# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

# FORM 8-K

**CURRENT REPORT**
**Pursuant to Section 13 or 15(d)**
**of the Securities Exchange Act of 1934**

Date of Report (Date of earliest event reported): **February 15, 2022**

# APPLIED THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

| **Delaware** | **001-38898** | **81-3405262** |
|---|---|---|
| (State or Other Jurisdiction of Incorporation) | (Commission File Number) | (I.R.S. Employer Identification No.) |

| **545 Fifth Avenue, Suite 1400**<br>**New York, NY 10017**<br>(Address of Principal Executive Offices) | **10017**<br>(Zip Code) |
|---|---|

Registrant's telephone number, including area code: **(212) 220-9226**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

| **Title of each class** | **Trading Symbol(s)** | **Name of each exchange on which registered** |
|---|---|---|
| Common stock | APLT | The Nasdaq Global Market |

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

**Item 7.01 Regulation FD Disclosure.**

On February 15, 2022, Applied Therapeutics, Inc. released a presentation that contains company information to be used by members of management from time to time in a series of meetings with analysts, investors and other third parties. The presentation is attached to this Current Report on Form 8-K as Exhibit 99.1 and is incorporated herein by reference.

The information included in this Current Report on Form 8-K, including Exhibit 99.1 incorporated by reference herein, shall not be deemed "filed" for purposes of Section 18 of the Securities and Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that Section, or incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in such filing.

**Item 9.01 Financial Statements and Exhibits.**

(d) Exhibit:

The following exhibit is attached with this current report on Form 8-K:

| Exhibit No. | Description |
|---|---|
| 99.1 | February 2022 Corporate Overview Presentation |
| 104 | Cover Page Interactive Data File (embedded within the Inline XBRL document) |

**SIGNATURE**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

**APPLIED THERAPEUTICS, INC.**

Dated: February 15, 2022

By: /s/ Shoshana Shendelman
Name: Shoshana Shendelman.
Title: President and Chief Executive Officer

Exhibit 99.1

# Applied Therapeutics

## Corporate Presentation

February 2022

APPLIED THERAPEUTICS

# Disclaimer

**This presentation is made by Applied Therapeutics, Inc. (the "Company"). Nothing contained in this presentation is, or should be co promise or representation by the presenter or the Company or any director, employee, agent, or adviser of the Company. This present inclusive or to contain all of the information you may desire. This presentation shall not constitute an offer to sell or the solicitation o securities, nor shall there be any sale of the Company's securities in any state or jurisdiction in which such offer, solicitation or s registration or qualification under the securities laws of any such state or jurisdiction.**

Various statements in this presentation concerning the Company's future expectations, plans and prospects, including without limitation, the regarding its strategy, its product candidate selection and development timing, its management team capabilities, and the ability of the Compar clinically meaningful effect on the target patient populations, constitute forward-looking statements. The use of words such as "may," "might "anticipate," "believe," "estimate," "project," "intend," "future," "potential," or "continue," the negative of these and other similar expressions are intenc statements. Such statements, based as they are on the current analysis and expectations of management, inherently involve numerous risks and u many of which are beyond the Company's control. Such risks include, but are not limited to: the impact of general economic conditions, general c industries, changes in the global and regional regulatory environments in the jurisdictions in which the Company does or plans to do business, ma and changes to the competitive environment. Consequently, actual future results may differ materially from the anticipated results expressed in the case of forward-looking statements regarding investigational product candidates and continuing further development efforts, specific risks which materially from the Company's current analysis and expectations include: failure to demonstrate the safety, tolerability and efficacy of our pro controlled verification of data and the related analyses; the expense and uncertainty of obtaining regulatory approval, including from the U.S. F European Medicines Agency; the possibility of having to conduct additional clinical trials and our reliance on third parties such as our licensors ar our suite of technologies and product candidates. Further, even if regulatory approval is obtained, biopharmaceutical products are genera 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 Excha uncertainties of which the Company is not currently aware may also affect Company's forward-looking statements. The reader should not place und statements included in this presentation. These statements speak only as of the date made and the Company is under no obligation and disavows 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 patien 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

### M

Fatal or d with no a

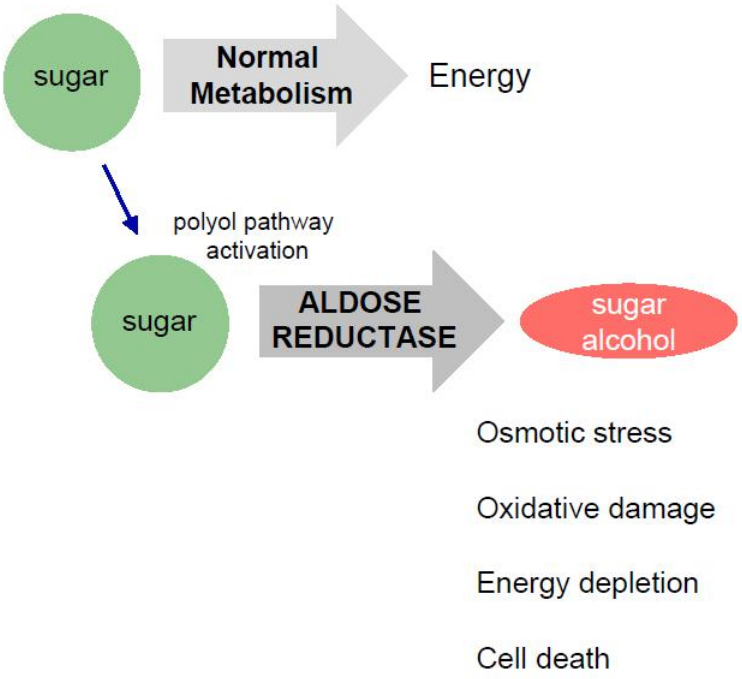
Limited

# Innovative Pipeline with Near-Term Milestones

| Compound | Preclinical | Phase 1 | Phase 2 | Phase 3 | Dosing | Target Tissue | Milestones |
|---|---|---|---|---|---|---|---|
| **ALDOSE REDUCTASE FRANCHISE** | | | | | | | |
| AT-007 | Galactosemia | | | | QD Oral | CNS | Positive adult and pediat pediatric Phase 3 outcor |
| AT-007 | SORD Deficiency | | | | Oral | CNS | Positive pilot study data; trial ongoing |
| AT-007 | PMM2-CDG | | | | Oral | CNS | Phase 2 ready; Expandec |
| AT-001 | Diabetic Cardiomyopathy | | | | BID Oral | Systemic | Ph 3 registrational trial ir expected 2023 |
| AT-001 | Diabetic Peripheral Neuropathy | | | | Oral | Peripheral Nerve | Sub-study embedded in I |
| AT-003 | Diabetic Retinopathy | | | | Oral | Retina | Ph 1 expected 2022 |
| **PI3 KINASE FRANCHISE** | | | | | | | |
| AT-104 | PTCL, CTCL, TALL† | | | | SC / Oral | Selective δ/γ inhibitor | Proof of concept preclini |

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

# Aldose Reductase Inhibitor Overview




**Aldose Reductase is an enzyme implicated in mul**

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

Converts sugar to reduced sugar alcohols, which are

Leads to cell death through osmotic dysregulation, re formation, and energy deficiencies

Prior attempts to inhibit Aldose Reductase were hinde selectivity and off-target tox issues

Applied Therapeutics' compounds are 1,000 X more p and highly selective; no off-target inhibition of aldehyc

# AT-007: Blockbuster Opportunity with Late-Stage Progr
# Rare Diseases with High Unmet Need and No Approved

## Galactosemia

- Positive adult and pediatric biomarker data
- Orphan Drug Designation
- Pediatric Rare Disease Designation
- Fast-Track Designation
- **Phase 3 pediatric outcomes study ongoing; powered for statistical significance at 18 months**

## SORD Deficienc

- Preclinical proof of concept
- Positive pilot study results in SORD
- **Phase 3 study ongoing**
- **Biomarker data expected H2 202 for accelerated approval**

*~7,000 patients in US + EU in each indication (14,000 total)*
*Near-term revenue opportunity with Composition of Matter patent exclusivity through 2*

- Validated mechanism of action
- US payer feedback supports pricing/coverage
- Strong patient, caregiver, HCP interest
- Convenient, once-daily oral dosing
- Favorable safety and tolerability profile
- Small commerci
- Commercializati
- Low cost of gooc

# AT-001: Potential First Therapy in Diabetic Cardiomyop
# Highly Prevalent Disease with Blockbuster Potential

## Diabetic Cardiomyopathy

- Heart Failure affecting ~20% of diabetics
- Positive proof of concept in Phase 1/2
- ARISE-HF global Phase 3 trial ongoing; data expected 2023
- No drugs approved; potential first disease-modifying treatment in DbCM

*DbCM potential market ~6M patients US; 5M EU5*

## Diabetic Peripheral Neurop

- Affects >30% of diabetics
- Proof of concept with "old" ARIs
- Phase 2 sub-study embedded in ARIS Phase 3
- Although pain drugs are approved for treatment, no disease-modifying treat Potential first disease-modifying treat

*DPN potential market ~9M patients U*

- Validated mechanism of action
- Demonstrated proof of concept
- Patent exclusivity through 2031
- Convenient, twice-daily oral dosing
- Favorable safety and tolerability profile
- Strong KOL support
- Low cost of go
- Payer feedbac on par with En

# 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

APPLIED THERAPEUTICS

# Galactosemia is a Rare Metabolic Disease With No App 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/ Diag

- No approved therapies to treat Galac
- Mandatory newborn screening in US countries
- Galactose-restricted diet implemente birth and adhered to for life
- Dietary restriction prevents newborn not prevent long-term CNS complica endogenous galactose production by
- Patients are primarily seen by metab

### 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

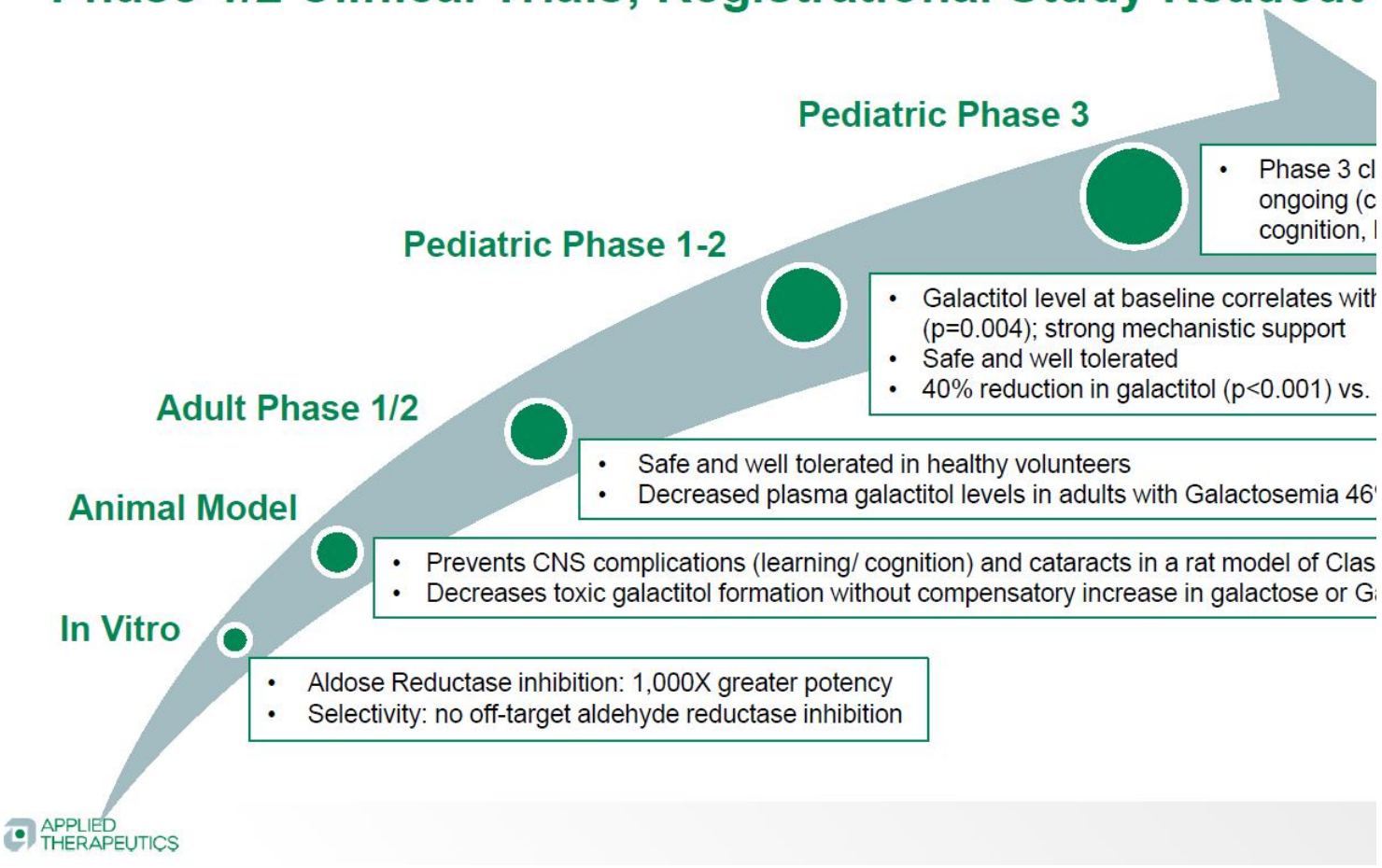
### Market Size / Opportu

- $1.25B+ WW peak sales potential (U
- Known prevalent and addressable po ~7K WW)
- Small commercial footprint focused c of Excellence
- Strong patient community engageme
- Payer feedback supports access/pric
- Composition of matter IP through 20

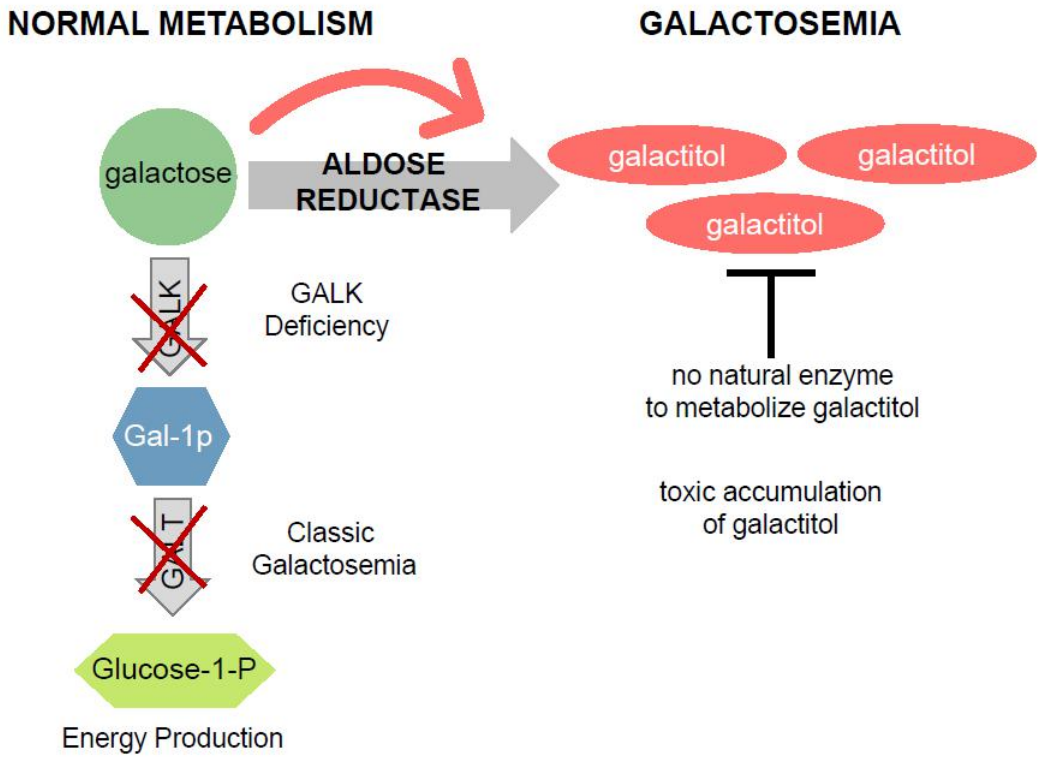
APPLIED THERAPEUTICS

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 ra* Swaiman et al. *Pediatric Neurology*. 2018.

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



# Deficiency in GALT or GALK Leads to Inability to Metab
# Galactose; AR Converts Excess Galactose to Toxic Gala



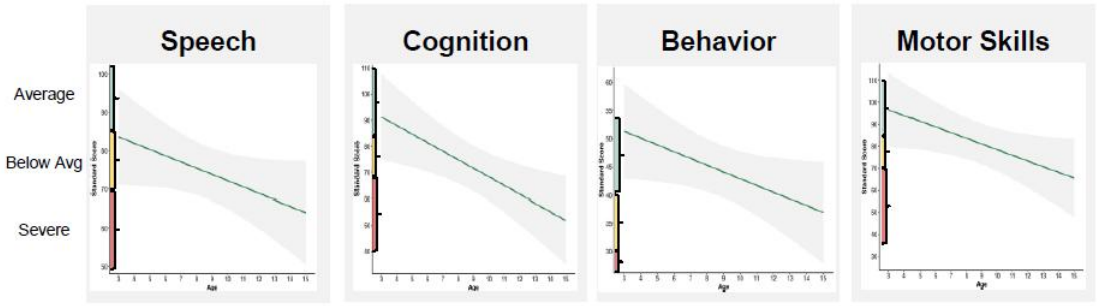

- **CNS C**
  - Spe
  - Cog Mer
  - Beh
  - Mot Ata
  - Sei
- **Other**
  - Ova
  - Cat



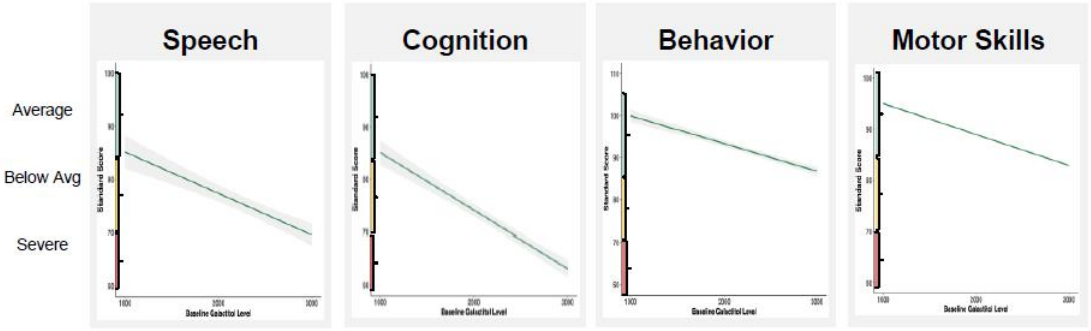
AR = Aldose Reductase

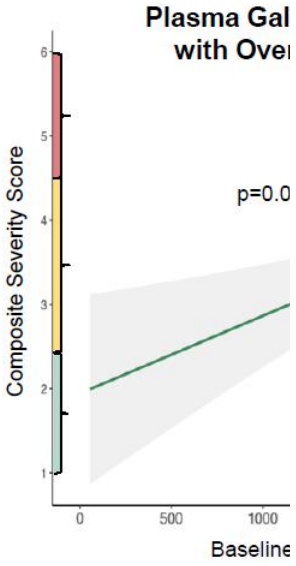
# Natural History: Galactosemia is a Progressive Disease with Age; Disease Severity Correlates with Plasma Gala

**Natural history of disease demonstrates progressive worsening with age**




**Baseline galactitol level correlates with severity of clinical functional outcomes**




*Overall severity based on con

***No correlation d and d***

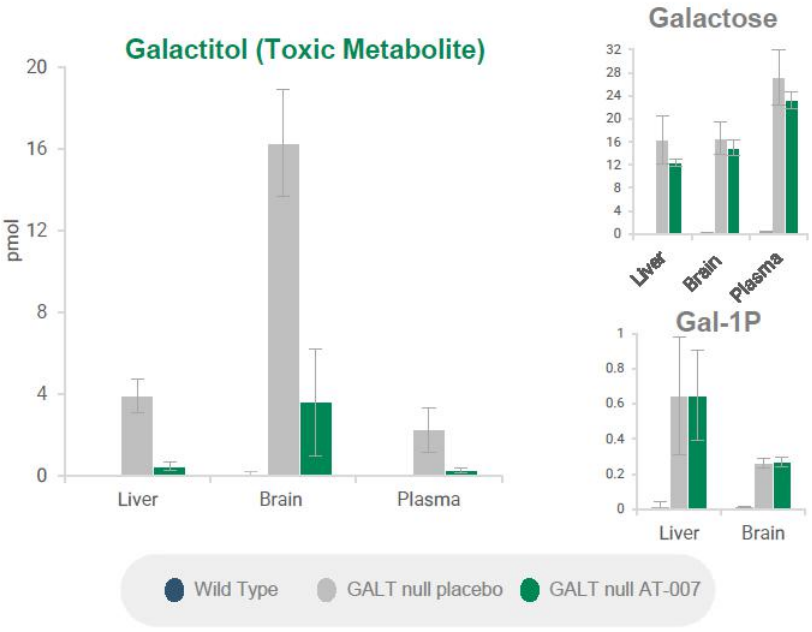


Abstract eP011: Progressive Worsening of Central Nervous System Phenotype in Children with Classic Galactosemia: a Cross-Sectional Analysis; ACMG 2021 conference; Per
Disease Severity in Children with Classic Galactosemia on Galactose Restricted Diet. Poster presented at: International Congress Inborn Errors of Metabolism Annual Meeting;

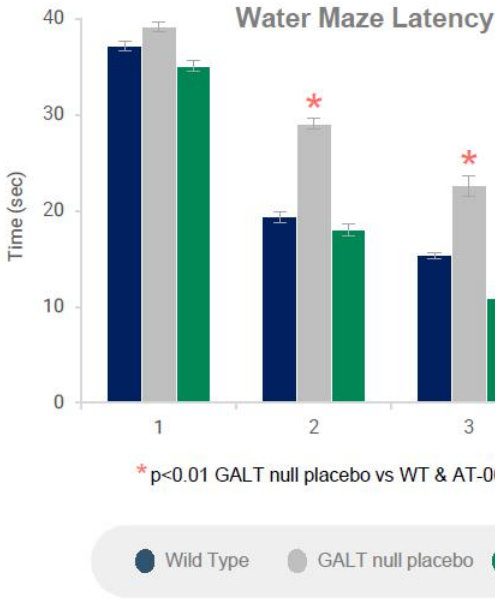
PRE-CLINICAL

# In a Rat Model of Galactosemia, AT-007 Significantly Reduced Galactitol Levels in All Target Tissues and Normalized the CN

**AT-007 treatment decreased galactitol levels in liver, brain and plasma; no compensatory increase in galactose or Gal-1p**



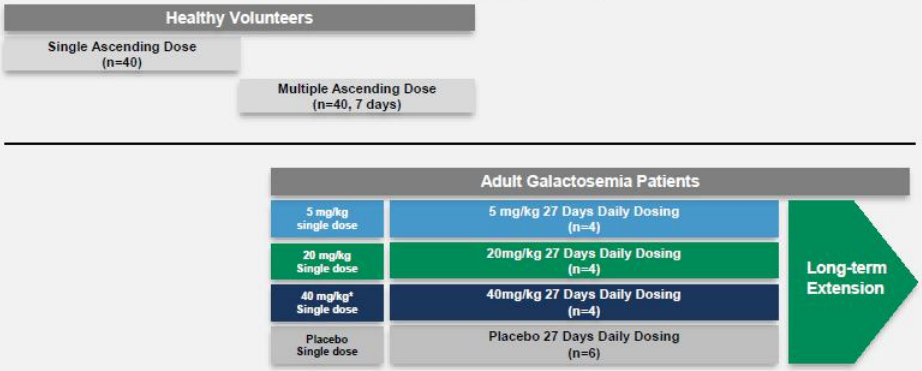

**AT-007 treatment normalized Cl on both water maze and r**




* p<0.01 GALT null placebo vs WT & AT-0

# AT-007 Significantly Reduced Galactitol Levels in the G
# Adult Phase 1/2 Study (ACTION-Galactosemia); Safe an

## Adult Phase 1/2 Study Design



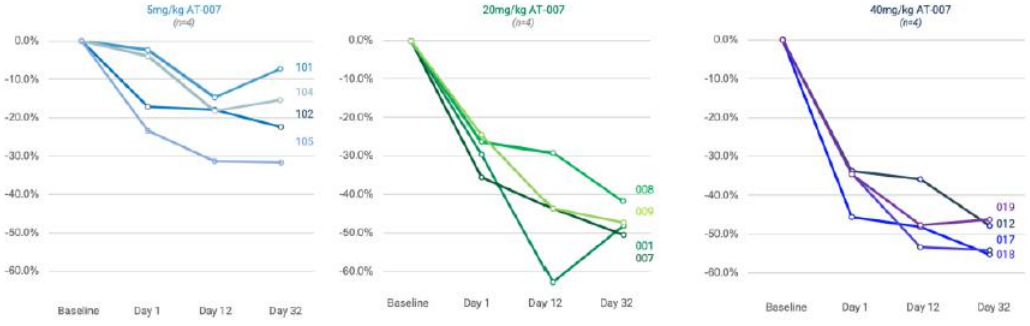

### Safety

- Favorable safety and tolerability

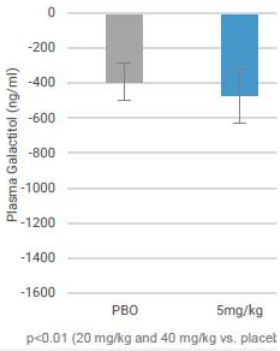
### Pharmacokinetics/ Pharmacody

- 20mg/kg dose selected as optim
- PK supports once-daily dosing
- Rapid, sustained and significant
- Galactitol reduction in the brain
- No compensatory increase in ga

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

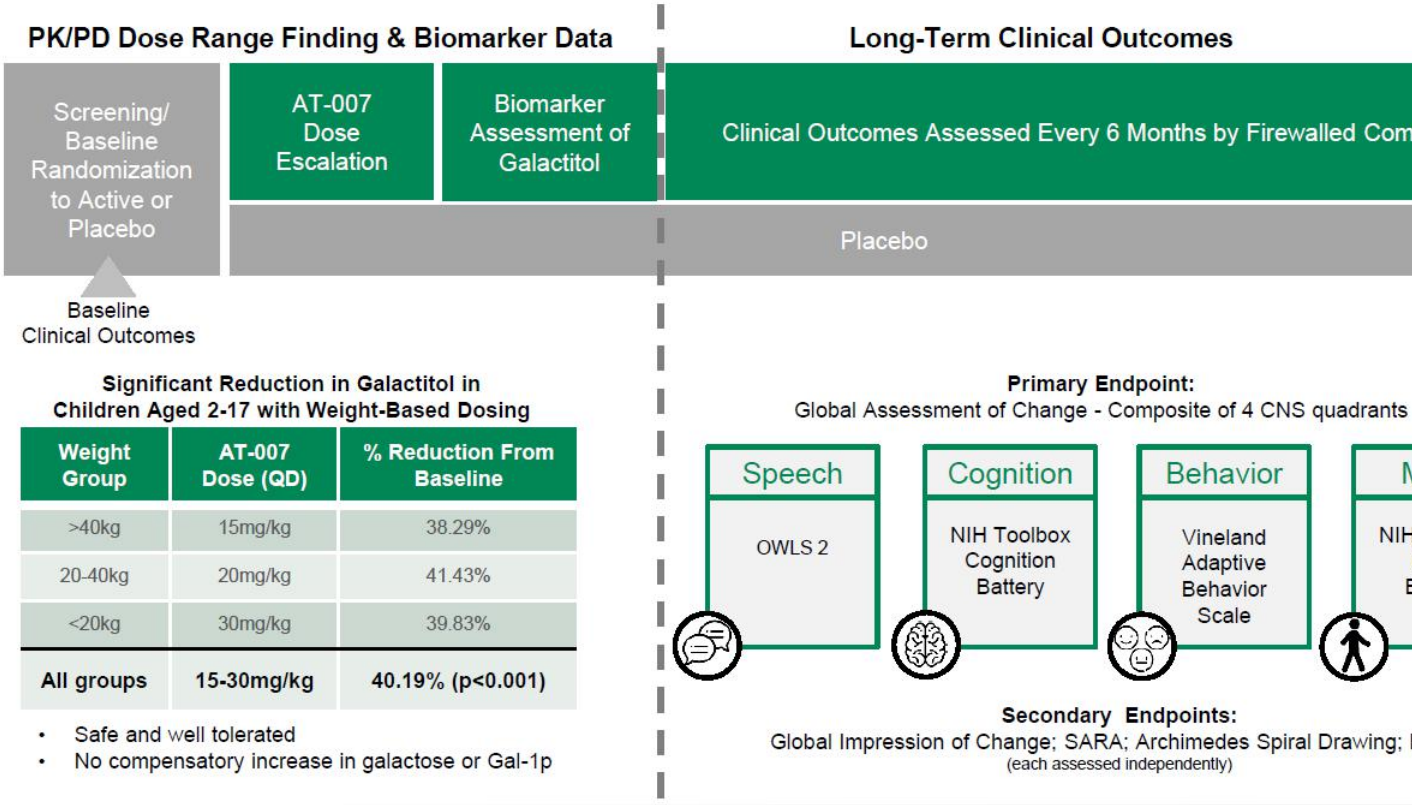



## Maximum Galactitol R




APPLIED THERAPEUTICS

# AT-007 Significantly Reduced Galactitol Levels in the A
# Galactosemia Kids Pediatric Registrational Clinical Stu




**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

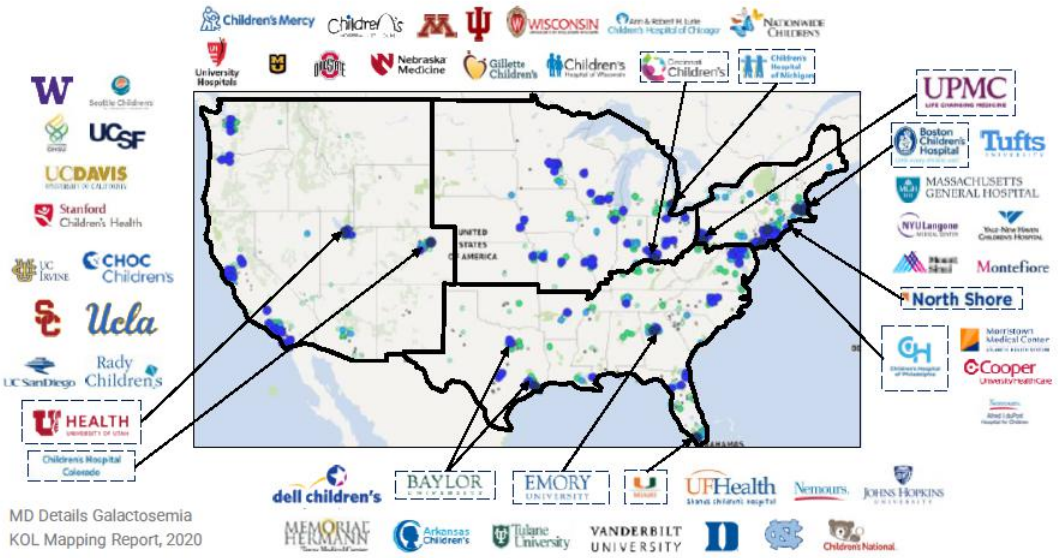
**Primary Endpoint:**
Global Assessment of Change - Composite of 4 CNS quadrants




**Secondary Endpoints:**
Global Impression of Change; SARA; Archimedes Spiral Drawing;
(each assessed independently)

# Commercial Preparations On-Track for U.S. Galactose

## U.S. Map of Galactosemia KOL Medical Genetics Centers of Excellence (COEs)*




MD Details Galactosemia KOL Mapping Report, 2020

## Commercialization Prep Optimized Launch at Ap

- Sales force segmentation mapping completed; focu
- Claims Data Analysis sup patients
- Cross-functional brand pl awareness, trial, usage o
- Market research shows s treatment
- Single-source Specialty F ready to begin infrastructu
- Payer research indicates rare-disease level pricing

APPLIED THERAPEUTICS

* >90% of KOLs are Medical Geneticists; Pediatricians comprise majority of remaining KOLs

# Award Winning DSA Campaign Performance Reflects U
# Strong Demand for Galactosemia Education and Treatm

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 Gala & 3D M**

**48,0** com video

## Awards





APPLIED THERAPEUTICS

Metrics as of December 2021; DSA = Disease State Awareness

# AT-007

# SORD DEFICIENCY

- Orphan Drug Designation

Preclinical proof of concept demonstrated

Positive pilot study completed

Registrational Phase 2/3 study ongoing

# SORD Deficiency is a Rare Neurological Disease with I 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/ Dia

- No approved therapies to treat SO
- Genetic testing commercially avail
- Prior to 2020, patients were diagn as CMT2 or dHMN; new screening categorizing CMT2/dHMN patients
- Primarily treated by neurologists/ n specialists at Inherited Neuropathy 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

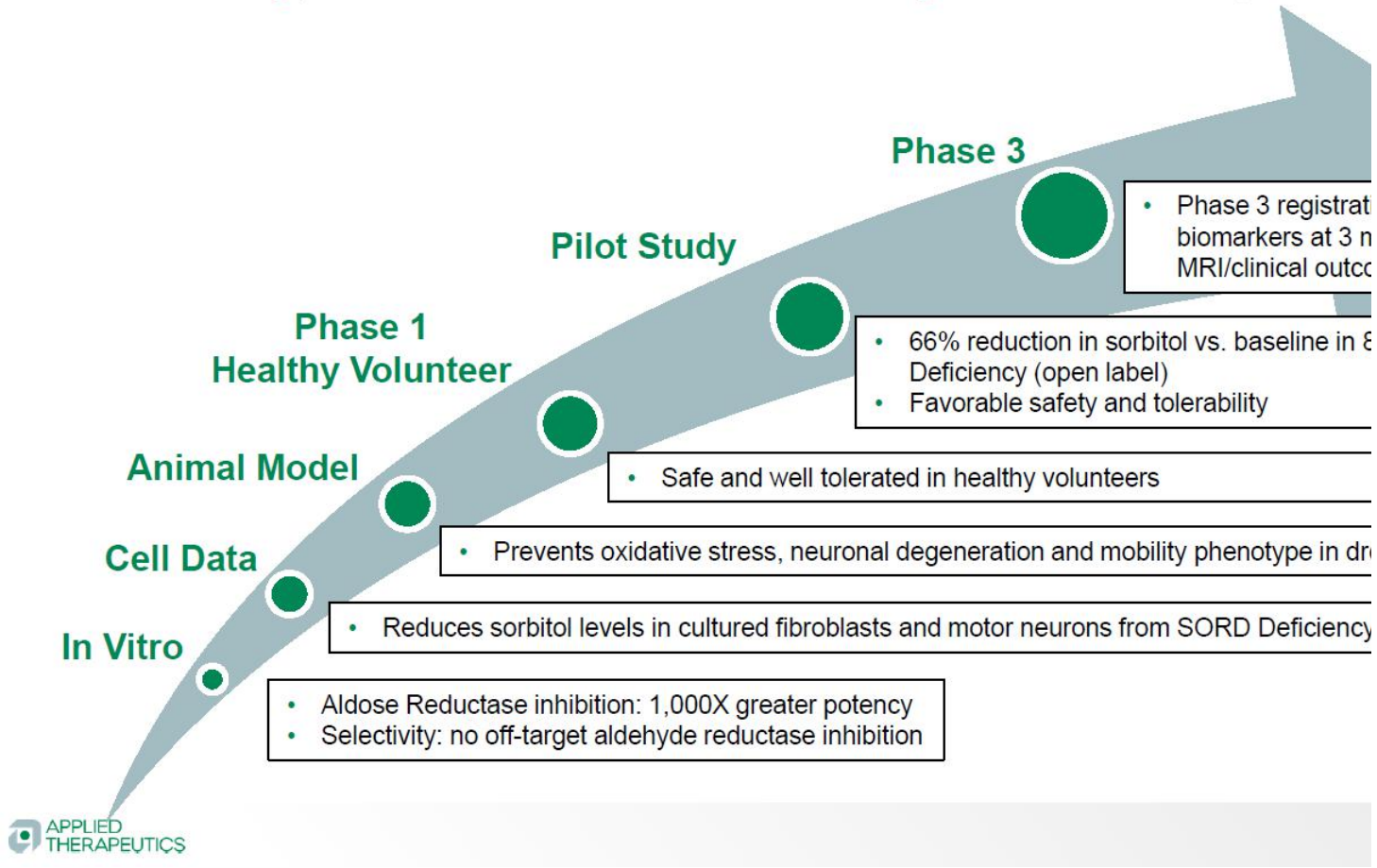
### Market Size/ Oppor

- $1.9B+ WW peak sales potential,
- ~3,300 individuals in the US with S 7,000 US+EU combined
- Small commercial footprint focuse
- Strong patient community engage
- Payer feedback supports access/p
- Composition of matter IP through 2 treatment of SORD Deficiency thro

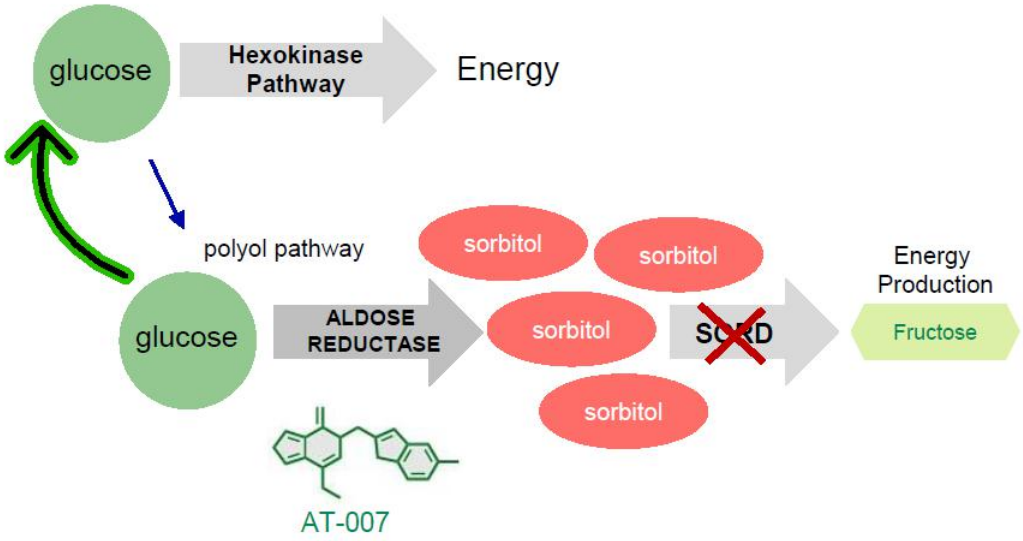
APPLIED THERAPEUTICS

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, an
# Pilot Study; Phase 3 Biomarker Data Expected in 2022; Outc



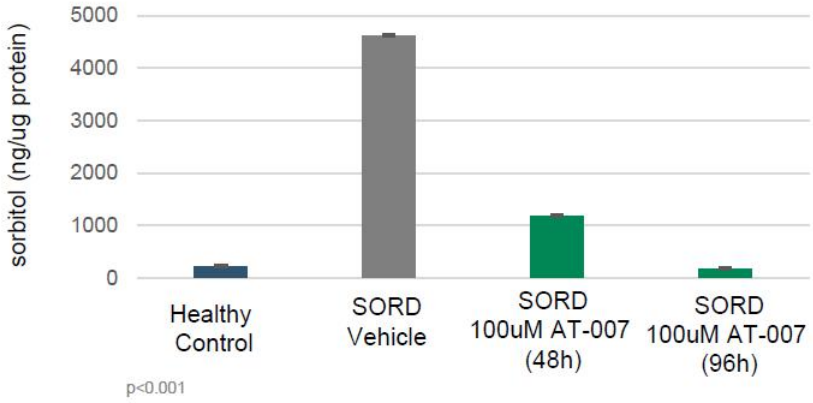
# Aldose Reductase Inhibition Addresses the Underlying SORD Neuropathy by Preventing Conversion of Gluco




- People with SORD
  the SORD enzyme
  Reductase in the p
  - As a result,
    Deficiency a
    metabolize s
  - Sorbitol accu
    and tissues
  - High toxic so
    cell death ar
    leading to ne

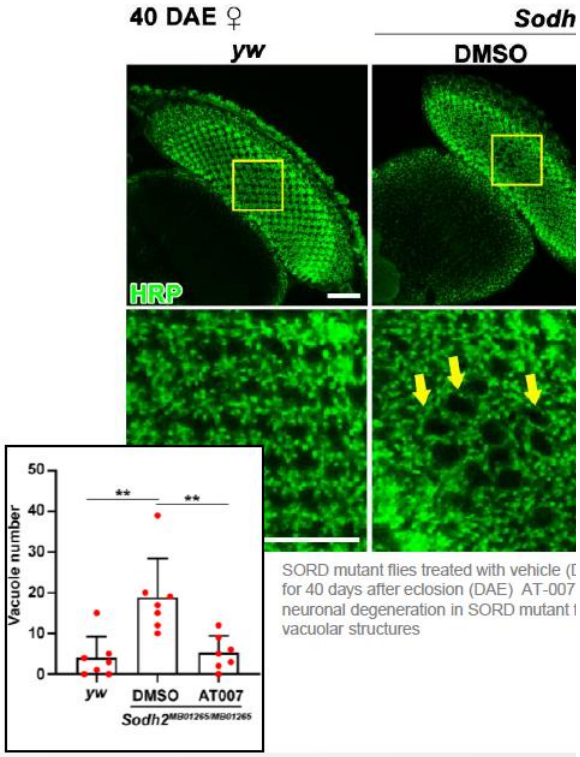
# AT-007 Treatment Reduces Sorbitol Levels in SORD Pa
# Prevents CNS Phenotype in a Drosophila SORD Deficie

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




- Cultured fibroblasts from SORD patients accumulate sorbitol levels up to 100X higher than healthy controls
- Treatment with AT-007 in culture significantly reduced sorbitol levels

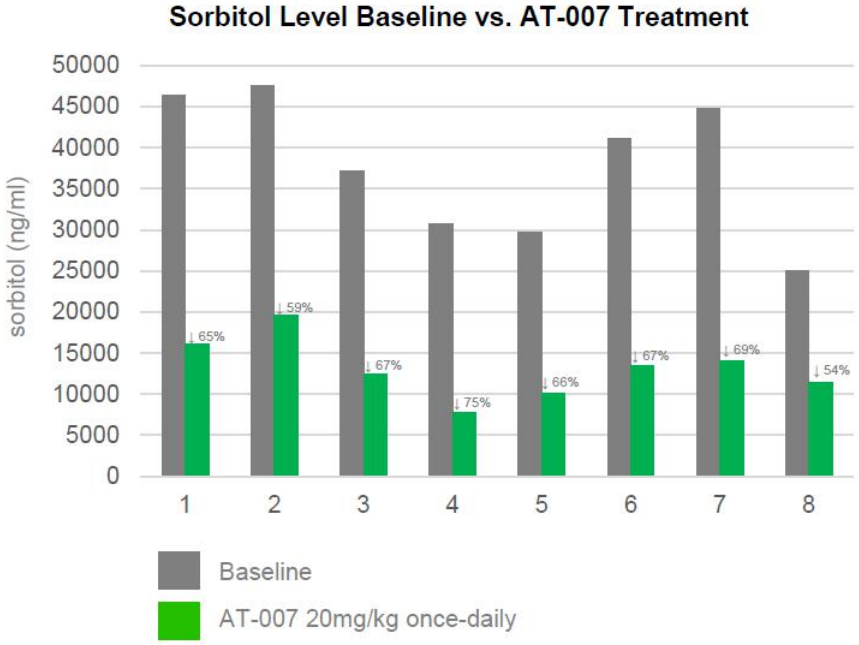
## AT-007 Prevents the SORD Disease P




SORD mutant flies treated with vehicle (D
for 40 days after eclosion (DAE) AT-007
neuronal degeneration in SORD mutant
vacuolar structures

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

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




Mean baseline sorbitol level was ~38,000ng/ml; individual % reduction from baseline noted above green bar

## Safety

- AT-007 safe and well tol

## Pharmacokinetics/ I

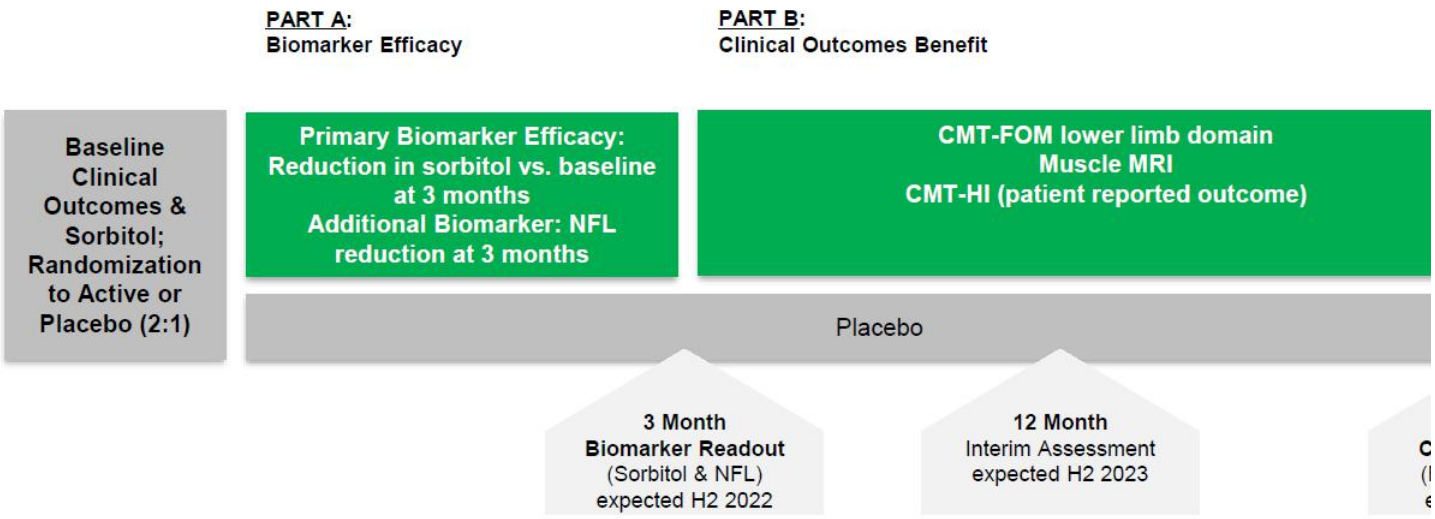
- Rapid and sustained rec
- No compensatory increa

APPLIED THERAPEUTICS

PHASE 2/3

# SORD Neuropathy Phase 2/3 Registrational Study (INSP

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



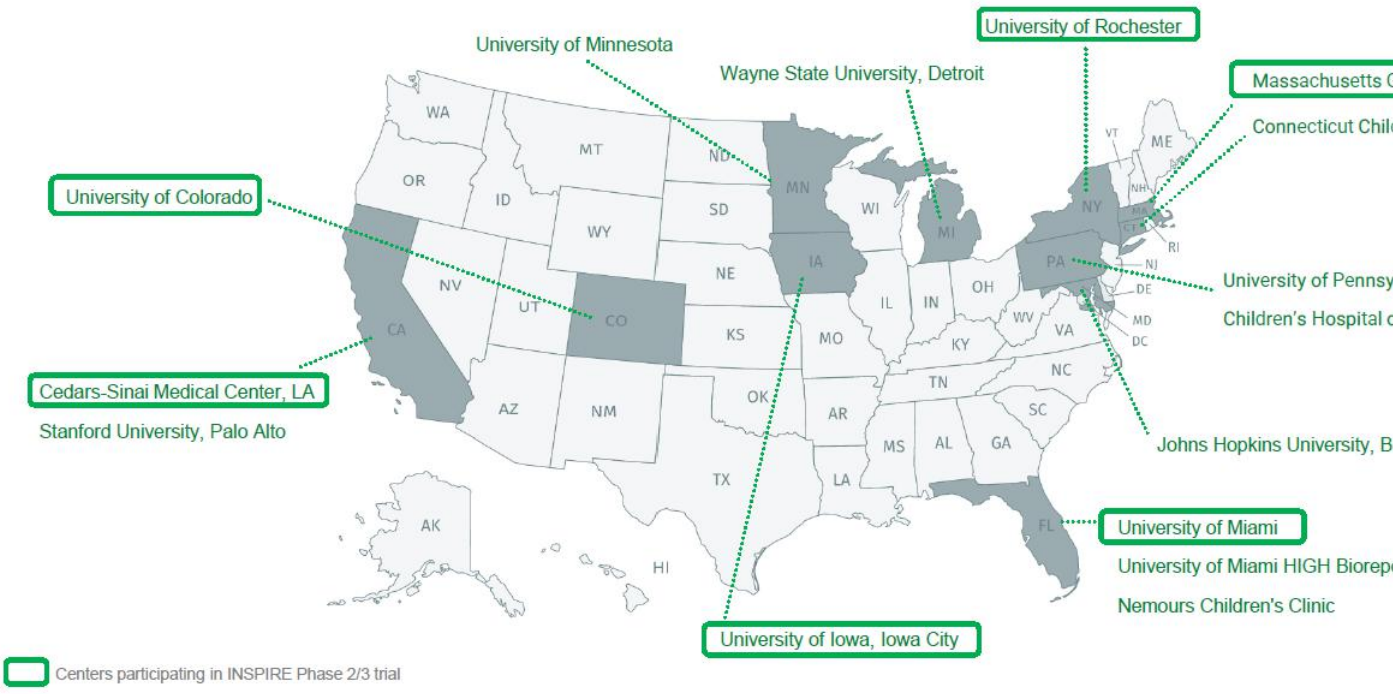

Global clinical sites: US, EU, UK

*CMT-FOM lower limb domain includes: 10m walk/run; timed stairs; timed up-and-go



CMT = Charcot-Marie-Tooth, FOM = Functional Outcomes Measure, HI = Health Index, MRI = Magnetic Resonance Imaging

# Inherited Neuropathy Consortium Centers of Excellenc
# CMT Registries Exist to Support Trial Enrollment & Trea

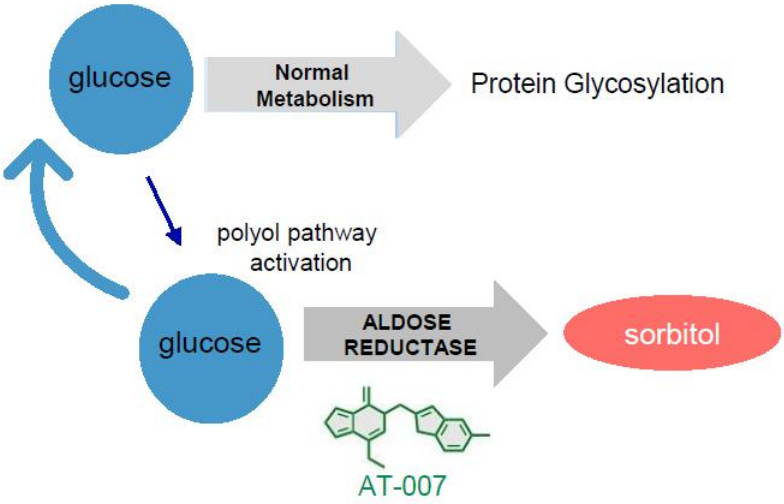


# PMM2-CDG

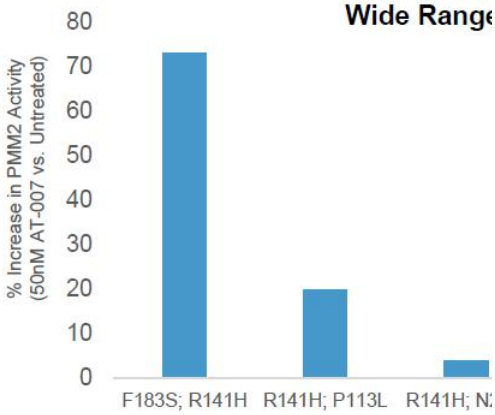
## Aldose Reductase Inhibition Improves PMM2 Act
## AT-007 Granted Orphan & Pediatric Rare Disease
## PMM2-CDG; Single-Patient IND Open – Phase 2 F

**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 Incr**
**Wide Range**




- AR inhibition blocks the polyo glucose flow through normal r
  - Promotes proper balance necessary for protein glyc
  - Results in increased PMM glycosylation

***High unmet need with no ap***
***cases WW, 20% int***

APPLIED THERAPEUTICS

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 Affe of Diabetics; Significant Unmet Need with No Approved

### 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 progression to overt heart failure/ de
- Once DbCM patients have develope eligible for standard HF therapies in 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

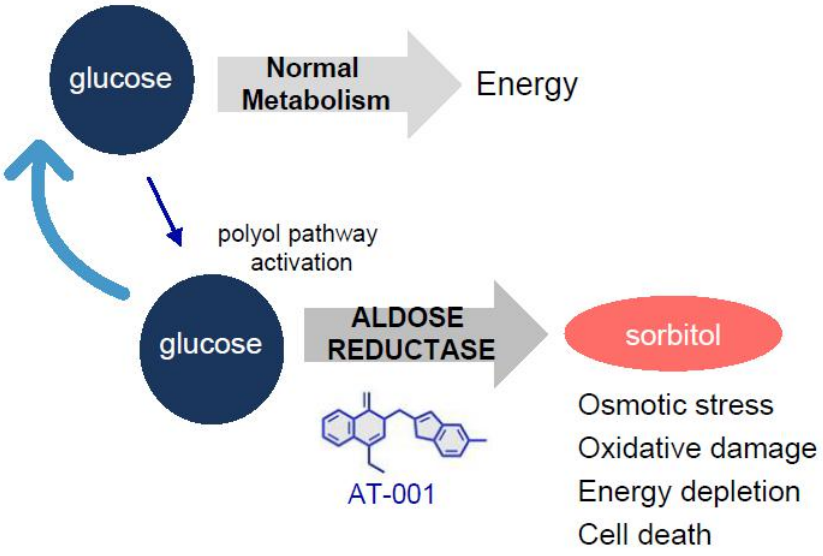
### Market Size/ Opportu

- Blockbuster potential
- Addressable population of ~6M patie
- Anticipated pricing in line with Entres
- Composition of matter IP through 20

APPLIED THERAPEUTICS

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 hyp
pathway is then hyperactivated to rid the body c

Aldose Reductase, the first and rate limiting enz
converts this glucose into sorbitol and eventuall

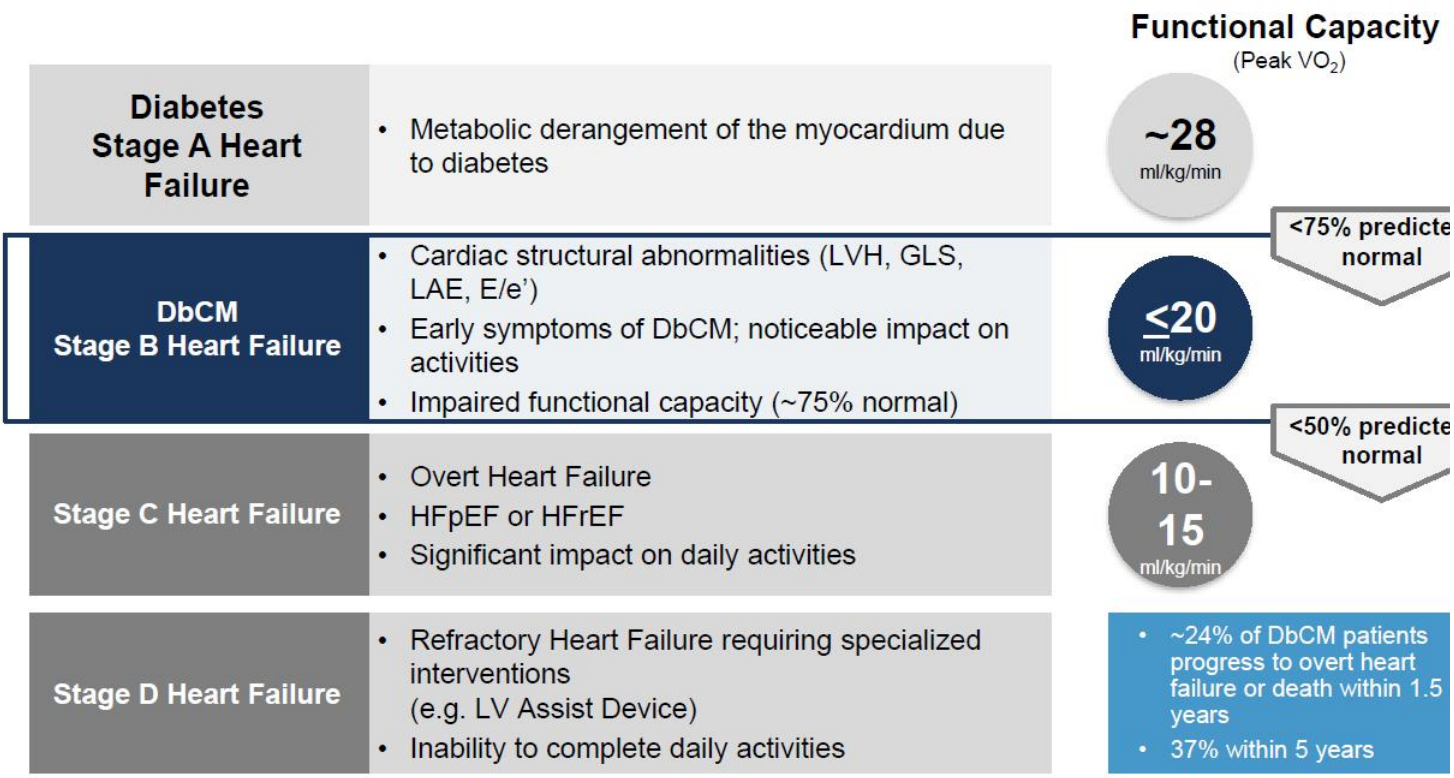
Excess sorbitol and fructose cause several dow
in cell death, including osmotic dysregulation ar

AR activation also detracts glucose from the en
hexokinase/glycolytic pathway, resulting in less
cardiomyocytes

This results in heart fibrosis, a “hardening” of th
means it cannot effectively pump blood to the re


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

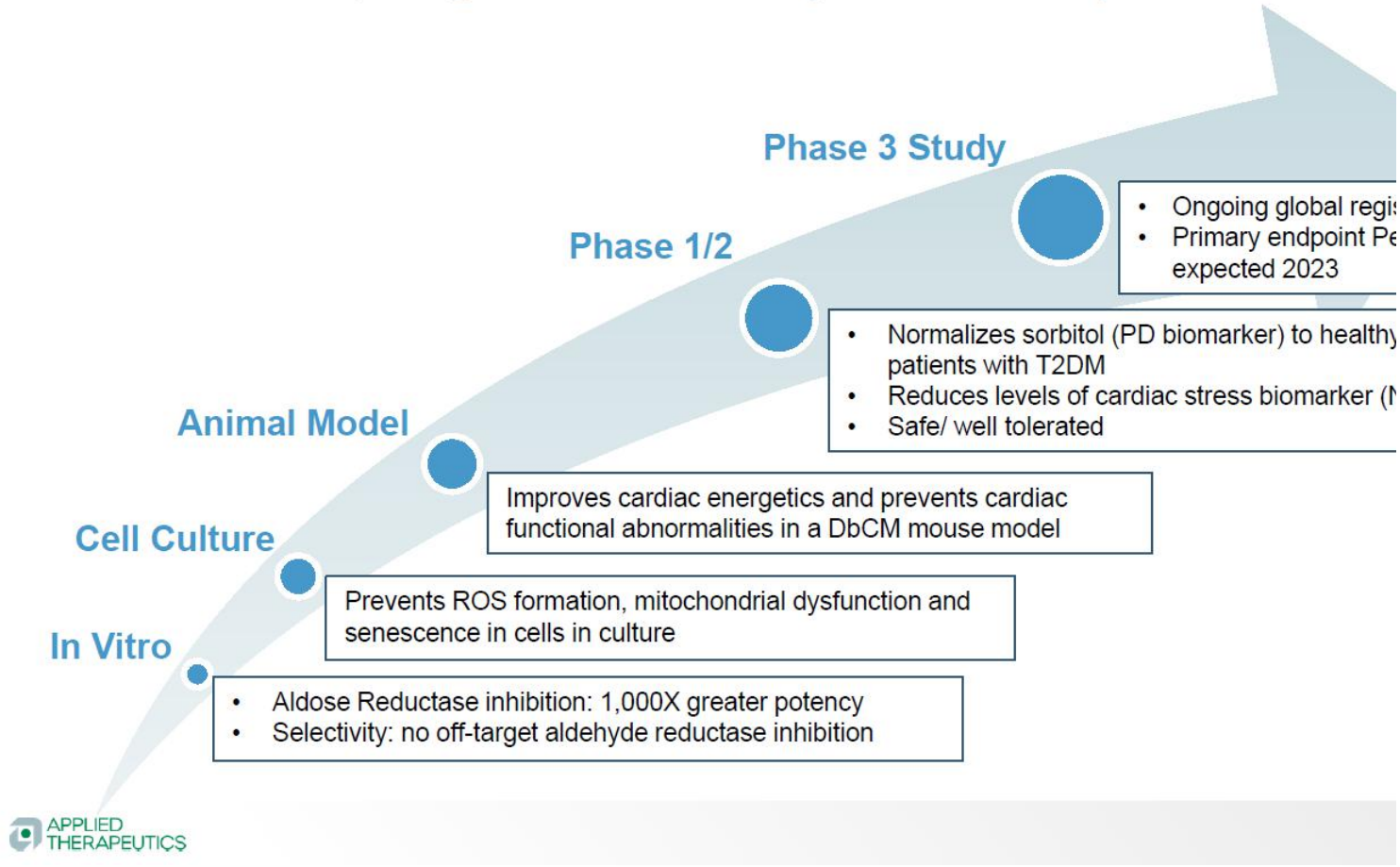
# Diabetic Cardiomyopathy is a Form of Stage B Heart Fa




APPLIED THERAPEUTICS

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

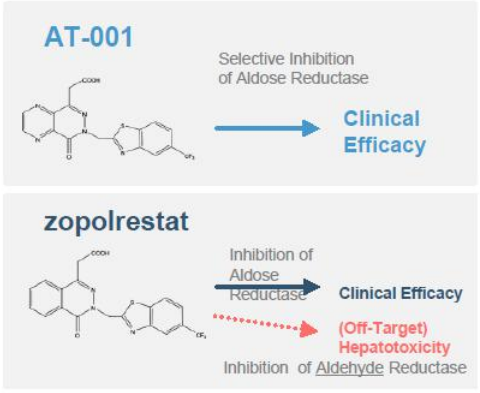
# AT-001 Has Demonstrated Effectiveness In Vitro, In Vivo, and Clinical Trials; Registrational Study Readout Expected 2023



PRE-CLINICAL

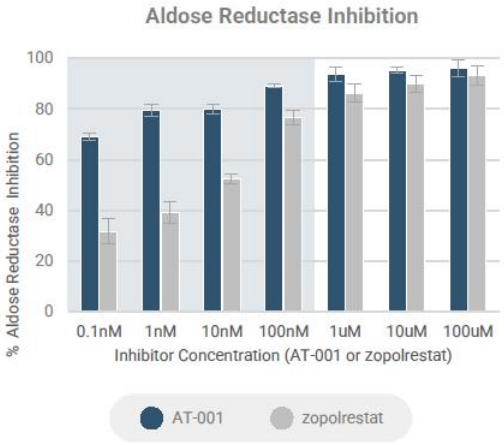
# In Vitro: AT-001 Provides Greater Potency and Improve Selectivity vs. "Old" Aldose Reductase Inhibitors

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

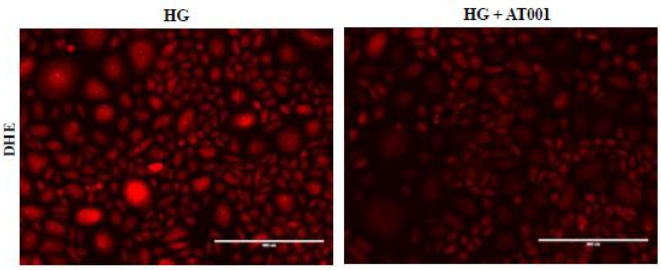


Poster # 632: "Addressing safety and specificity with aldose reductase inhibition: development of AT-001 for diabetic cardiomyopathy" 56th Annual Meeting of the European Association for the Study of Diabetes (EASD) Sept 2020

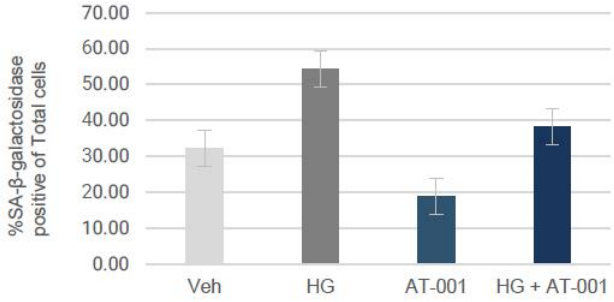
PRE-CLINICAL

# AT-001 Treatment Prevents Reactive Oxygen Species G
# Mitochondrial Stress & Cell Aging Caused by High Gluc

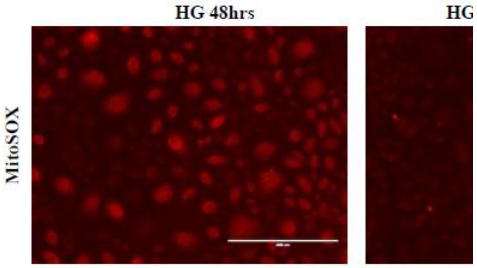
## Dihydroethidium (DHE) Staining for Cytosolic ROS




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




## MitoSOX™ Staining for Mitocl




**HG**- NHK cells exposed to 25mM glucose (high glucose)
**HG + AT-001** - cells treated with 0.18nM AT-001 along w

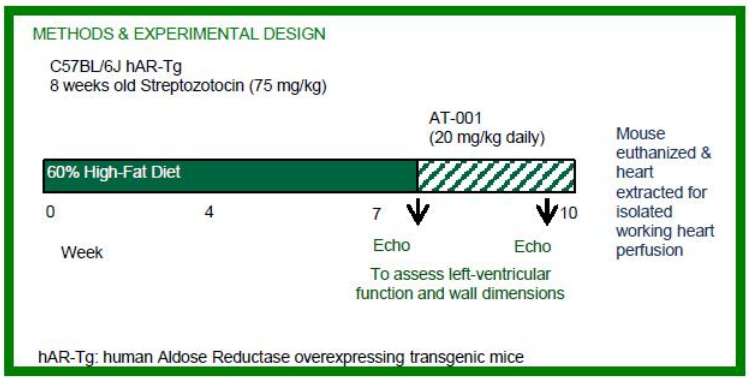
- In patients with diabetes, metabolism of glucose in generation of Reactive Oxygen Species (ROS key mediator of tissue damage and causal in dia inhibition of AR reduces oxidative stress and mit
- AT-001 prevents the production and accumulatio DHE quantitation and MitoSOX™ staining, demo oxidative damage in the cytosol and mitochondri
- Evaluation of cellular aging via SA-β-gal staining exposed to high glucose in the presence of AT-0

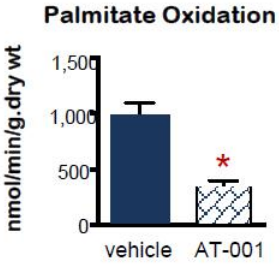
APPLIED THERAPEUTICS

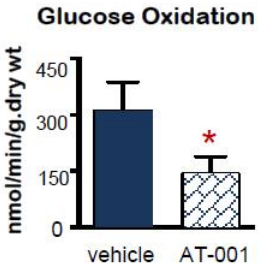
Poster #629: "AT-001 a new aldose reductase inhibitor with improved selectivity and specificity protects from cellular damage" 56th Annual Meeting of the European Associatio for the Study of Diabetes (EASD) Sept 2020

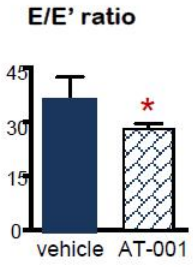
# AT-001 Prevents Abnormal Cardiac Energy Metabolism Heart Function in an Animal Model of DbCM

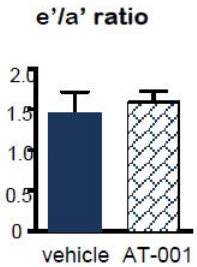
- AT-001 treatment prevents cardiac structural and functional abnormalities in a mouse model of DbCM, and normalizes cardiac energetics by shifting cardiac metabolism towards a non-diabetic metabolic state

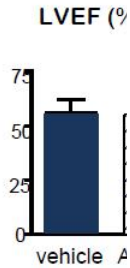


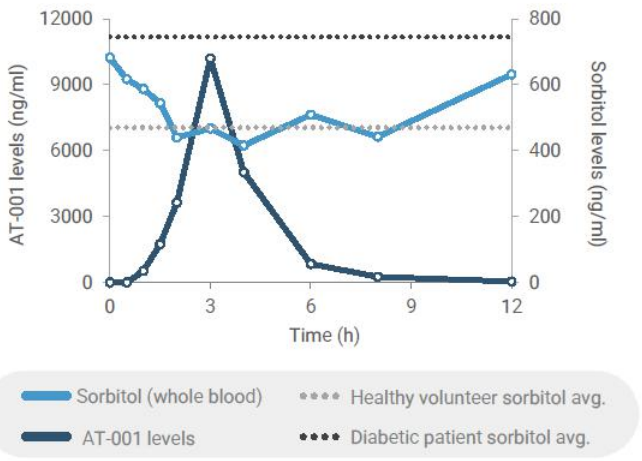




* = p<0.01

PHASE 1/2

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

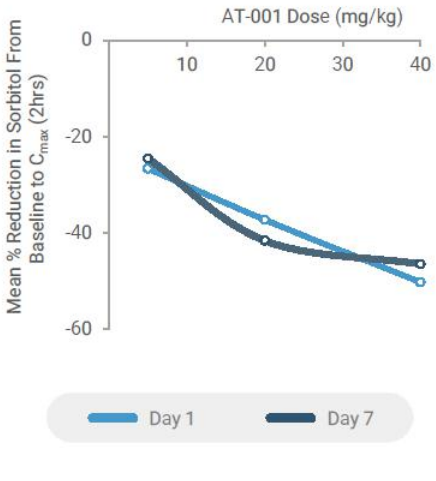
### Proof of Biological Activity




AT-001 normalized sorbitol in diabetics to healthy volunteer levels

No compensatory increase in glucose level

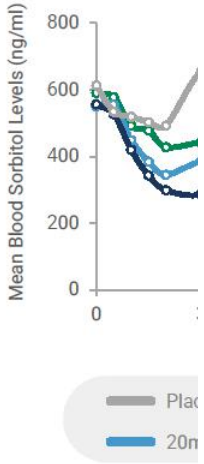
### Sorbitol Reduction by Dose




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 N



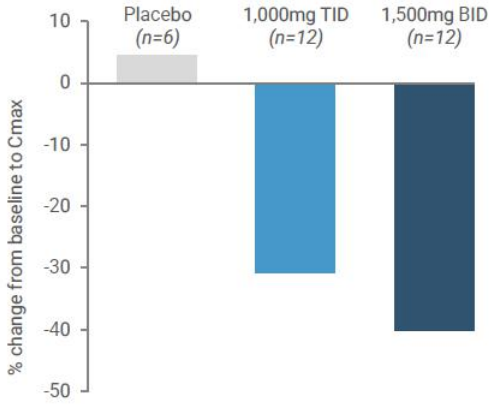

Rapid release cap
normalization effe
**10-12hrs post-do**

Includes protectio
during times of po

PHASE 1/2

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

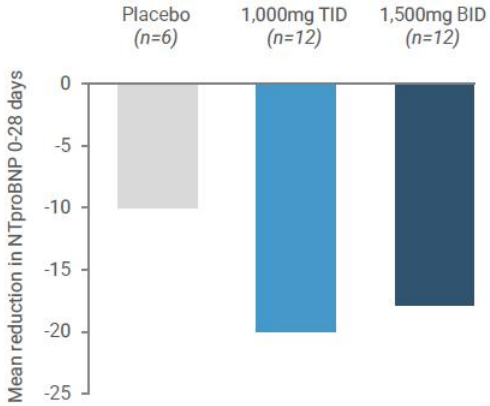
**Sorbitol Normalization**




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

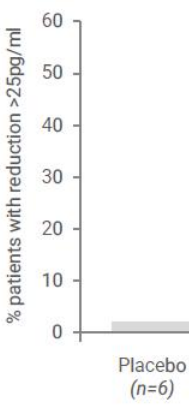
**Mean Reduction in NTproBNP**




Mean reduction in NTproBNP seen over 28 days vs. placebo

Mean baseline NTproBNP was 65pg/ml

**Clinic**



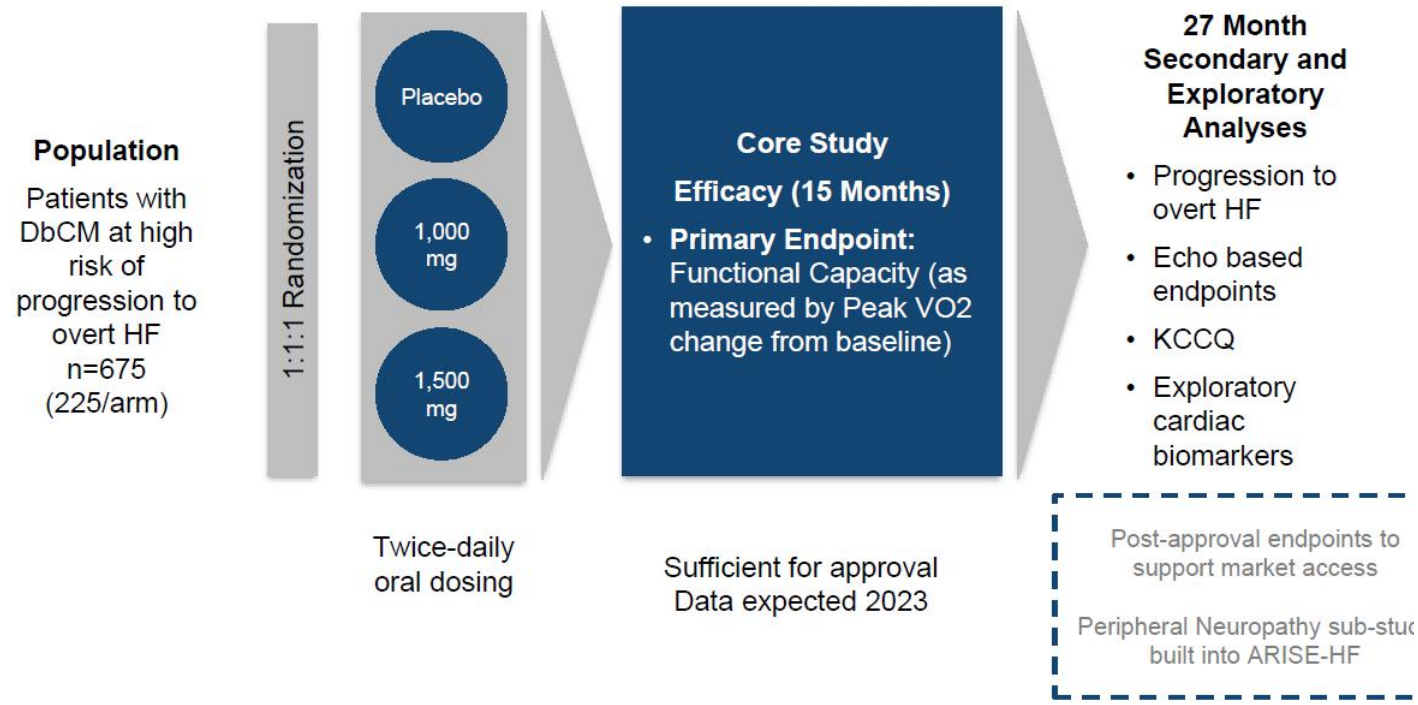

~50% AT-001
a clinically me
NTproBNP ov

>25pg/ml redu

PHASE 3

# DbCM Phase 3 Registrational Study (ARISE-HF)

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



# Key Projected Milestones by Program