

Applied Therapeutics

Corporate Presentation

April 2021



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Applying Science to Transform Lives

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

SCIENCE



Targeting pathways with known roles in pathogenesis

Novel compounds with improved potency/selectivity

DEVELOPMENT



Clinical efficacy confirmed via biomarkers

Pursuing expedited regulatory pathways








MARKET



Fatal or debilitating diseases with no approved therapies

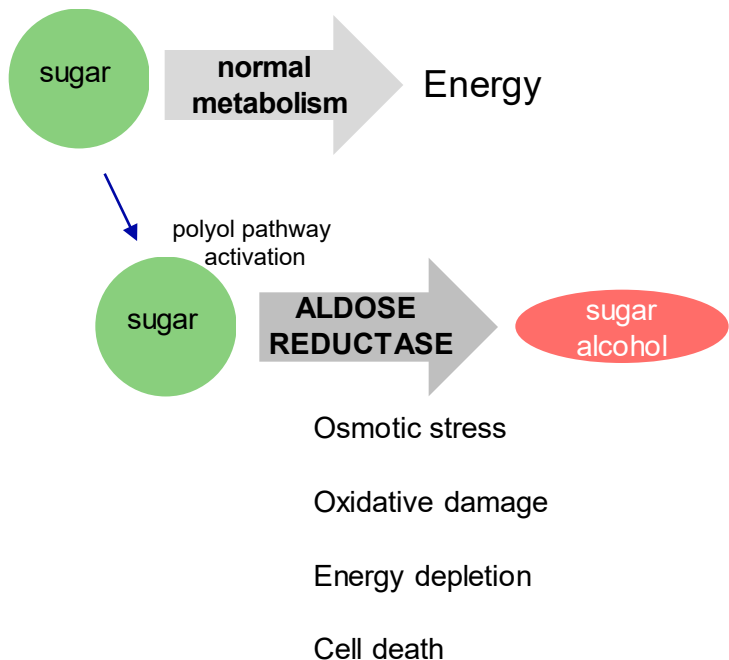
Limited / no competition

Innovative Pipeline with Near-Term Milestones

Compound	Preclinical	Phase 1	Phase 2	Phase 3	Dosing	Target Tissue	Milestones	WW Rights
ALDOSE REDUCTASE FRANCHISE								
AT-007	Galactosemia – Pivotal Phase 2 Study				QD Oral	CNS	Adult study completed; pediatric study ongoing NDA expected Q3 2021	
AT-007	SORD Deficiency				Oral	CNS	Phase 2 pilot study initiated	
AT-007	PMM2-CDG				Oral	CNS	Phase 2 ready; clinical study start in 2021	
AT-001	Diabetic Cardiomyopathy – Pivotal Phase 3 Study				BID Oral	Systemic	Ph 3 trial initiated in Q3 2019; data in 2022	
AT-001	Diabetic Peripheral Neuropathy				Oral	Peripheral Nerve	Sub-study embedded in DbCM Ph 3 trial	
AT-003	Diabetic Retinopathy				Oral	Retina	Ph 1 expected 2021	
PI3 KINASE FRANCHISE								
AT-104	PTCL, CTCL, TALL [†]				SC / Oral	Selective δ/γ inhibitor	Proof of concept preclinical 2021	

[†]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 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

AT-007

GALACTOSEMIA

Positive adult biomarker data; LTE ongoing

Pediatric trial ongoing

NDA expected ~Q3 2021



Galactosemia: a Rare Metabolic Disease With No Approved Therapies

Galactosemia is a **rare, slowly progressing metabolic disease** caused by a **genetic inability to break down the sugar galactose**. Galactose is found in foods, but the human body also naturally produces galactose on its own

~3,000 patients in the US with Galactosemia; ~80 new births per year; Mandatory newborn screening in US and most EU countries

Aldose Reductase (AR) enzyme converts galactose into **galactitol, an aberrant toxic metabolite that builds up in tissues and organs** and causes long-term disease complications

AT-007, a novel CNS penetrant Aldose Reductase inhibitor, **prevents galactitol formation and accumulation** in adult Galactosemia patients; pediatric study ongoing

Low burden of development due to biomarker-based program under new FDA guidance for low prevalence diseases; **Low commercial footprint** required to launch quickly and effectively;

Patent exclusivity through 2037; Orphan and Pediatric Rare Disease designations granted

Galactosemia: Disease Progression is Slow But Debilitating



Newborn

- Liver failure
- Kidney problems
- Sepsis
- Brain edema
- Pseudotumor cerebri
- Feeding difficulties
- Growth problems
- Cataracts



Infants/Toddlers

- Speech/language delays
- Coordination problems (fine and gross motor skills)
- Developmental delays
- Attention issues
- Growth problems
- Cataracts



Young Children

- Learning delays
- Issues with fine and gross motor skills (e.g., handwriting)
- Growth problems
- Speech/language problems
- Behavioral and emotional issues
- Tremor



Teen

- Puberty and fertility problems (females)
- Growth delays
- Anxiety
- Social problems
- Learning difficulties
- Tremor



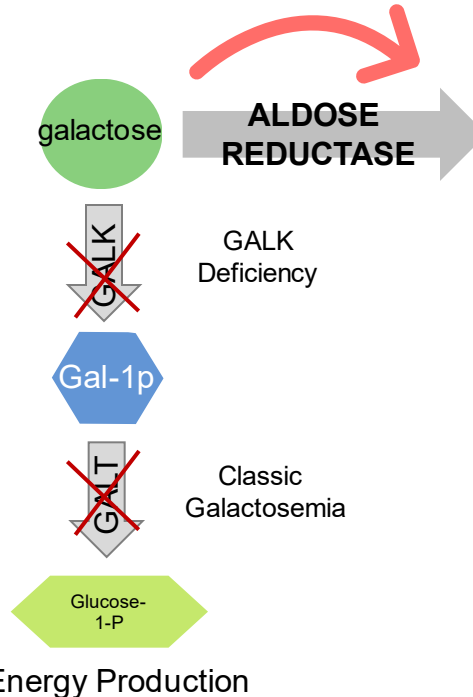
Adult

- Tremor
- Seizures
- Anxiety
- Depression
- Attention Deficit Hyperactivity Disorder (ADHD)
- Cataracts

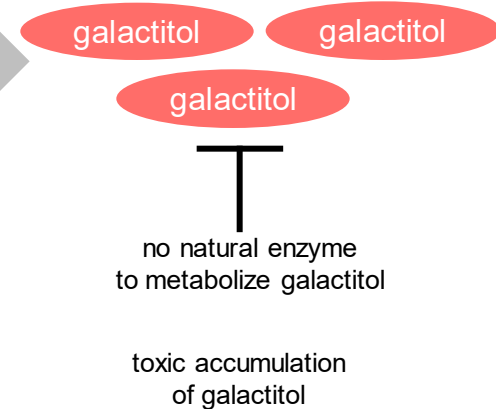
Galactosemia: Deficiency in GALT or GALK Leads to Inability to Metabolize Galactose

Aldose Reductase Converts Excess Galactose to Toxic Galactitol

NORMAL METABOLISM

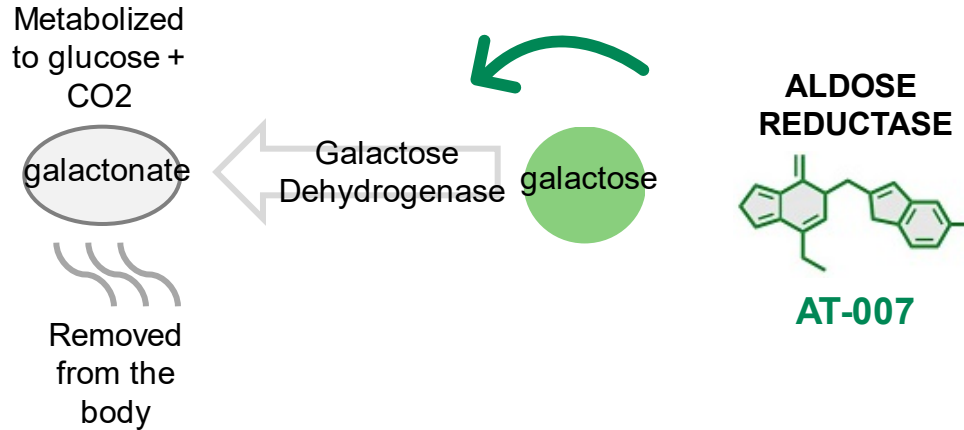


GALACTOSEMIA



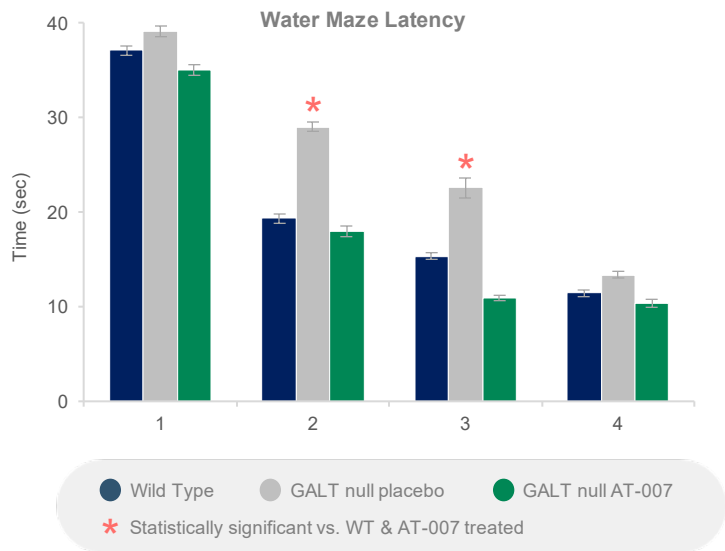
AT-007 Blocks Aldose Reductase Conversion of Galactose to Galactitol

Galactose is then shunted through a nontoxic pathway for metabolism and excretion

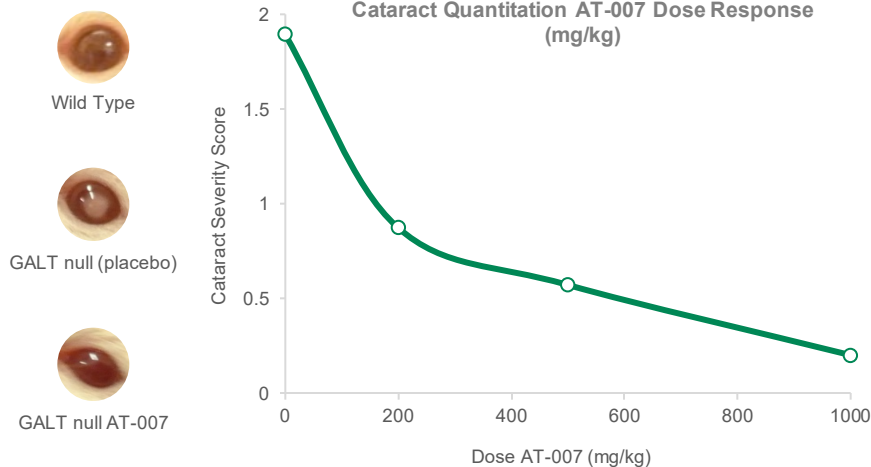


In a Rat Model of Galactosemia, AT-007 Treatment Prevented the CNS Phenotype of Disease, Including Learning, Cognition and Motor Deficiencies, and Prevented Cataracts

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

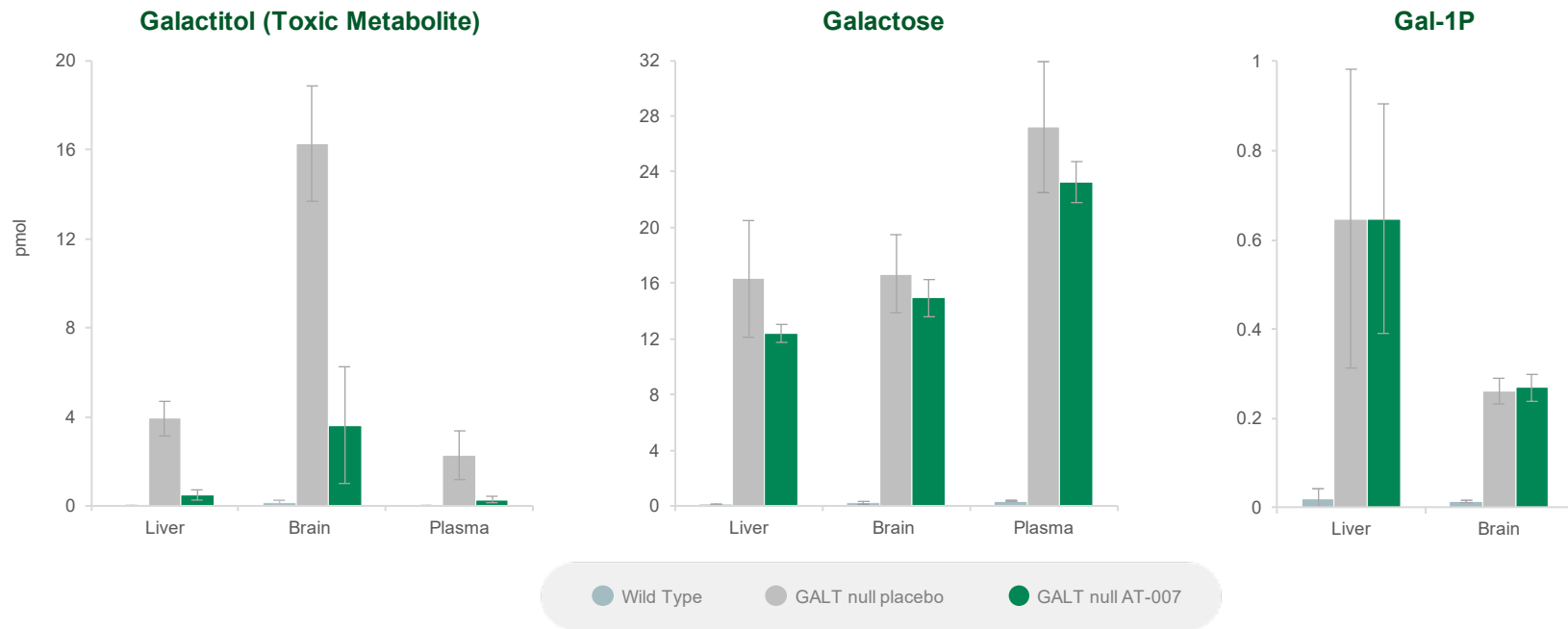


AT-007 treatment prevented galactitol accumulation in tissues, resulting in absence of cataracts



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

AT-007 Significantly Reduces Toxic Galactitol Levels in All Target Tissues Without Increasing Galactose or Gal-1P



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

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

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

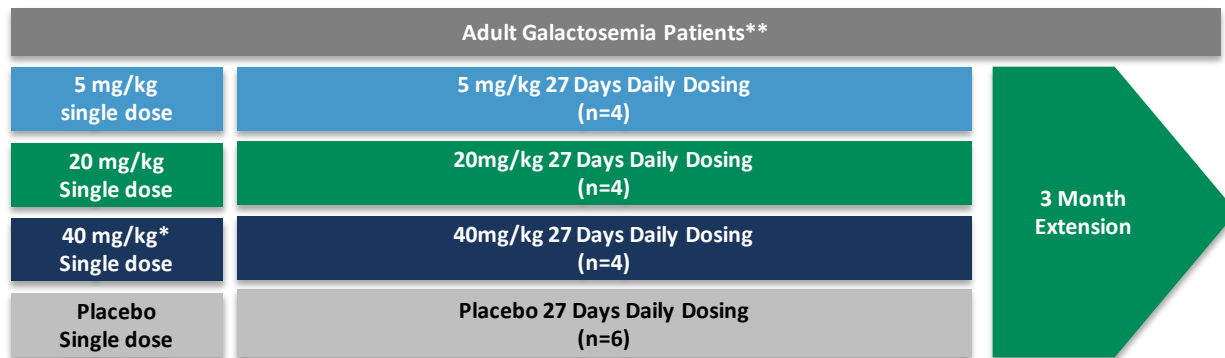


Endpoints:

- Safety
- Pharmacokinetics
- CNS Penetrance (via CSF sample)

Endpoints:

- Safety
- Pharmacokinetics/
Pharmacodynamics
- **Efficacy Biomarker - Galactitol**



*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 ≥ 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

Healthy Volunteer Data Demonstrated Safety, CNS Penetrance, PK Supportive of QD Dosing

Safety

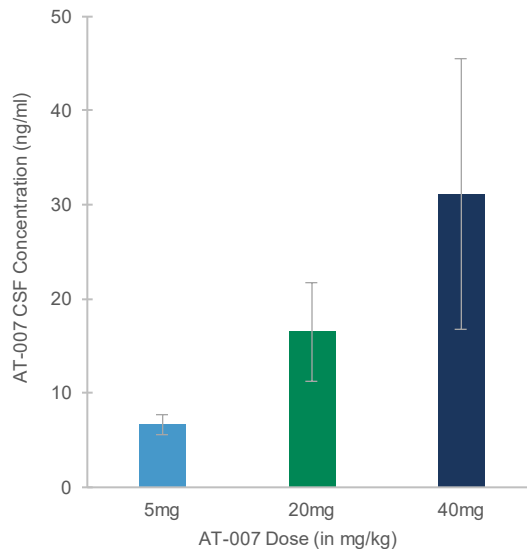
~80 healthy volunteers treated

AT-007 was safe and well tolerated at all doses



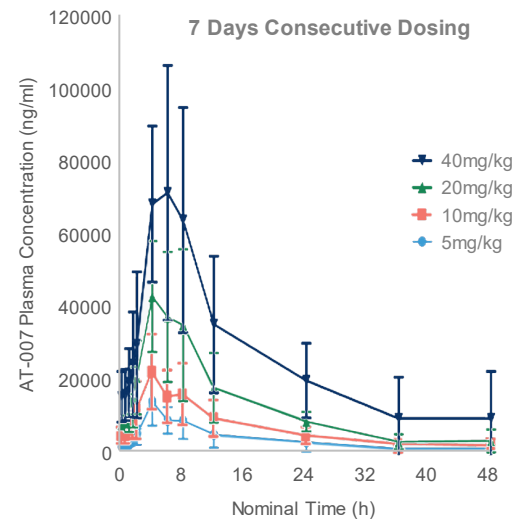
Brain Penetrance

Drug crosses into brain when dosed orally (CNS penetrant)



Pharmacokinetics

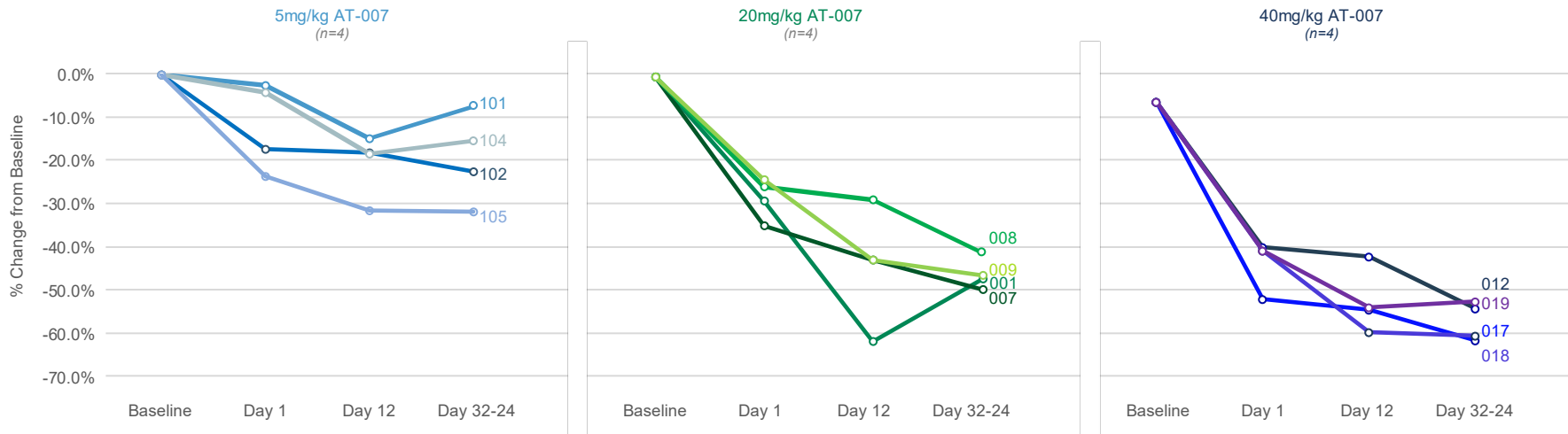
Dose-dependent increase in exposure; supportive of once daily oral dosing



AT-007 Decreased Galactitol Levels in All Treated Patients

Decrease was dose-dependent, rapid and sustained; statistically significant at 20 & 40mg/kg

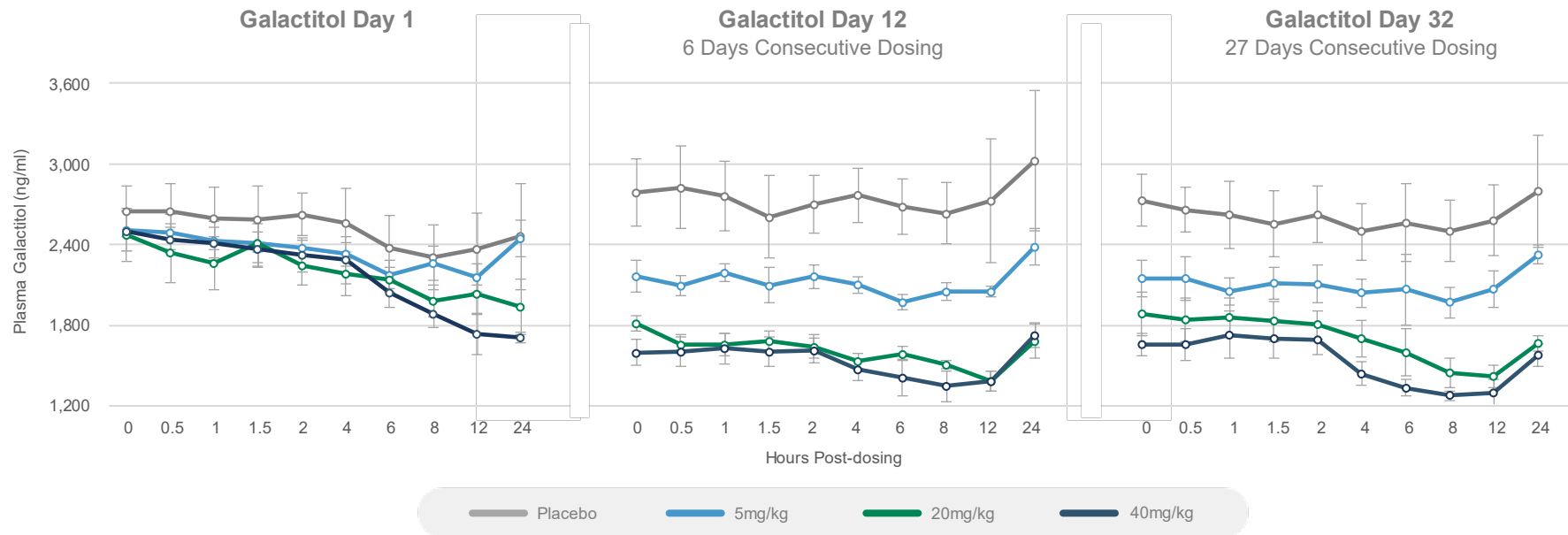
Individual Maximum Reduction in Galactitol Percent Change From Baseline



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

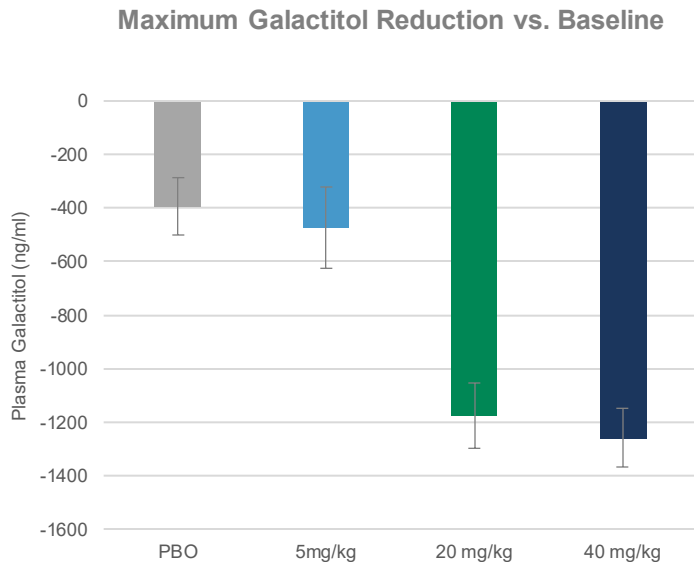
AT-007 Galactitol Reduction is Rapid and Sustained, Beginning on 1st Day of Treatment and Sustained Over 1 Month of Treatment

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

AT-007 Significantly Decreased Galactitol Levels; Safe and Well Tolerated



$P < 0.01$ 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

Safety

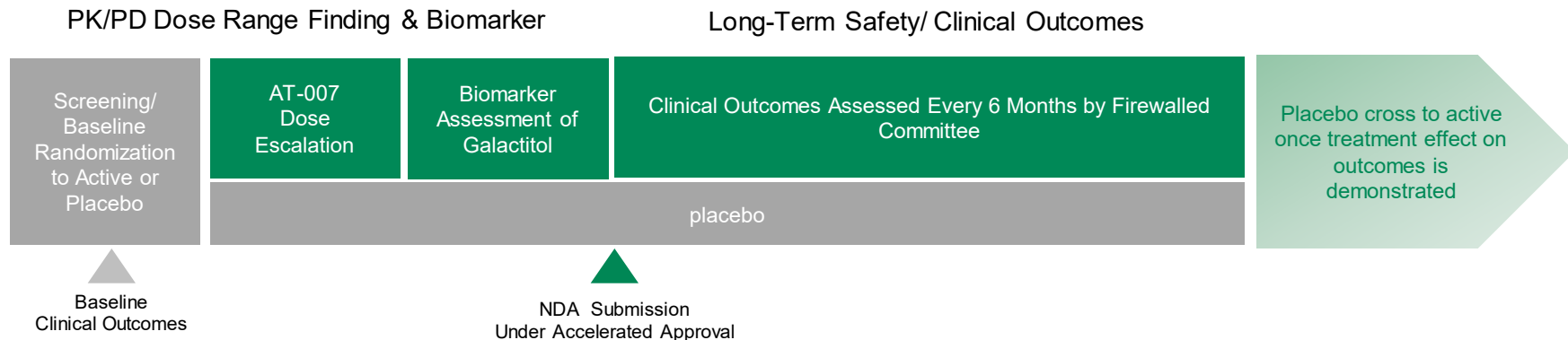
- Favorable safety and tolerability in core study and 3-month extension

Pharmacokinetics/ Pharmacodynamics

- PK supports once-daily dosing
- Rapid and sustained reduction in plasma galactitol
- Galactitol reduction in the brain demonstrated by MR Spectroscopy

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

ACTION-Galactosemia Kids Pediatric Registrational Clinical Study Design



- Dose range finding PK/PD study to determine optimal dose in children and biomarker-based assessment of galactitol reduction for NDA submission under Accelerated Approval
- Long-term clinical outcomes to assess impact on how patients feel and function and to provide long-term safety data

Outcomes Assessed by Composite Endpoint Consisting of 4 Quadrants: Speech, Cognition, Behavior, Motor Skills



Speech

- Expressive Language
- Receptive Language

OWLS-2 (Oral & Written Language Skills 2);
Picture Vocabulary Test; Oral Reading Recognition Test



Cognition & Learning

- Cognitive and Intellectual Development
- Attention
- Executive Function
- Memory (episodic and working memory)
- Processing speed

NIH Toolbox Cognition Battery: Flanker Inhibitory Control & Attention Test; Dimensional Change Card Sort; Picture Sequence Memory; List Sorting; Pattern Comparison Processing Speed



Behavioral / Psychosocial

- Atypical Behavior
- Mental Health (Anxiety/Depression)
- Adaptive/Behavior Social Skills
- Communication

Behavior Assessment System for Children (BASC) Vineland Adaptive Behavior Scales



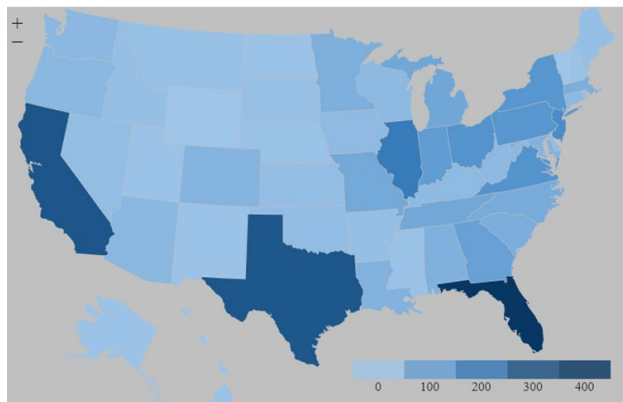
Motor Skills

- Dexterity
- Balance
- Gait Coordination
- Tremor

9-Hole Pegboard; Standing Balance; Scale for Assessment & Rating of Ataxia (SARA); Spiral Drawing Test

Claims Data Analysis Supports US Market Opportunity: ~3,000 Galactosemia Patients

Distribution of US Galactosemia Population Based on Claims Data



~60% of Claims in Top 10 States

State	Projected Population	Projected Population %
FL	358	12%
CA	283	9%
TX	281	9%
IL	191	6%
NJ	146	5%
OH	129	4%
VA	129	4%
NY	122	4%
PA	122	4%
IN	107	3%

Key Claims Data Analysis Findings:

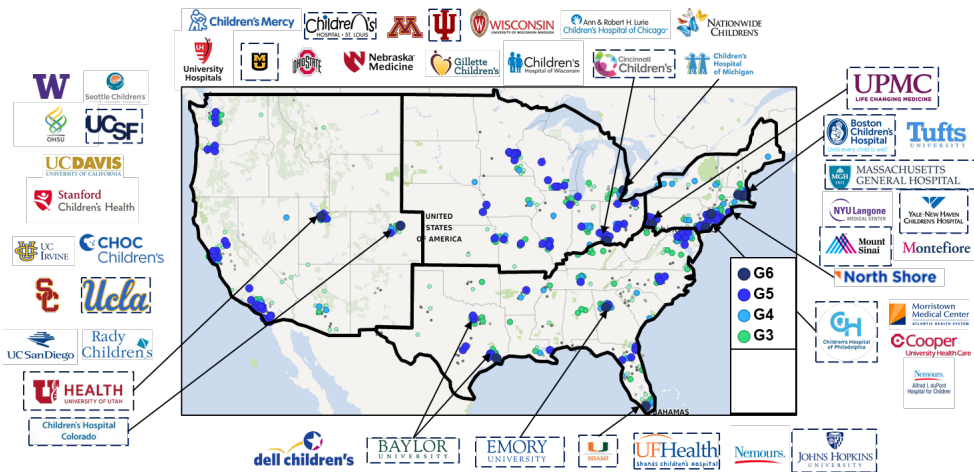
- Majority of claims coding for Galactosemia ≤ 18 yr
- Top 3 states (FL, CA, TX) have ~30% of all claims

Projected Claims by Age and Sex (All States)

Age Group	Female	Male	Grand Total
<2	313	264	577
2-6	456	543	999
7-12	210	204	414
13-18	155	138	294
19-34	219	192	410
35-54	112	82	194
55-64	43	38	81
65+	60	54	114
Grand Total	1568	1515	3083

Focus on Centers of Excellence; Small Commercial Footprint Required

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



Key Findings

- KOLs are concentrated at Medical Genetics Centers of Excellence
- >90% of KOLs are Medical Geneticists
- Pediatricians comprise majority of remaining KOLs



AT-007 Commercial Opportunity

Significant unmet need with no approved treatment

Potential for pricing in-line with other rare diseases

Caregiver / patient and HCP enthusiasm and willingness to ask for / Rx at launch

Appealing product profile, including oral once-daily dosing and favorable safety profile

Relatively small commercial footprint to be focused on Centers of Excellence

Exclusivity through 2037 and possible regulatory extension of term

Potential to be the first disease-modifying therapy for Galactosemia

AT-007 SORD DEFICIENCY

Preclinical proof of concept demonstrated

Phase 2 pilot study initiated



SORD Deficiency is One of the Most Common Recessive Causes of Hereditary Neuropathy, Impacting ~3,000 US Patients

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

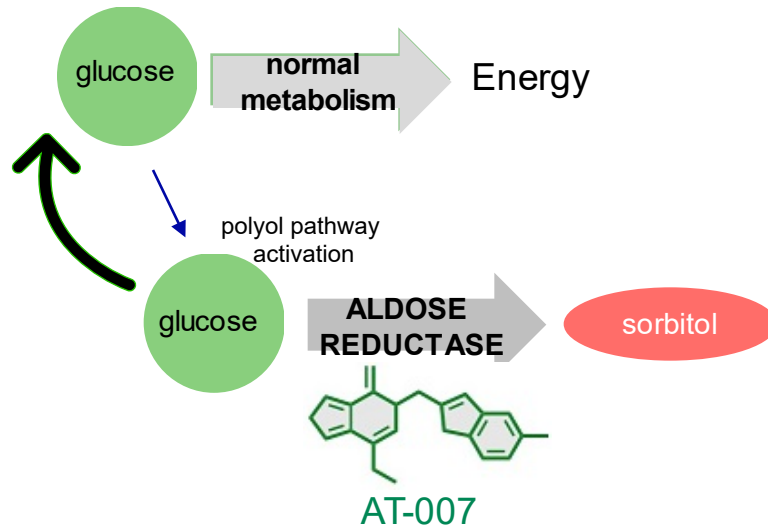
Recently identified mutations in the SORD gene resulting in **loss of enzyme Sorbitol Dehydrogenase (SORD) function** and consequent **intracellular sorbitol accumulation**

Previously, these patients were diagnosed as a subset of patients with Charcot-Marie-Tooth disease Type 2 (CMT2) or Distal Hereditary Motor Neuropathy (dHMN)

~3,300 individuals in the US with SORD Deficiency (~7-9% CMT2/dHMN patients)

SORD's **role in metabolism is well defined**, and an understanding of this genetic and biochemical basis of disease offers **new opportunities for treatment** of patients with neuropathy caused by SORD deficiency

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



- Patients have very high levels of sorbitol in their cells and tissues as a result of SORD enzyme deficiency
- High toxic sorbitol levels results in cell death and tissue degeneration, such as neuropathy.
- AT-007 significantly reduces sorbitol levels in SORD patient fibroblasts



Applied Therapeutics, data on file; pilot study

AT-007: Potential First Therapy for SORD Deficiency

High Unmet Need in SORD

- No approved therapies; limited pipeline for generalized CMT2
- Causes substantial decrease in patient QoL
- Diagnosed in early stage, where treatment may prevent disability progression and positively impact prognosis and QoL

AT-007 Opportunity

- Validated mechanism of action, penetrates CNS
- Favorable safety & tolerability profile
- Convenient oral dosing to optimize adherence and minimize patient burden
- Sorbitol reduction biomarker based clinical development for Accelerated Approval
- Ph 2 pilot trial initiated in SORD patients; larger registrational study design underway

AT-007 is expected to be the first disease-modifying therapy for SORD, targeting the underlying cause of disease

AT-007

PMM2-CDG

Preclinical proof of concept

Phase 2 expected 2021



What is PMM2-CDG?

Glycosylation is a process by which sugars are chemically attached to proteins to form glycoproteins, which are required by crucial functions within the human body

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**

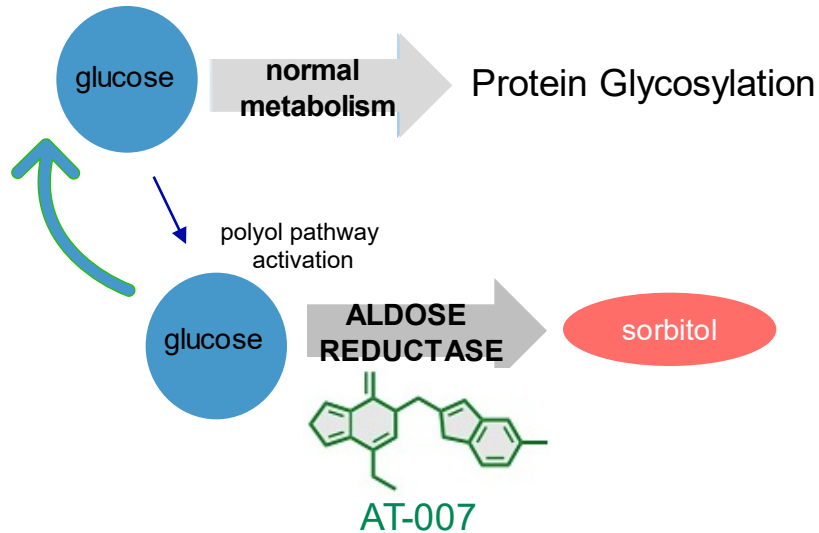
Level of PMM2-CDG activity correlates with severity of disease

PMM2-CDG is the most common congenital disorder of glycosylation

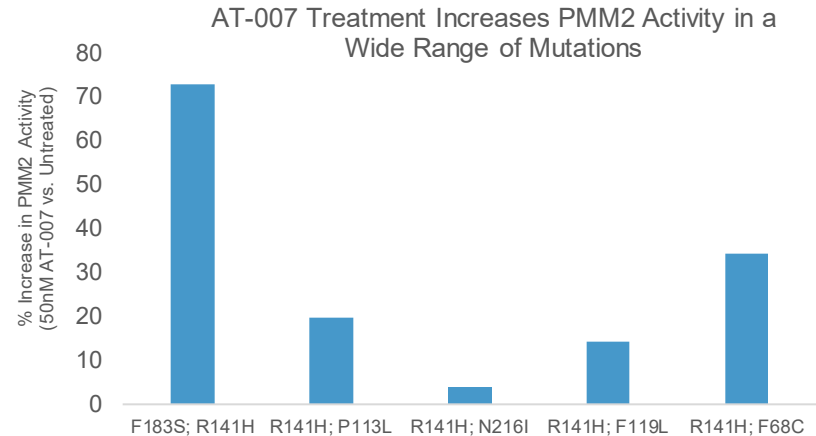
Diagnosed within the **first year of life** by pediatrician or pediatric neurologist based on clinical presentation; confirmed by medical geneticist at center of excellence

[†]PMM2-CDG = Phosphomannomutase-2 Deficiency, a Clinical Disorder of Glycosylation disease

Aldose Reductase Inhibition Improves PMM2 Activity, Addressing the Underlying Cause of PMM2-CDG¹⁻³



- 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



AT-007: Potential First Therapy for PMM2-CDG

High Unmet Need in PMM2-CDG

- No approved therapies
- ~1,000 cases worldwide, with ~20% infant mortality
- Significant impact on QoL and patient morbidity/mortality
- Disease management is complex: symptoms are managed through supportive multidisciplinary care – nothing to prevent underlying pathogenesis of disease

AT-007 Opportunity

- Validated MOA, penetrates CNS
- Favorable safety & tolerability profile
- Convenient oral dosing to optimize adherence and minimize patient burden
- Low burden of development due to biomarker-based program under new FDA guidance for low prevalence diseases[†]
- Relatively small commercial footprint to be focused on COEs

Proof of concept preclinical study and single patient compassionate use with epalrestat supports the rationale for clinical development
Clinicians and regulators are working together to develop a robust study

AT-007 is expected to be the first disease-modifying therapy for PMM2-CDG, directly targeting the underlying cause of disease

[†]Diseases with less than 5,000 US patients are termed "low prevalence"

AT-001

DIABETIC CARDIOMYOPATHY

Ph 3 initiated in Q3 2019

Data read-out expected YE 2022



What is Diabetic Cardiomyopathy (DbCM)?

DbCM is a **form of heart failure (Stage B)**, diagnosed by echocardiogram, in which structural cardiac damage has occurred, resulting in decreased cardiac functional capacity

Hyperactivation of the **polyol pathway is a key underlying mechanism in DbCM and other diabetic complications**. In hyperglycemic and ischemic conditions, this pathway — **via Aldose Reductase (AR)** — causes intracellular sorbitol accumulation, osmotic stress, cell death, and generation of ROS

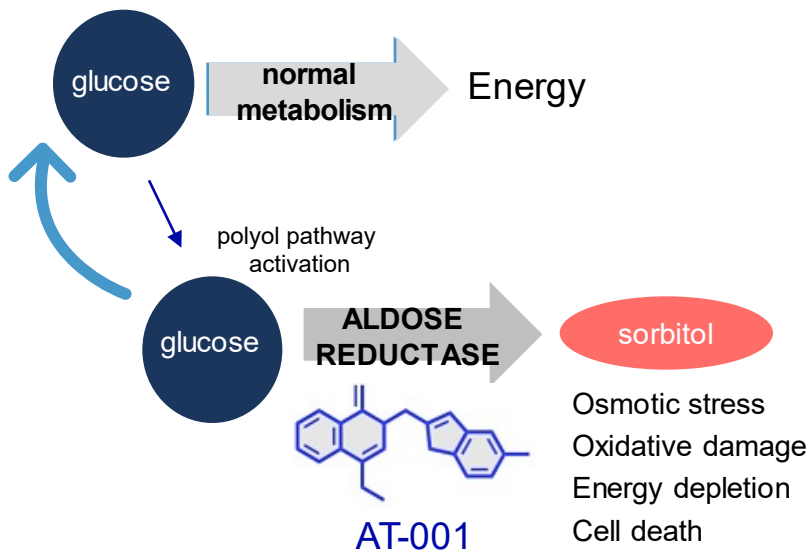
There are no approved therapies for DbCM, which affects ~17% of people with diabetes

~25% of patients with DbCM progress to overt heart failure or death within 1.5 years of diagnosis

Previous AR inhibitors studied in diabetic complications (including DbCM) **demonstrated clinical efficacy**, but were **associated with off-target safety signals** due to lack of selectivity and specificity

In Phase 1/2 trials, **AT-001 significantly reduced levels of sorbitol, a key toxic biomarker of Aldose Reductase function**, to the same levels as healthy volunteers

DbCM: Mechanism of Disease



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

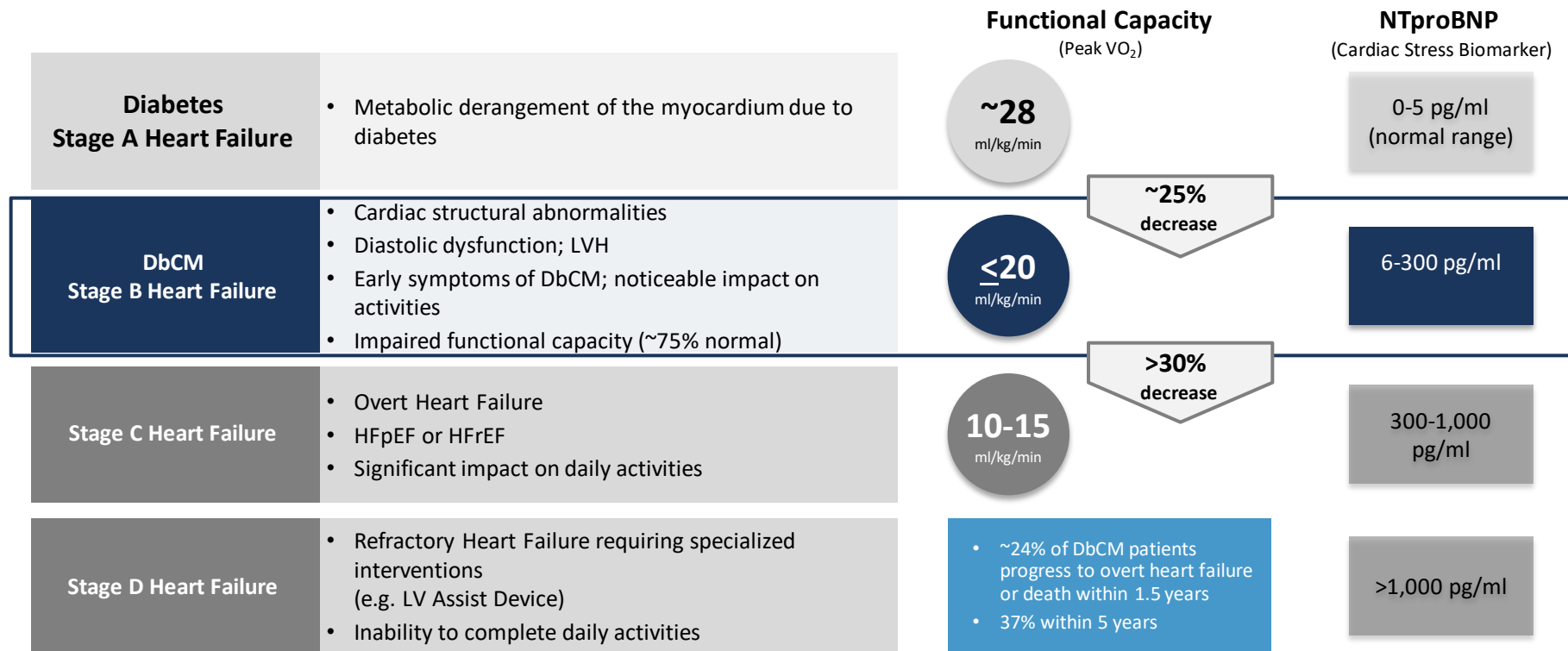
Aldose Reductase (the first and rate limiting enzyme in the polyol pathway) converts this glucose into **sorbitol** and eventually **fructose**

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

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

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

Diabetic Cardiomyopathy is a Form of Stage B Heart Failure



No Current Treatments for DbCM

Patients present clinically with shortness of breath on exertion due to decreased cardiac functional capacity

Structural heart disease confirmed/ DbCM diagnosed by echocardiogram

No treatments exist; patients counseled on lifestyle modification to improve compounding risk factors

DbCM occurs in both Type 1 and Type 2 diabetics, despite glucose control

AT-001 Phase 1/2 Trial in Type 2 Diabetes Demonstrated Safety, Clinical Proof-of-Concept via Normalization of Sorbitol & Effect on NTproBNP

Dose Range Finding

80 T2D Participants[†] | 7 Days

Endpoints / Results

Safe and well tolerated

Normalization of sorbitol (PD biomarker)

Single Ascending Dose (n=40)

5mg/kg
10mg/kg
20mg/kg
40mg/kg
Placebo

Multiple Ascending Dose (n=40, 7 days)

QD: 5mg/kg – 20mg/kg – 40mg/kg
BID: 20mg/kg
Placebo

Biomarker-Based Outcome

26 DbCM Participants | 28 Days

Endpoints/ Results

Safety: No drug-related AEs or abnormal labs[†]

Effect on cardiac biomarker NTproBNP

1,500mg BID Dosing (n=10)

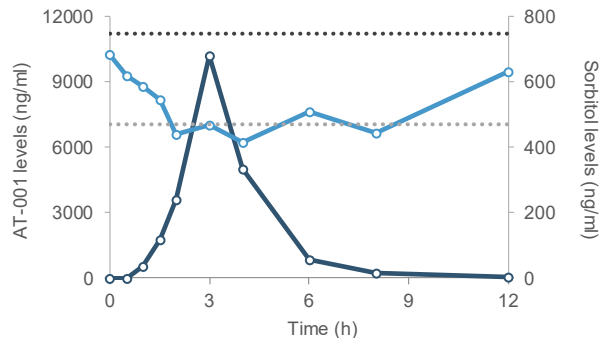
1,000mg TID Dosing (n=10)

Placebo (n=6)

[†]All participants remained on concomitant medications

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

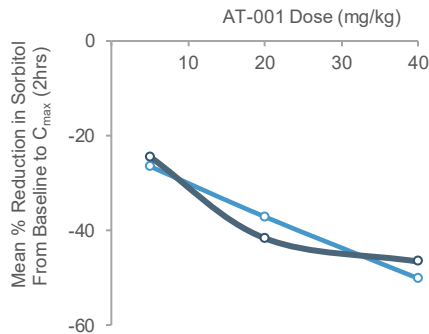
Proof of Biological Activity



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

AT-001 normalized sorbitol in diabetics to healthy volunteer levels

Sorbitol Reduction by Dose

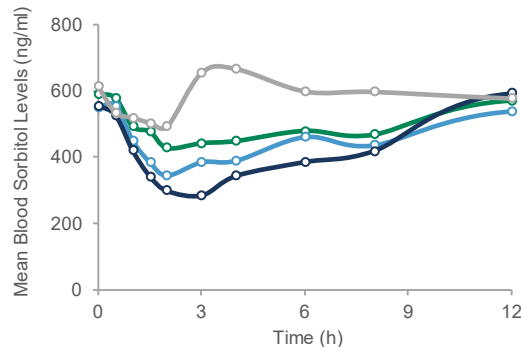


— Day 1 — Day 7

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

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

Sorbitol Normalization Over Time



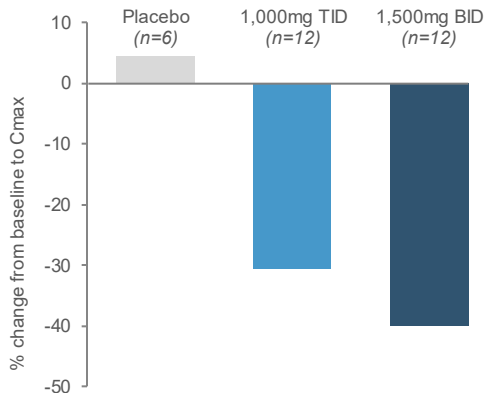
— Placebo — 5mg/kg
 — 20mg/kg — 40mg/kg

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

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

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

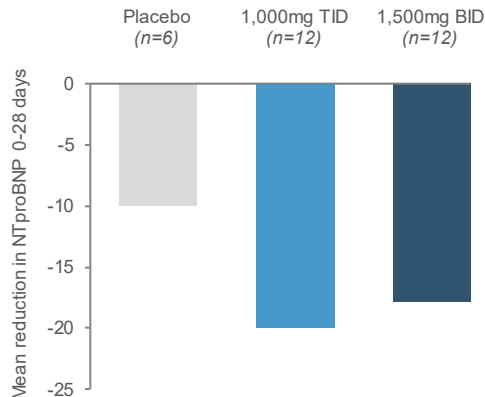
Sorbitol Normalization



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

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

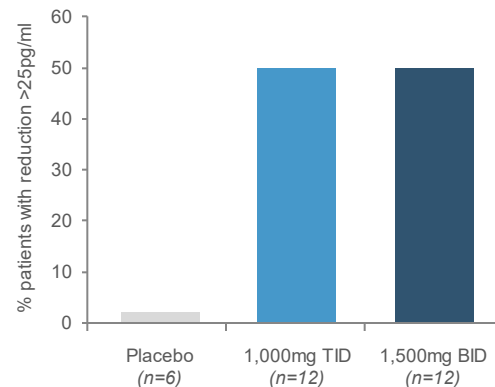
Mean Reduction in NTproBNP



Mean reduction in NTproBNP seen over 28 days vs. placebo

Mean baseline NTproBNP was 65pg/ml

Clinical Responder Analysis

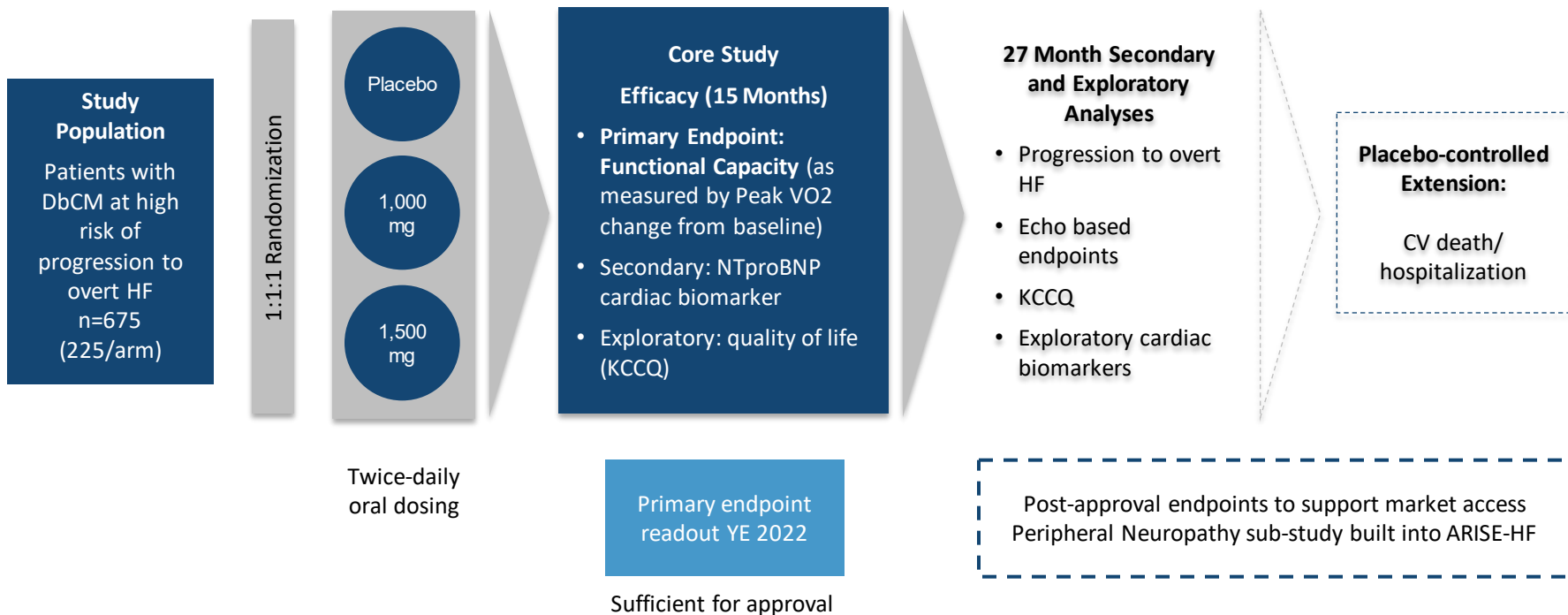


~50% AT-001 treated patients demonstrated a clinically meaningful reduction in NTproBNP over 28 days

>25pg/ml reduction from baseline

DbCM Phase 3 Registrational Study (ARISE-HF)

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



ARISE-HF: Study Objectives

Primary Efficacy Objective

To demonstrate that AT-001 improves or prevents the decline of cardiac functional capacity in patients with Diabetic Cardiomyopathy (DbCM) at high risk of progression to overt heart failure

Secondary Efficacy Objective

To demonstrate that AT-001 decreases the progression to overt heart failure (Stage C HF)

The background features a faded image of a smiling couple, a man and a woman, looking towards the left. Overlaid on this are faint chemical structures, including a benzene ring with a substituent, a water molecule (H₂O), and a molecular framework with arrows indicating electron flow or reaction pathways.

AT-001 Has Potential to be First Product to Treat DbCM, a Form of HF Affecting 17% of Diabetics

Appealing product profile, with convenient oral dosing; safe and well-tolerated

Significant unmet need with no approved treatment

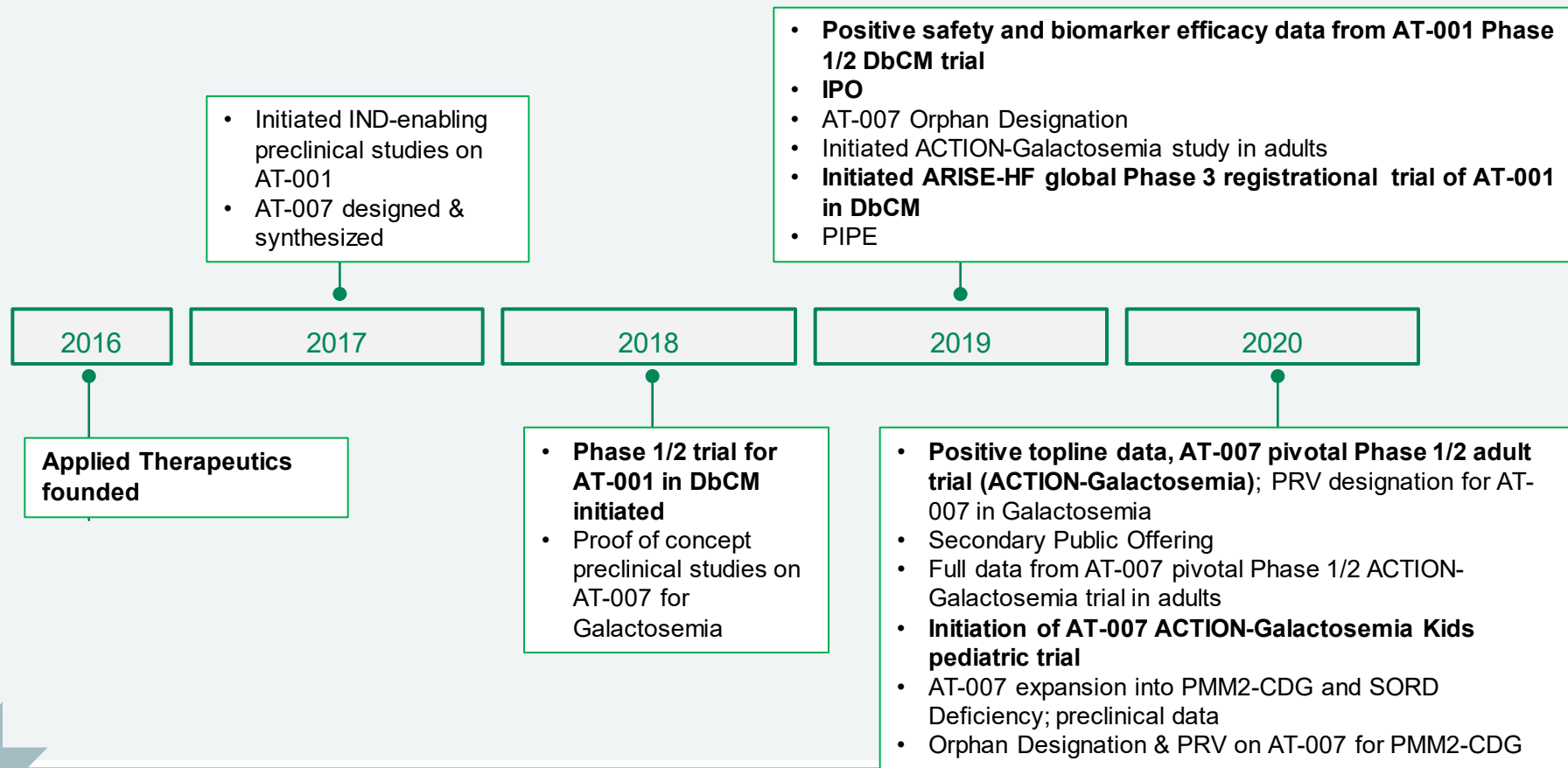
Potential for pricing in-line with SGLT2s and Entresto

Diagnosis confirmed by echocardiogram

Exclusivity through 2031 and possible regulatory extension of term

Potential to be first product approved to treat DbCM

Significant Progress Over Four Years Supports Strategy and Execution



Intellectual Property Summary

Composition of matter patents and freedom to operate on key compounds

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

In-licensed composition of matter patents that cover AT-007 and related compounds (US)

- 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

In-licensed composition of matter patents that cover AT-001 and related compounds (US, EP, JP, CA and AU)

- Patent protection through 2031, regulatory extension of term possible
- Method claims obtained or currently being pursued

Company-owned patent applications that cover methods for treating Galactosemia are pending in 13 countries, and a company-owned international application (PCT) that covers additional compound derivatives is pending

Company-owned provisional patent applications that cover methods for treating PMM2 deficiency and other indications are pending