

# Applied Therapeutics

January 2024



# Forward Looking Statements

Various statements in this presentation concerning the Company's future expectations, plans and prospects constitute forward-looking statements. The use of words such as "may," "might," "will," "should," "expect," "plan," "anticipate," "believe," "estimate," "project," "intend," "future," "potential," or "continue," the negative of these and other similar expressions are intended to identify such forward looking statements. Such statements, based as they are on the current analysis and expectations of management, inherently involve numerous risks and uncertainties, known and unknown, many of which are beyond the Company's control. Such risks include, but are not limited to: the impact of general economic conditions, general conditions in the biopharmaceutical industries, changes in the global and regional regulatory environments in the jurisdictions in which the Company does or plans to do business, market volatility, fluctuations in costs and changes to the competitive environment, the Company's ability to fund its working capital requirements and expectations regarding the sufficiency of our capital resources and the Company's ability to achieve the anticipated benefits from the agreements entered into in connection with our partnership with Advanz Pharma. Consequently, actual future results may differ materially from the anticipated results expressed in the forward-looking statements. In the case of forward-looking statements regarding investigational product candidates and continuing further development efforts, specific risks which could cause actual results to differ materially from the Company's current analysis and expectations include: failure to demonstrate the safety, tolerability and efficacy of our product candidates; final and quality controlled verification of data and the related analyses; the expense and uncertainty of obtaining regulatory approval, including from the U.S. Food and Drug Administration and European Medicines Agency; the possibility of having to conduct additional clinical trials and our reliance on third parties such as our licensors and collaboration partners regarding our suite of technologies and product candidates; the Company's ability to take advantage of expedited regulatory pathways for any of our product candidates; the Company's intellectual property position and the duration of its patent rights; developments or disputes concerning the Company's intellectual property or other proprietary rights. Further, even if regulatory approval is obtained, biopharmaceutical products are generally subject to stringent on-going governmental regulation, challenges in gaining market acceptance and competition.

These risks and uncertainties are described more fully under the caption "Risk Factors" in the Company's filings with the Securities and Exchange Commission. Other risks and uncertainties of which the Company is not currently aware may also affect Company's forward-looking statements. The reader should not place undue reliance on any forward-looking statements included in this presentation. These statements speak only as of the date made and the Company is under no obligation and disavows any obligation to update or revise such statements as a result of any event, circumstances or otherwise, unless required by applicable legislation or regulation.

# 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

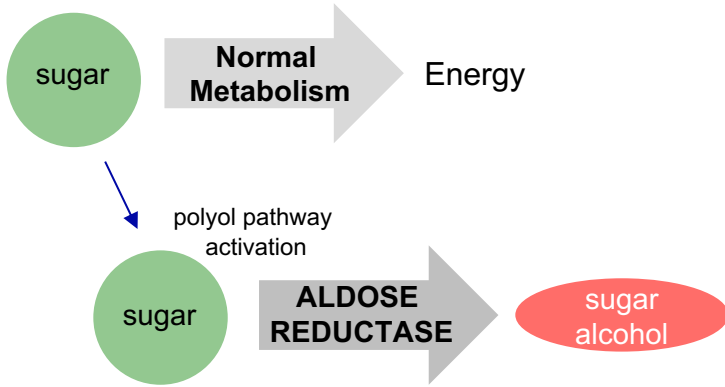
Limited / no competition

# Innovative Pipeline with Near-Term Milestones

Compound	Preclinical	Phase 1	Phase 2	Phase 3	Dosing	Target Tissue	Milestones	Rights
<b>ALDOSE REDUCTASE FRANCHISE</b>								
<b>AT-007</b> (govorestat)	Galactosemia 				QD Oral	CNS	Pediatric Phase 3 outcomes trial completed; NDA submitted & MAA validated Q4 2023	 
	SORB Deficiency 				QD Oral	CNS	Positive pilot study data; Phase 3 registrational trial ongoing	 
	PMM2-CDG				QD Oral	CNS	Phase 2 ready; Expanded Access open	
<b>AT-001</b>	Diabetic Cardiomyopathy 				BID Oral	Systemic	Ph 3 trial topline data available	
	Diabetic Peripheral Neuropathy				BID Oral	Peripheral Nerve	Sub-study embedded in DbCM Ph 3 trial	
<b>AT-003</b>	Diabetic Retinopathy				Oral	Retina	Phase 1 ready	



# 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

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Converts sugar to reduced sugar alcohols, which are toxic

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

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Osmotic stress

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

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Oxidative damage

Energy depletion

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

Cell death

# 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 completed

Regulatory submissions under review (MAA validated; NDA submitted)



# 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 behavior and motor skills deficiencies, cognitive issues; tremor, speech problems; ovarian insufficiency in females
- Progressively worsens with age

## 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

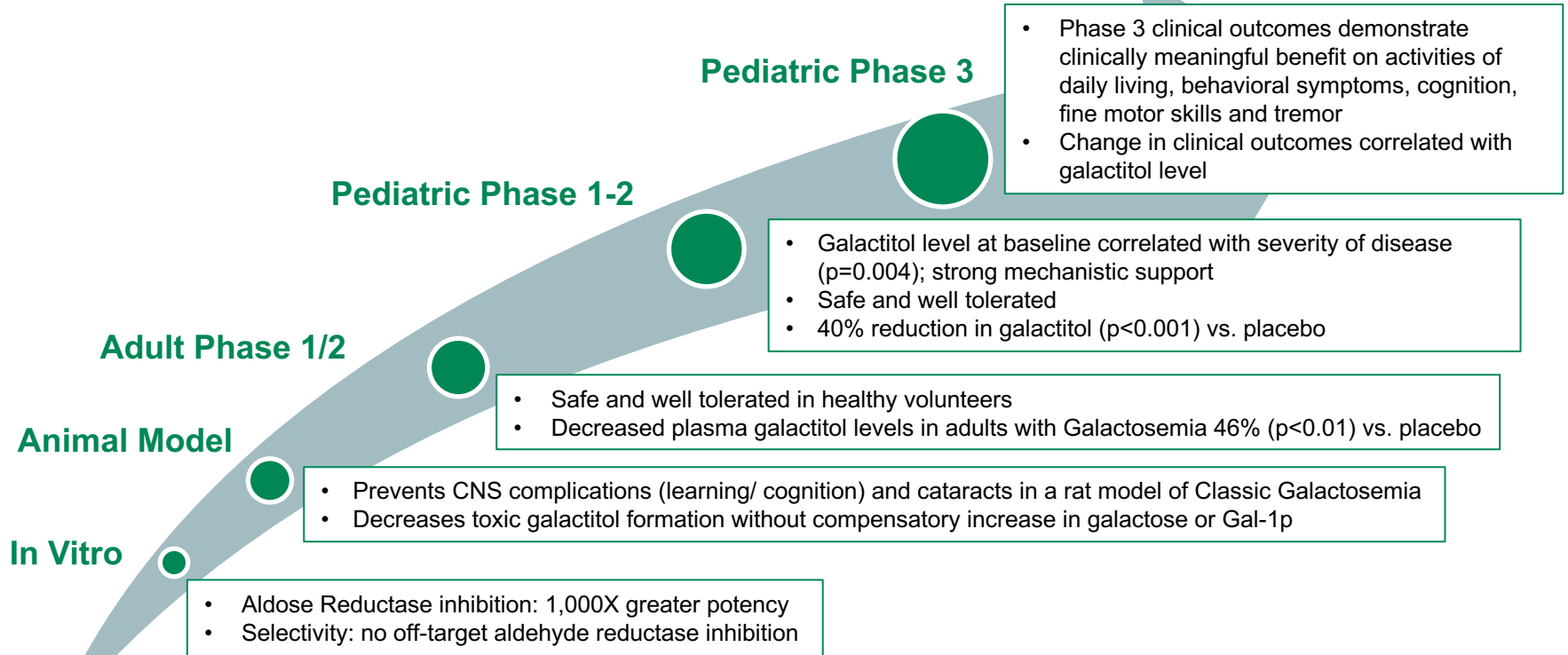
## Standard of Care/ Diagnosis

- 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

## Market Size / Opportunity

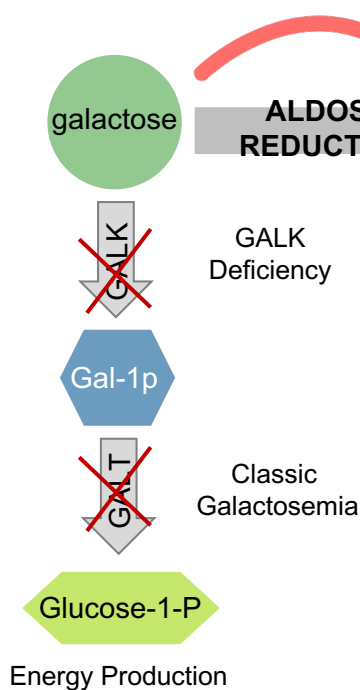
- Known prevalent and addressable population (~3K US, ~7K WW)
- Small commercial footprint focused on KOLs at Centers of Excellence
- Strong patient community engagement
- Payer feedback supports access/pricing
- Composition of matter IP through 2037 (not including extensions)

# AT-007 Has Demonstrated Effectiveness In Vitro, In Vivo, and in Clinical Trials

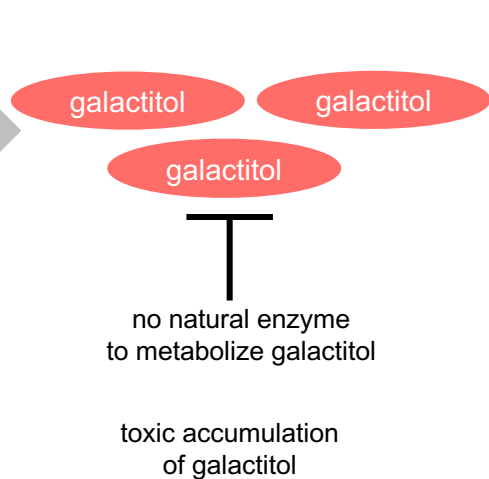


# Deficiency in GALT or GALK Leads to Inability to Metabolize Galactose; AR Converts Excess Galactose to Toxic Galactitol

## NORMAL METABOLISM



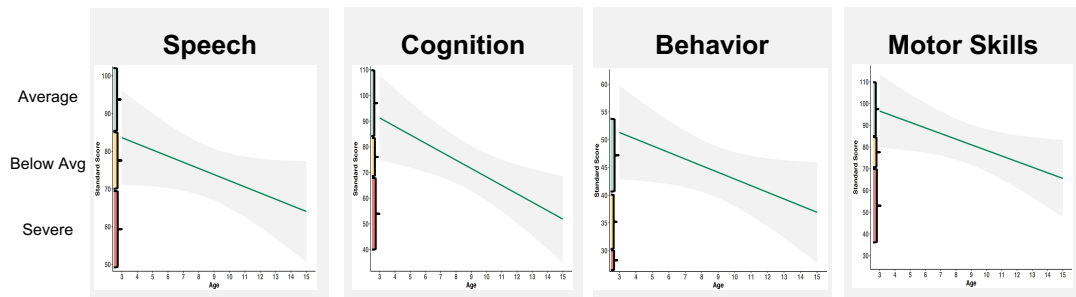
## GALACTOSEMIA



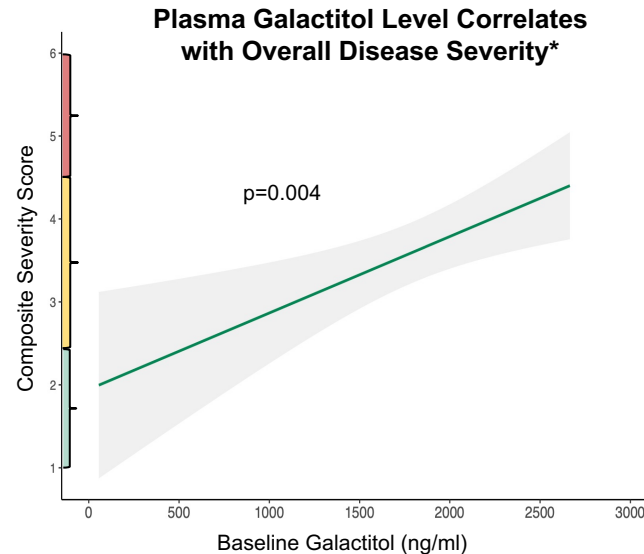
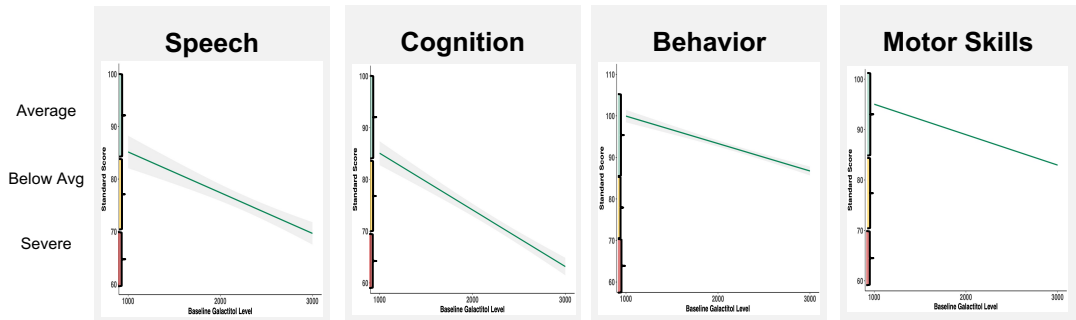
- **CNS Complications:**
  - Cognition/ Learning/ IQ/ Memory
  - Behavior/ Psychiatric
  - Motor Skills (Tremor, Ataxia)
  - Seizures
  - Speech Deficiencies
- **Other Complications:**
  - Ovarian Insufficiency
  - Cataracts

# 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



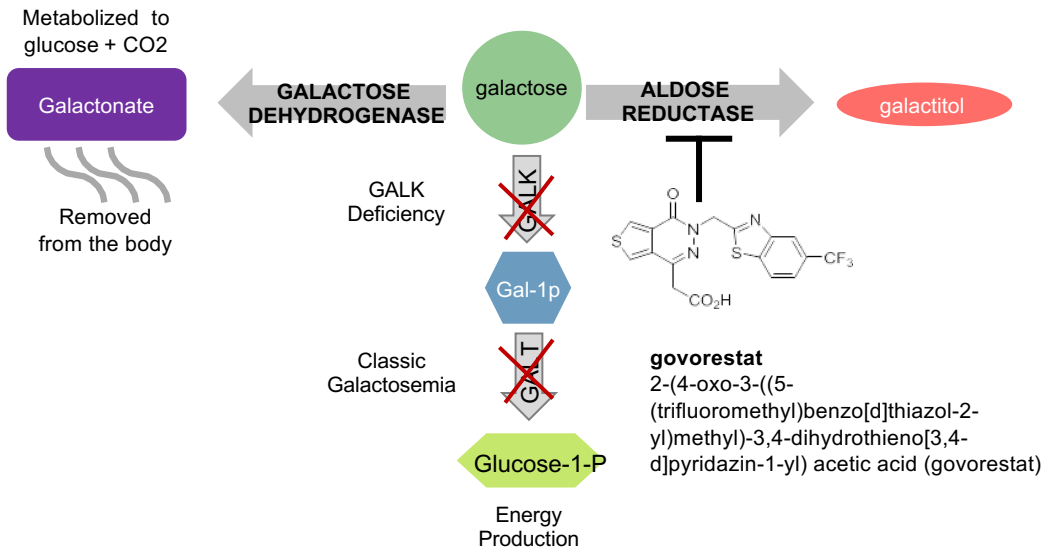
\*Overall severity based on composite score comprised of 4 CNS quadrants

**No correlation observed between Gal-1p and disease severity**



# Govorestat (AT-007) is a Selective, CNS Penetrant Aldose Reductase Inhibitor

## Blocks Production of the Toxic Metabolite Galactitol

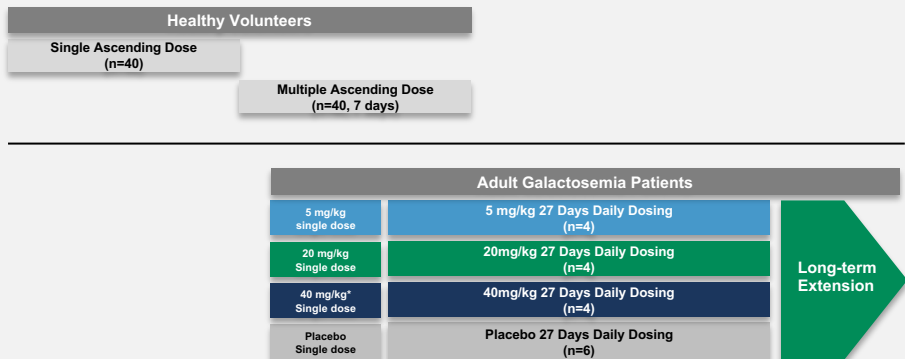


Population	Dose
Adults	20mg/kg
Children >40kg	15mg/kg
Children 20-40kg	20mg/kg
Children <20kg	30mg/kg

- Govorestat is provided as a 200mg/ml oral suspension (for once-daily dosing)
- Dosed by weight to achieve uniform exposure in both pediatric patients and adults

# 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



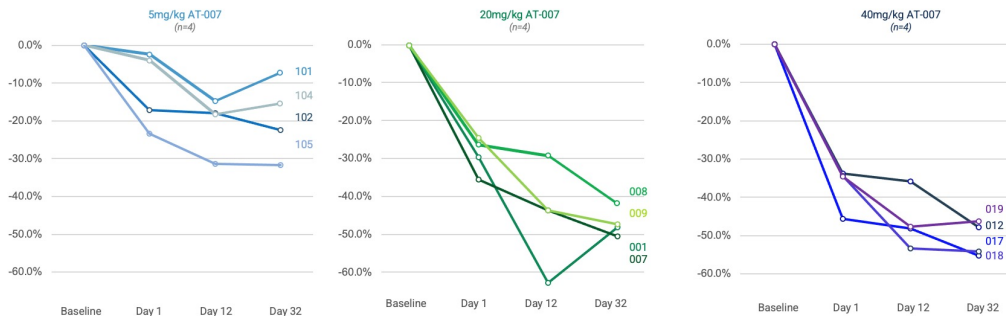
## Safety

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

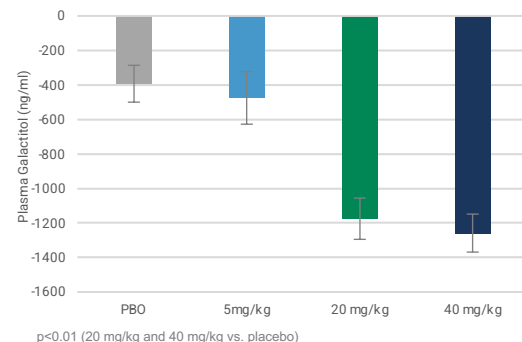
## Pharmacokinetics/ Pharmacodynamics

- 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

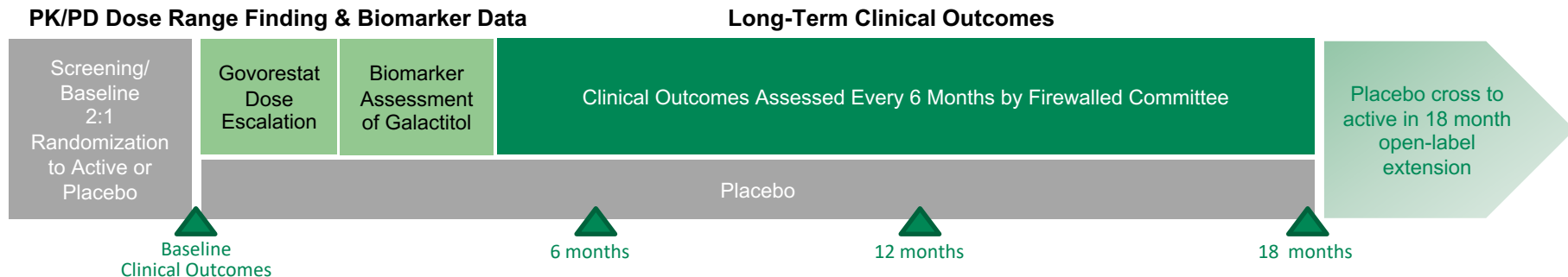
## Galactitol Reduction vs. Baseline (Individual Patient Values)



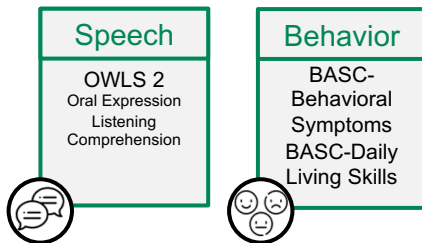
## Maximum Galactitol Reduction vs. Baseline



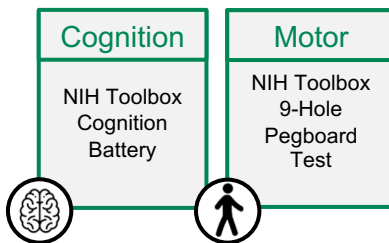
# ACTION-Galactosemia Kids Pediatric Registrational Clinical Study Design (47 Children Age 2-17)



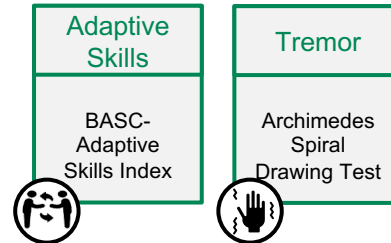
**Primary Endpoint:**  
Global Assessment of Change (Global Statistical Test)  
Composite Sum of Change in CNS function



**Primary Sensitivity Analysis**



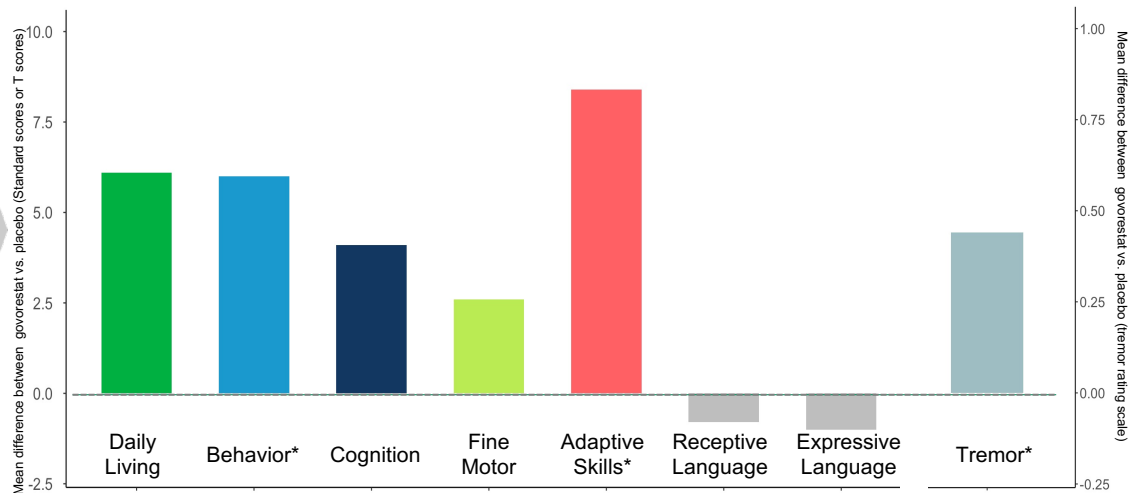
**Key Secondary Endpoints**



# Govorestat Treatment Reduced Plasma Galactitol Levels by 40% ( $p < 0.001$ vs. placebo); Improvement in Galactitol Biomarker Provided Clinical Benefit Across Activities of Daily Living, Behavior, Cognition, Adaptive Skills and Tremor

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%
<b>All groups</b>	<b>15-30mg/kg</b>	<b>40.19% (<math>p &lt; 0.001</math>)</b>

- Significant improvement in galactitol biomarker vs. placebo
- Sustained over time through 18 months of treatment
- No compensatory increase in galactose or Gal-1p

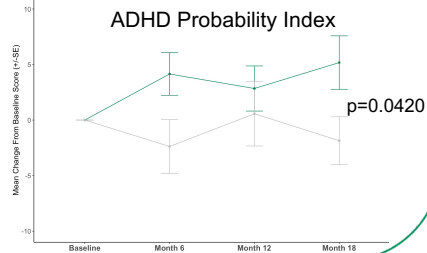
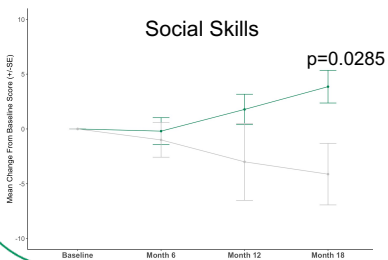
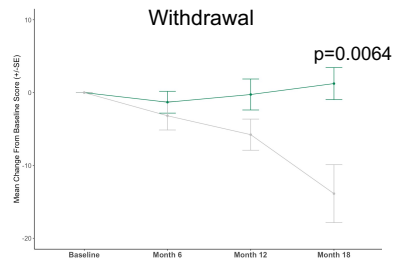
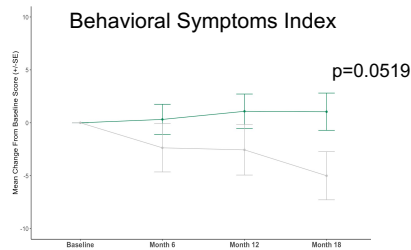


\*Several components of the BASC test (prespecified secondary endpoints) demonstrated statistically significant benefit of govorestat treatment vs. placebo at 18 months, including adaptive skills ( $p=0.0265$ ); adaptability ( $p=0.0109$ ); withdrawal ( $p=0.0064$ ), social skills ( $p=0.0285$ ); ADHD index ( $p=0.0420$ ); functional impairment ( $p=0.0085$ ). Tremor (another prespecified secondary endpoint) was also statistically significant at 18 months ( $p=0.0428$ ).

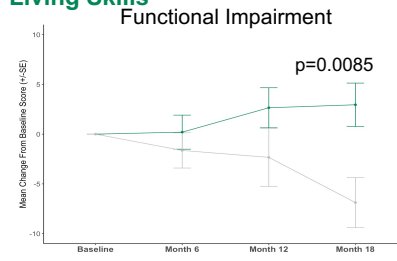
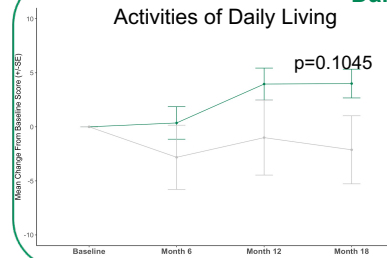
Speech endpoints were not impacted by govorestat treatment, which is suspected to be due to lack of progression in the placebo group and concomitant speech therapy received by almost all children in the trial. Of note, patients with severe speech deficits showed a favorable trend towards improvement with AT-007 vs. placebo. Tremor is measured on a different scale vs. other tests, and is referenced by the right-hand y axis.

# Govrostat Treatment Positively Impacted Behavior, Daily Living Skills, Adaptive Skills, Cognition, Fine Motor Skills & Tremor; Clinical Outcomes Declined in the Placebo Group, While Govrostat Treated Patients Stabilized or Improved Over 18 Months

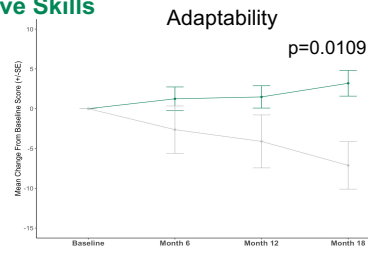
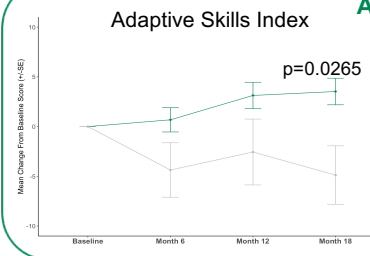
## Behavior



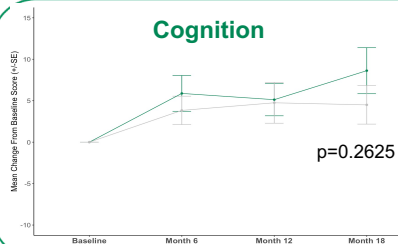
## Daily Living Skills



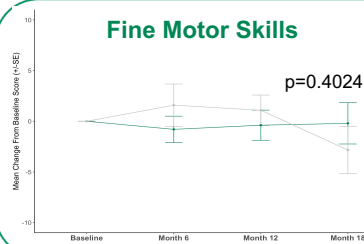
## Adaptive Skills



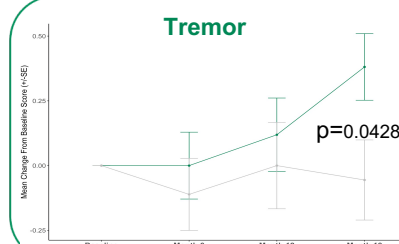
## Cognition



## Fine Motor Skills

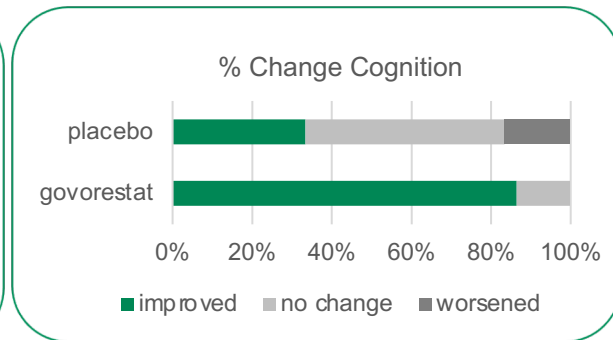
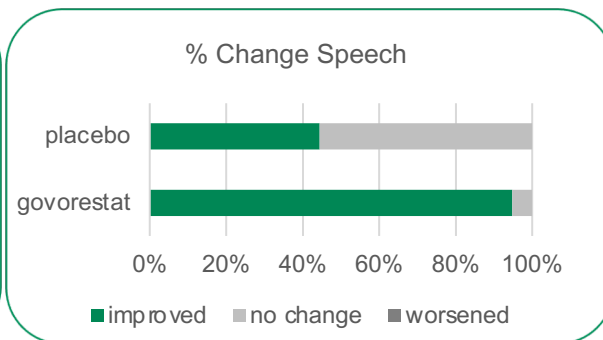
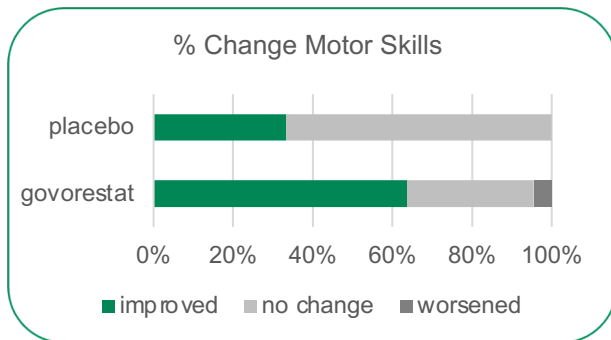
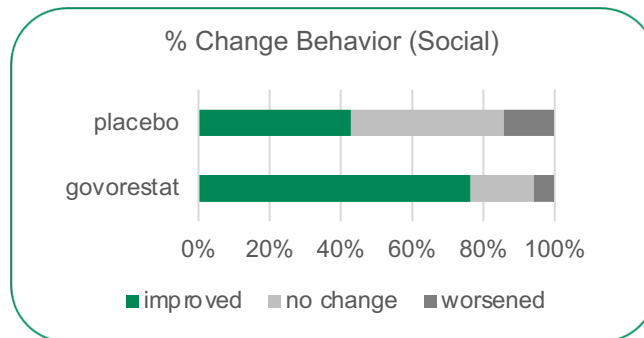
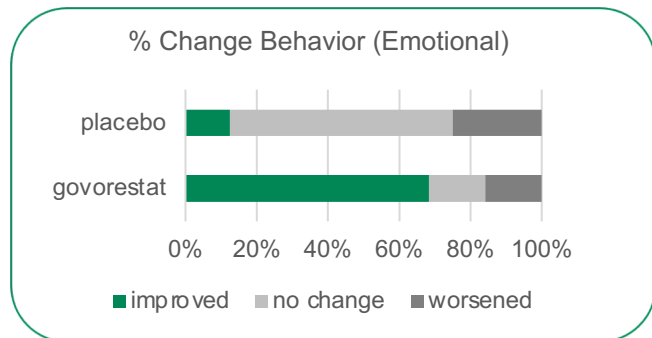


## Tremor



● AT-007 ● Placebo

# Caregiver Exit Interviews Support the Clinical Meaningfulness of Govorestat Treatment

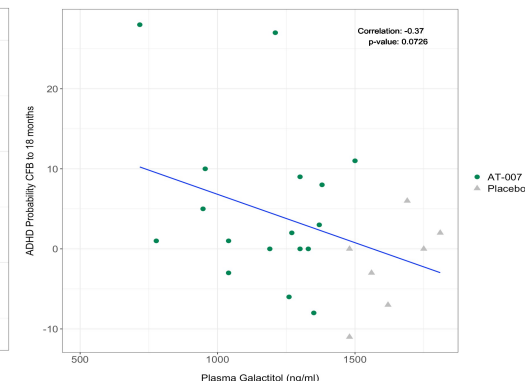
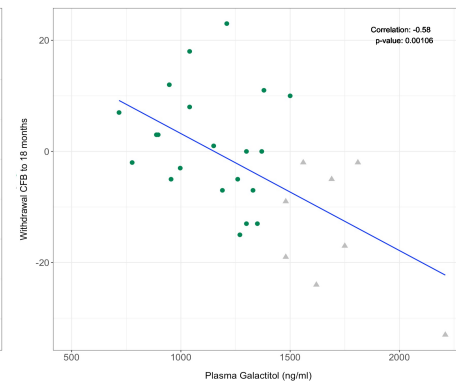
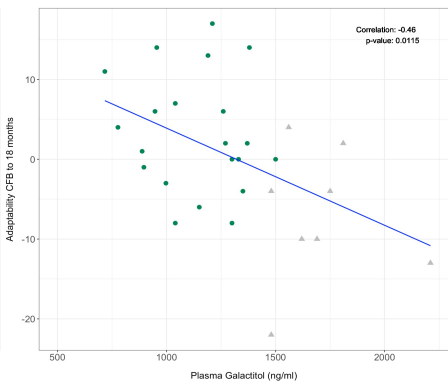
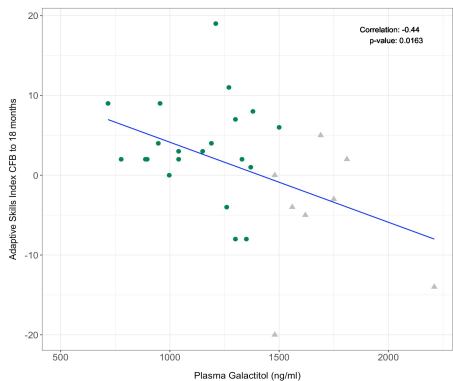
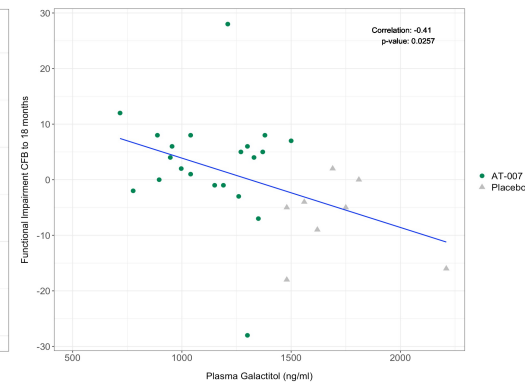
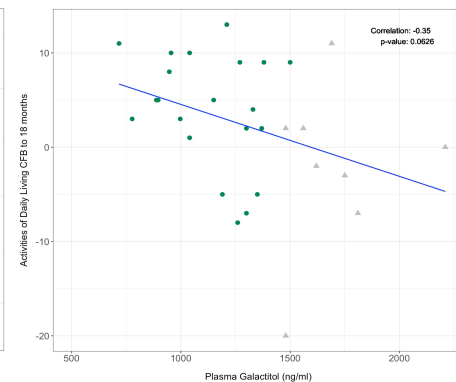
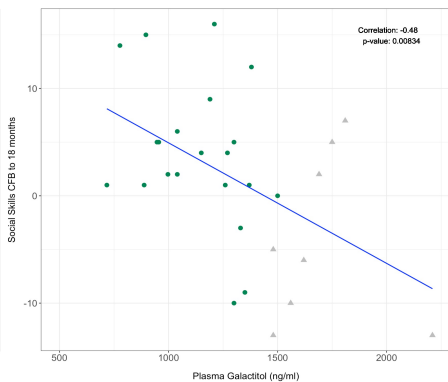
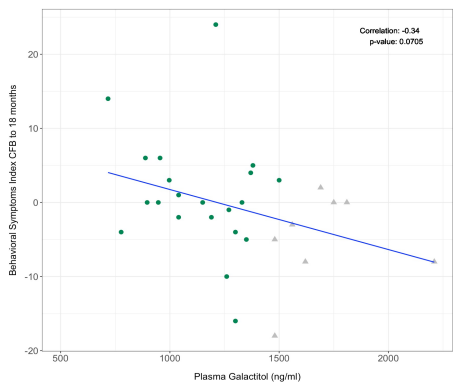


Caregivers noted an improvement or stabilization of disease on all categories of symptoms in the govorestat treated group vs. placebo.\*



# Galactitol Reduction Correlated with Clinical Outcomes Benefit

Galactitol level at 3 months statistically correlated with change in clinical outcomes at 18 months



# Safety Summary

- Govorestat was safe and well-tolerated with no serious adverse events
- All adverse events were mild to moderate
- Adverse events & lab values were balanced between govorestat and placebo groups

	Placebo (N=16) Number (%) of Subjects	Govorestat (N=31) Number (%) of Subjects
Subjects Reporting at Least One TEAE	16 (100%)	30 (96.8%)
Gastrointestinal disorders	11 (68.8%)	23 (74.2%)
Hepatic enzyme increased	2 (12.5%)	8 (25.8%)
Urine albumin/creatinine ratio increased	7 (43.8%)	5 (16.1%)
Urine protein/creatinine ratio increased	3 (18.8%)	2 (6.5%)
Renal & Urinary Disorders	1 (6.3%)	3 (9.7%)
Infections and infestations	10 (62.5%)	18 (58.1%)

TEAE= treatment emergent adverse event; Refers to patients having reported at least 1 term in AE category; AE, adverse event

# Strong Demand for Galactosemia Education and Treatment from Caregivers and HCPs

## GALACTOSEMIA TOGETHER



Engaging the Galactosemia Community through Social

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



Support and Education at Galactosemia.com

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



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

**48,000+**  
complete video views

### Awards



WEBAWARDS 2021



# 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

## 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

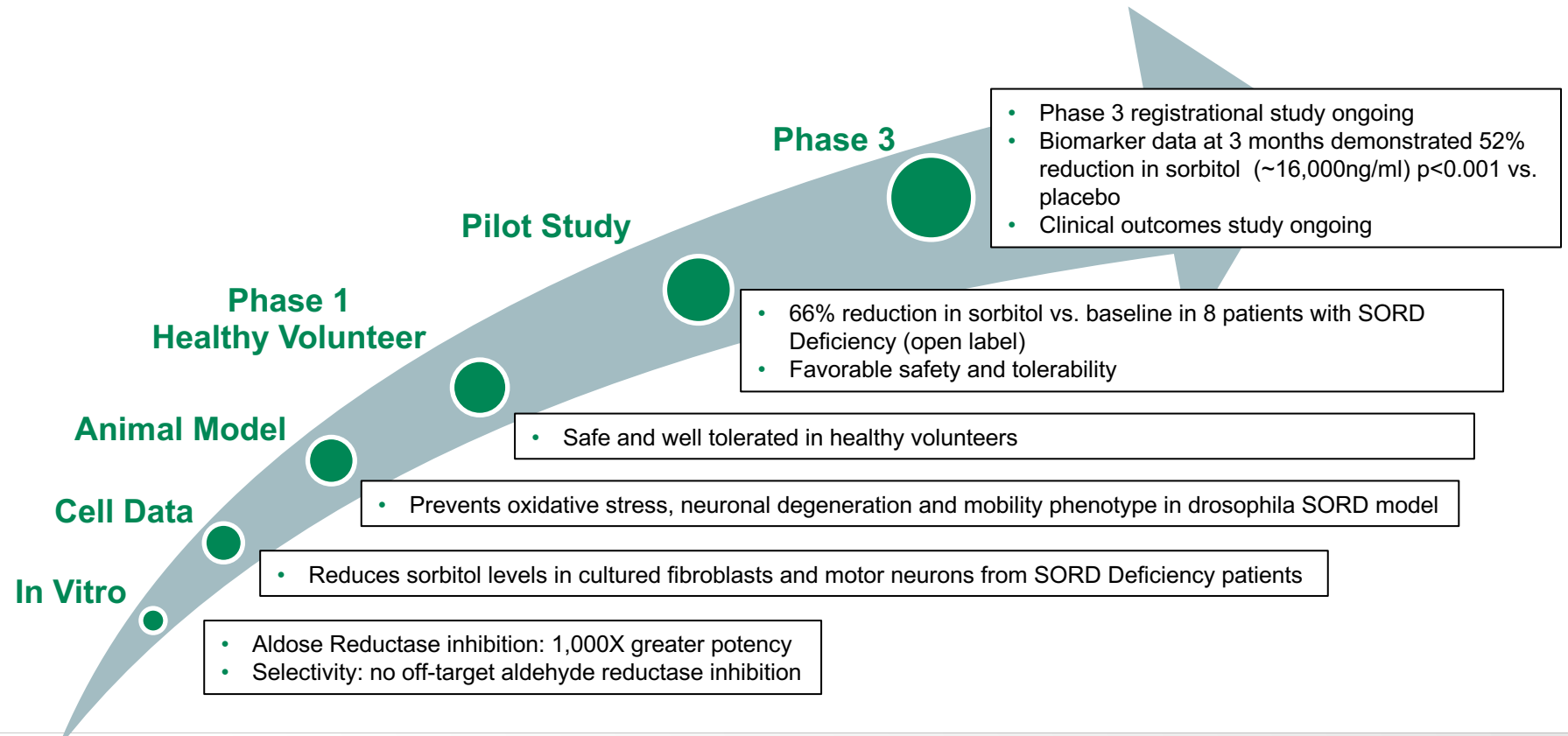
## Standard of Care/ Diagnosis

- 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

## Market Size/ Opportunity

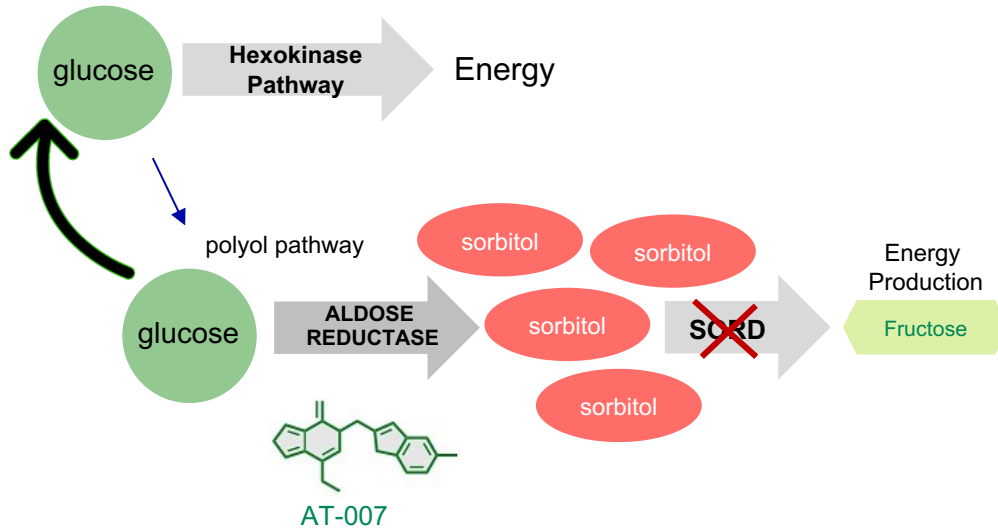
- ~3,300 individuals in the US with SORD Deficiency; 7,000 US+EU combined
- Small commercial footprint focused on KOLs at COEs
- Strong patient community engagement
- Payer feedback supports access/pricing
- Composition of matter IP through 2037; IP covering ARI treatment of SORD Deficiency through 2040

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





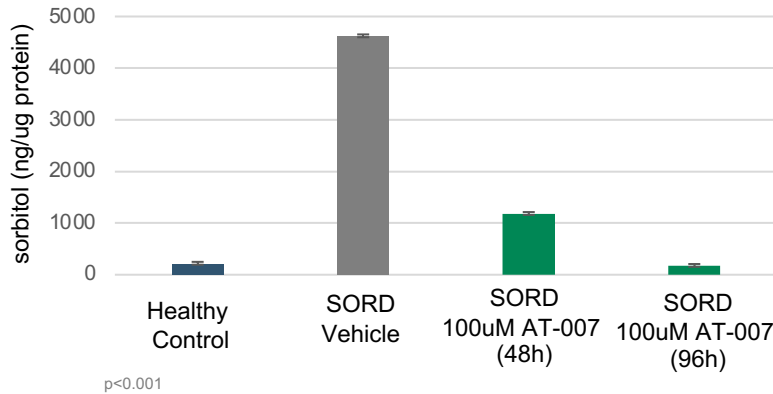
# Aldose Reductase Inhibition Addresses the Underlying Cause of SORD Neuropathy by Preventing Conversion of Glucose to Sorbitol



- 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

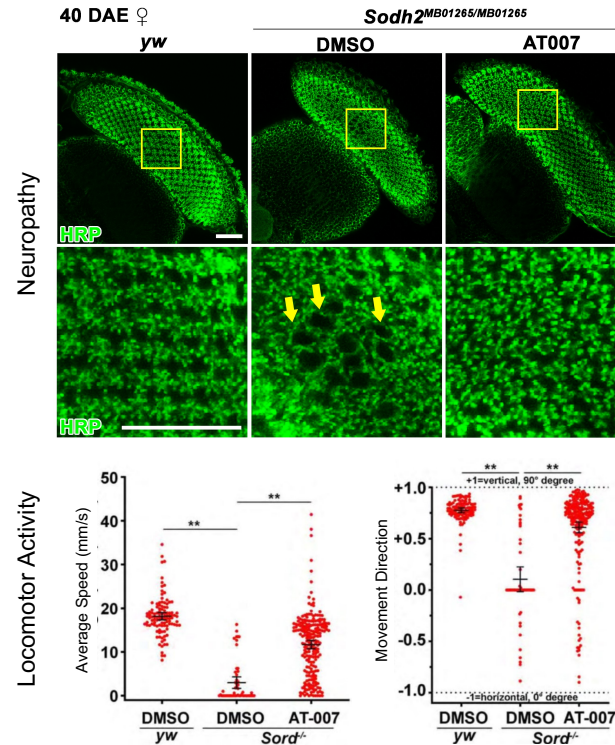
# AT-007 Treatment Reduces Sorbitol Levels in SORD Patient Cells; Prevents CNS Phenotype in a Drosophila SORD Deficiency Model

## Sorbitol Reduction in Patient Fibroblasts with AT-007 Treatment

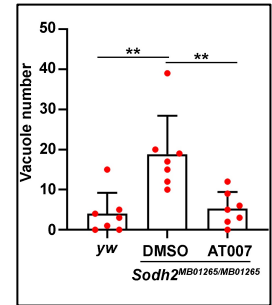


- Sorbitol accumulation causes mitochondrial dysfunction and reactive oxygen species formation, resulting in axonal neuropathy
- Treatment with AT-007 reduces sorbitol and prevents downstream neuronal damage
- AT-007 treatment normalizes lower limb function in drosophila

## 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

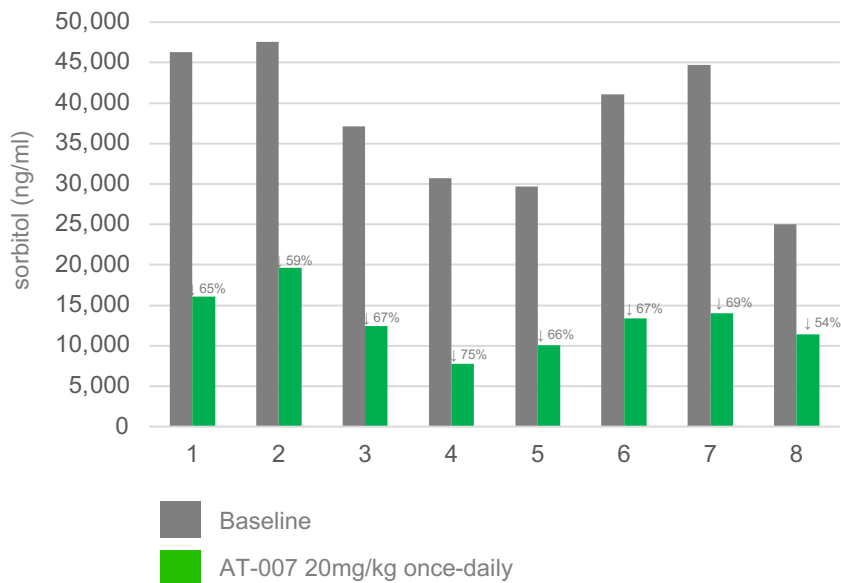


Fly geotactic activity was recorded using an automated monitoring system. *yw* flies (control) treated with DMSO and SORD deficient flies treated with DMSO or 10 µg/ml AT-007 at 10 DAE. Data are presented as mean ± SE. \*\*p < 0.01 from trial-by-trial comparisons.

# 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%)

**Sorbitol Level Baseline vs. AT-007 Treatment**



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

## Safety

- AT-007 safe and well tolerated; no SAEs

## Pharmacokinetics/ Pharmacodynamics

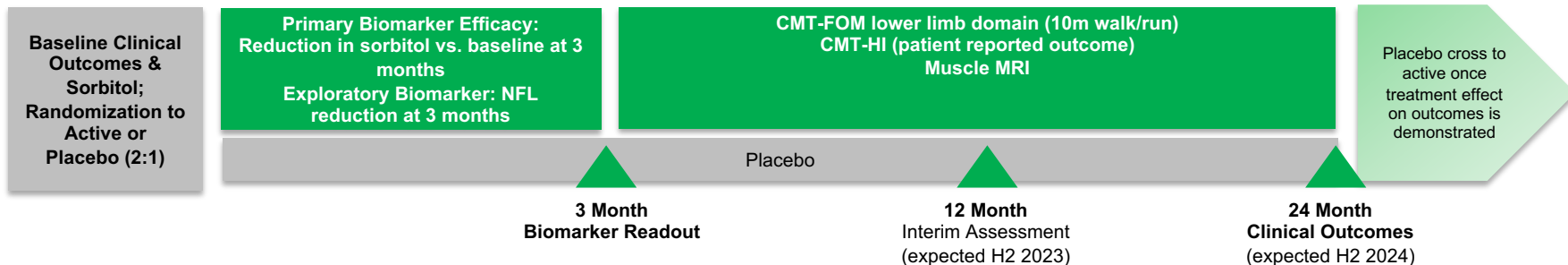
- Rapid and sustained reduction in sorbitol
- No compensatory increase in glucose level

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

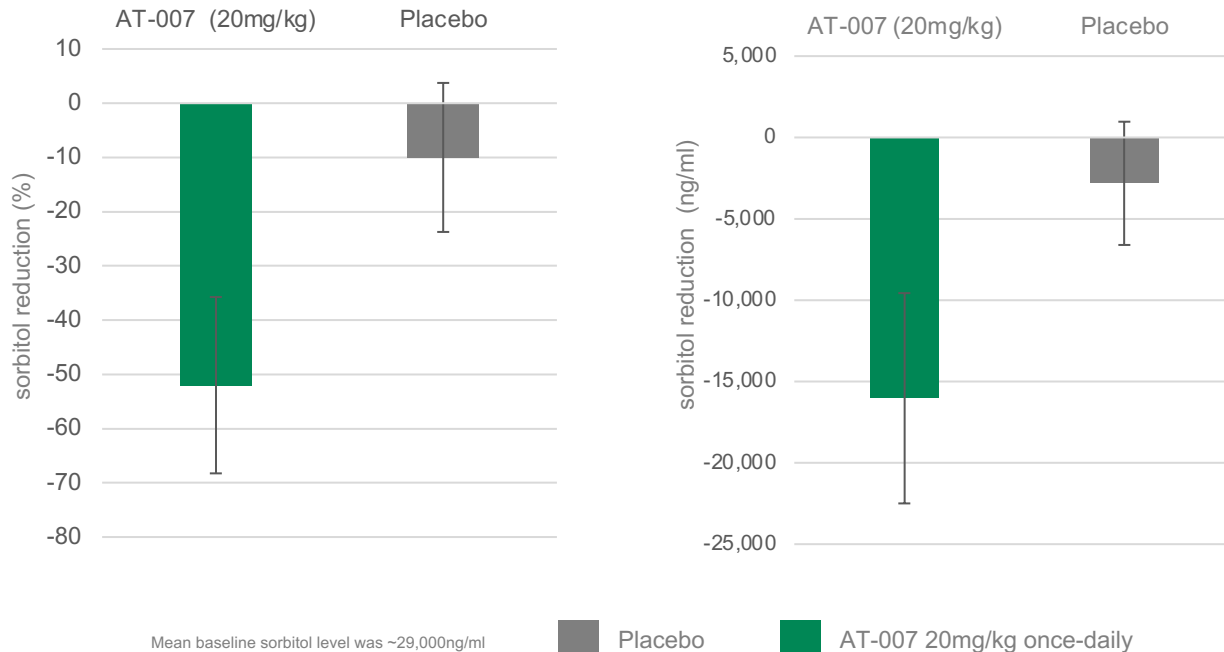
outcome	variable	constant	p value
10MWR	sorbitol	age	p<0.05
4-stair-climb	sorbitol	age	p<0.05
sit-to-stand	sorbitol	age	p<0.05

- 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

# 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



### Safety

- AT-007 safe and well tolerated

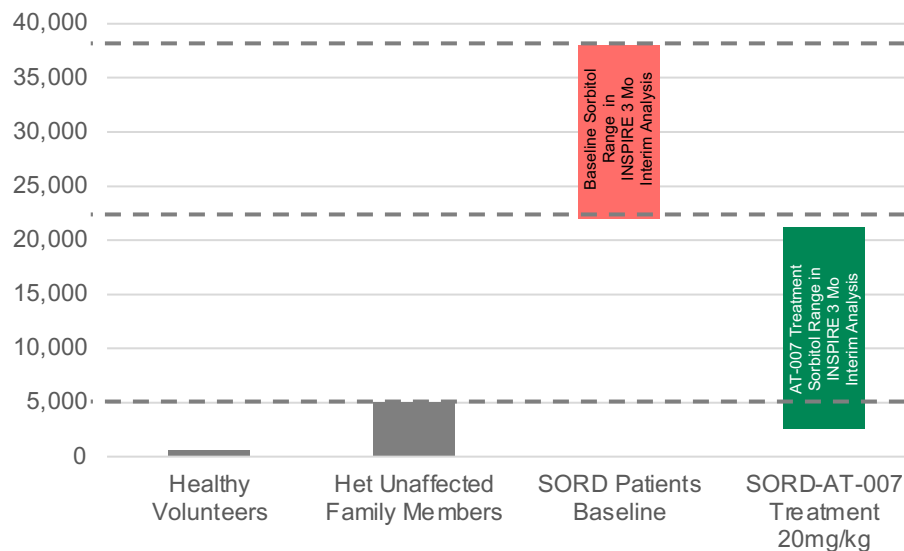
### Clinical Impact of Sorbitol Reduction

- Sorbitol reduction expected to impact clinical outcomes, including primary clinical outcome measure 10m walk/run test
- **NFL:** Neurofilament Light Chain (NFL) decreased in the AT-007 treated group but increased in the placebo group ( $p = 0.027$ )\*

\*percent change from baseline ANCOVA analysis

# 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



- Faster disease progression
- Need for leg braces early
- Inability to climb stairs
- Upper limb symptoms

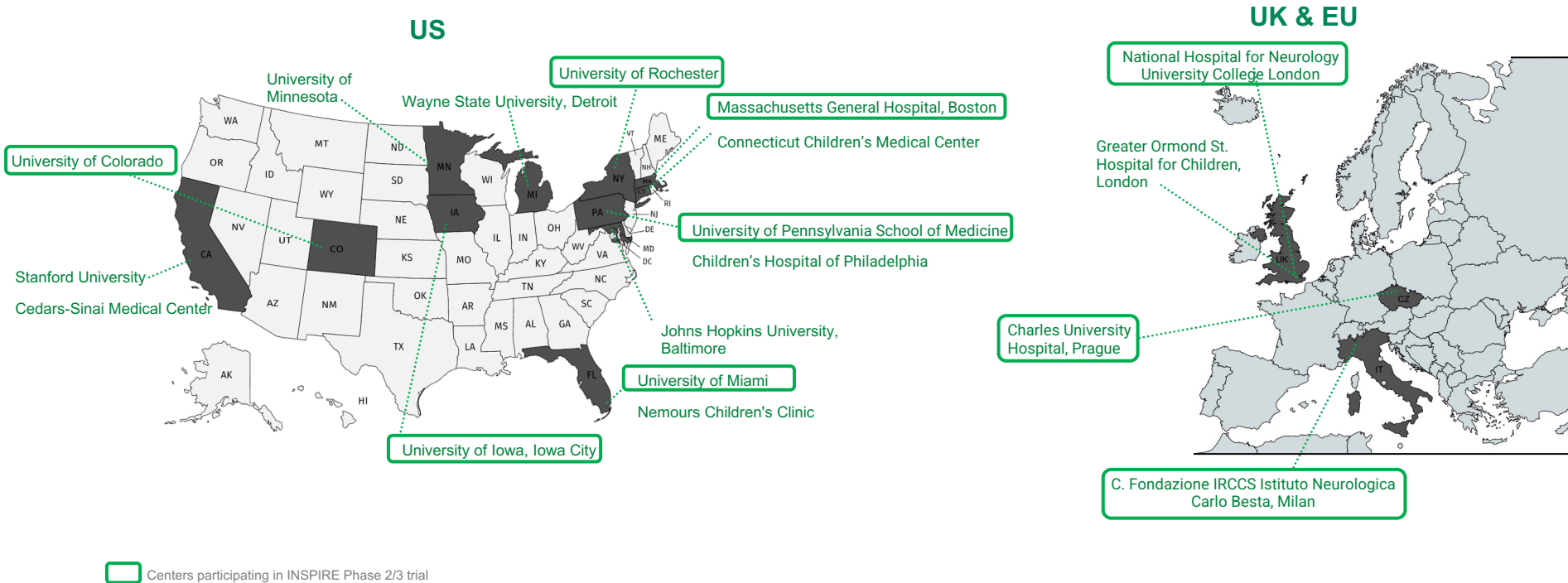
- Slower disease progression
- Difficulty walking
- Difficulty climbing stairs
- No upper limb symptoms

- No Axonal Neuropathy

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



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

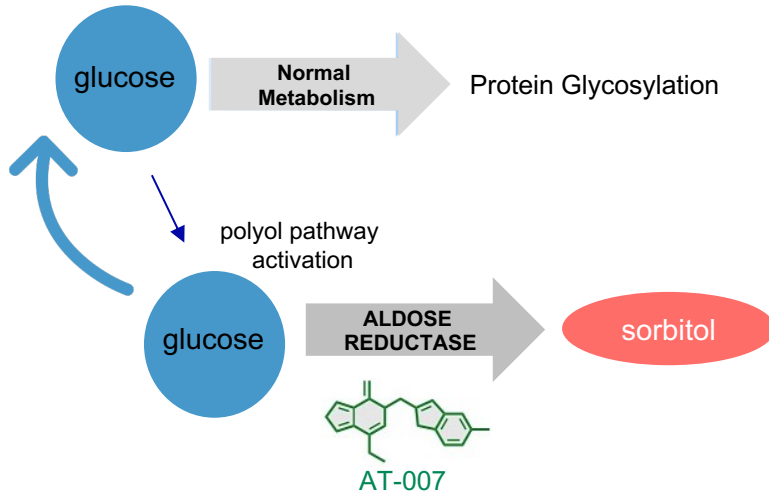


# PMM2-CDG

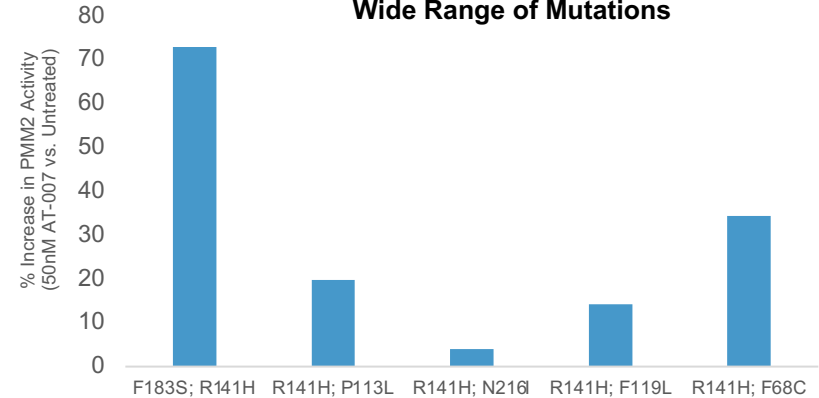
## Aldose Reductase Inhibition Improves PMM2 Activity AT-007 Granted Orphan & Pediatric Rare Disease Designation for PMM2-CDG; Single-Patient IND Open – Phase 2 Ready

**PMM2-CDG<sup>†</sup>**, 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*

# AT-001

# DIABETIC

# CARDIOMYOPATHY

Phase 1/2 pilot study completed

Phase 3 study completed



# 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

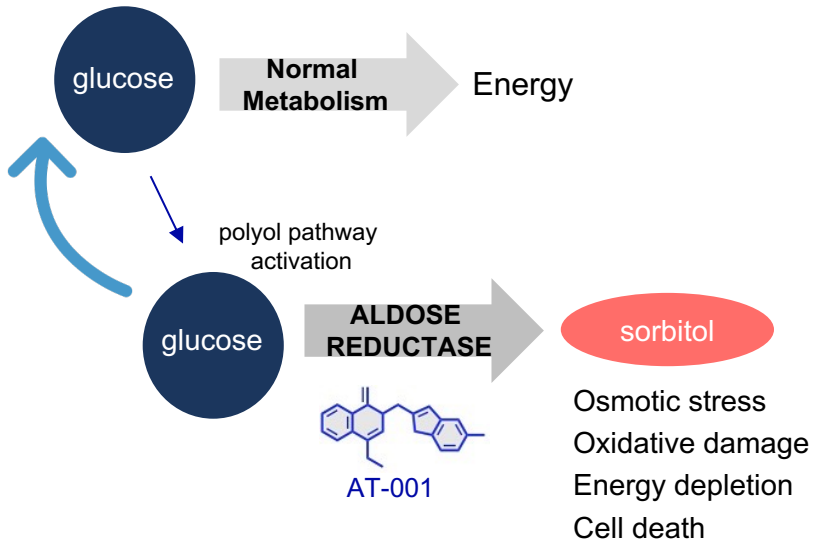
## Mechanism of Disease

- 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)

# 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

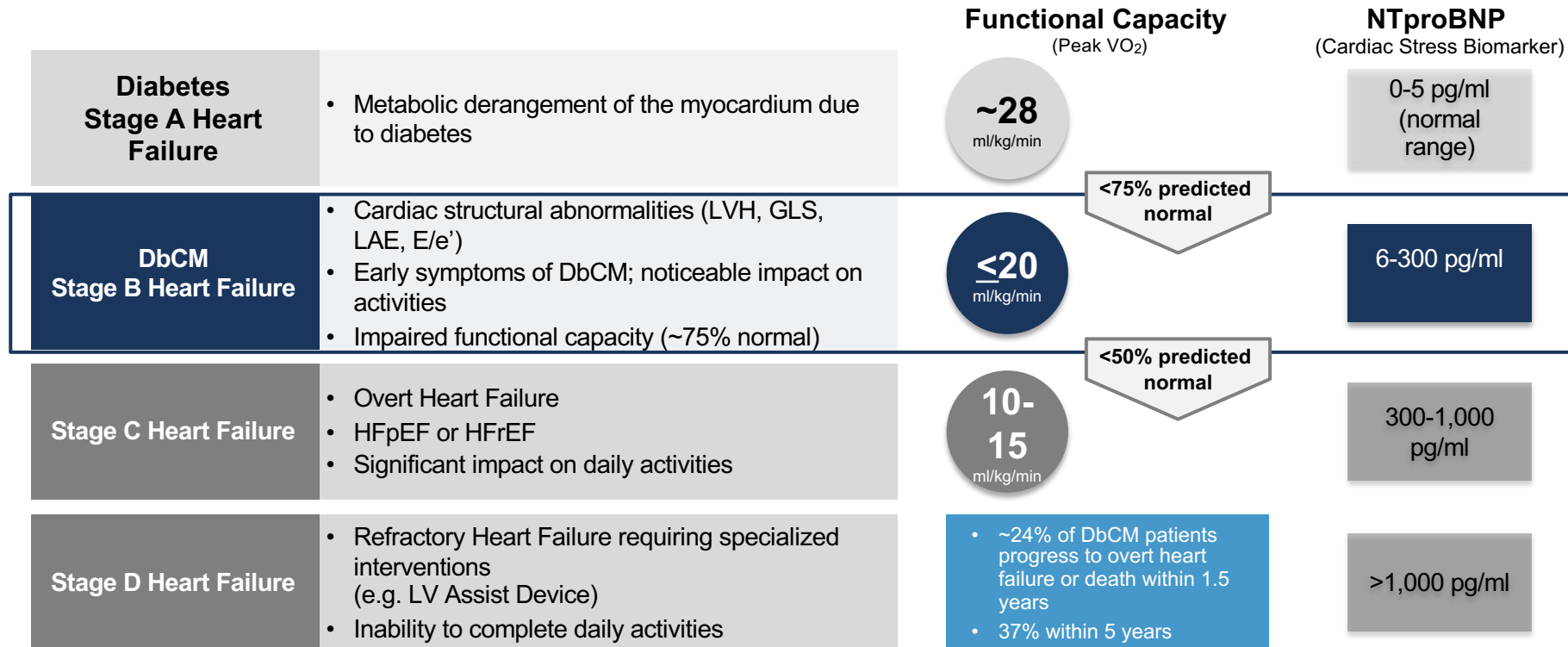
Aldose Reductase, the first and rate limiting enzyme in the polyol pathway, converts this glucose into sorbitol and eventually fructose

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

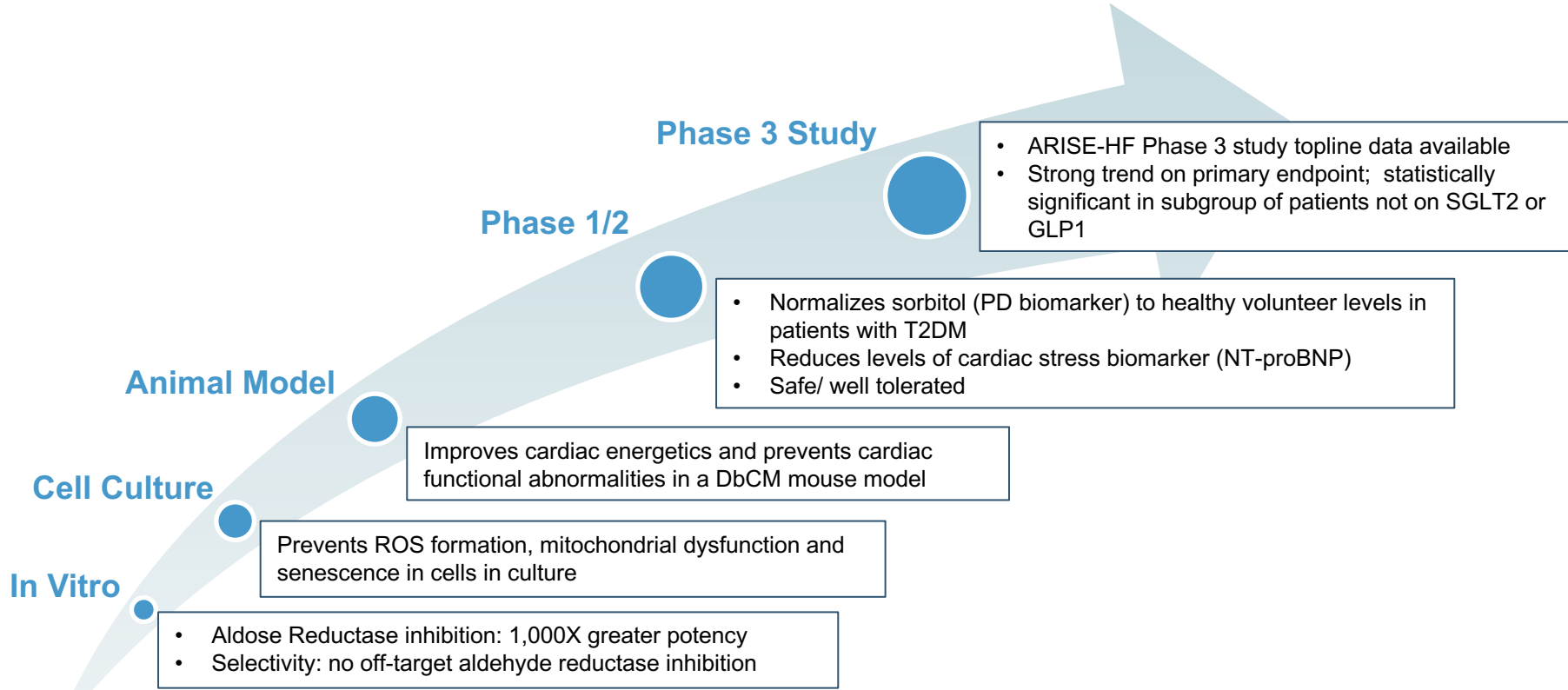
AR activation also detracts glucose from the energy efficient hexokinase/glycolytic pathway, resulting in less energy production for cardiomyocytes

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

# Diabetic Cardiomyopathy is a Form of Stage B Heart Failure



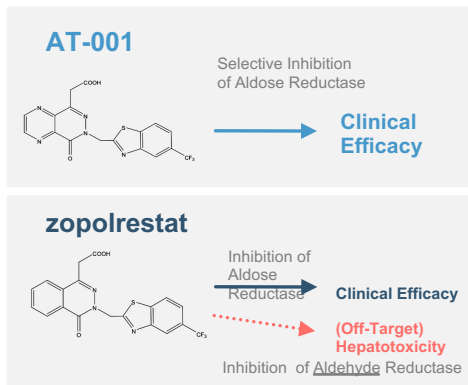
# AT-001 Has Demonstrated Effectiveness In Vitro, In Vivo, and in Phase 1/2 Clinical Trials; Registrational Study Readout Expected 2023





# 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<sup>2</sup>



Tissue Penetration (in rats)

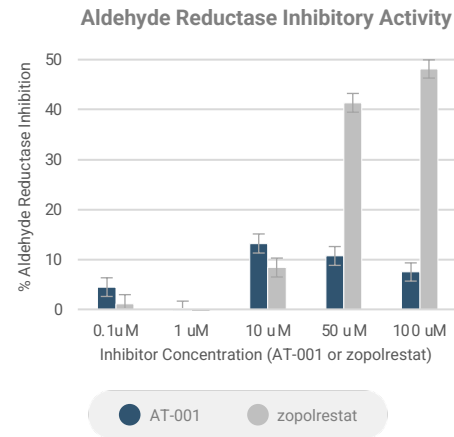
Compound	IC <sub>50</sub>	MTD in animals	Systemic/Heart			
			Nerve	Retina	CNS	
AT-001	30pM	>2,000mg/kg	✓	✓	✓	✗
zopolrestat	10nM	100mg/kg	✓	✓	✗	✗

AT-001 demonstrated improved IC<sub>50</sub> and IC<sub>90</sub> vs. zopolrestat



Data based on In Vitro Enzyme Inhibition & Cultured Hepatocytes

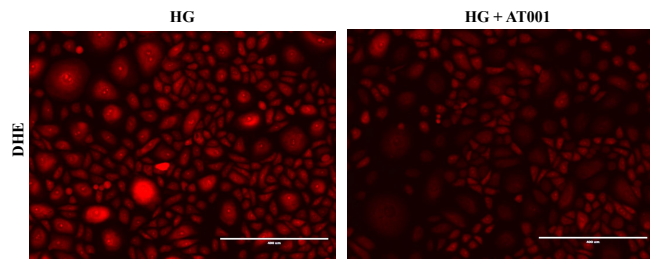
Unlike zopolrestat, AT-001 does not inhibit Aldehyde Reductase



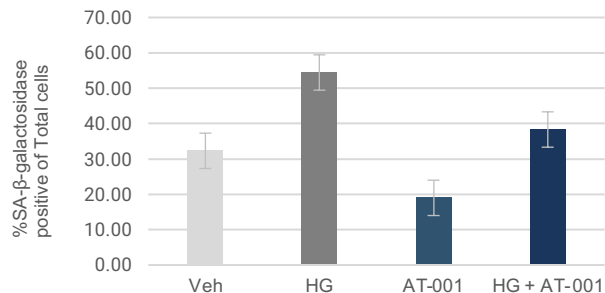


# AT-001 Treatment Prevents Reactive Oxygen Species Generation & Mitochondrial Stress Caused by High Glucose Exposure

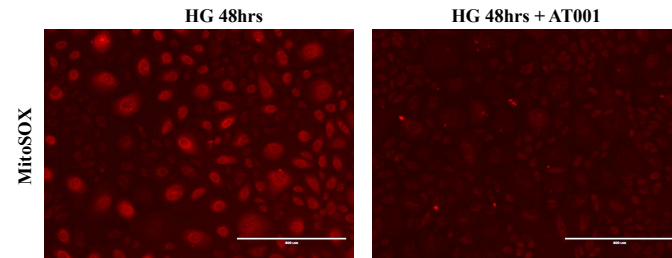
## Dihydroethidium (DHE) Staining for Cytosolic ROS



## Quantitation of Cell Senescence Via SA-β-gal Staining



## MitoSOX™ Staining for Mitochondrial ROS



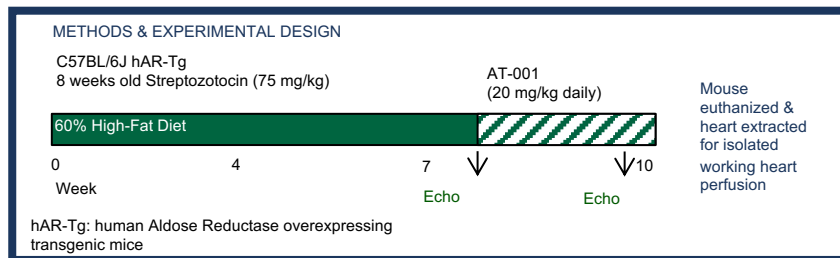
**HG**- NHK cells exposed to 25mM glucose (high glucose) for 48hrs

**HG + AT-001** - cells treated with 0.18nM AT-001 along with above mentioned HG exposure

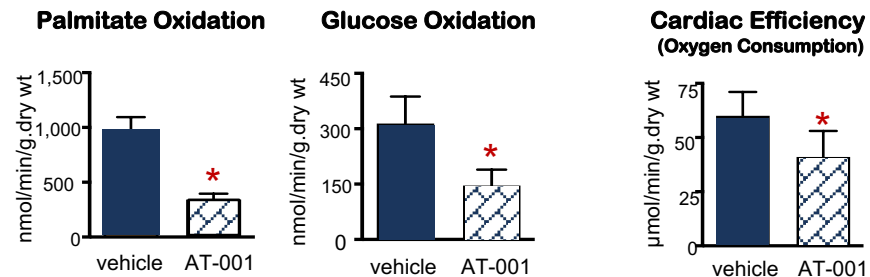
- In patients with diabetes, metabolism of glucose through the polyol pathway results in generation of Reactive Oxygen Species (ROS), which has been identified as a key mediator of tissue damage and causal in diabetic complications. Selective inhibition of AR reduces oxidative stress and mitigates these 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

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

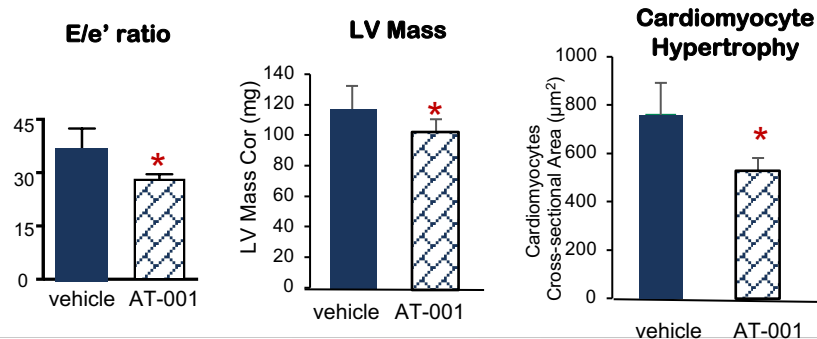
## AT-001 Treatment in a DbCM Mouse Model (Design)



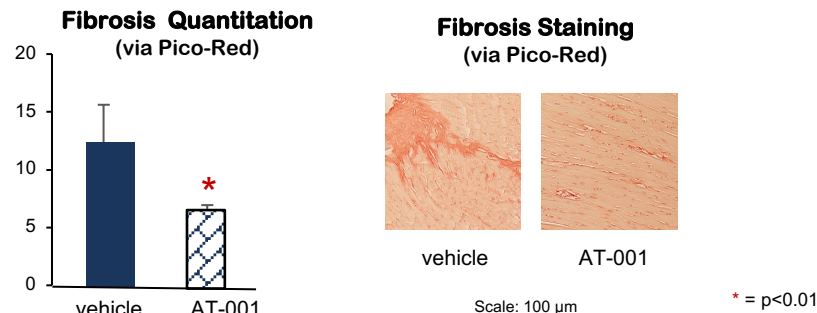
## AT-001 Improves Cardiac Energetics



## AT-001 Improves Cardiac Function and Prevents LVH

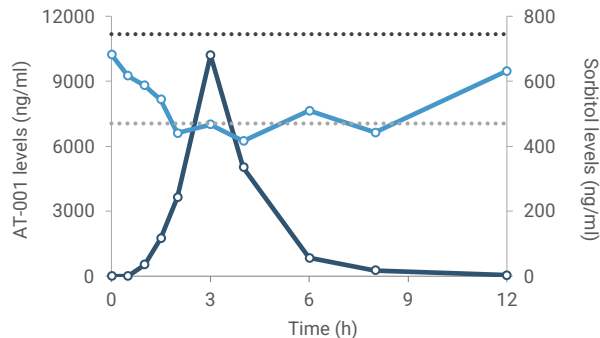


## AT-001 Prevents Fibrosis and Adverse Remodeling



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

**Proof of Biological Activity**

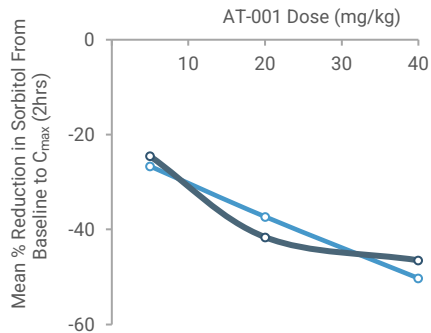


—●— Sorbitol (whole blood)     —●— Healthy volunteer sorbitol avg.  
—●— AT-001 levels             - - - Diabetic patient sorbitol avg.

AT-001 normalized sorbitol in diabetics to healthy volunteer levels

No compensatory increase in glucose level

**Sorbitol Reduction by Dose**

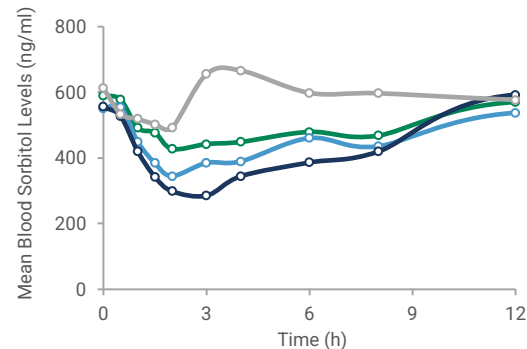


—●— Day 1     —●— Day 7

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**



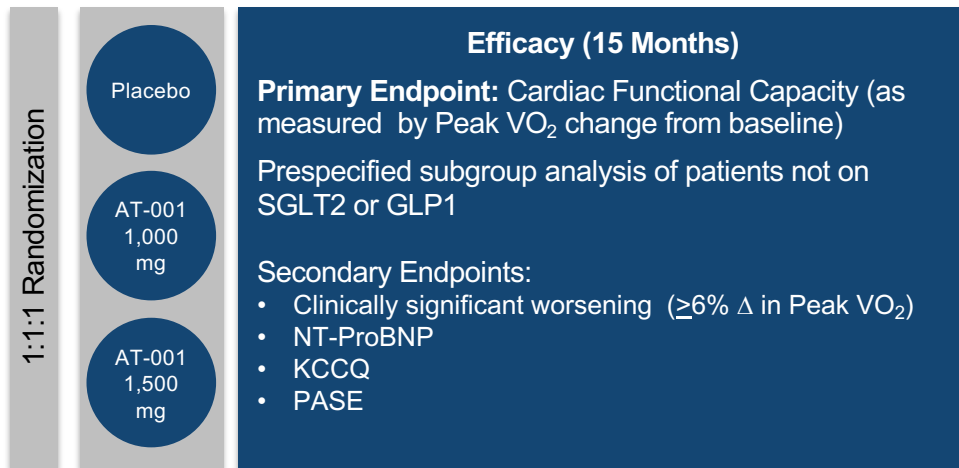
—●— Placebo                     —●— 5mg/kg  
—●— 20mg/kg                     —●— 40mg/kg

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

# DbCM Phase 3 Study (ARISE-HF) Design

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



- Enrolled patients with DbCM at high risk of progression to overt heart failure
- n=675 (225/arm)
- Twice-daily oral dosing
- Add-on to standard of care diabetes therapies

## Key Inclusion Criteria:

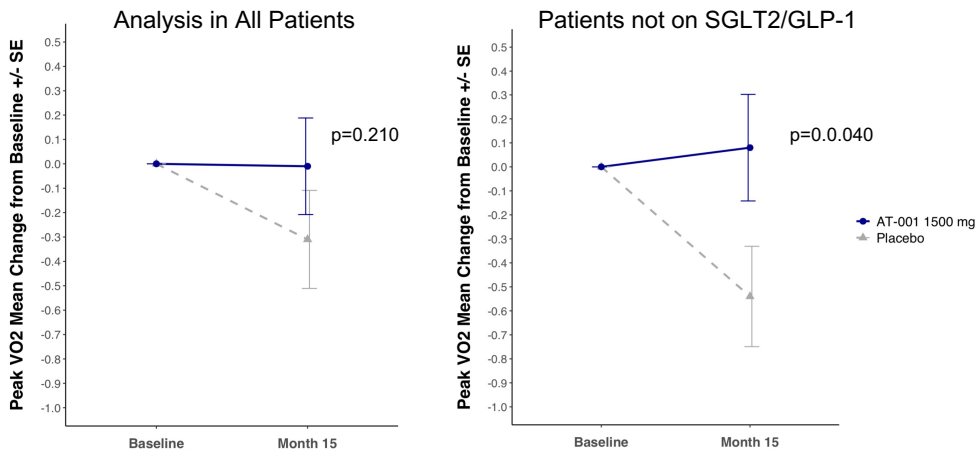
- Diagnosis of Type 2 Diabetes
- Age:  $\geq 60$  years, or  $\geq 40$  years with duration of diabetes  $>10$  years
- Demonstration of DbCM/ Stage B Heart Failure
- LVEF  $> 45\%$  and at least one of the following: echocardiographic abnormalities or NTProBNP  $> 50$  pg/ml, or HsTNT  $> 6$  ng/L
- RER  $> 1.05$
- Peak  $\text{VO}_2$   $< 75\%$  of age/gender predicted normal

## Key Exclusion Criteria:

- Diagnosis or signs of overt/symptomatic heart failure
- Use of a loop diuretic
- History of CAD, MI, ACS, CABG, PCI, stroke
- History of severe valve disease, clinically significant arrhythmia, or other cause of cardiomyopathy
- Severe disease impacting implementation of the protocol or performance of a CPET
- SBP  $> 140$  mmHg or DBP  $> 90$  mmHg
- BMI  $> 45$  kg/m<sup>2</sup>
- HbA1c  $> 8.5\%$
- eGFR  $< 45$  mL/min/1.73 m<sup>2</sup>

# DbCM Phase 3 Topline Results

Positive Effect of AT-001 on Cardiac Functional Capacity; Statistically Significant in Patients not on SGLT2/GLP1



	Placebo (N=230)	AT-001 1000mg (N=228)	AT-001 1500mg (N=231)
Serious Adverse Events (SAEs)	33 (14%)	28 (12%)	40 (17%)
Treatment- Emergent Adverse Events (TEAEs)	182 (79%)	186 (82%)	187 (81%)
Treatment-Related Discontinuations	9 (3.9%)	22 (9.6%)	22 (9.5%)

- AT-001 1500mg stabilized cardiac functional capacity, as measured by Peak VO<sub>2</sub>, (-0.01 ml/kg/min) while the placebo group declined (-0.31 ml/kg/min) (p=0.210)
- Impact of AT-001 was statistically significant in a prespecified subgroup analysis of patients not on SGLT2 or GLP1 treatment: placebo declined (-0.54 ml/kg/min), while the AT-001 high dose group improved (+0.08 ml/kg/min) (p=0.040)
- Patients with clinically significant worsening ( $\geq 6\%$  on Peak VO<sub>2</sub>) was substantially higher in the placebo group (46%) as compared to the AT-001 high dose group (32.7%), odds ratio 0.56 (p=0.035).
- Effect of AT-001 was dose dependent; low dose demonstrated an intermediate effect between the high dose and placebo
- Favorable safety and tolerability profile