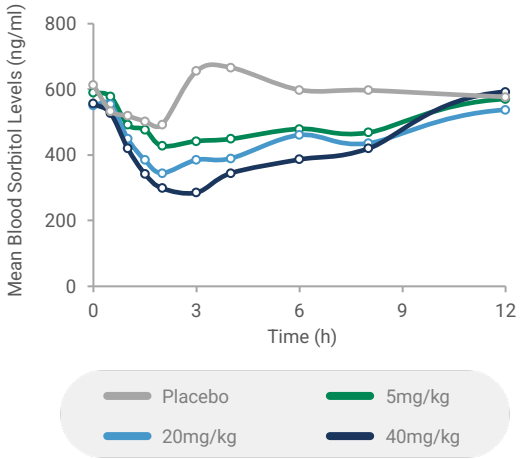
Sorbitol Reduction by Dose



Mean reduction in sorbitol at Day 1 and Day 7: Results are persistent over 1 week of treatment

At 40mg/kg patients were normalized to healthy volunteer sorbitol levels, demonstrating complete AR inhibition

Sorbitol Normalization Over Time



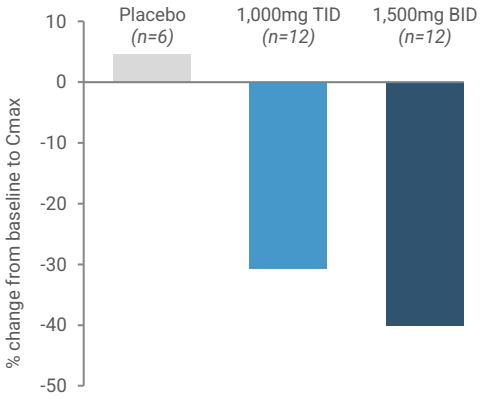
Rapid release capsule provides sorbitol normalization effects (PD biomarker) through **10-12hrs post-dose** at >10mg/kg

Includes protection from food-related sorbitol spikes during times of post-prandial hyperglycemia

Poster, "Phase 1/2 Safety and Proof of Biological Activity Study of AT-001, an Aldose Reductase Inhibitor in Development for Diabetic Cardiomyopathy" American Diabetes Association 79th Scientific Sessions in San Francisco (June 7-11, 2019); Poster "Clinical Assessment of AT-001, an Aldose Reductase Inhibitor in Development for Diabetic Cardiomyopathy: a 28 day proof of concept study" American Heart Association (AHA) Scientific Sessions

Phase 2: AT-001 Reduced Levels of NTproBNP Cardiac Stress Biomarker Over 28 Days

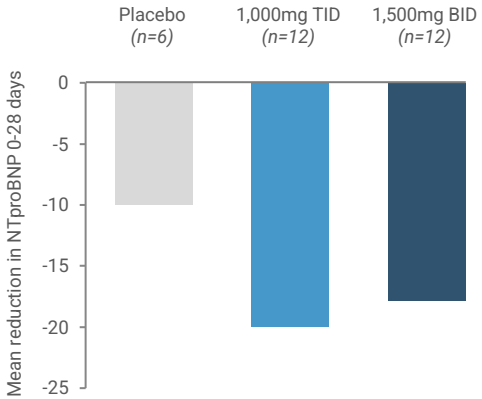
Sorbitol Normalization



Significant sorbitol reduction achieved by both 1,000mg TID and 1,500mg BID AT-001

Higher Cmax achieved with BID slightly beneficial — normalizes sorbitol to healthy volunteer levels

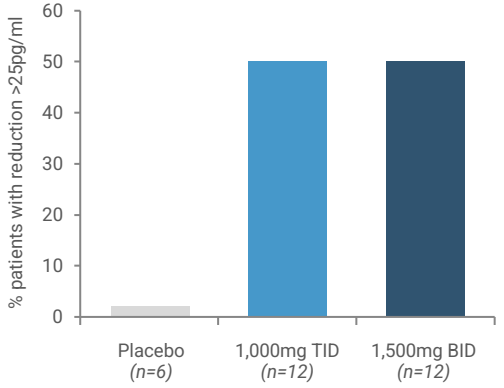
Mean Reduction in NTproBNP



Mean reduction in NTproBNP seen over 28 days vs. placebo

Mean baseline NTproBNP was 65pg/ml

Clinical Responder Analysis



~50% AT-001 treated patients demonstrated a clinically meaningful reduction in NTproBNP over 28 days

>25pg/ml reduction from baseline

PHASE 3

DbCM Phase 3 Registrational Study (ARISE-HF)

Randomized, Placebo-Controlled Study in DbCM Patients at High Risk of Progression

Population

Patients with DbCM at high risk of progression to overt HF n=675 (225/arm)

1:1:1 Randomization

- Placebo
- 1,000 mg
- 1,500 mg

Twice-daily oral dosing

Core Study

Efficacy (15 Months)

- **Primary Endpoint:** Functional Capacity (as measured by Peak VO2 change from baseline)

Sufficient for approval
Data expected YE 2023

27 Month Secondary and Exploratory Analyses

- Progression to overt HF
- Echo based endpoints
- KCCQ
- Exploratory cardiac biomarkers

Post-approval endpoints to support market access

Peripheral Neuropathy sub-study built into ARISE-HF

Placebo-controlled Extension:

CV death/ hospitalization

Key Projected Milestones by Program