**CORPORATE OVERVIEW JULY 9, 2020**

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# Investment Highlights

**2 Pivotal programs in high unmet need indications with near-term milestones**

- Positive Ph2 (pivotal) Galactosemia data announced April 2020; Pediatric trial underway; NDA expected ~YE 2020

- Diabetic Cardiomyopathy pivotal data expected 2021

**Distinct late-stage commercial opportunities**

- Galactosemia - easily commercialized orphan indication based on biomarker data

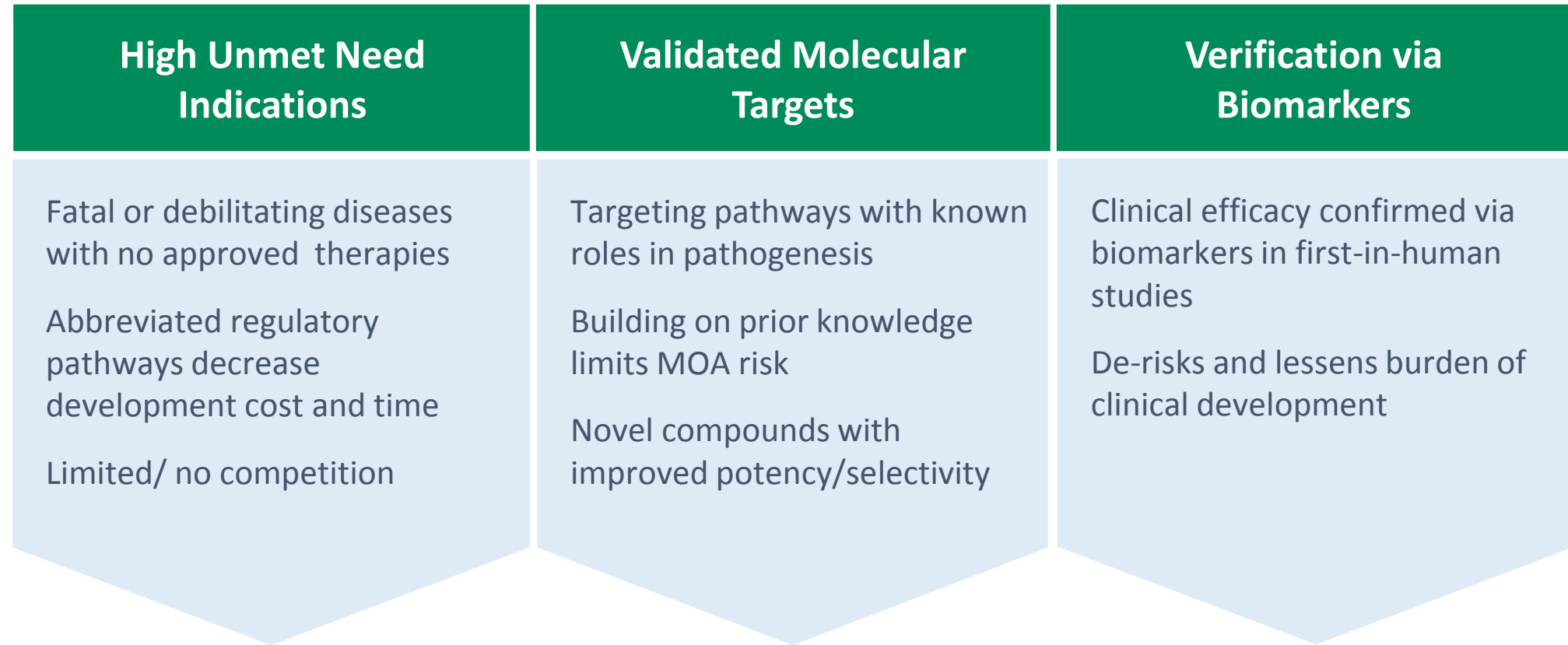- Diabetic Cardiomyopathy - potential blockbuster indication supported by deep science

**Reproducible discovery and development strategy**

- Additional rare metabolic diseases targeting aldose reductase (SORD Deficiency, PMM2-CDG)

- Early stage pipeline in orphan oncology indications targeting PI3k

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

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# Applying Science to Transform Lives

| High Unmet Need Indications | Validated Molecular Targets | Verification via Biomarkers |
|---|---|---|
| Fatal or debilitating diseases with no approved therapies<br><br>Abbreviated regulatory pathways decrease development cost and time<br><br>Limited/ no competition | Targeting pathways with known roles in pathogenesis<br><br>Building on prior knowledge limits MOA risk<br><br>Novel compounds with improved potency/selectivity | Clinical efficacy confirmed via biomarkers in first-in-human studies<br><br>De-risks and lessens burden of clinical development |

*We develop drugs quickly at a lower cost:*
*A significant benefit to patients in need of treatment*

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# Pipeline

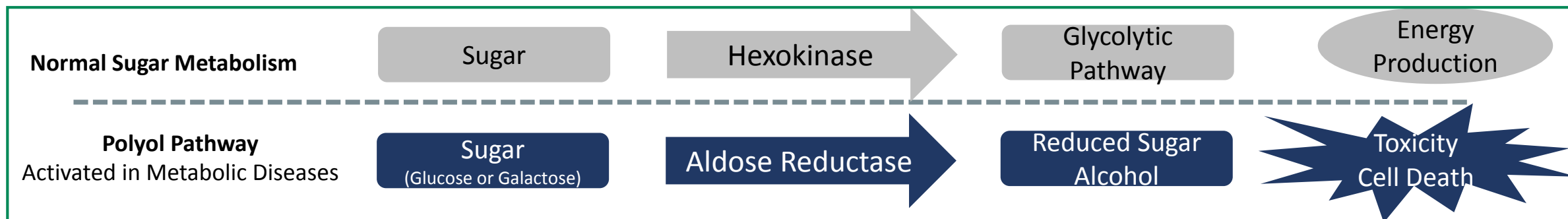| Compound | Preclinical | Phase 1 | Phase 2 | Phase 3 | Dosing Route | Target Tissue | Milestones |
|----------|-------------|---------|---------|---------|--------------|---------------|------------|

**Aldose Reductase Franchise**

| Compound | Preclinical | Phase 1 | Phase 2 | Phase 3 | Dosing Route | Target Tissue | Milestones |
|----------|-------------|---------|---------|---------|--------------|---------------|------------|
| AT-007 | Galactosemia – Pivotal Ph 2 Study | | | | Oral | CNS | Full results of pivotal Ph 2 adult ACTION-Galactosemia released; pediatric study initiated June 2020 |
| AT-007 | SORD Deficiency | | | | Oral | CNS | Phase 2 ready; clinical study start 2021 |
| AT-007 | PMM2-CDG | | | | Oral | CNS | Phase 2 ready |
| AT-001 | Diabetic Cardiomyopathy – Pivotal Ph 3 Study | | | | Oral | Systemic | Ph 3 trial initiated in Q3 2019; data in 2021 |
| AT-001 | Diabetic Peripheral Neuropathy | | | | Oral | Peripheral Nerve | Sub-study embedded in DbCM Ph 3 trial |
| AT-003 | Diabetic Retinopathy | | | | Oral | Retina | Preclinical data 2019; Initiate Ph 1 2021 |

**PI3 Kinase Franchise**

| Compound | Preclinical | Phase 1 | Phase 2 | Phase 3 | Dosing Route | Target Tissue | Milestones |
|----------|-------------|---------|---------|---------|--------------|---------------|------------|
| AT-104 | PTCL, CTCL, TALL* | | | | SC / Oral | Selective $\delta/\gamma$ inhibitor | Initiate Ph 1 2021 |

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

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# Unlocking the Potential of Aldose Reductase Inhibition Across Multiple Metabolic Diseases

**Normal Sugar Metabolism**

| Sugar | Hexokinase → | Glycolytic Pathway | Energy Production |

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**Polyol Pathway**
Activated in Metabolic Diseases

| Sugar (Glucose or Galactose) | Aldose Reductase → | Reduced Sugar Alcohol | Toxicity Cell Death |

**Validated Target Resistant to Therapeutic Development**
- AR known to play a key role in diabetic complications and heart disease
- Past efforts failed to produce sufficiently potent, selective and tolerable drugs

**Recent Advances Enable Improved ARI's**
- New understanding of structural changes within the active site of AR following enzymatic activation
  - Novel structures; all drugs are new chemical entities
- Increased potency and selectivity compared to prior compounds with none of the prior off-target safety issues to date

**R&D and Regulatory Opportunities**
- High unmet need in numerous AR-mediated diseases
- Leverage prior ARI programs for streamlined, abbreviated development of our novel compounds
- Potential to utilize regulatory pathways designed for accelerated drug development

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# AT-007 for CNS Rare Metabolic Diseases

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# AT-007 for CNS Rare Metabolic Diseases
## Galactosemia, SORD Deficiency, PMM2-CDG

Glucose

Galactose

**Galactosemia**

GALK
GALT

🚫 **AT-007**
Aldose Reductase

[chemical structure with S, N, CO₂H, CF₃ labels]

Sorbitol (toxic)

Galactitol (toxic)

Reduced Sugar Alcohols

SORD

**SORD Deficiency**

Fructose

**PMM2-CDG**

PMM2

Mannose-1-P

Protein Glycosylation
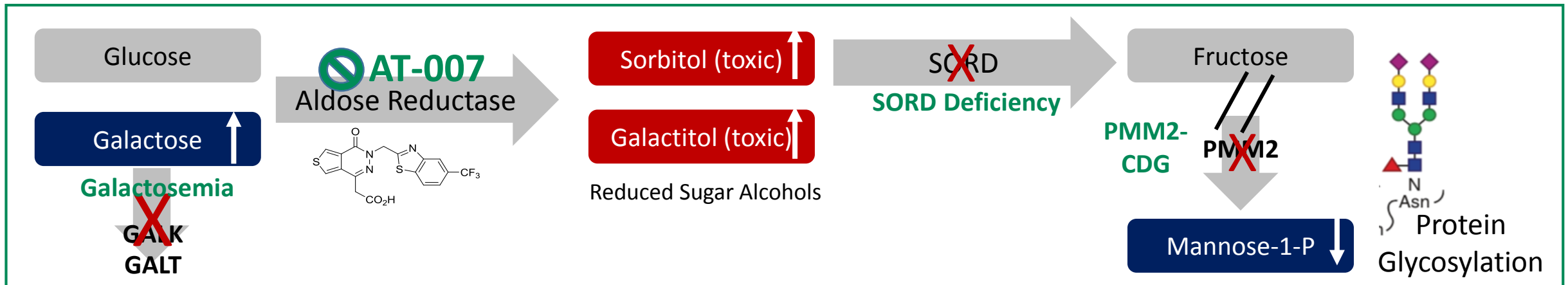
| Galactosemia<br>(pivotal study complete) | SORD Deficiency<br>(biomarker Ph 2 pivotal study 2021) | PMM2-CDG<br>(Ph 2 ready) |
|---|---|---|
| • GALT/ GALK deficiency (enzymes required for galactose metabolism)<br><br>• Results in galactitol formation (aberrant metabolite of galactose)<br><br>• Galactitol toxicity results in CNS complications (cognitive, motor, seizures, tremor) & cataracts<br><br>• ~2,900 patients in US (~7,000 worldwide) | • Deficiency in Sorbitol Dehydrogenase (SORD)[1]<br><br>• High sorbitol levels (>1,000X)<br><br>• Sorbitol toxicity results in severe peripheral neuropathy and motor neuron disease<br><br>• 3,500-5,000 patients in US (~10,000 worldwide) | • Decreased PMM2 enzyme activity (catalytic site or dimerization mutations)[2,3]<br><br>• Decreased protein glycosylation results in systemic and CNS complications; severe disease<br><br>• Polyol pathway (AR) feeds into glycosylation pathway<br><br>• ~1,000 patients worldwide |

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1. Cortese et al Nature Genetics 2020; 2. Morava editorial Nature Genetics 2020; 3. Iyer et al Disease Models & Mechanisms 2019

# Galactosemia

## Pathogenesis of Disease

- Rare genetic metabolic disease caused by inability to break down galactose

- Galactose is a sugar produced naturally by the body

- **In patients with Galactosemia, Aldose Reductase converts galactose to galactitol, an aberrant toxic metabolite**

- Clinical presentation:
  - Significant CNS complications - motor, speech, cognitive, and psychiatric impairments, tremor, and seizures
  - Cataracts
  - Ovarian insufficiency in females

## Standard of Care

- Mandatory newborn screening and initiation of dairy free diet; dietary restriction prevents fatalities, but **does not prevent long term consequences of disease**

- No approved therapies

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# Galactosemia Commercial Opportunity

- **Easily identifiable patients & substantial population**

- Newborn screening and patient registry

- "Low Prevalence" but not ultra-rare

  - ~2,800 US patients; ~3,500 patients in Europe; supported by newborn screening peer reviewed publications and 3rd party epidemiology studies[1]

  - ~80 new births per year in the US; more in Europe

- **Low burden of development due to biomarker-based program under new FDA guidance**

- **Opportunity to launch quickly with high market penetration; comparatively low commercial investment required**

  - >90% patients seen by ~20 specialists worldwide

  - High prescriber awareness of Applied clinical development program

1. Reference: Pyhtila et al. Newborn Screening for Galactosemia. JIMD. 2014.pdf; Decision Resources Group epidemiological assessment data on file

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# AT-007, a CNS-Penetrant Novel Aldose Reductase Inhibitor, Prevents Galactitol Formation and Accumulation

Galactose

TYPE II
**GALK**

Gal-1-Phosphate

Classic Galactosemia
**GALT**

Glu-1-Phosphate

**AT-007**
Aldose Reductase

Galactitol
Toxic Aberrant Metabolite

Sorbitol Dehydrogenase

Sorbitol dehydrogenase, the next enzyme in the polyol pathway, can't reduce galactitol

- Galactosemia results in accumulation of galactose, which becomes an aberrant substrate for AR
- AR converts galactose to galactitol, which causes toxic complications in many tissues

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# AT-007 Treatment Corrects All 3 Aspects of Disease in the Galactosemia Rat Model

## Biochemical Effects

*AT-007 treatment significantly reduced galactitol levels in all tissues without increasing galactose or Gal1p*



Galactitol

Galactose

Wild Type | GALT null placebo | GALT null AT-007
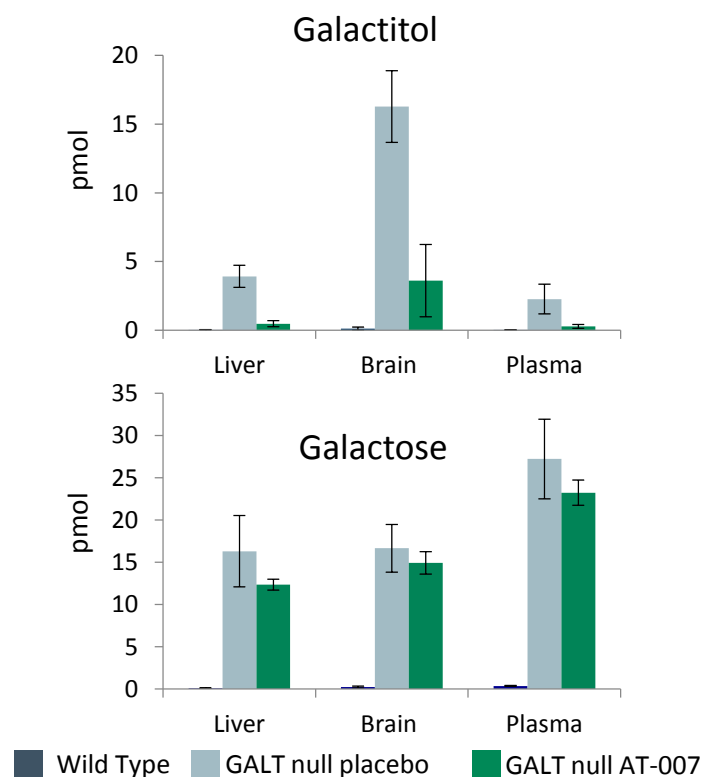
## Tissue Deposition of Galactitol

*AT-007 treatment prevented galactitol accumulation in tissues, resulting in absence of cataracts*



WT | GALT null (placebo) | GALT null AT-007

Cataract Quantitation AT-007 Dose Response
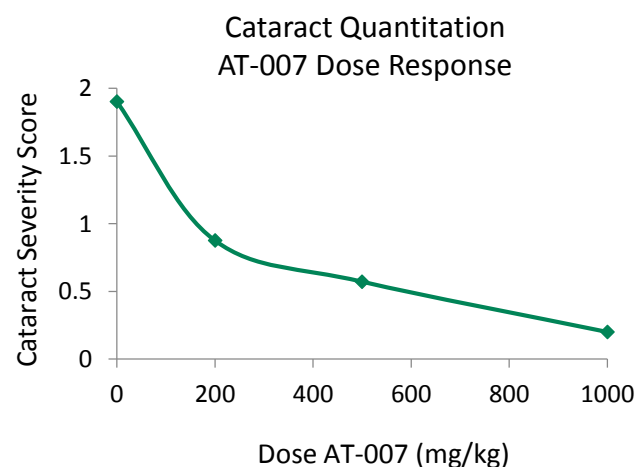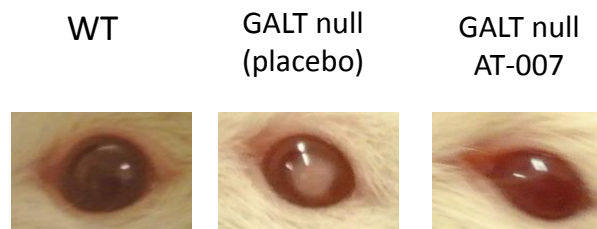
## CNS Outcomes

*AT-007 treatment normalized CNS outcomes on both water maze and rotarod*

Water Maze Latency



WT
GALT null placebo
GALT null AT-007
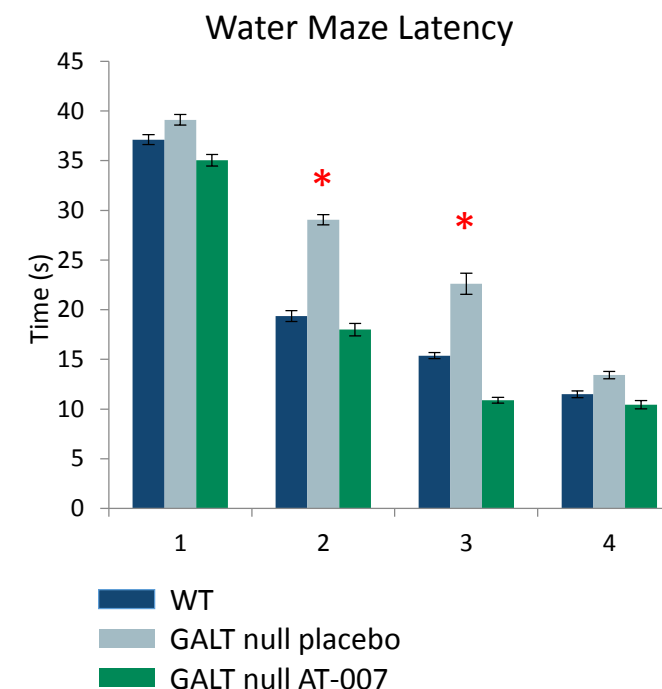
* Statistically significant vs. WT & AT-007 treated

Rats were on a lactose-restricted diet similar to humans; rat breast milk contains very low lactose levels; supplemented with soy formula; rat chow has low galactose levels similar to allowed foods such as legumes

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# A Closer Look: AT-007 Significantly Reduces Galactitol Levels in all Target Tissues Without Increasing Galactose or Gal-1P



Galactitol (Aberrant Toxic Metabolite)

Galactose

Gal-1P

Plasma vs. Brain Galactitol

R² = 0.9596
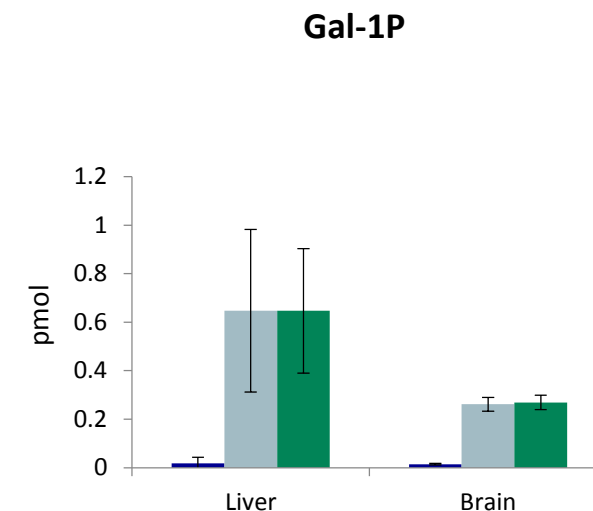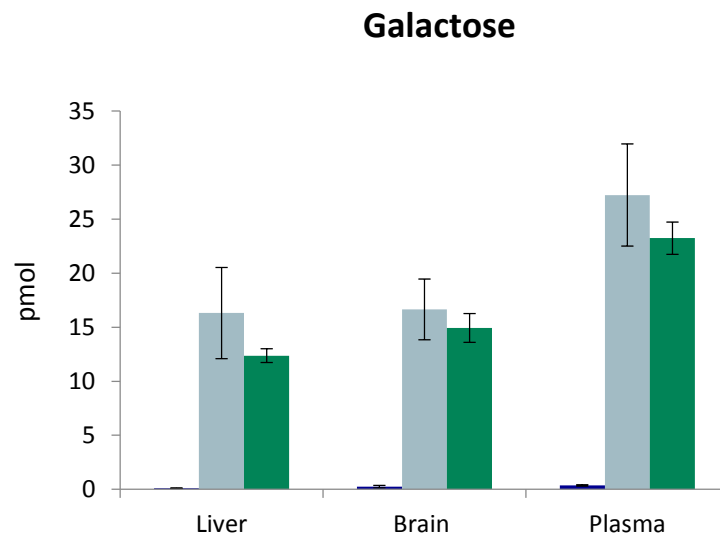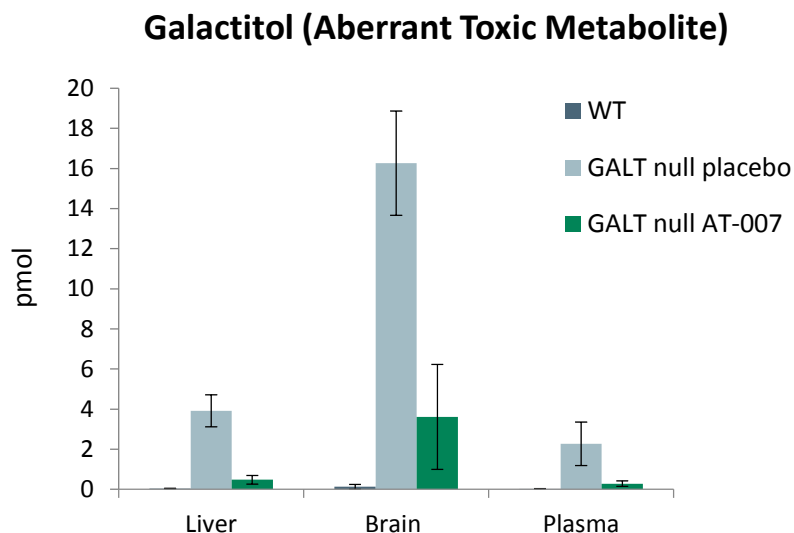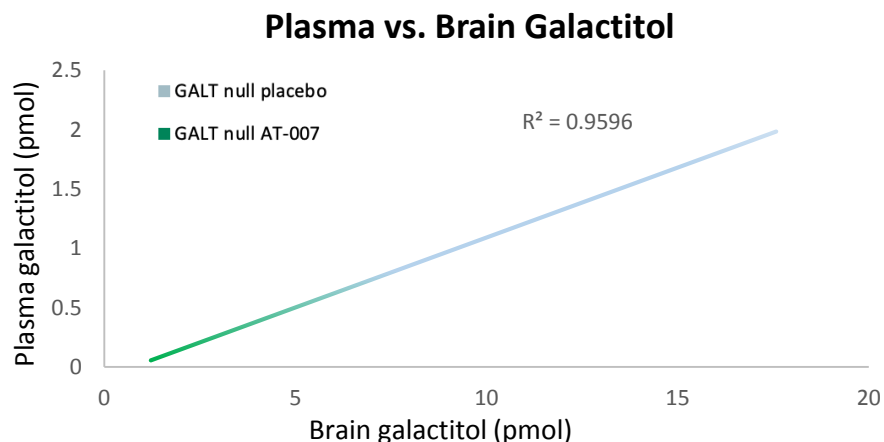
- AT-007 treatment from neonatal Day 1 to Day 10 significantly reduced galactitol in liver, brain and plasma

- AT-007 treatment did not increase galactose or Gal-1P levels; similar results seen at Day 22 and age 5 months

- Levels of galactitol in plasma and brain correlated in individual animals; reduction in galactitol induced by AT-007 treatment correlated in plasma and brain

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# Galactosemia Phase 1/2 Registrational Study (ACTION-Galactosemia)

Multi-Center Placebo-Controlled Study in Healthy Volunteers & Adult Galactosemia Patients

**Healthy Volunteers**

Single Ascending Dose
(n=40)

Multiple Ascending Dose
(n=40, 7 days)

Healthy Volunteer Endpoints:
- Safety
- Pharmacokinetics
- CNS Penetrance (via CSF sample)

Galactosemia Endpoints:
- Safety
- Pharmacokinetics/ Pharmacodynamics
- **Efficacy Biomarker - Galactitol**

**Adult Galactosemia Patients****

| | | |
|---|---|---|
| 5 mg/kg single dose | 5 mg/kg 27 Days Daily Dosing (n=4) | |
| 20 mg/kg Single dose | 20mg/kg 27 Days Daily Dosing (n=4) | 3 Month Extension |
| 40 mg/kg* Single dose | 40mg/kg 27 Days Daily Dosing (n=4) | |
| Placebo Single dose | Placebo 27 Days Daily Dosing (n=6) | |

*Based on initial topline data from Jan 2020, the study was expanded to include a 40mg/kg dose in healthy volunteers and then Galactosemia patients. This cohort also included 2 additional placebo patients

**Due to the small size of the population and burden of study participation (travel, missed work for caregivers  etc), the protocol proactively allowed for patients to participate in more than 1 cohort. If participating in a second cohort, the patient had to remain blinded, washout for $\geq$ 1 month, and a new baseline was taken. (Crossover design is in line with FDA guidance)

Patients were on lactose-restricted diet prior to enrollment and throughout study

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# AT-007 Significantly Decreased Galactitol Levels; Safe and Well Tolerated at All Doses Tested

**Maximum Galactitol Reduction vs. Baseline**



Y-axis: Plasma Galactitol (ng/ml), from 0 to -1600
X-axis categories: PBO, 5mg/kg, 20 mg/kg, 40 mg/kg

**Pharmacokinetics**
- PK supports once-daily dosing
- Linear increase in AT-007 dose-dependent plasma concentration
- Similar exposure levels in Galactosemia patients and healthy volunteers

**Safety**
- AT-007 was safe and well-tolerated
- No treatment-related discontinuations
- No treatment-related Adverse Events
- No treatment-related lab abnormalities

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

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

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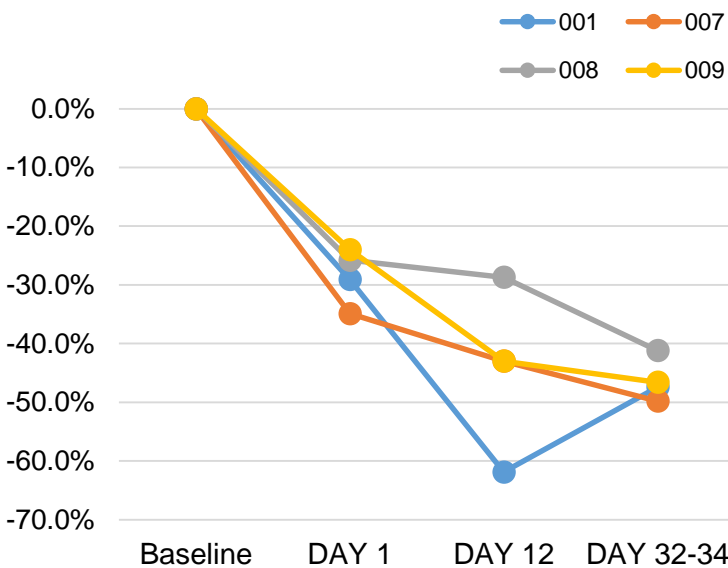# AT-007 Decreased Galactitol Levels in All Treated Patients

Decrease was Dose-Dependent, Rapid and Sustained; Statistically Significant at 20 & 40mg/kg

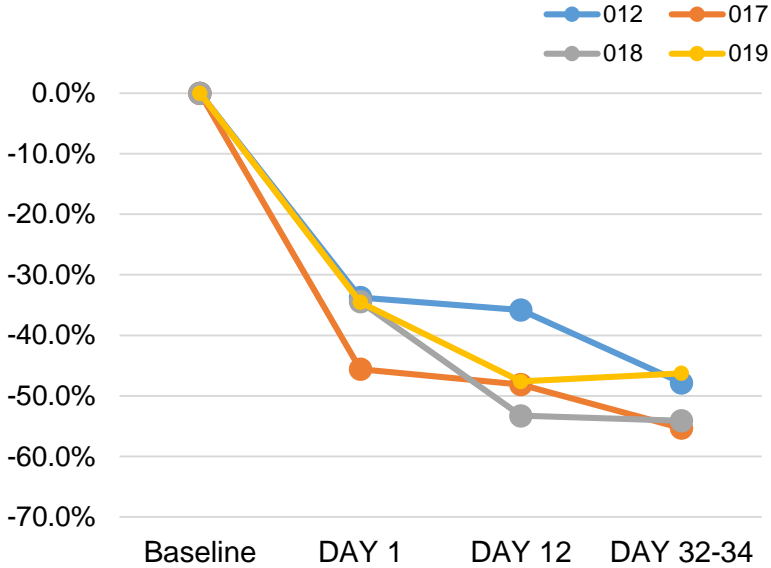**Individual Maximum Reduction in Galactitol Percent Change From Baseline**
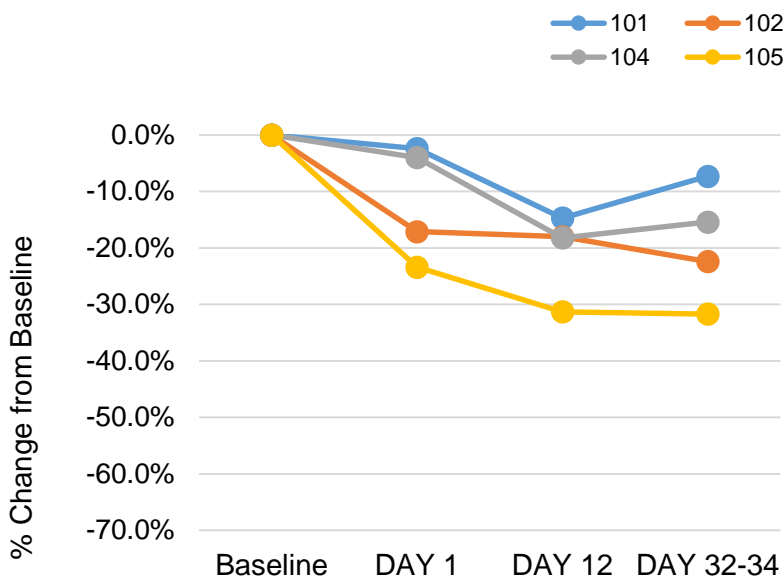


Further Characterization of AT-007 in adult Galactosemia patients in ongoing long-term safety study

# AT-007 Galactitol Reduction is Rapid and Sustained
## Reduction Begins on 1st Day of Treatment and is Sustained Over 1 Month of Treatment

Galactitol Reduction is Sustained Over the 24hr Dosing Period at Steady State (Day 12 and Day 32), Supporting Once Daily Oral Dosing
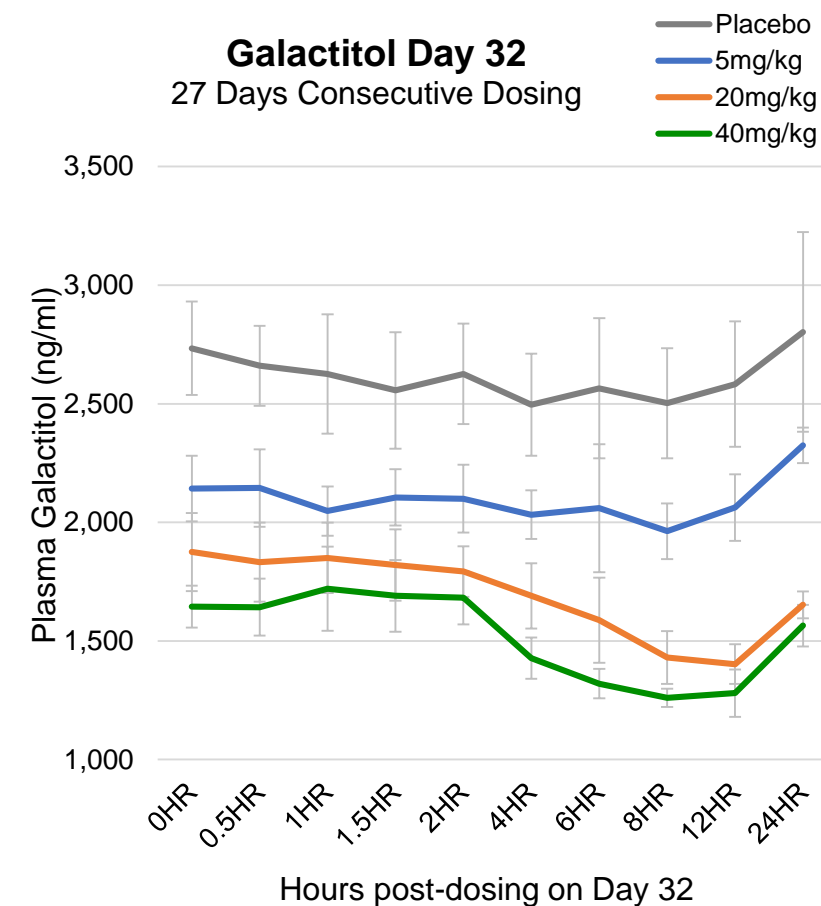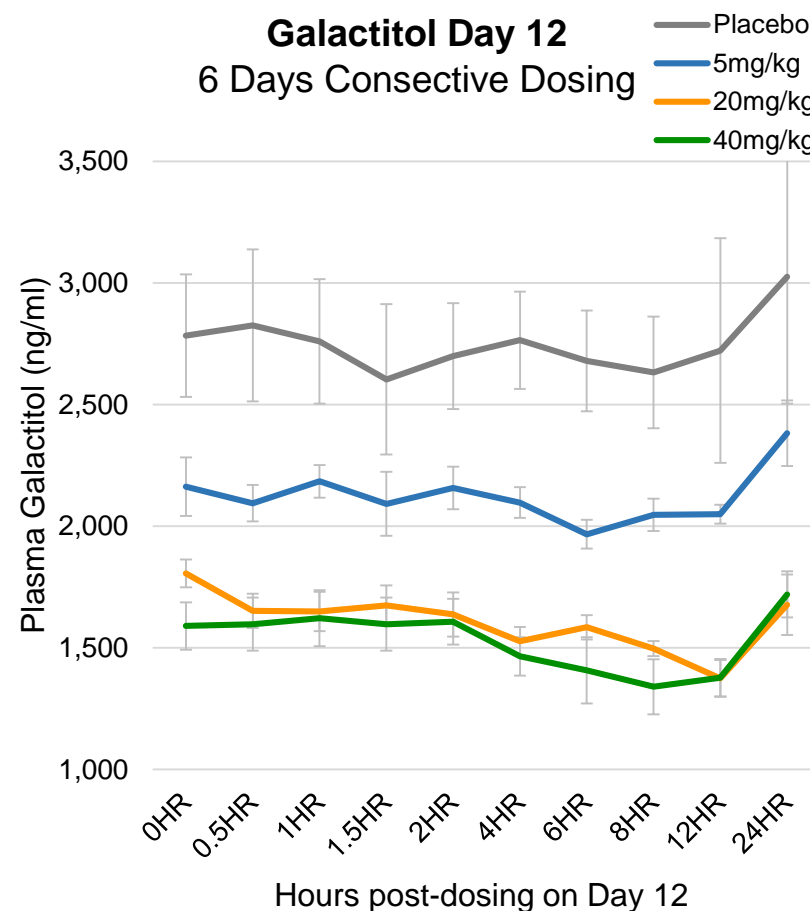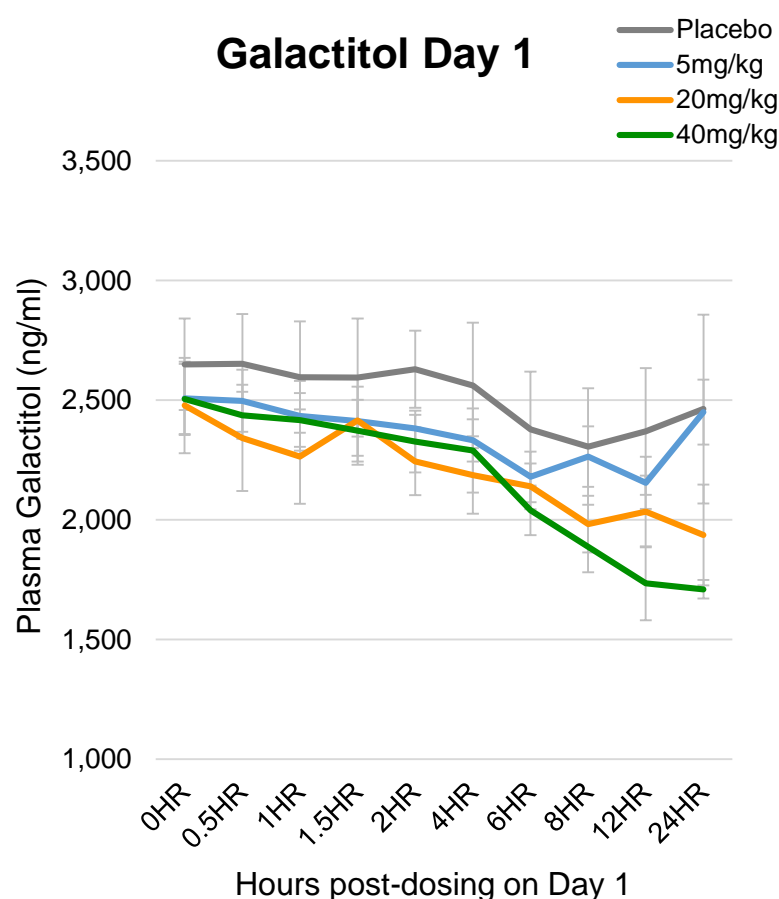


Data for each cohort is shown as mean ±SEM; Baseline mean galactitol was not statistically different between cohorts

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# Galactitol Quantitation in the Brain by 3T MR Spectroscopy

- Galactitol can be quantitatively assessed in the brain by MR Spectroscopy

- Galactitol is not present in the brain of healthy volunteers and is only present in Galactosemia patients

- In "old" studies with low power magnets, the aberrant galactitol peak was only visible in patients who were not on a compliant diet

- Higher power 3T MRI/MRS now allows detection and quantitation of galactitol in the brain of patients on a galactose-free diet, representing galactitol in the brain formed by endogenous galactose production

Effects of AT-007 on brain galactitol will be presented at upcoming conference
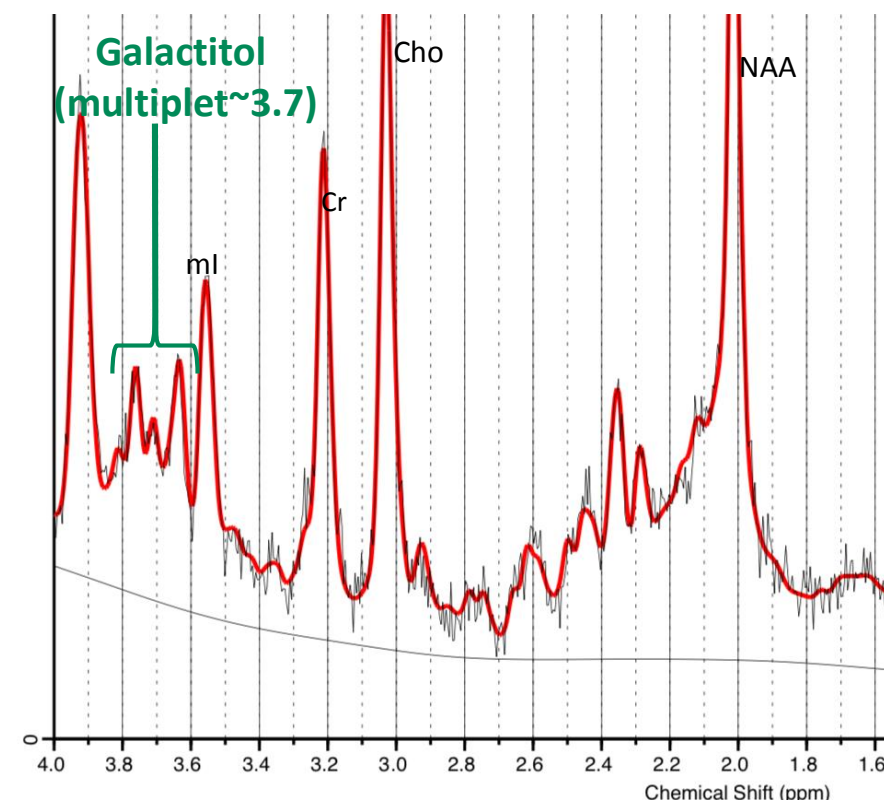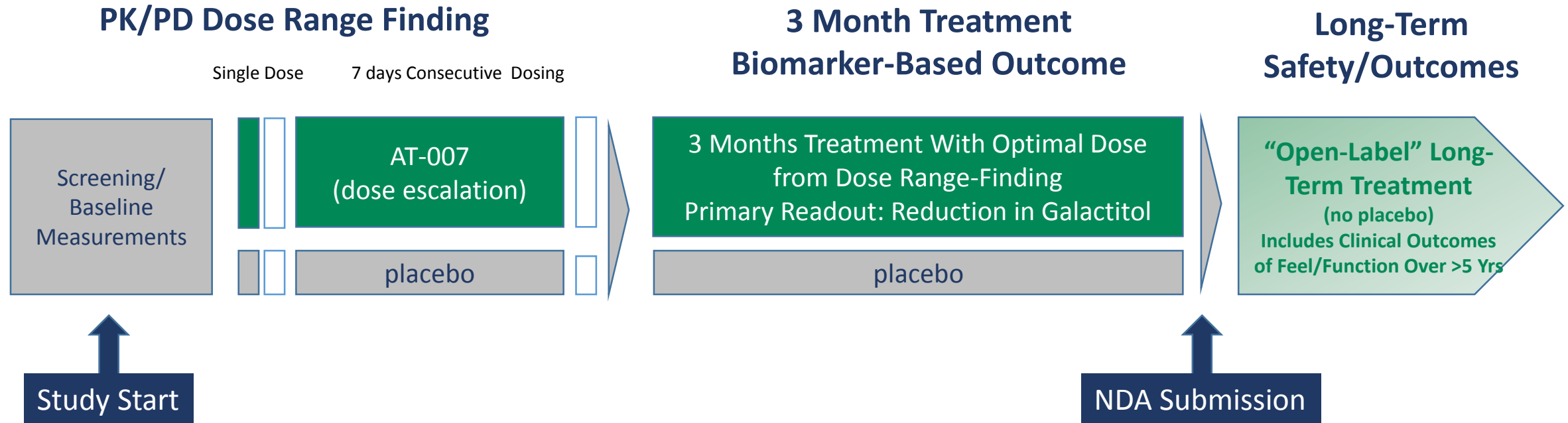


Representative baseline MRS of adult Galactosemia patient from ACTION-Galactosemia study
(on galactose-free diet; 3T MRI)
ml=myoinositol; Cr=creatine; Cho=choline; NAA=N-acetyl aspartate

# ACTION-Galactosemia Kids Pediatric Registrational Clinical Study

**PK/PD Dose Range Finding**

Single Dose      7 days Consecutive Dosing

**3 Month Treatment
Biomarker-Based Outcome**

**Long-Term
Safety/Outcomes**

| Screening/ Baseline Measurements | AT-007 (dose escalation) | 3 Months Treatment With Optimal Dose from Dose Range-Finding Primary Readout: Reduction in Galactitol | "Open-Label" Long-Term Treatment (no placebo) Includes Clinical Outcomes of Feel/Function Over >5 Yrs |
| --- | --- | --- | --- |
| | placebo | placebo | |

**Study Start**

**NDA Submission**

- Dose range finding PK/PD study to determine optimal dose in children, followed by 3-month biomarker-based assessment of galactitol reduction for NDA submission
    - Initial study (pre-NDA) will enroll children ages 2-17
    - Additional cohort will enroll infants age 2 mo-2 yrs (timing TBD)
- A long-term clinical outcomes study (not required for approval) will follow post-NDA submission to assess impact on how patients feel and function and provide long-term safety data to to support long-term market access, adherence and persistence on therapy

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# AT-007: Oral CNS Penetrant Aldose Reductase Inhibitor

| **Drug Profile** | • Structurally distinct molecule with potent AR inhibition and unique PK profile<br><br>• Exposure to all Galactosemia target tissues – CNS, nerve and retina penetrant<br><br>• Oral once-daily dosing (half life 12-18 hrs) |
|---|---|
| **Safety** | • No drug-related safety or tolerability issues in Phase 2 adult Galactosemia patient study<br><br>• No safety issues in newborn rat treatment studies, supporting eventual infant/pediatric use |
| **Path to Registration** | • Prevented complications of disease in Galactosemia rat model<br><br>• Biomarker effects correlate with clinical endpoints<br><br>• Did not increase galactose levels or levels of other galactose metabolites (Gal1P)<br><br>• Initiate pediatric study in Q2 2020<br><br>• Ongoing 90-day long-term safety extension of ACTION-Galactosemia in adult Galactosemia patients |

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# Sorbitol Dehydrogenase (SORD) Deficiency

## Burden of Disease

- Progressive hereditary neuropathy
- Pediatric-to-adolescent onset of disease
- Manifestations include difficulty walking, lower limb atrophy, and distal muscle weakness predominantly in lower limbs and frequently upper limbs
- Often diagnosed symptomatically as a subtype of CMT2

## Standard of Care

- No approved therapies

## Building on Prior Body of Evidence

- Patients with SORD have very high levels of sorbitol in their cells and tissues as a result of the enzyme deficiency, which results in tissue toxicities such as neuropathy
- Recent research in drosophila and cell models demonstrates that treatment with an ARI that blocks sorbitol production may provide benefit in this disease

## Development

- Preclinical studies initiated
- Leverage prior Phase 1 development work in healthy volunteers – Phase 2 ready asset
- Plan to initiate SORD deficiency clinical study in 2021; potential for biomarker-based pivotal study (reduction in sorbitol)

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# Phosphomannomutase 2 deficiency (PMM2-CDG)

## Burden of Disease

- Most common congenital disorder of glycosylation
- Classical presentation includes cognitive deficiencies, developmental delay, severe encephalopathy with axial hypotonia, psychomotor retardation, and cerebellar hypoplasia
- Many patients present with abnormal fat distribution and cardiomyopathy in infancy and childhood
- High infant mortality rate in the first few years of life

## Standard of Care

- No approved therapies

## Building on Prior Body of Evidence

- PMM2-CDG patients have high levels of Sorbitol in blood and urine, presumably because PMM2 deficiency deranges the homeostatic feedback mechanisms involved in the polyol pathway
- Epalrestat (old ARI) shown to be potent activator of enzyme activity in PMM2-CDG patient fibroblasts
  - Data suggest Aldose Reductase inhibition act post-translationally to increase PMM2 enzyme activity

## AT-007 in Preclinical Development

- Initial data in fibroblast cell lines derived from PMM2-CDG patients; AT-007 increases phosphomannomutase 2 activity
- Potential to pursue clinical development in 2021

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# AT-001 for Diabetic Cardiomyopathy

# AT-001 for Diabetic Cardiomyopathy

## Pathogenesis of Disease

- Fatal fibrosis of the heart; cardiac tissue "hardens" and limits contractility

- Caused by aberrant metabolism of glucose to sorbitol in cardiomyocytes (by Aldose Reductase)

- Affects 17-24% of diabetics (77M patients worldwide)

- Occurs in both Type 1 and Type 2 diabetes

## Standard of Care

- No treatments exist for DbCM

- Patients are counseled on glucose control and lifestyle

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# DbCM Commercial Opportunity: Blockbuster Potential with Limited Capital Requirement

| Regulatory | Commercial Market | Point of Care |
|---|---|---|
| • Clear path to registration based on functional capacity endpoint (exercise tolerance)<br><br>• Single Phase 3 trial required | • 10M patients in the US; 77M worldwide<br><br>• Sufficiently narrow heart failure population - can be targeted with limited commercial investment<br><br>• High disease awareness | • Easily diagnosed and tracked by cardiologists (echo)<br><br>• Easily identified for referral- endocrinologists/PCPs can identify probable patients through a simple blood test (NTproBNP cardiac stress biomarker) |

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# Strong Rationale for AT-001 Development in Diabetic Cardiomyopathy: First-in-Class Potential

## Building on Prior Body of Evidence

- The role of AR in DbCM is well supported by preclinical and clinical evidence
- Proof of mechanism: Pfizer's zopolrestat achieved proof-of-concept on LVEF in Phase 2 Diabetic Cardiomyopathy trial
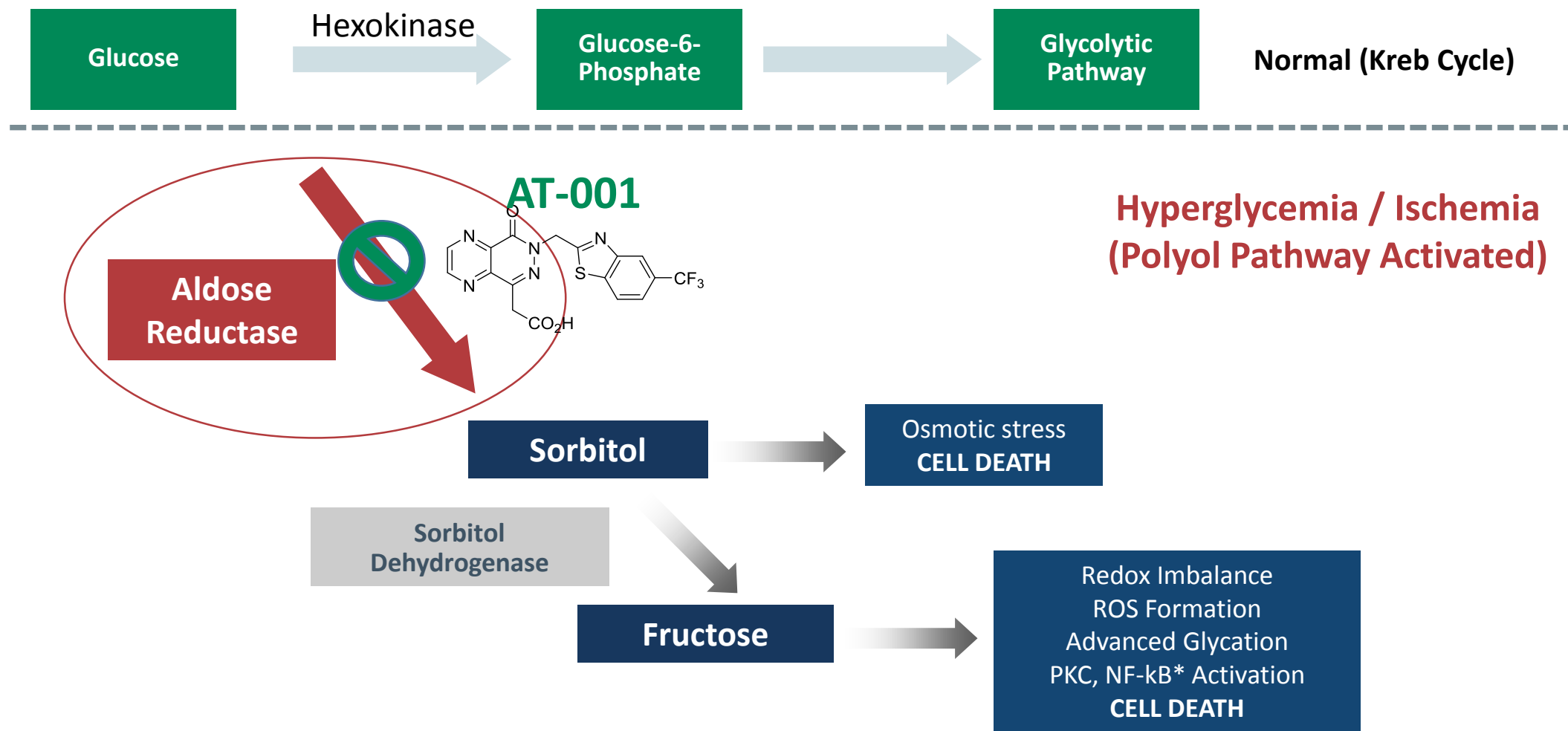
## AT-001's Robust Pre-Clinical Profile

- 1,000X more potent than prior best-in-class ARI (zopolrestat), in vitro and in vivo
- Broad exposure: Cardiac and nerve tissue
- Highly favorable preclinical profile: MTD>2,000mg/kg

## AT-001's Robust Clinical Profile (Ph 1/2 trial)

- Clinical proof-of-concept via sorbitol biomarker observed in T2D patients
- No drug related AEs observed at any dose; well tolerated
- Heart inflammatory biomarkers in 28 day arm in DbCM patients informed dose selection for pivotal study
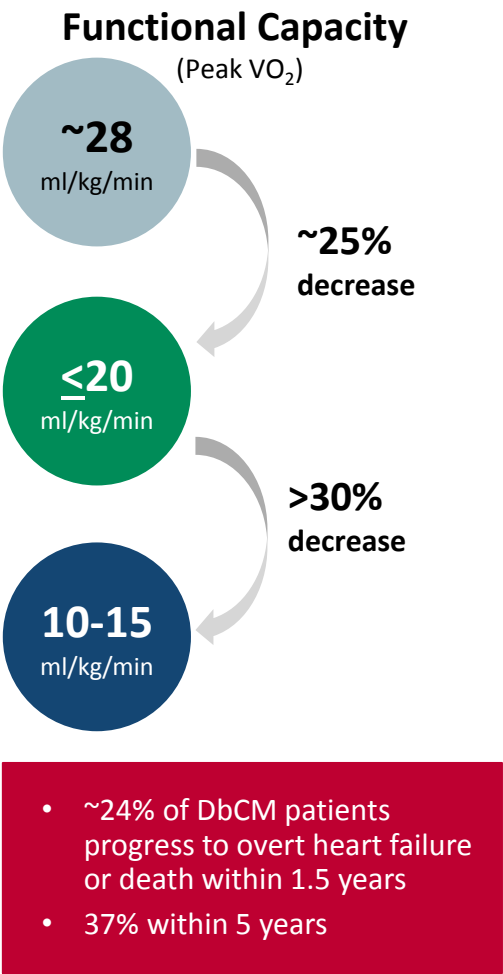
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# Aldose Reductase Causes Damage to Tissues (Including Cardiomyocytes) Under Oxidative Stress



Glucose → (Hexokinase) → Glucose-6-Phosphate → Glycolytic Pathway — **Normal (Kreb Cycle)**

**AT-001**

Aldose Reductase

**Hyperglycemia / Ischemia (Polyol Pathway Activated)**

Sorbitol → Osmotic stress **CELL DEATH**

Sorbitol Dehydrogenase

Fructose → Redox Imbalance / ROS Formation / Advanced Glycation / PKC, NF-kB* Activation / **CELL DEATH**

*Nf-kB is a protein complex that controls transcription of DNA, cytokine production and cell survival

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# Understanding Diabetic Cardiomyopathy as a Form of Heart Failure

| | |
|---|---|
| **Diabetes**<br>**Stage A Heart Failure** | • Metabolic derangement of the myocardium due to diabetes |
| **DbCM**<br>**Stage B Heart Failure** | • Cardiac structural abnormalities<br>• Diastolic dysfunction; LVH<br>• Early symptoms of DbCM; noticeable impact on activities<br>• Impaired Functional capacity (~75% normal) |
| **Stage C Heart Failure** | • Overt Heart Failure<br>• HFpEF or HFrEF<br>• Significant impact on daily activities |
| **Stage D Heart Failure** | • Refractory Heart Failure requiring specialized interventions (e.g. LV Assist Device)<br>• Inability to complete daily activities |

**Functional Capacity**
(Peak VO$_2$)

**~28** ml/kg/min

**~25% decrease**

**≤20** ml/kg/min

**>30% decrease**

**10-15** ml/kg/min

- ~24% of DbCM patients progress to overt heart failure or death within 1.5 years
- 37% within 5 years

References: Kosmala et al, JACC V O L . 6 5 , NO . 3 , 20 1 5; Swank et al. Circ HF 2012; Wang et al. JACC: Cardiovasc Imaging 2018; From et al. JACC 2010

APPLIED THERAPEUTICS

# AT-001 Phase 1/2 Trial in Type 2 Diabetic Patients

| Parts A & B |
|---|

**Design**

- 80 Type 2 Diabetic Patients
- All patients remained on concomitant meds
- 40 patients in SAD – (5, 10, 20, 40mg/kg)
- 40 patients in MAD – (5, 20, 40mg/kg; 20mg/kg BID)
- 8 drug treated & 2 placebo in each cohort

**Results**

- No drug-related AEs in entire study (up to 7 days treatment)
- No abnormal labs
- Normalization of sorbitol (PD biomarker)
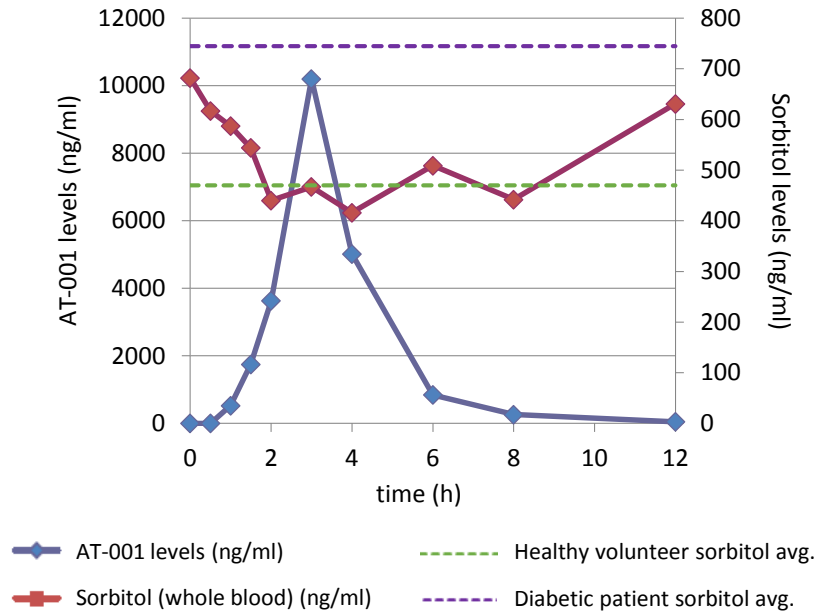
| Part C |
|---|

**Design**

- 30 DbCM patients
- 10 patients per cohort (8 drug treated, 2 placebo)
  - Placebo
  - 1,500mg BID
  - 1,000mg TID

**Results**

- No drug-related AEs in entire study (up to 28 days treatment)
- No drug-related lab abnormalities
- Effect on cardiac biomarker NTproBNP

**APPLIED THERAPEUTICS**

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

## Proof of Biological Activity



- AT-001 levels (ng/ml)
- Sorbitol (whole blood) (ng/ml)
- Healthy volunteer sorbitol avg.
- Diabetic patient sorbitol avg.

- Drug treatment with AT-001 normalized sorbitol in diabetics to healthy volunteer levels

## Sorbitol Reduction by Dose
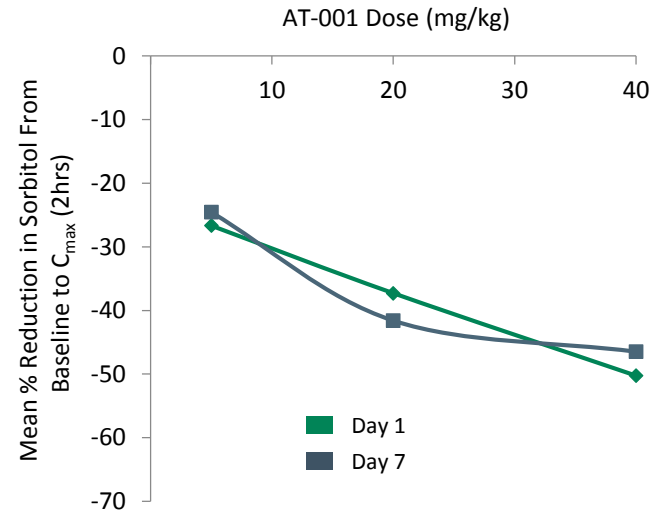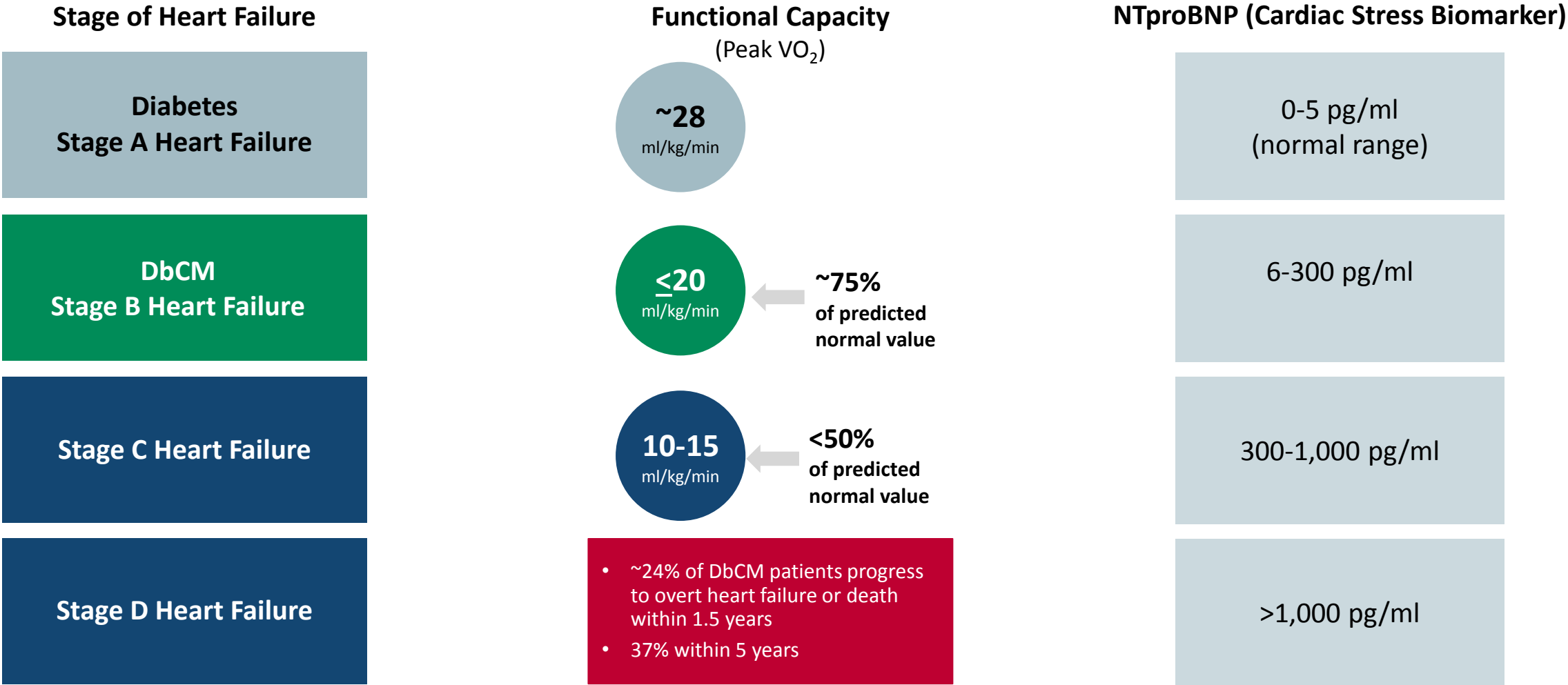


- Day 1
- Day 7

- 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



- 5mg/kg
- 20mg/kg
- 40mg/kg
- placebo
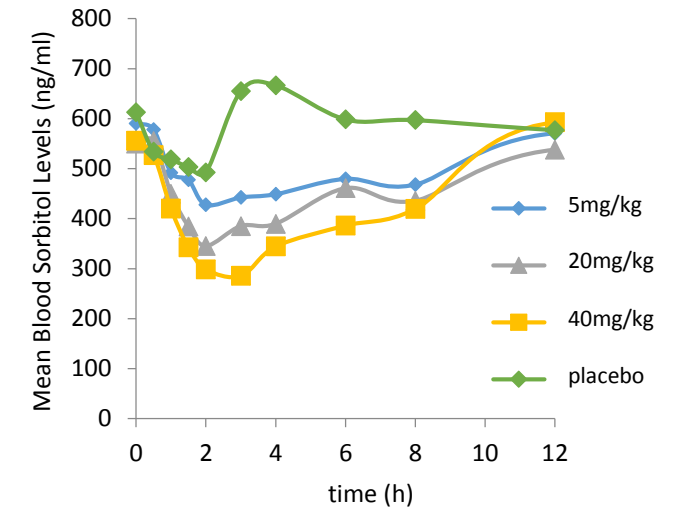
- Rapid release capsule provides sorbitol normalization effects (PD biomarker) through 10-12hrs post-dose at >10mg/kg

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

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# NTproBNP Levels are Elevated in DbCM Patients (Blood-based cardiac stress biomarker)

| Stage of Heart Failure | Functional Capacity (Peak VO$_2$) | NTproBNP (Cardiac Stress Biomarker) |
|---|---|---|
| Diabetes Stage A Heart Failure | ~28 ml/kg/min | 0-5 pg/ml (normal range) |
| DbCM Stage B Heart Failure | ≤20 ml/kg/min — ~75% of predicted normal value | 6-300 pg/ml |
| Stage C Heart Failure | 10-15 ml/kg/min — <50% of predicted normal value | 300-1,000 pg/ml |
| Stage D Heart Failure | • ~24% of DbCM patients progress to overt heart failure or death within 1.5 years<br>• 37% within 5 years | >1,000 pg/ml |

References: Kosmala et al, JACC V O L . 6 5 , NO . 3 , 20 1 5; Swank et al. Circ HF 2012; Wang et al. JACC: Cardiovasc Imaging 2018; From et al. JACC 2010
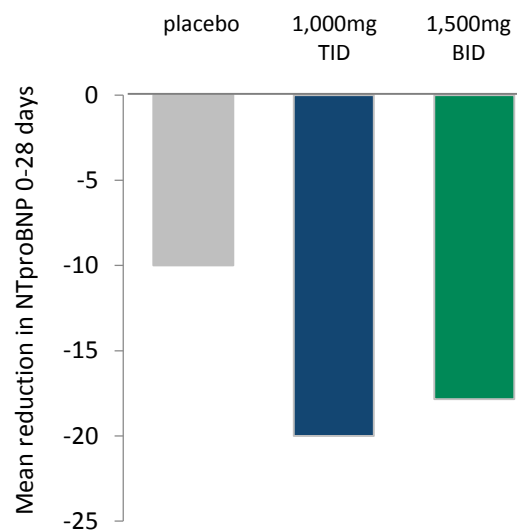
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# AT-001 Reduced Levels of NTproBNP Cardiac Stress Biomarker Over 28 Days of Treatment
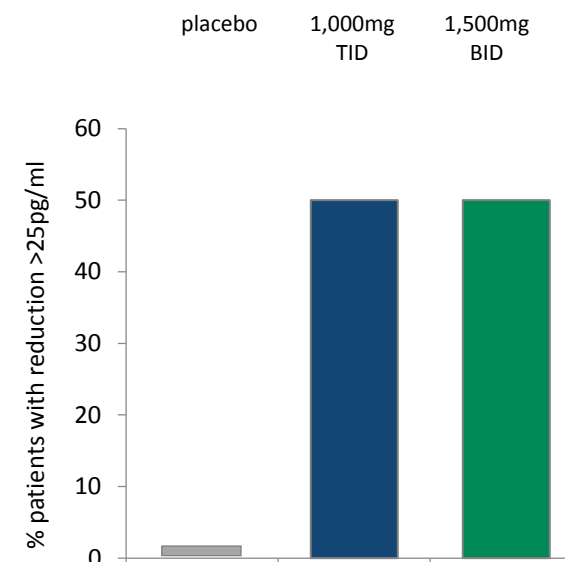
## Sorbitol Normalization
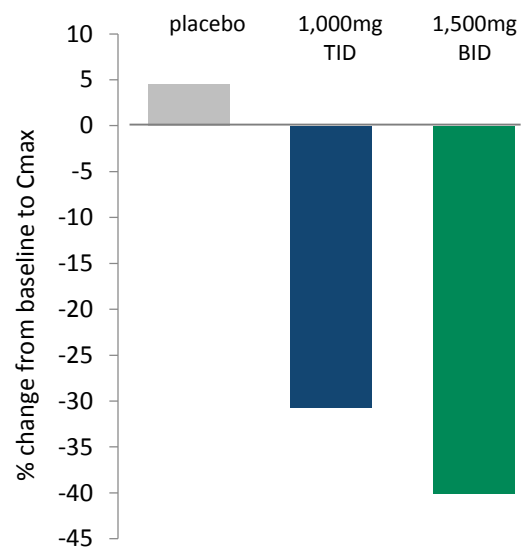


- Significant sorbitol reduction achieved by both 1,000mg TID and 1,500mg BID AT-001

- Higher $C_{max}$ achieved with BID slightly beneficial – normalizes sorbitol to healthy volunteer levels

## Mean Reduction in NTproBNP



- Mean reduction in NTproBNP seen over 28 days vs. placebo
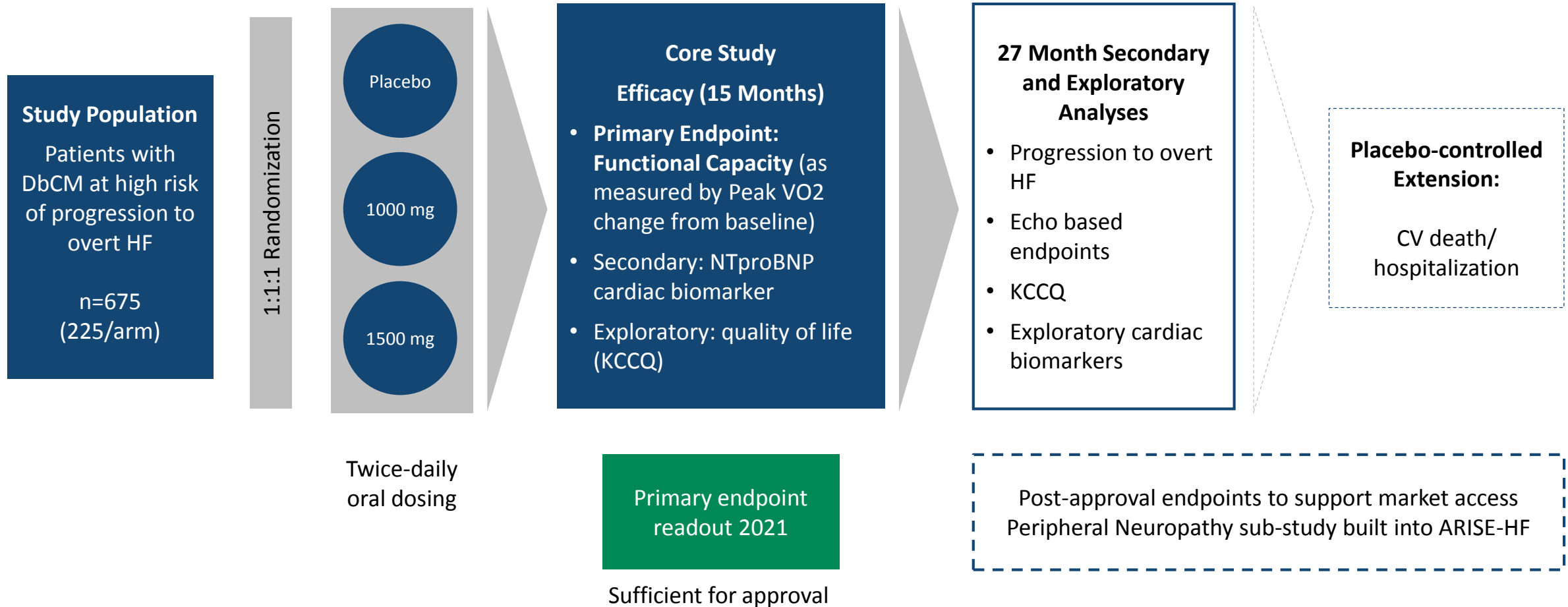  - Mean baseline NTproBNP was 65pg/ml

## Clinical Responder Analysis



- ~50% AT-001 treated patients demonstrated a clinically meaningful reduction in NTproBNP over 28 days
  - >25pg/ml reduction from baseline

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# DbCM Phase 3 Registrational Study (ARISE-HF)

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

**Study Population**

Patients with DbCM at high risk of progression to overt HF

n=675 (225/arm)

1:1:1 Randomization

- Placebo
- 1000 mg
- 1500 mg

Twice-daily oral dosing

**Core Study**

**Efficacy (15 Months)**

- **Primary Endpoint: Functional Capacity** (as measured by Peak VO2 change from baseline)
- Secondary: NTproBNP cardiac biomarker
- Exploratory: quality of life (KCCQ)

Primary endpoint readout 2021

Sufficient for approval

**27 Month Secondary and Exploratory Analyses**

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

**Placebo-controlled Extension:**

CV death/ hospitalization

Post-approval endpoints to support market access
Peripheral Neuropathy sub-study built into ARISE-HF

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Appendix / Backup Slides

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# Addressing Large Indications in Areas of High Unmet Medical Need – Opportunities for Abbreviated Clinical Development

| Indication | Prevalence | Market | Unmet Need | Development Strategy |
|---|---|---|---|---|
| Diabetic Cardiomyopathy | 17-24% Diabetics | ~77M patients worldwide | • No therapies approved<br>• No known drugs in development<br>• Entresto approved in stage 4 disease | Abbreviated Development |
| Retinopathy | 35% Diabetics | ~158M patients worldwide | • 2 therapies approved (intravitrial injection)<br>• Anti-VEGFs only for late stage disease | Abbreviated Development |
| Diabetic Peripheral Neuropathy | 50% Diabetics | ~226M patients worldwide | • No disease-modifying therapies approved<br>• Only symptomatic treatments available (Lyrica)<br>• Epalrestat, an off-patent ARI, approved in Japan, China, India | Strategic Partner; Standard Development |
| Galactosemia | 1/50k to 1/90k | ~2,800 patients in the US | • No therapies approved; lactose dietary restriction not sufficient<br>• No known drugs in development | Abbreviated Development (includes PRV) |
| SORD Deficiency | >1/100k | ~3,300 patients in the US | • No therapies approved<br>• No known drugs in development | Abbreviated Development (eligible for PRV) |
| PMM2-CDG | <1/1M | ~1,000 patients worldwide | • No therapies approved<br>• No known drugs in development | Abbreviated Development (eligible for PRV) |

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# Novel Chemistry For Better Drugs

## Backbone
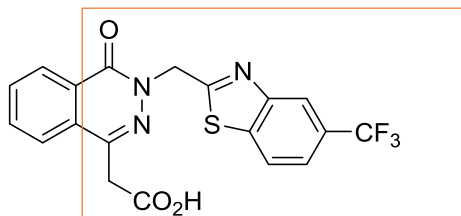


**zopolrestat**

Similar backbone to zopolrestat (prior best in class efficacy, but liver tox issues)

## Technological Advancements

- Advanced crystallography provided novel understanding of structural changes within AR active site
- Many prior ARIs were unable to inhibit redox-activated AR
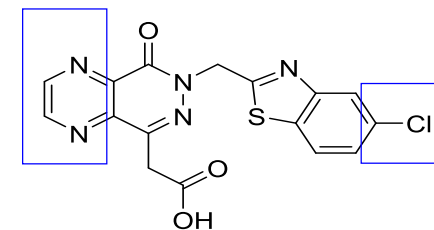
## Impact of Modified Structure

- Functional modifications improve compound's binding affinity and specificity
- Novel dimeric binding within the catalytic core
- Higher enzymatic inhibitory activity
- Increased selectivity leads to less off-target activity and potentially better safety



**AT-001**



**AT-007**



**AT-003**

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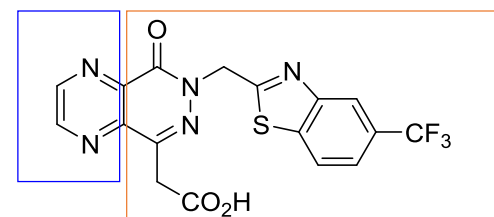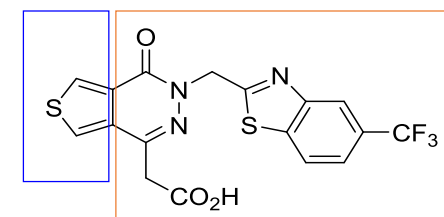
# Intellectual Property Summary

- Dominant IP and Freedom to Operate on all compounds & all target indications

- Expected IP runway of at least 10 years post-launch in key indications

- Composition of matter patents obtained in the US that cover AT-007 and related compounds

    - Patent protection through 2037, regulatory extension of term possible

    - European patent application has been allowed (patent has not yet issued); patent applications are pending in other countries

- Composition of matter patents that cover AT-001 and related compounds obtained US, EP, JP, CA and AU

    - Patent protection through 2031, regulatory extension of term possible

    - Method claims obtained or currently being pursued

- Company-owned international applications (PCT) cover methods for treating Galactosemia and additional compound derivatives

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# For Reference: Prior Galactitol Time Course Graphs Not Including 40mg/kg Cohort
## (and without 2 new placebo patients; Day 12/ 32 data previously from April 2020)
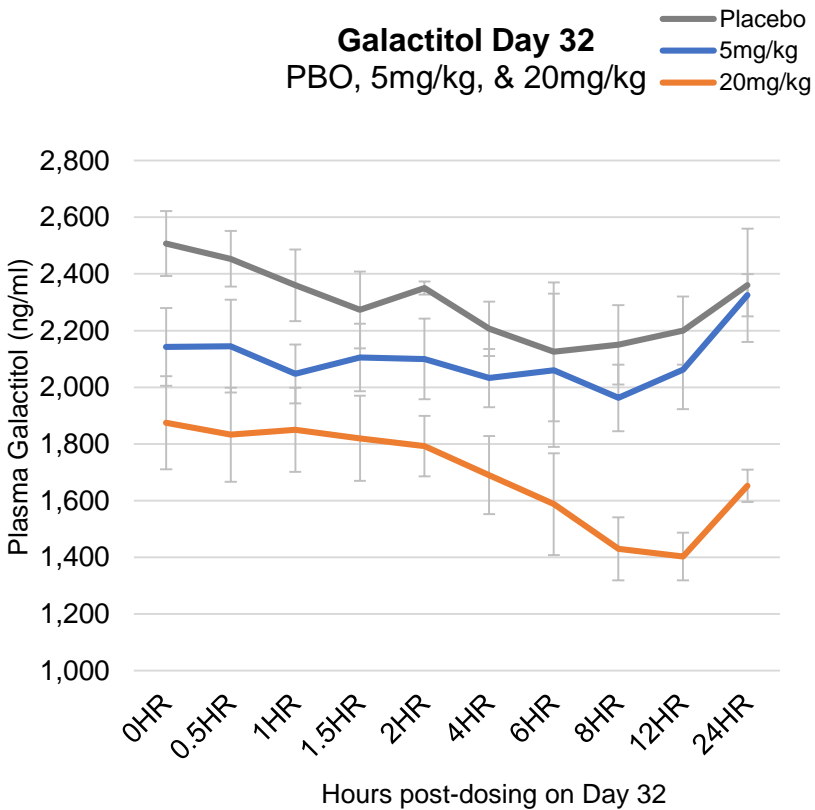


**Galactitol Day 1**
PBO, 5mg/kg, & 20mg/kg
— Placebo
— 5mg/kg
— 20mg/kg
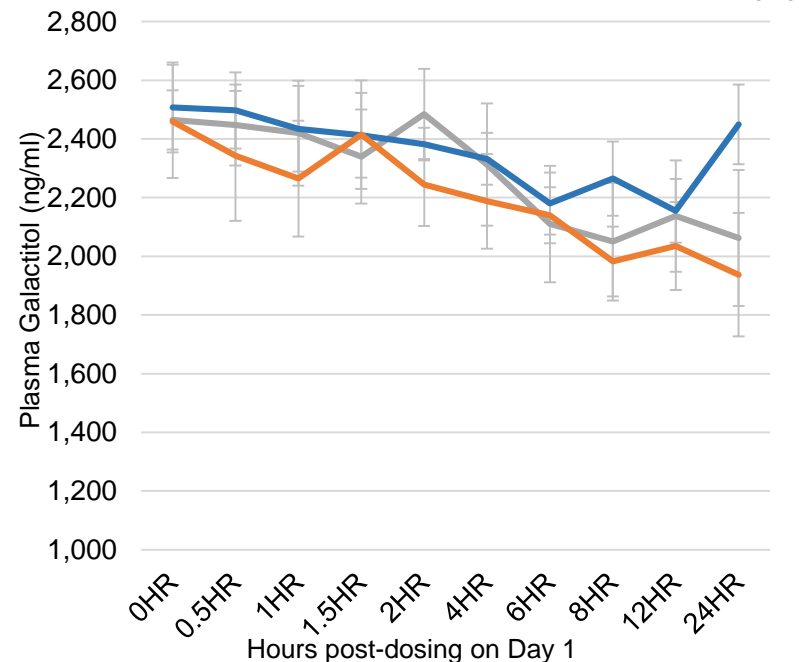
**Galactitol Day 12**
PBO, 5mg/kg, & 20mg/kg
— Placebo
— 5mg/kg
— 20mg/kg
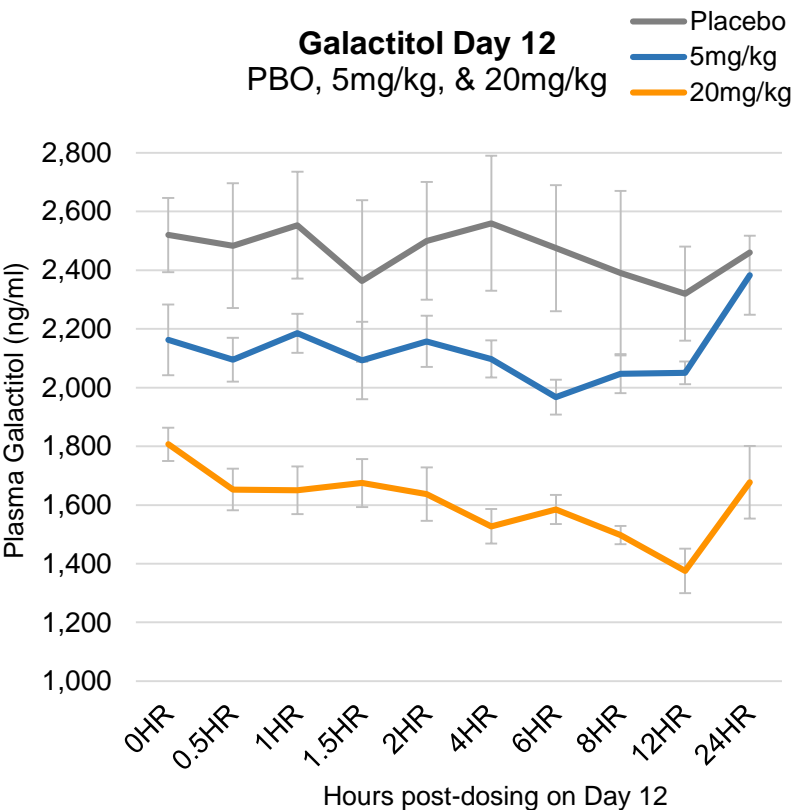
**Galactitol Day 32**
PBO, 5mg/kg, & 20mg/kg
— Placebo
— 5mg/kg
— 20mg/kg

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# If Blocking AR Doesn't Increase Galactose or Gal-1P.....
# Where Does the Extra Substrate Go?



**Galactonate** ← **Galactose Dehydrogenase** --- **Galactose**

Removed in Urine or converted to Xylulose and metabolized to glucose + $CO_2$

**TYPE II GALK**

**Gal-1-Phosphate**

**TYPE I GALT**

**Glu-1-Phosphate**

**Glycolytic Pathway**

**Aldose Reductase** → **Galactitol** — Galactitol accumulates

**Sorbitol Dehydrogenase**

Sorbitol dehydrogenase, the next enzyme in the polyol pathway, can't reduce galactitol

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# Galactosemia History Timeline

**1980's** — Newborn screening initiated

**2004** — Discovery of endogenous galactose production; dietary restriction does not prevent problems

**2011** — First GalK deficient patient study published: supports galactitol as causative of CNS complications

**2018** — First GalT knockout rat model developed: biochemical + CNS abnormalities

**2019** — AT-007 treatment/ reduction in galactitol prevents biochemical + CNS abnormalities in GalT rat model

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# Anticipated Changes in Functional Capacity and Progression to Overt Heart Failure in Study Population

Anticipated mean baseline functional capacity (Peak VO2) <6 METS (21ml/kg/min) represents a steep slope of decline and strong relationship between changes in functional capacity and ability to perform everyday tasks

## Progression to Overt Heart Failure

| Peak VO2 | Metabolic 'Cost' of Activity |
|----------|------------------------------|
| 3.5 | Rest |
| 7.0-10.5 | Walking 2mph, eating, dressing |
| 14.0-17.5 | Walking 4mph, household tasks |
| 21.0-24.5 | Walking up stairs, Stage 2 Bruce: 2.5mph, 12% |
| 28.0-31.5 | Swimming, tennis |
| 35.0-38.5 | Jogging 10 min/miles, Stage 3 Bruce: 3.4mph, 14% |
| 42.0-49.0 | Intense aerobic sports, squash Stage 4 Bruce: 4.2mph, 16% |
| >70.0 | Professional athletes/Olympians |

*Light and moderate intensity* (rows: 3.5 through 21.0-24.5)
*Vigorous intensity* (rows: 28.0-31.5 through >70.0)



Survival Functions

0 SBHF feature
1 SBHF feature
2 SBHF features
≥3 SBHF features

Cum Survival (y-axis: 0.0, 0.2, 0.4, 0.6, 0.8, 1.0)
Months (x-axis: 6, 12, 18, 24, 30, 36)

AMA Guides to the Evaluation of Permanent Impairment, Sixth Edition. Author: Robert D. Rondinelli, MD, PhD
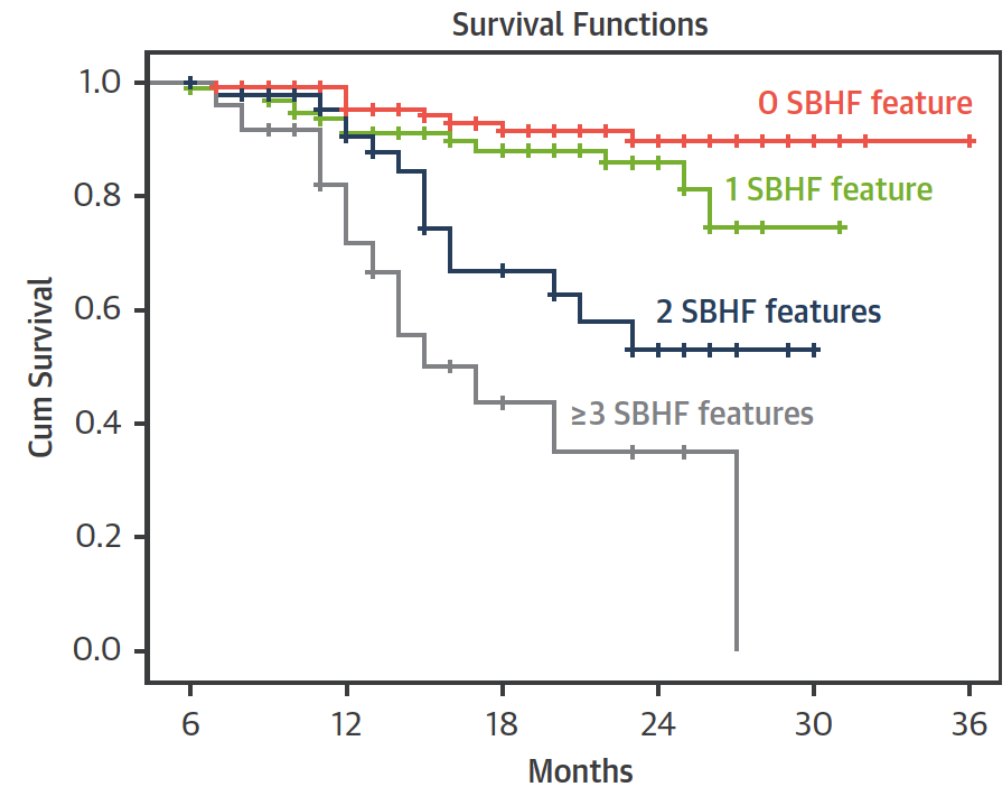
Wang Y, Marwick TH. JACC: CV Imaging 2018

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