Applied Therapeutics

March 2024

APPLIED THERAPEUTICS

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

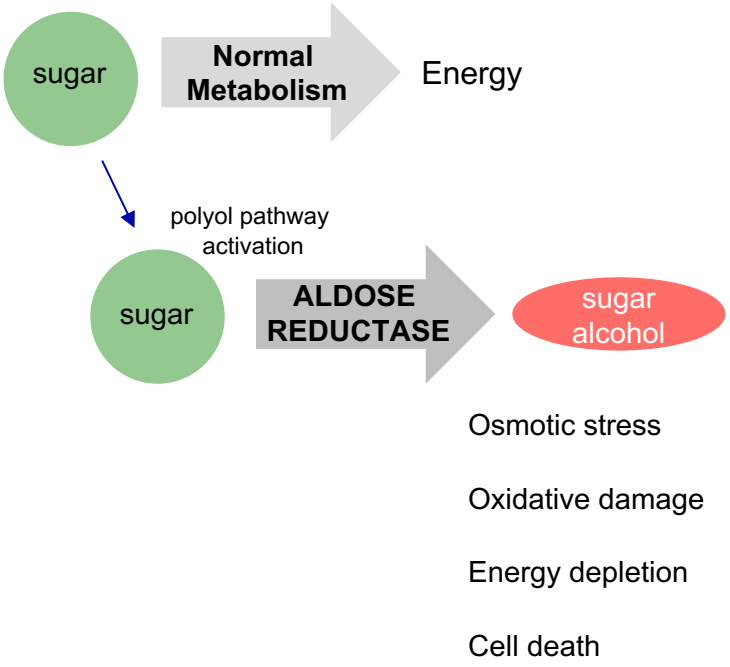
Fatal or debilitating diseases with no approved therapies

Limited / no competition

Innovative Pipeline with Near-Term Milestones

Compound	Preclinical	Phase 1	Phase 2	Phase 3	Dosing	Target Tissue	Status	Rights
ALDOSE REDUCTASE FRANCHISE								
AT-007 (govorestat)	Galactosemia (ACTION)				QD Oral	CNS	Pediatric Ph 3 outcomes trial completed; MAA validated Q4 2023 & NDA accepted Q1 2024; PDUFA date Aug 2024	ROW; ADVANZ PHARMA EU
	SORD Deficiency (INSPIRE)				QD Oral	CNS	Positive pilot study data; Phase 3 12-month interim data positive; 24 months ongoing	ROW; ADVANZ PHARMA EU
	PMM2-CDG				QD Oral	CNS	Phase 2 ready; Expanded Access open	WW
AT-001	Diabetic Cardiomyopathy (ARISE-HF)				BID Oral	Systemic	Ph 3 trial topline data reported	WW
	Diabetic Peripheral Neuropathy				BID 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 1,000X more potent than "old" Aldose Reductase Inhibitors and highly selective; no off-target inhibition of aldehyde reductase

Govorestat (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 accepted)

APPLIED THERAPEUTICS

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

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

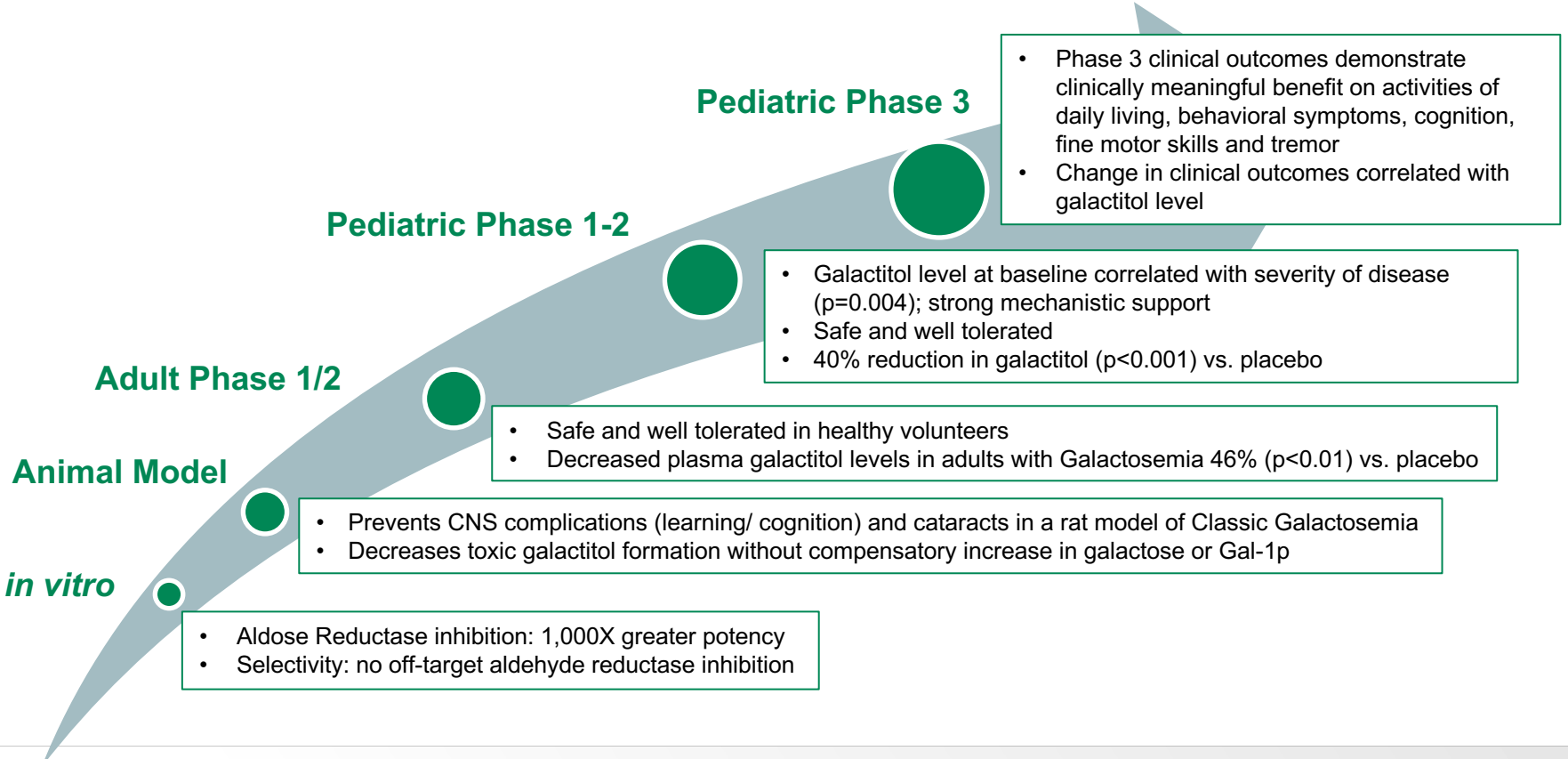
- People with Galactosemia are unable to metabolize galactose, which accumulates in cells and tissues
- At abnormally high levels, galactose becomes a substrate for Aldose Reductase, which converts galactose to a toxic and aberrant metabolite, galactitol
- Galactitol is highly toxic (especially to neurons)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

Market Size/ Opportunity

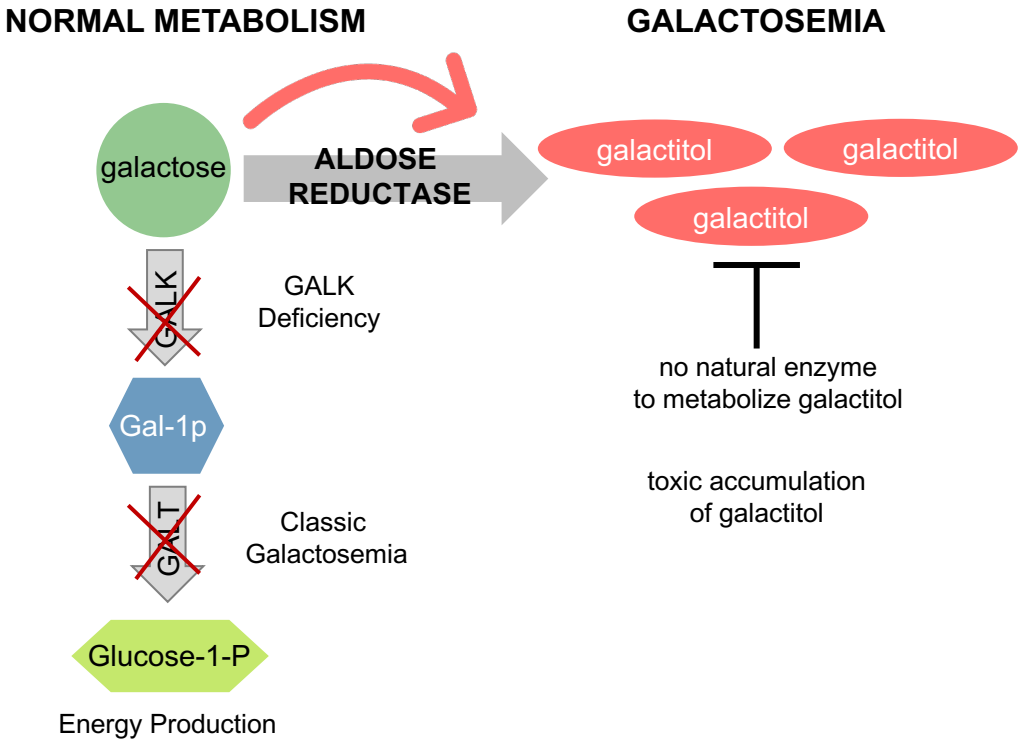
- Known prevalent and addressable population (~3K US, ~7K WW)
- Small commercial footprint focused on KOLs at Centers of Excellence
- Strong patient community engagement
- Payer feedback supports access/pricing
- Composition of matter IP through 2037 (not including extensions)

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.

Govorestat 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

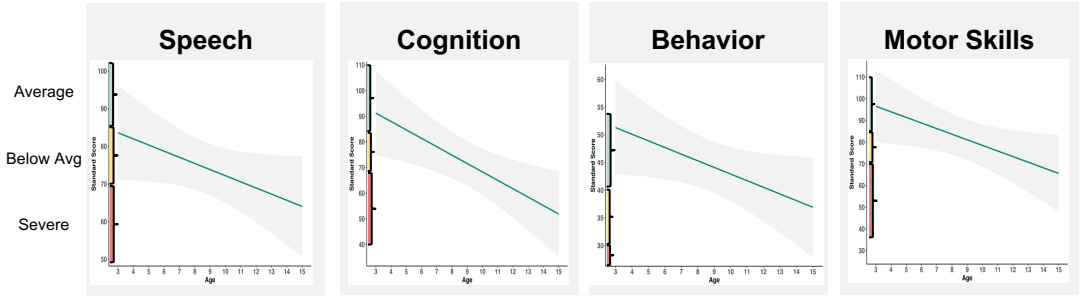


- **CNS Complications:**
  - Cognition/ Learning/ IQ/ Memory
  - Behavior/ Psychiatric
  - Motor Skills (Tremor, Ataxia)
  - Seizures
  - Speech Deficiencies
- **Other Complications:**
  - Ovarian Insufficiency
  - Cataracts

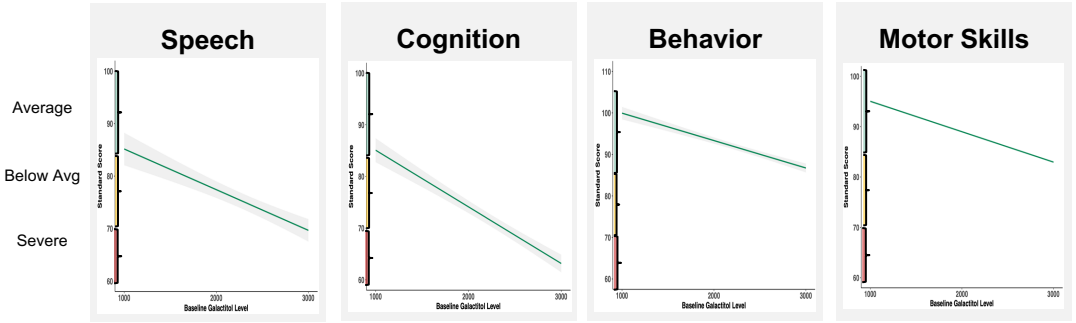
AR = Aldose Reductase

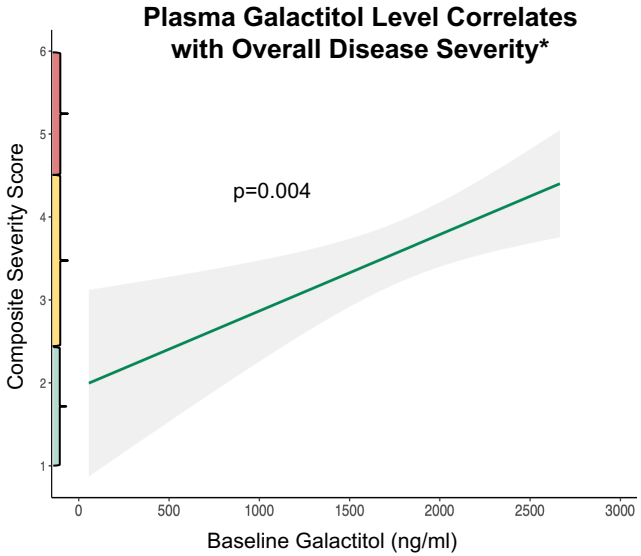
Natural History: Galactosemia is a Progressive Disease that Worsens with Age; Disease Severity Correlates with Plasma Galactitol Level

Natural history of disease demonstrates progressive worsening with age



Baseline galactitol level correlates with severity of clinical functional outcomes





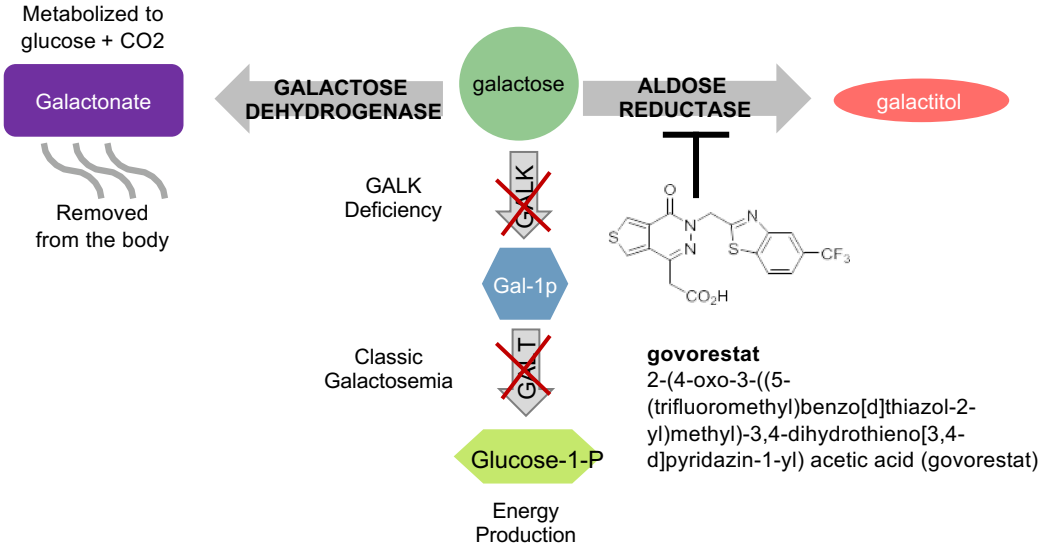
*Overall severity based on composite score comprised of 4 CNS quadrants

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.

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

Blocks production of the toxic metabolite galactitol



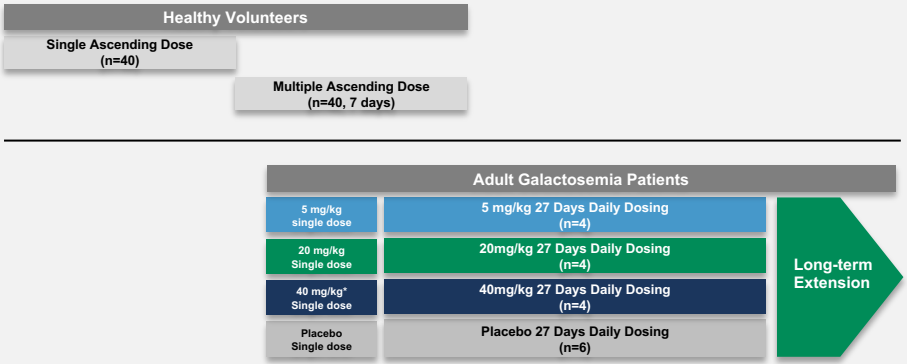
Population	Dose
Adults	20mg/kg
Children >40kg	15mg/kg
Children 20-40kg	20mg/kg
Children <20kg	30mg/kg

- 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

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.

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

Adult Phase 1/2 Study Design



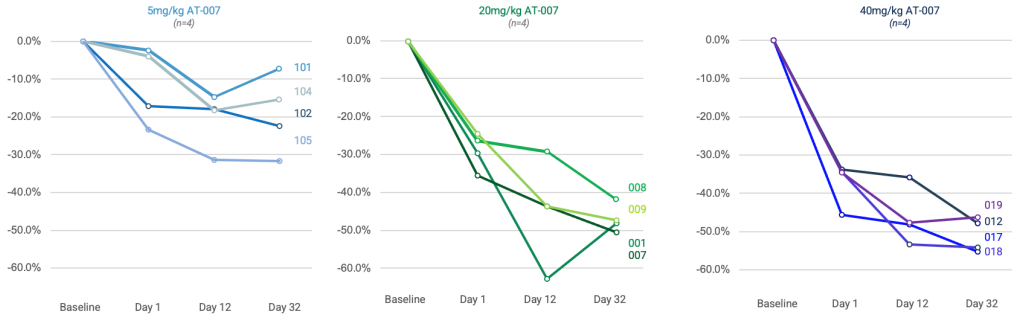
Safety

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

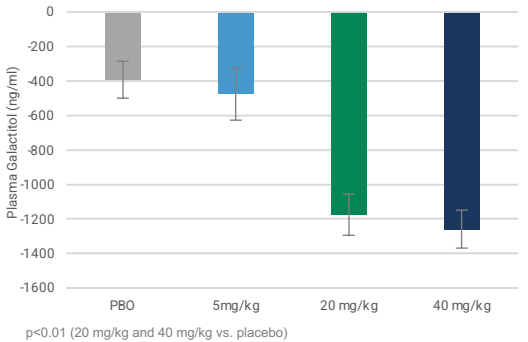
Pharmacokinetics/ Pharmacodynamics

- 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)

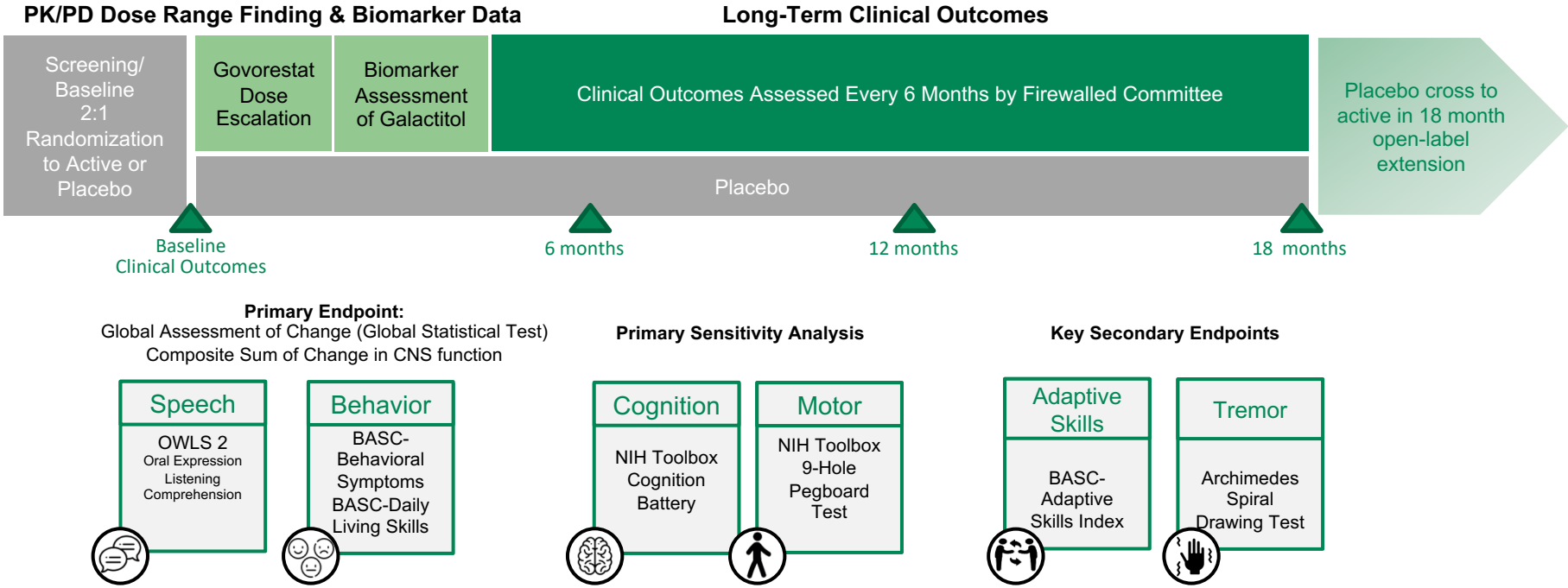


Maximum Galactitol Reduction vs. Baseline



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

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

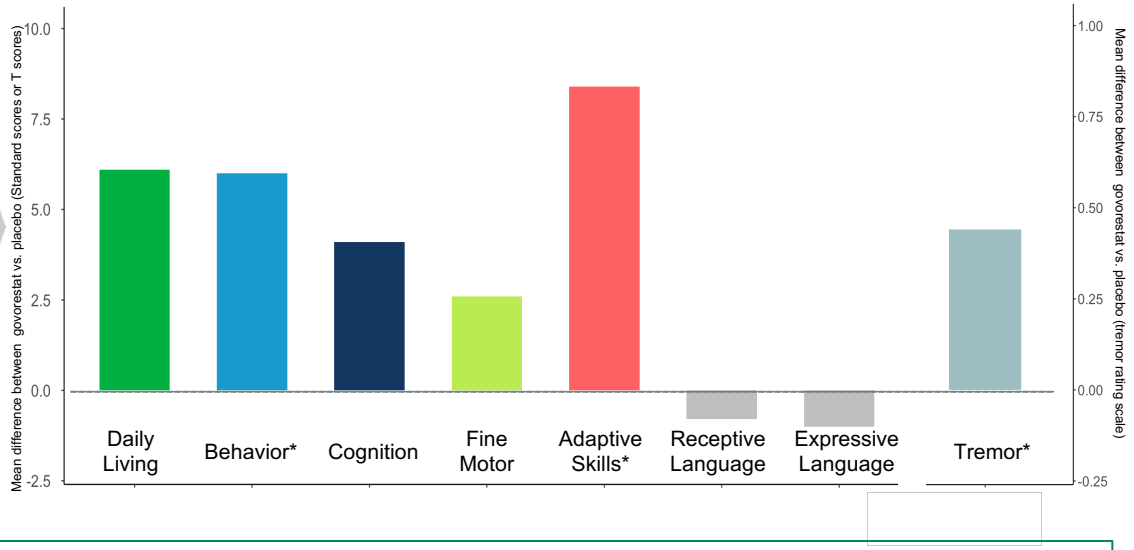


OWLS= Oral and Written Language Scales; BASC= Behavioral Assessment Scales for Children

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%
All groups	**15-30mg/kg**	**40.19% (p<0.001)**

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

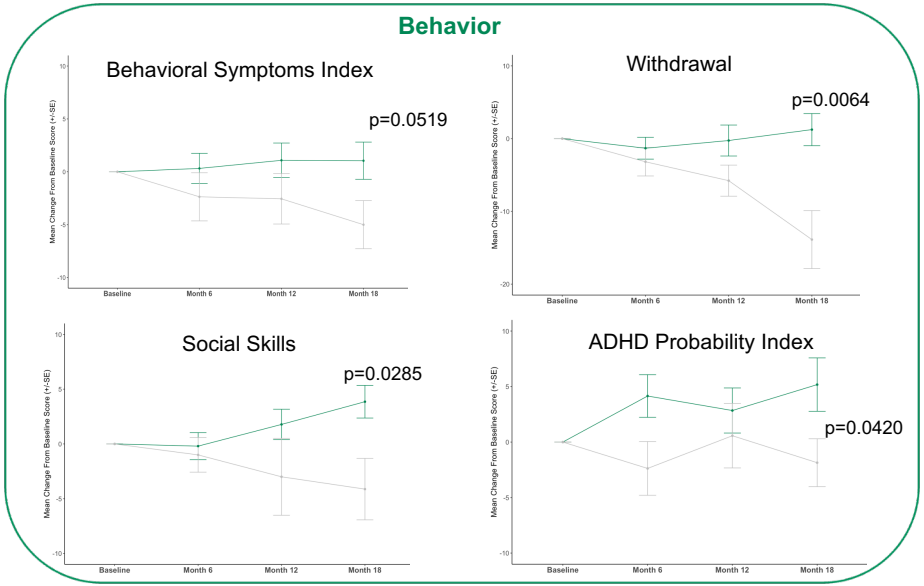


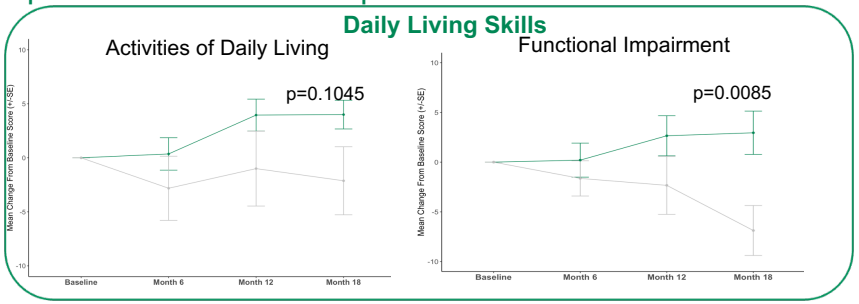
*Several components of the BASC test (prespecified secondary endpoints) demonstrated statistically significant benefit of govorestat treatment vs. placebo at 18 months, including adaptive skills (p=0.0265); adaptability (p=0.0109); withdrawal (p=0.0064), social skills (p=0.0285); ADHD index (p=0.0420);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

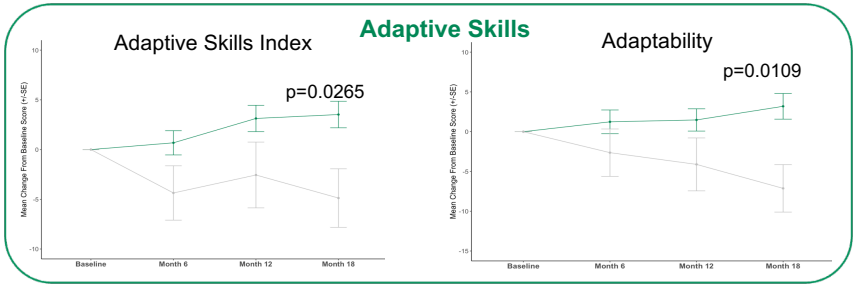
Speech endpoints were not impacted by govorestat treatment, which is suspected to be due to lack of progression in the placebo group and concomitant speech therapy received by almost all children in the trial. Of note, patients with severe speech deficits showed a favorable trend towards improvement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

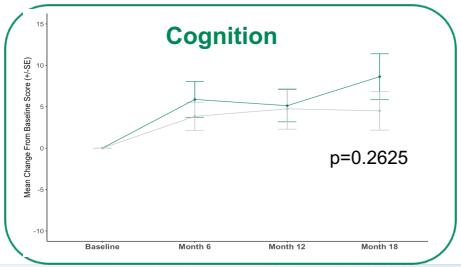
Govorestat Treatment Positively Impacted Behavior, Daily Living Skills, Adaptive Skills, Cognition, Fine Motor Skills & Tremor

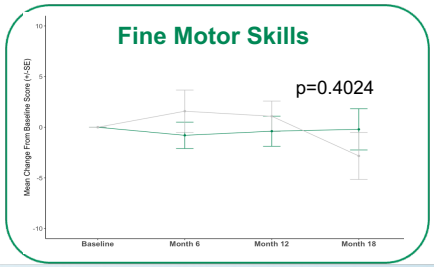
Clinical outcomes declined in the placebo group, while govorestat treated patients stabilized or improved over 18 months

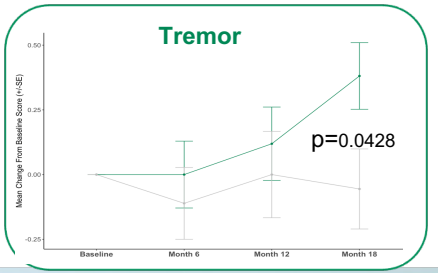






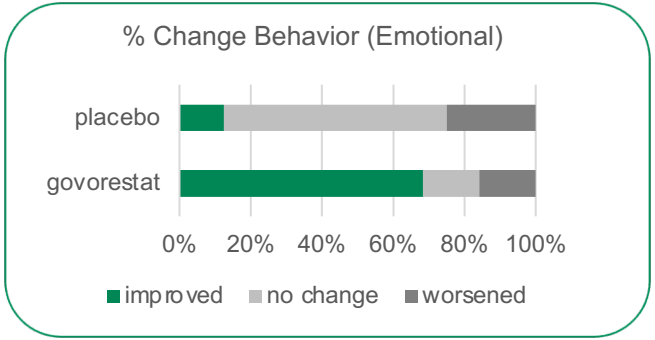


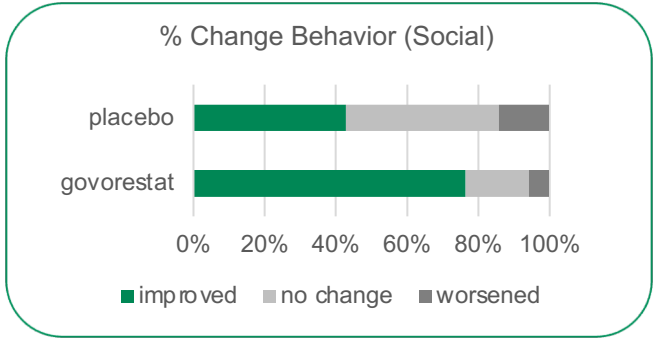


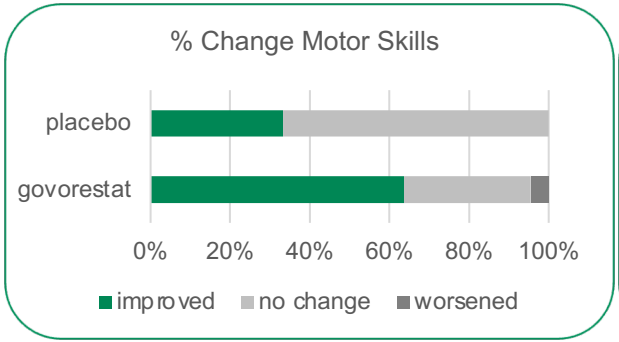


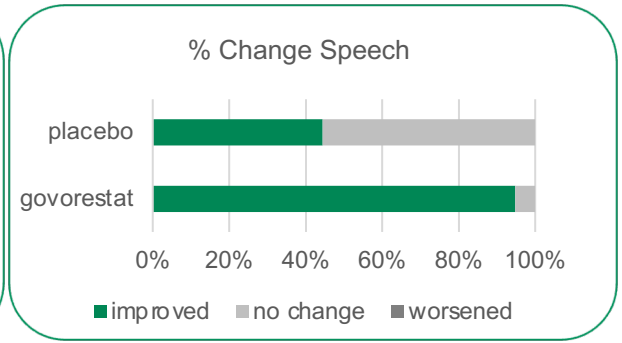
AT-007 Placebo

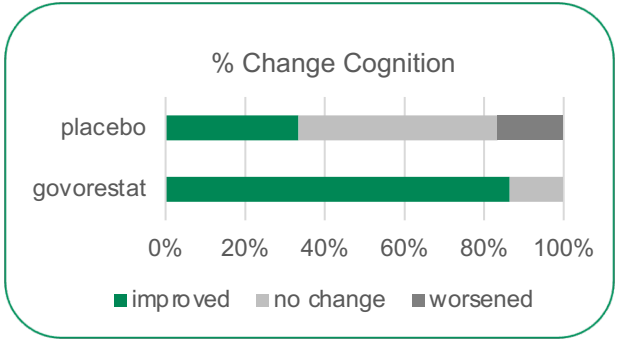
Caregiver Exit Interviews Support the Clinical Meaningfulness of Govorestat Treatment









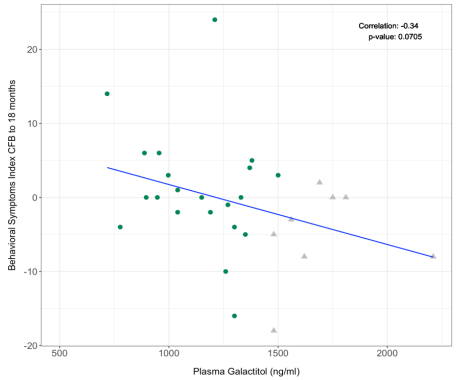


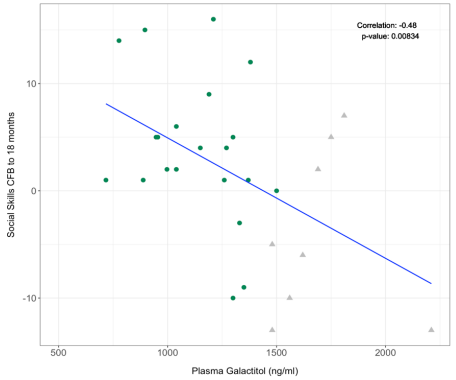
Caregivers noted an improvement or stabilization of disease on all categories of symptoms in the govorestat treated group vs. placebo.*

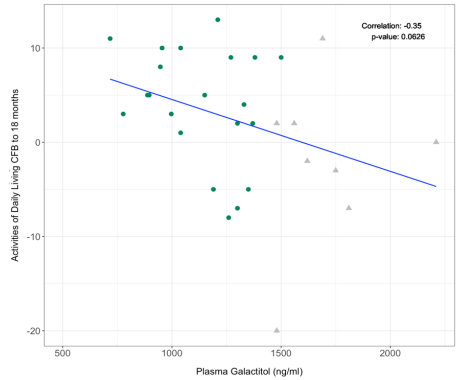
*Exit interviews were performed prior to study unblinding to prevent bias

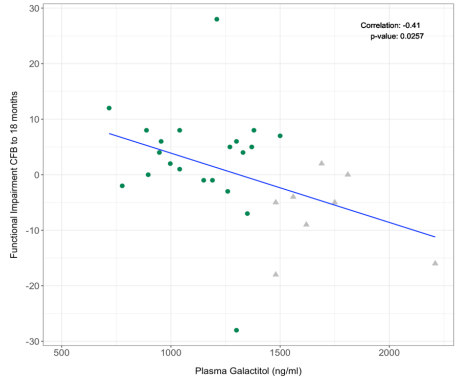
Galactitol Reduction Correlated with Clinical Outcomes Benefit

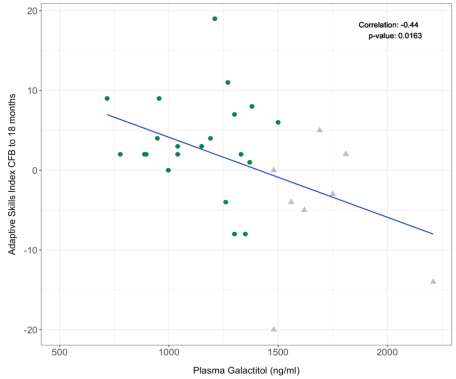
Galactitol level at 3 months statistically correlated with change in clinical outcomes at 18 months

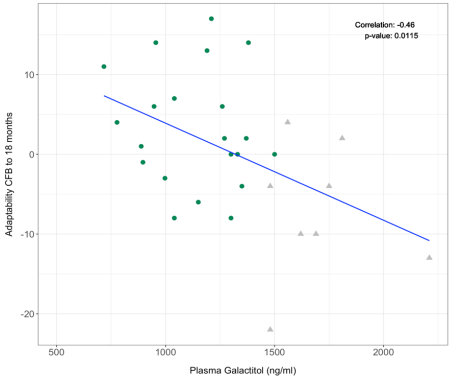


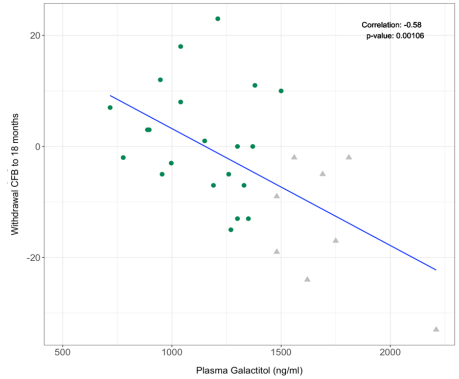


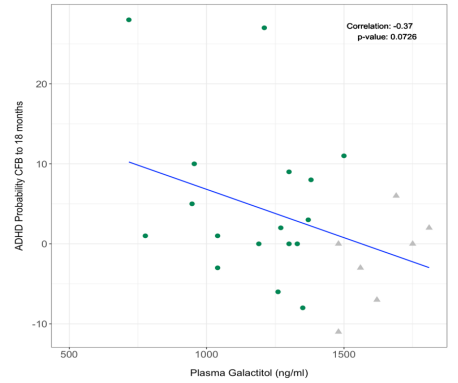












CFB= Change From Baseline; correlation plots include data for all subjects who completed the same BASC test at baseline and 18 months (e.g. preschool, child, adolescent)

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 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

Govorestat (AT-007)

SORD DEFICIENCY

- Orphan Drug Designation

Preclinical proof of concept demonstrated

Positive pilot study completed

Registrational Phase 3 study positive interim 12-month data

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

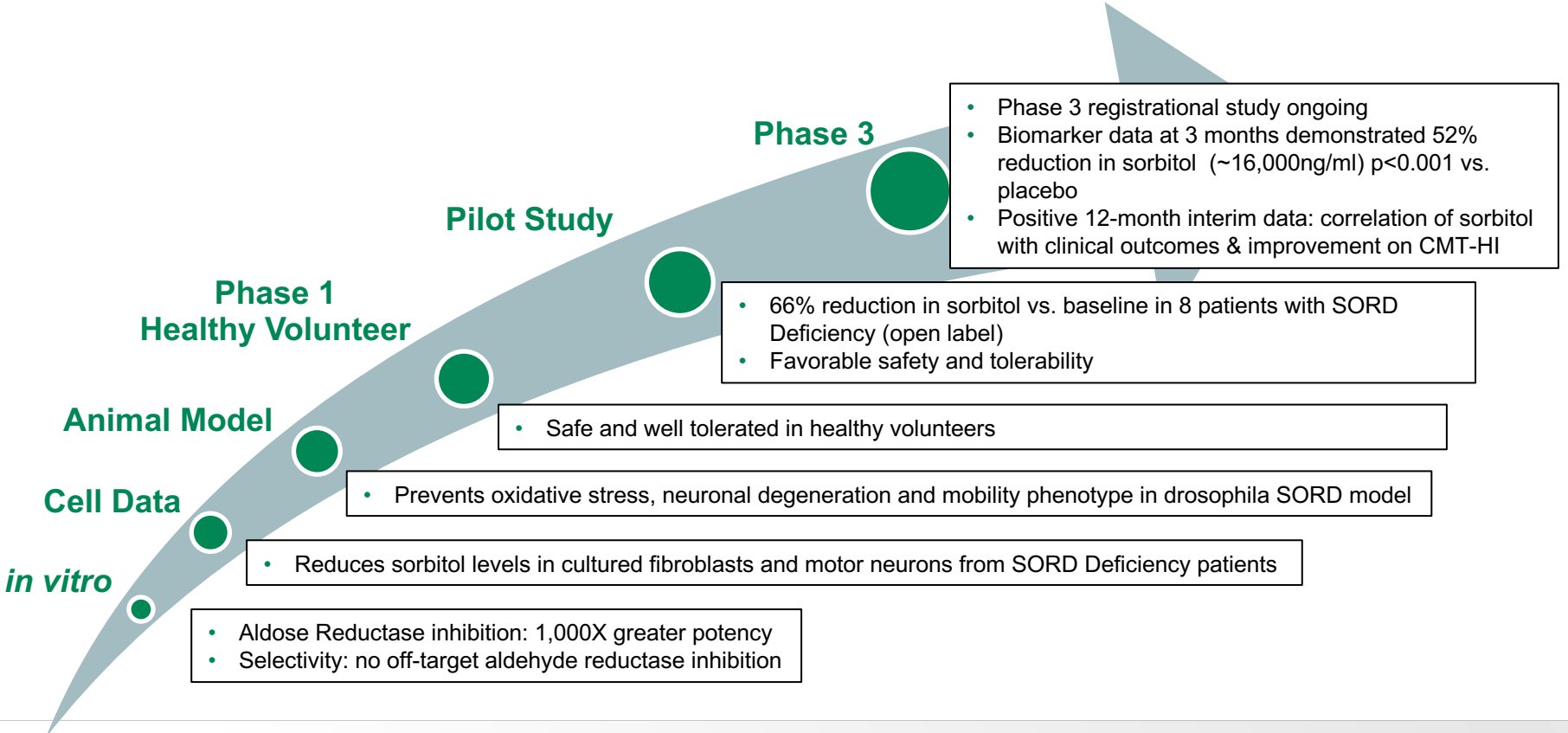
- Patients with SORD Deficiency are unable to metabolize sorbitol
- Aldose Reductase converts glucose to sorbitol, which then accumulates at up to 100X normal levels in patients with SORD Deficiency
- Sorbitol is toxic to cells (especially neurons), resulting in osmotic stress, redox derangement and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

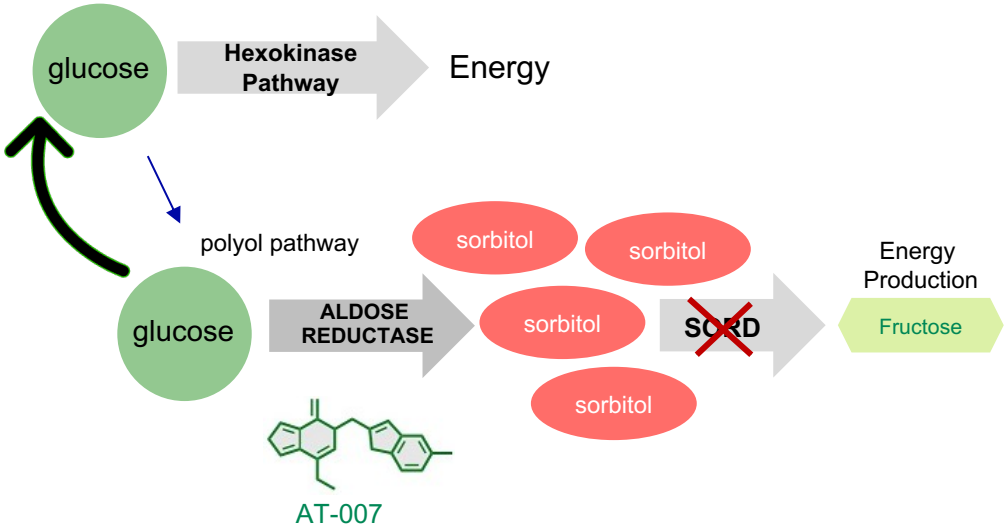
CMT2 = Charcot-Marie-Tooth Type 2; dHMN = distal Hereditary Motor Neuropathy; COE = Centers of Excellence; ARI = Aldose Reductase Inhibitor

Govorestat Has Demonstrated Effectiveness *in vitro*, *in vivo*, and in a SORD Pilot Study; Phase 3 12-Month Interim Data Positive



CMT-HI= CMT Health Index patient reported outcome measure; p=0.01 at 12 months

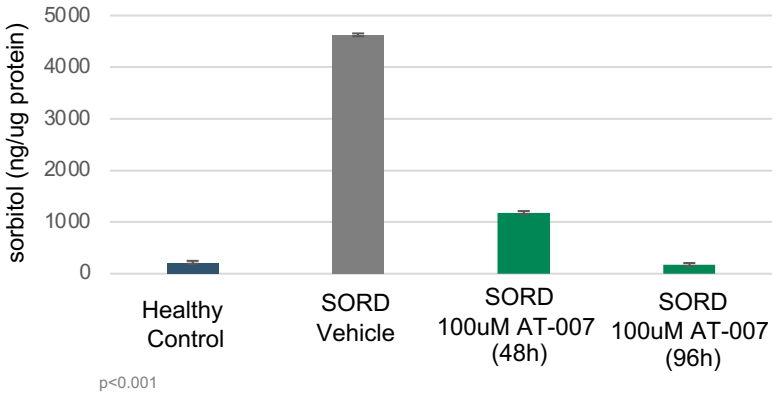
Aldose Reductase Inhibition Addresses the Underlying Cause of SORD Neuropathy by Preventing Conversion of Glucose to Sorbitol



- 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

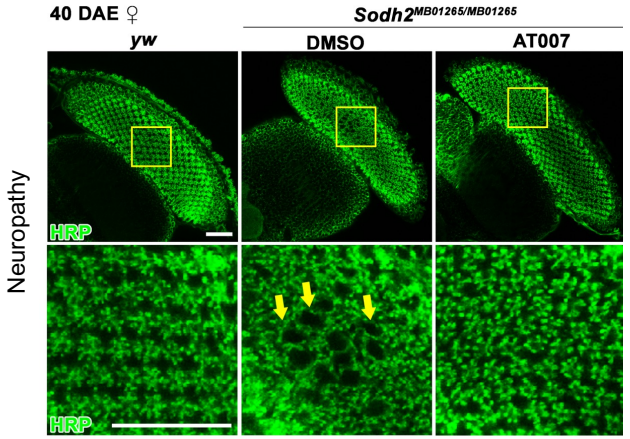
Govorestat Treatment Reduces Sorbitol Levels in SORD Patient Cells; Prevents CNS Phenotype in a Drosophila SORD Deficiency Model

Sorbitol Reduction in Patient Fibroblasts with Govorestat (AT-007) Treatment

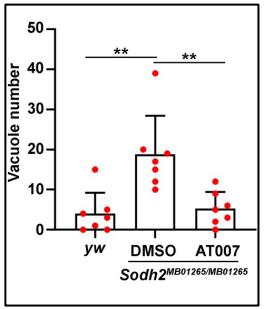


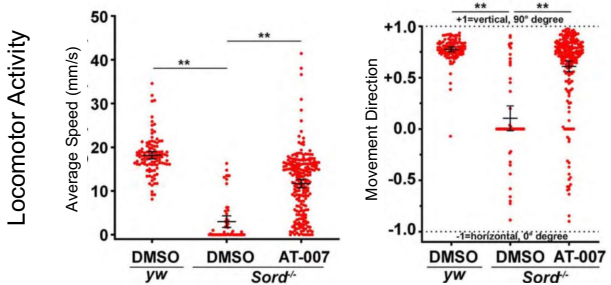
- Sorbitol accumulation causes mitochondrial dysfunction and reactive oxygen species formation, resulting in axonal neuropathy
- Treatment with govorestat (AT-007) reduces sorbitol and prevents downstream neuronal damage
- Govorestat treatment normalizes lower limb function in drosophila

Govorestat (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

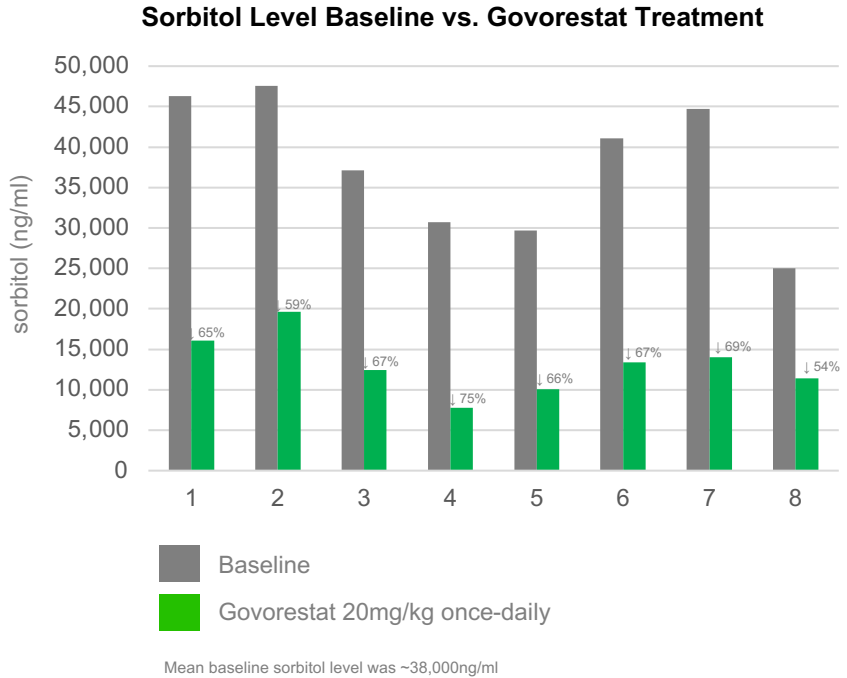




Fly geotactic activity was recorded using an automated monitoring system. *yw* flies (control) treated with DMSO and SORD deficient flies treated with DMSO or 10 µg/ml AT- 007 at 10 DAE. Data are presented as mean ± SE, $^{**}p < 0.01$ from trial-by-trial comparisons.

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

- Govorestat safe and well tolerated; no SAEs

Pharmacokinetics/ Pharmacodynamics

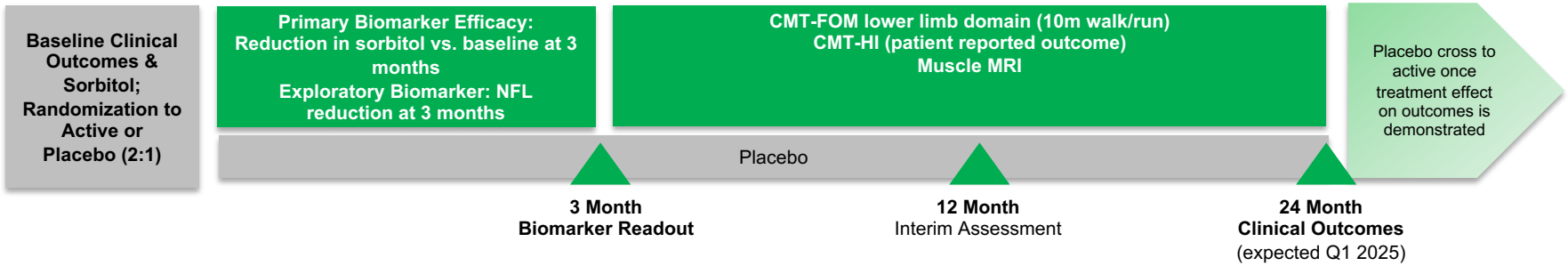
- Rapid and sustained reduction in sorbitol
- No compensatory increase in glucose level

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

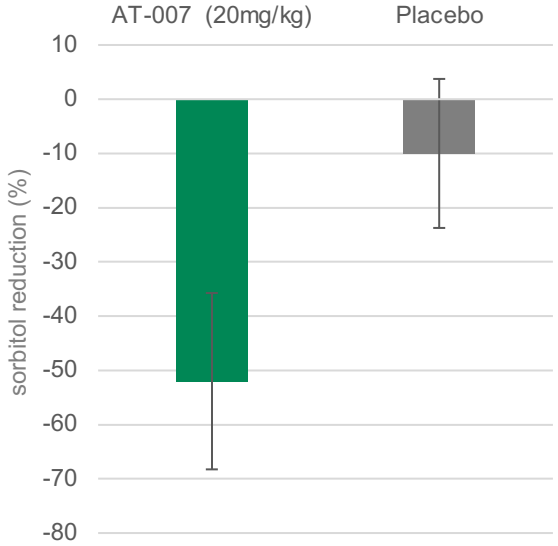
APPLIED THERAPEUTICS

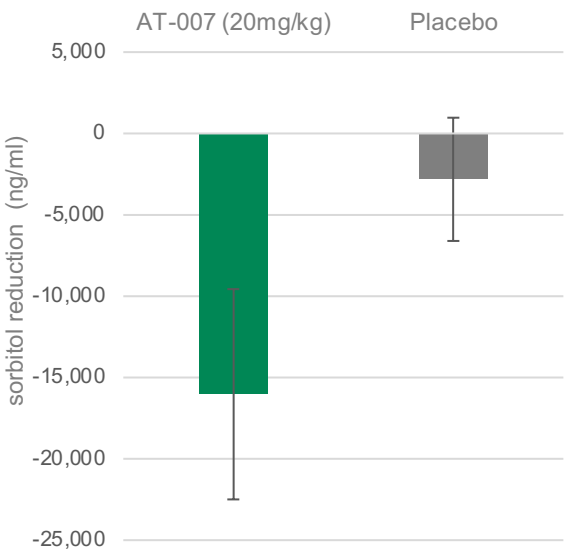
CMT = Charcot-Marie-Tooth, FOM = Functional Outcomes Measure, HI = Health Index, MRI = Magnetic Resonance Imaging, 10MWR = 10-Meter Walk/Run

Govorestat Significantly Reduced Sorbitol Levels in the Ph 3 INSPIRE Trial

3 Month Sorbitol Reduction Interim Analysis

Govorestat (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

- Govorestat 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 govorestat treated group but increased in the placebo group (p=0.027)*

*percent change from baseline ANCOVA analysis

INSPIRE Trial 12 Month Interim Data Overview

Co-primary endpoints at 12 month analysis:

- **Primary clinical efficacy endpoint**: Statistically significant correlation between sorbitol levels and change in clinical outcomes at 12 months of treatment on combined measures of the CMT Functional Outcome Measures (CMT-FOM) lower limb domain (10 meter walk-run test, 4 stair climb, and sit to stand test), 6-minute walk test and dorsiflexion (p=0.05)
- **Primary pharmacodynamic/ biomarker endpoint**: Sustained reduction in sorbitol level in patients treated with govorestat at 12 months, which was statistically significant compared to placebo (p<0.001).

Secondary Endpoints

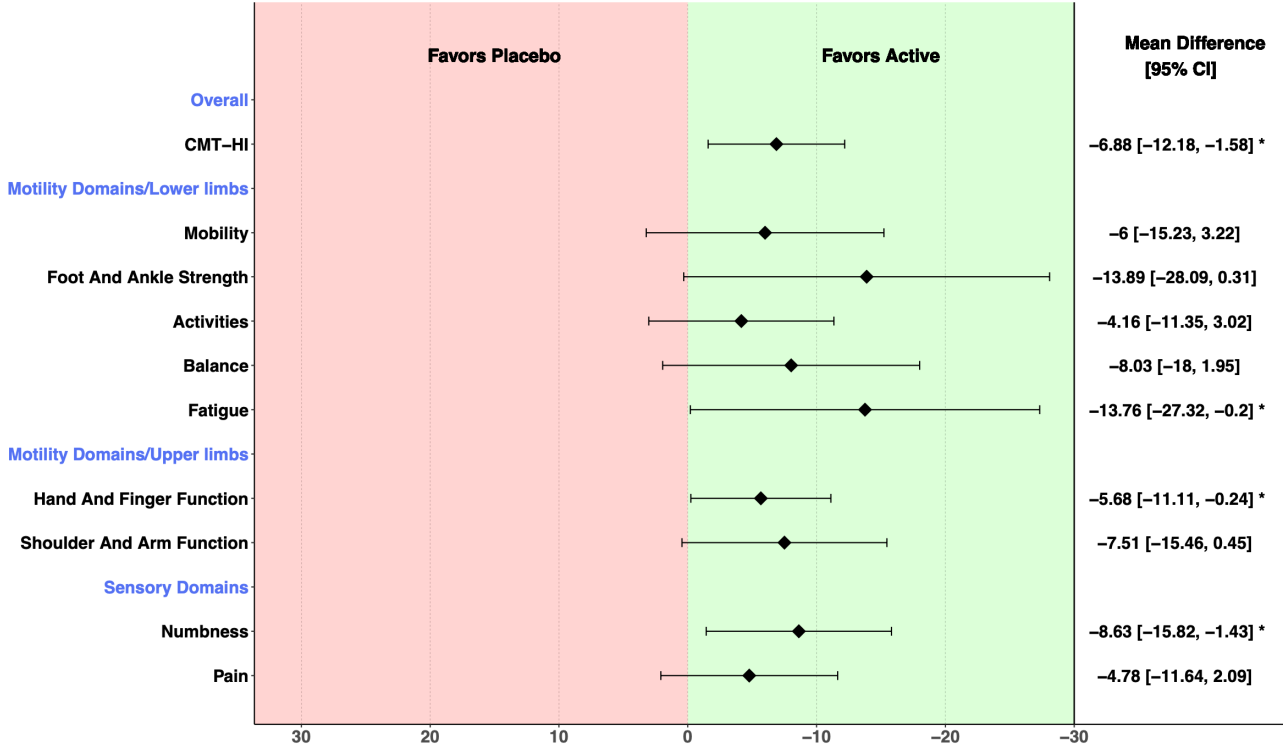
- Highly statistically significant effect (p=0.01) impact of govorestat on the CMT Health Index (CMT-HI), an important patient-reported outcome measure of disease severity and well-being; aspects of the CMT-HI that demonstrated a treatment effect included lower limb function, mobility, fatigue, pain, sensory function, and upper limb function.
- Trends (not statistically significant) on CMT-FOM measures linked to walking ability, such as 10MWR, dorsiflexion and 6 minute walk test
    - No substantial effect on stair climb or sit-to-stand test

Safety

- Govorestat was safe and well tolerated, with similar incidence of adverse events between active and placebo-treated groups

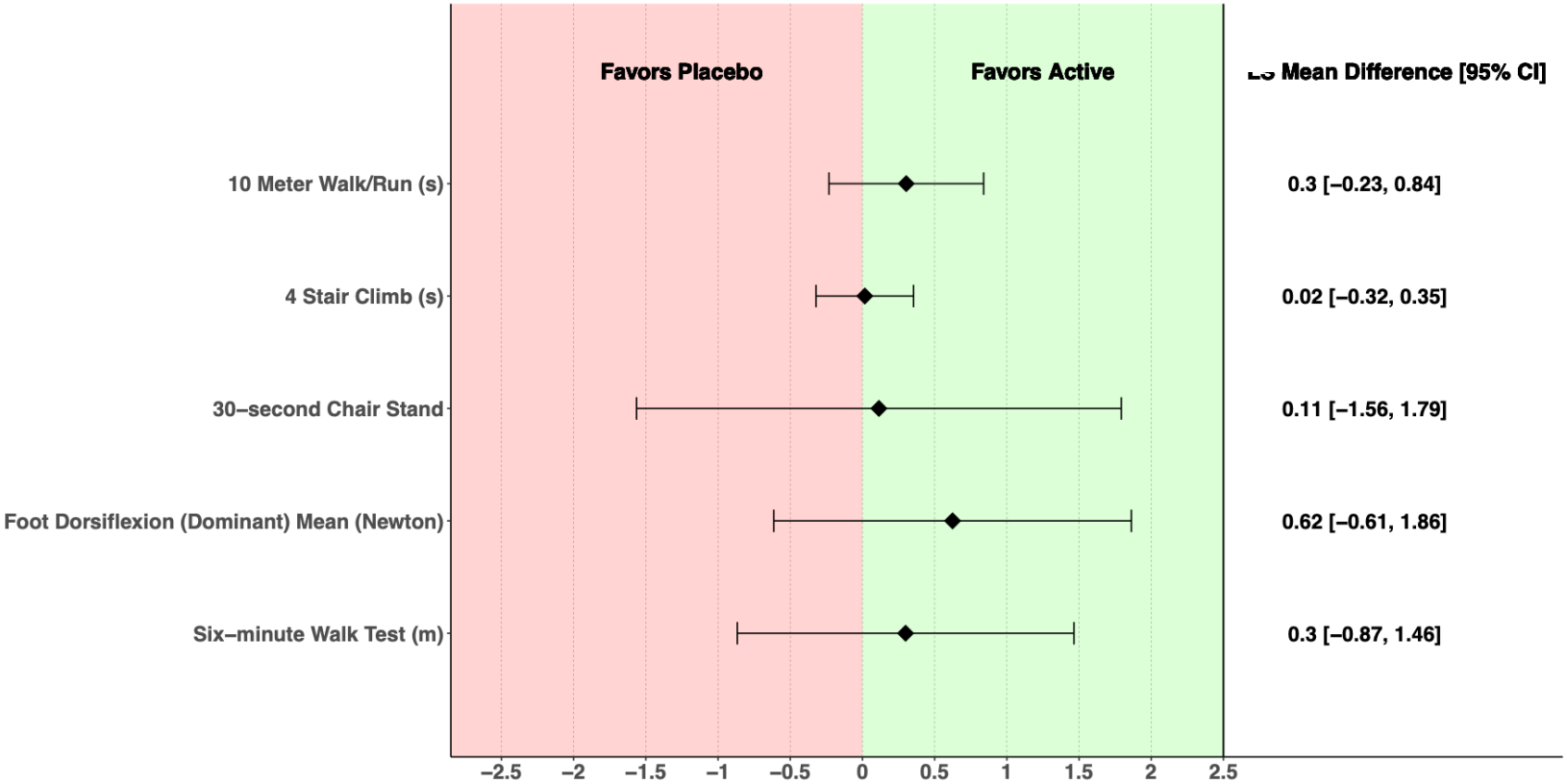
Study will continue in blinded format to 24 months

Govorestat Treated Patients Demonstrated a Statistically Significant Improvement in CMT-Health Index (CMT-HI) Scores at 12 Months (p=0.01 vs. placebo)



Lower score (negative change from baseline) represents improvement in disease symptoms; measures with “8” were statistically significant vs. placebo with p<0.05

Govorestat Treated Patients Demonstrated Trend Towards Improvement in 10MWR, Dorsiflexion and 6 Minute Walk at 12 Months



For foot Dorsiflexion, the estimate and the CI were divided by 10 in order to present within the x−axis range (actual values are 10X the values on the slide); For 6-minute walk, the estimate and the CI were divided by 50 in order to present within the x−axis range (actual values are 50X the values on the slide). For 10 Meter Walk/Run and 4 Stair Climb, the 'change from baseline' value has been reversed (multiplied by -1) in order to maintain consistency of direction of interpretation in the forest plot

Patient Disposition & Safety

Govorestat safe and well-tolerated; adverse events balanced between govorestat and placebo groups

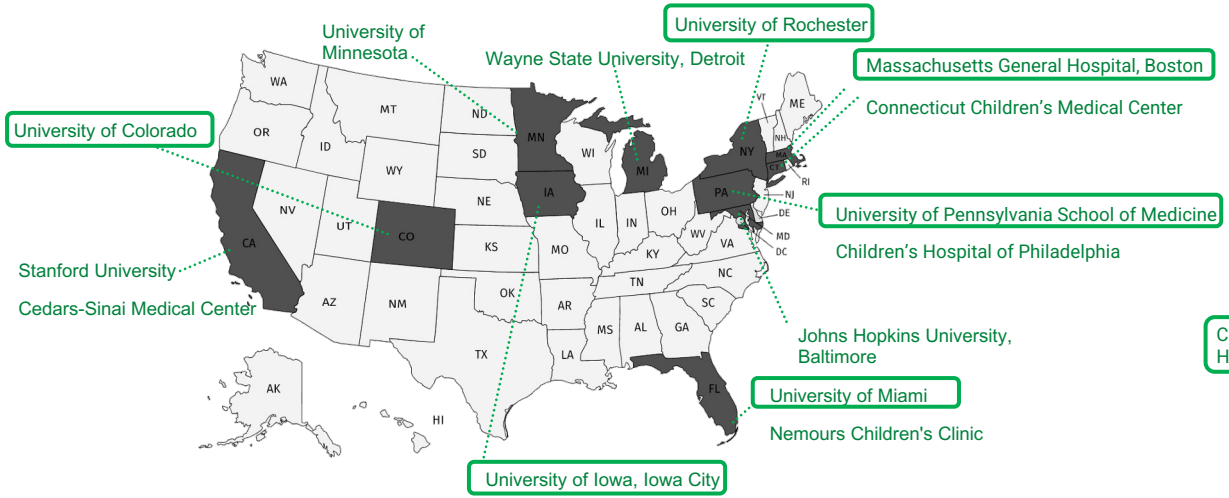
	Placebo N=18 n (%)	Govorestat N=38 n (%)	Combined N=56 n (%)
Randomized	18 (100.0%)	38 (100.0%)	56 (100.0%)
Ongoing	17 (94.4%)	34 (89.5%)	51 (91.1%)
Discontinued	1 (5.6%)	4 (10.5%)	5 (8.9%)
Reason for Discontinuation: Adverse Event	0 (0.0%)	3 (7.9%)	3 (5.4%)
Reason for Discontinuation: Withdrawal By Subject	1 (5.6%)	1 (2.6%)	2 (3.6%)

	Placebo (N=18) n (%)	Govorestat (N=38) n (%)	Overall (N=56) n (%)
Treatment Emergent Adverse Events (number of patients reporting any adverse event during the study)[1]	15 (83.3%)	34 (89.5%)	49 (87.5%)
Mild	12 (66.7%)	33 (86.8%)	45 (80.4%)
Moderate	5 (27.8%)	8 (21.1%)	13 (23.2%)
Severe	0 (0.0%)	1 (2.6%)[2]	1 (1.8%)[2]
Serious Adverse Events	0 (0.0%)	1 (2.6%)[3]	1 (1.8%)[3]
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)

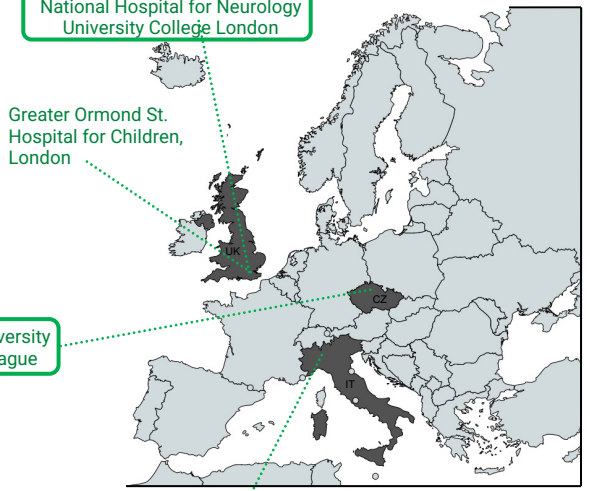
1.some patients reported more than one adverse event, so the sum of mild, moderate and severe is larger than the number of patients reporting an adverse event; 2. the severe adverse event was a recurrence of a pre-existing condition; 3. the serious adverse event was a motorcycle accident.

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

US



UK & EU



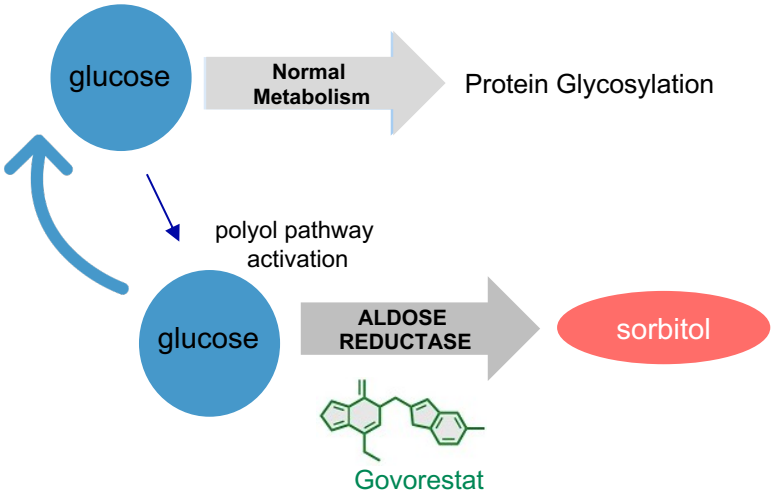
Centers participating in INSPIRE Phase 2/3 trial

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

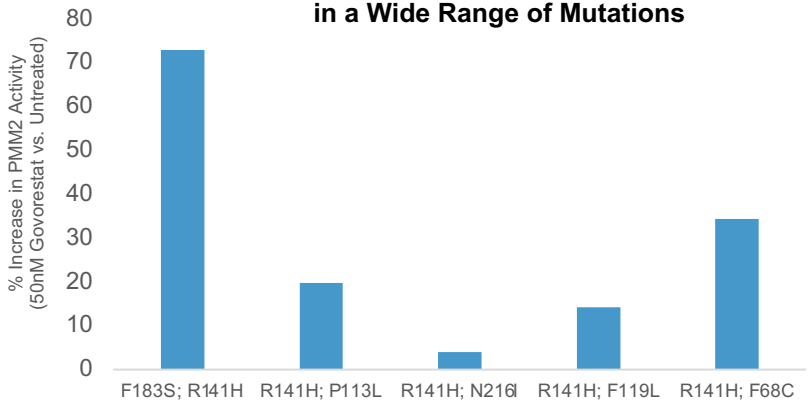
Aldose Reductase Inhibition Improves PMM2 Activity
Govorestart Granted Orphan & Pediatric Rare Disease Designation for PMM2-CDG; Single-Patient IND Open – Phase 2 Ready

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



Govorestat 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 (DbCM) 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

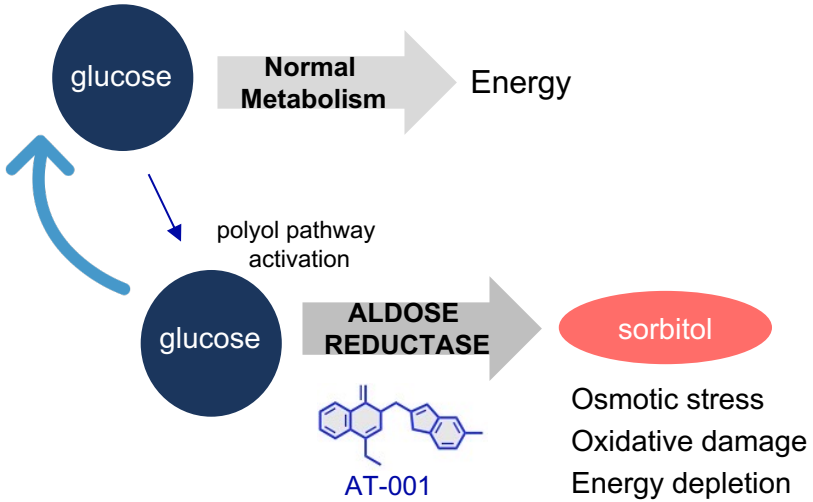
- Hyperactivation of the polyol pathway is a key underlying mechanism in DbCM
- Aldose Reductase activation causes intracellular sorbitol accumulation, osmotic stress, cell death, generation of ROS and impaired cardiac energetics
- Previous AR inhibitors demonstrated clinical efficacy, but were associated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

Diabetic Cardiomyopathy: 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

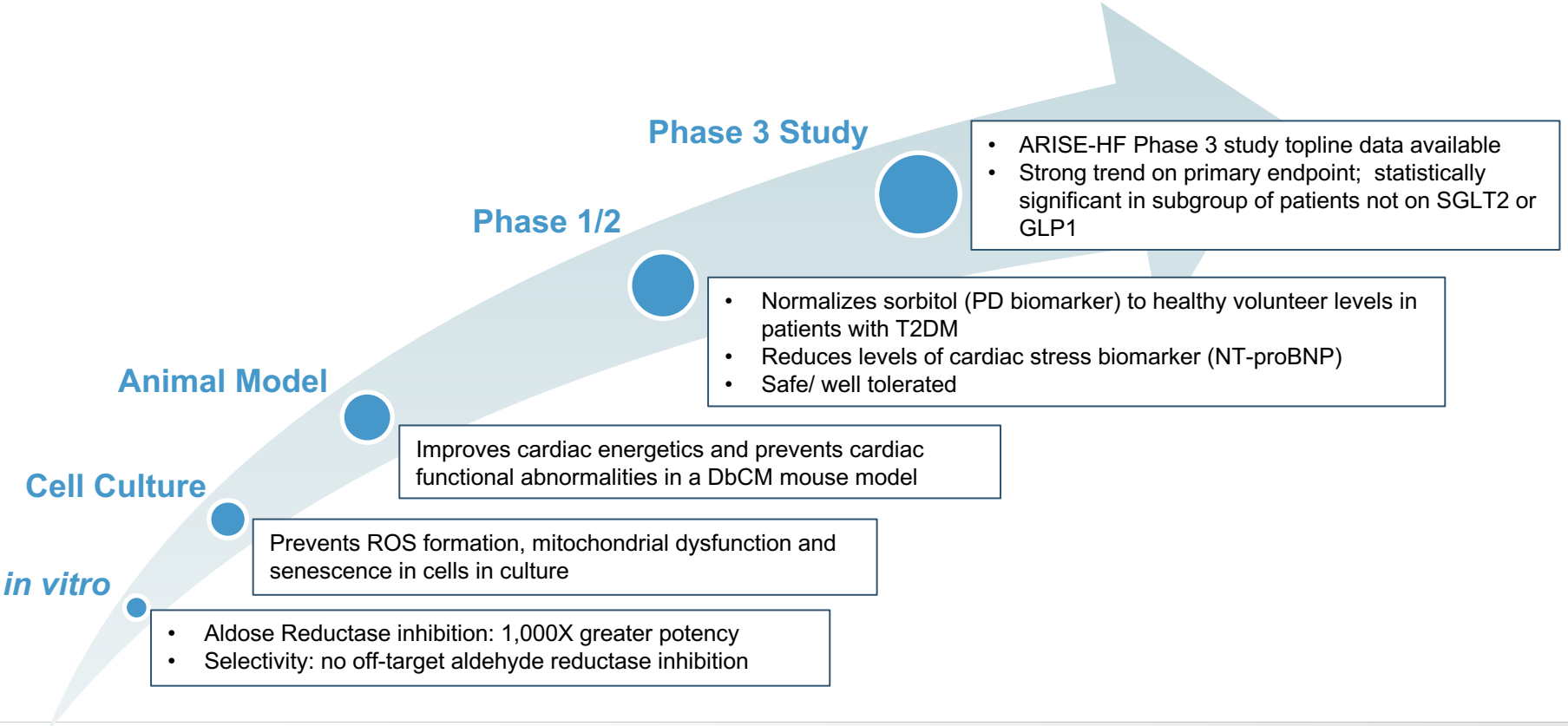
Excess sorbitol and fructose cause several downstream processes that result in cell death, including osmotic dysregulation and ROS formation

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

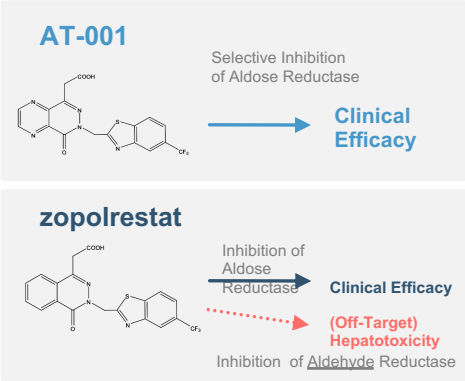
Brownlee M. Diabetes Care. 2005;54(6):1615-1625; Miki T, et al. Heart Fail Rev. 2013;18(2):149-166.

AT-001 Has Demonstrated Effectiveness *in vitro*, *in vivo*, and in Phase 1/2 Clinical Trials; Phase 3 Completed



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

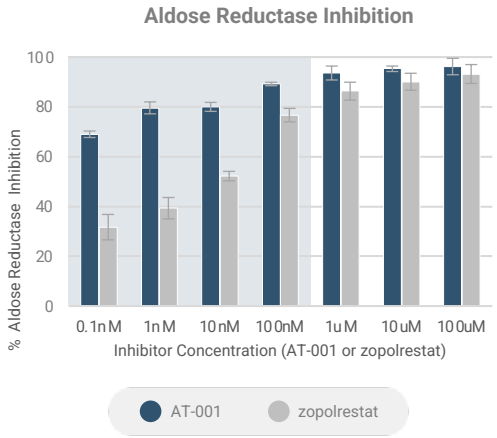
Applied Therapeutics' **AT-001 was developed to selectively inhibit Aldose Reductase with 1,000X greater potency and *without* off-target inhibition** of Aldehyde Reductase[2]



Tissue Penetration (in rats)

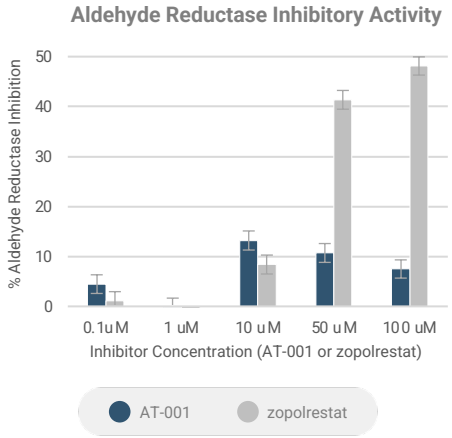
Compound	IC_{50}	MTD in animals	Systemic/ Heart	Nerve	Retina	CNS
AT-001	30pM	>2,000mg/kg	✓	✓	✓	X
zopolrestat	10nM	100mg/kg	✓	✓	X	X

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



Data based on In Vitro Enzyme Inhibition & Cultured Hepatocytes

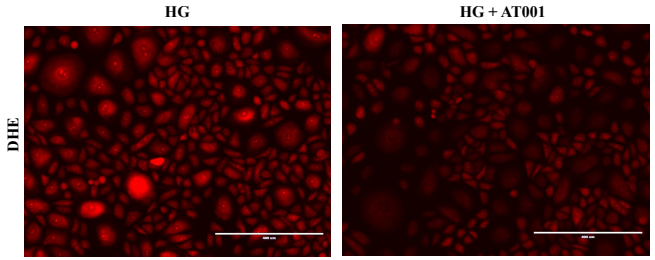
Unlike zopolrestrat, AT-001 does not inhibit Aldehyde Reductase



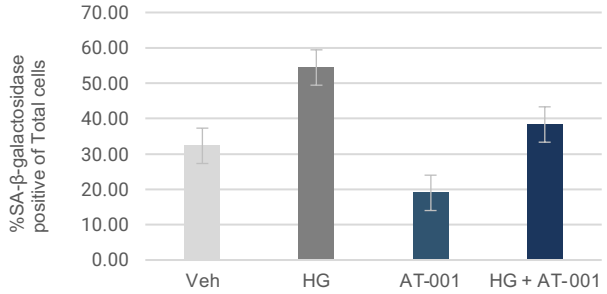
Poster # 632: "Addressing safety and specificity with aldose reductase inhibition: development of AT-001 for diabetic cardiomyopathy" 56th Annual Meeting of the European Association for the Study of Diabetes (EASD) Sept 2020

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

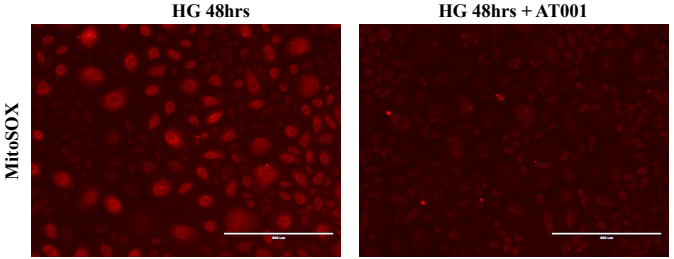
Dihydroethidium (DHE) Staining for Cytosolic ROS



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

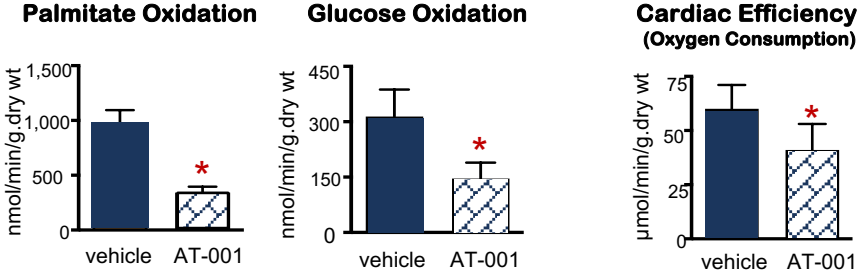
- In patients with diabetes, metabolism of glucose through the polyol pathway results in generation of Reactive Oxygen Species (ROS), which has been identified as a key mediator of tissue damage and causal in diabetic complications. Selective inhibition of AR reduces oxidative stress and mitigates these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

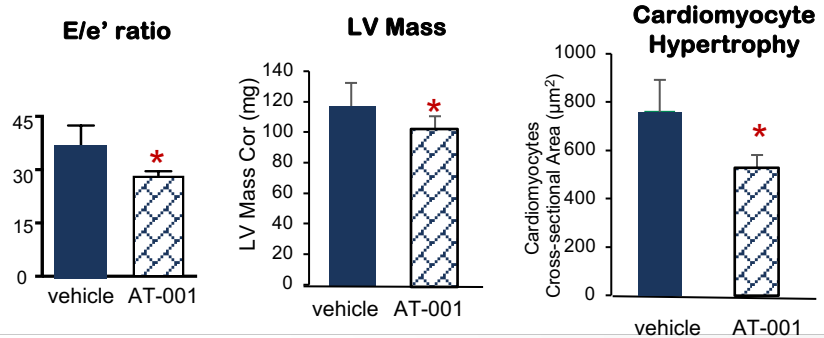
AT-001 Improves Cardiac Energetics, Prevents Cardiac Dysfunction and Prevents Fibrosis in an Animal Model of DbCM

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

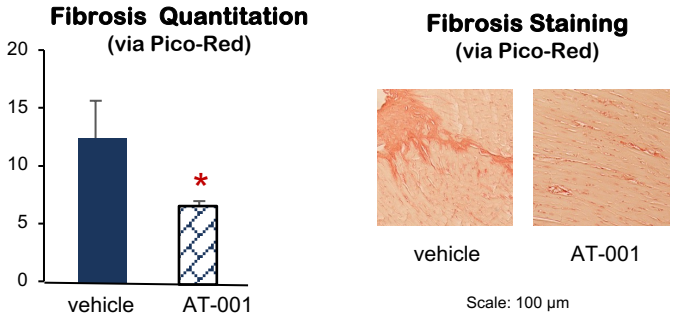
AT-001 Improves Cardiac Energetics



AT-001 Improves Cardiac Function and Prevents LVH



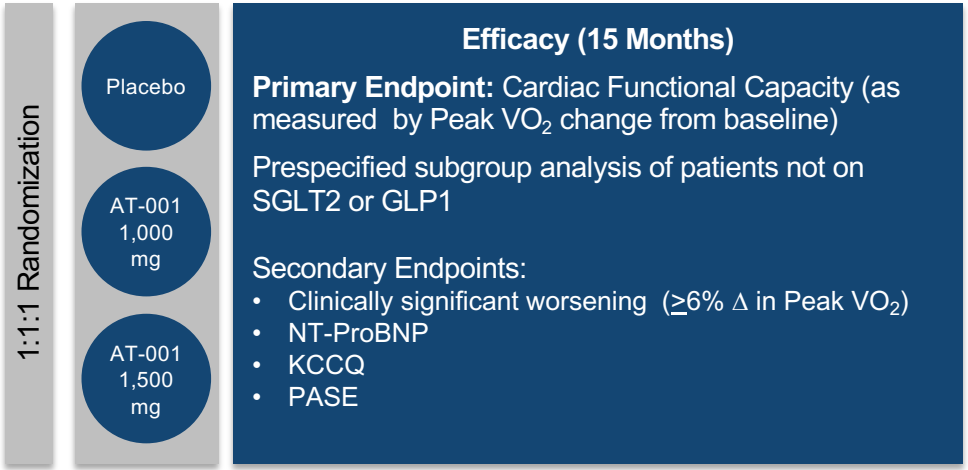
AT-001 Prevents Fibrosis and Adverse Remodeling



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

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: ≥60 years, or ≥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 VO2 <75% of age/gender predicted normal

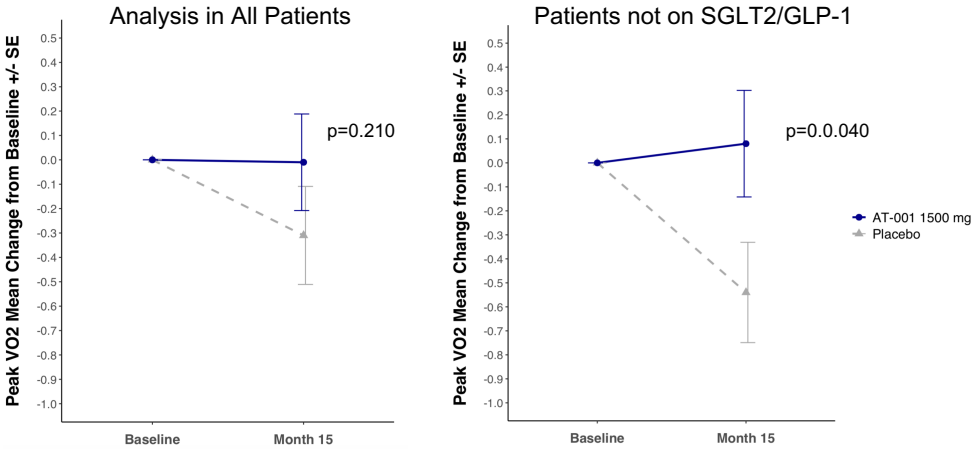
Key Exclusion Criteria:

- 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/m2
- HbA1c >8.5%
- eGFR <45 mL/min/1.73 m2

PHASE 3

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-001500mg stabilized cardiac functional capacity, as measured by Peak VO2, (-0.01ml/kg/min) while the placebo group declined (-0.31ml/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_2) 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

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