Applied Therapeutics

Corporate Presentation

September 2021

APPLIED THERAPEUTICS

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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

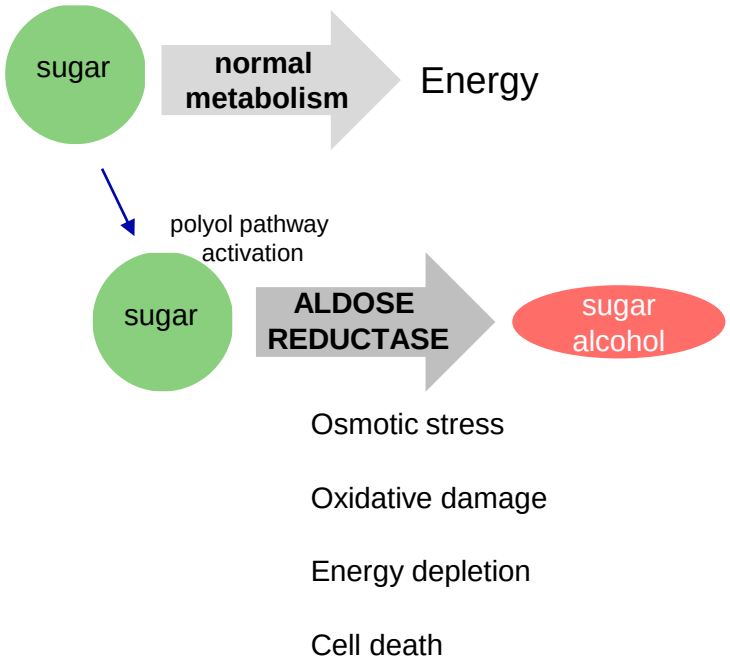
Limited / no competition

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 Q4 2021	
AT-007	SORD Deficiency				Oral	CNS	Pilot study underway; Registrational study Q4 2021	
AT-007	PMM2-CDG				Oral	CNS	Phase 2 ready- clinical study start 2021; Expanded Access open	
AT-001	Diabetic Cardiomyopathy – Pivotal Phase 3 Study				BID Oral	Systemic	Ph 3 trial initiated in Q3 2019; data 1H '23	
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

- Orphan Drug Designation
- Pediatric Rare Disease Designation (PRV)
- Fast-Track Designation

Positive adult biomarker data; LTE ongoing

Pediatric trial ongoing

NDA expected Q4 2021

APPLIED THERAPEUTICS

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
- **Small commercial footprint** required to launch quickly and effectively; strong community engagement with disease state awareness efforts reflects underlying demand
- Patent exclusivity through 2037; Orphan and Pediatric Rare Disease designations granted

Galactosemia Development History

1940-1956	LeLoir Pathway discovered; deficiency in galactose metabolism identified as cause of disease by Kalckar et al
1990s	2 different disease hypotheses emerge: 1) Gal-1p hypothesized to be responsible for disease pathogenesis due to absence of GALK patients with defined phenotype; 2) Galactitol hypothesized to be responsible for pathogenesis due to known toxicity of sugar alcohols and autopsies demonstrating high galactitol in the brain of Galactosemia infants
1995	GALT null mouse genetically engineered. Displays high galactose and Gal-1p, but no galactitol (mice don't express AR) resulting in no disease phenotype; suggests galactitol, not Gal-1p, responsible for disease.
2005	Newborn screening becomes mandatory in the US; Broad acceptance at the time that newborn screening + dietary implementation would prevent disease; Unfortunately this did prevent newborn deaths but not long-term complications.
2004	Endogenous galactose production discovered. As the body produces galactose at 10X levels ingested on a Galactosemia diet, this explained long-term complications and raised recognition that diet is not enough.
2011	First large study of GALK-deficient patients in Germany, demonstrating disease phenotype similar to GALT-deficient patients. GALK patients have high galactose and galactitol, but do not produce Gal-1p.
2018	GALT null rat genetically engineered. Displays high galactose, Gal-1p and galactitol and develops CNS abnormalities and cataracts; again, suggests galactitol (not Gal-1p) is responsible for disease phenotype.
2019	GALT null rat treated with Aldoses Reductase Inhibitor (AT-007). Galactitol reduction normalized CNS phenotype and prevented cataracts. Galactitol confirmed as pathogenic cause of Galactosemia.

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

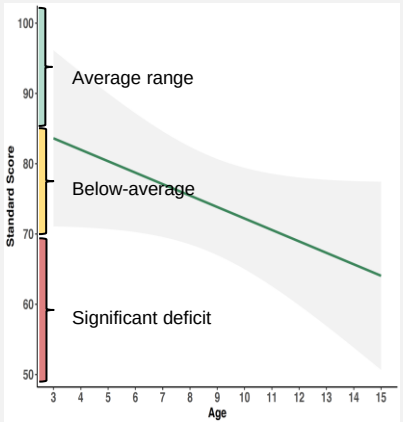
- Puberty and fertility problems (females)
- Growth delays
- Anxiety
- Social problems
- Learning difficulties
- Tremor

Adult

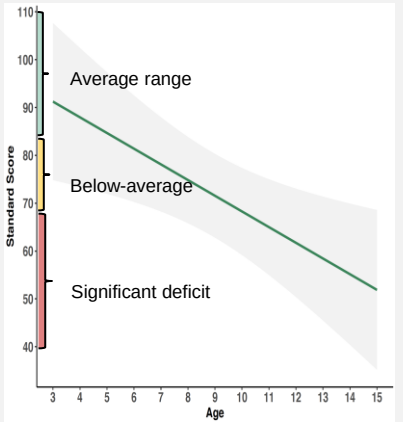
- Tremor
- Seizures
- Anxiety
- Depression
- Attention Deficit Hyperactivity Disorder (ADHD)
- Cataracts

Cross Sectional Analysis of Outcomes on 19 Children Age 3-15 Demonstrates Significant Progressive Worsening of Disease Over Time

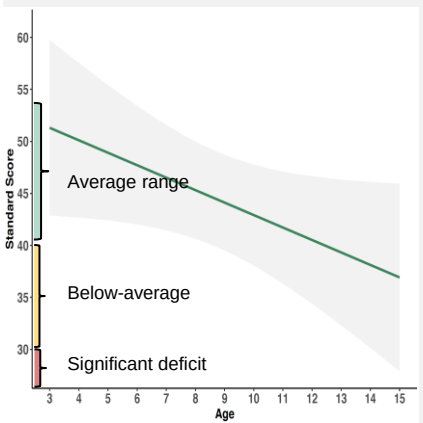
Speech



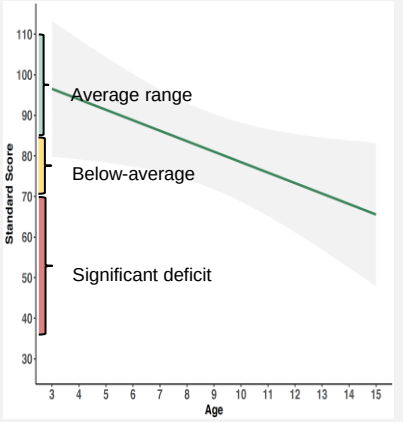
Cognition



Adaptive Behavior



Motor Skills



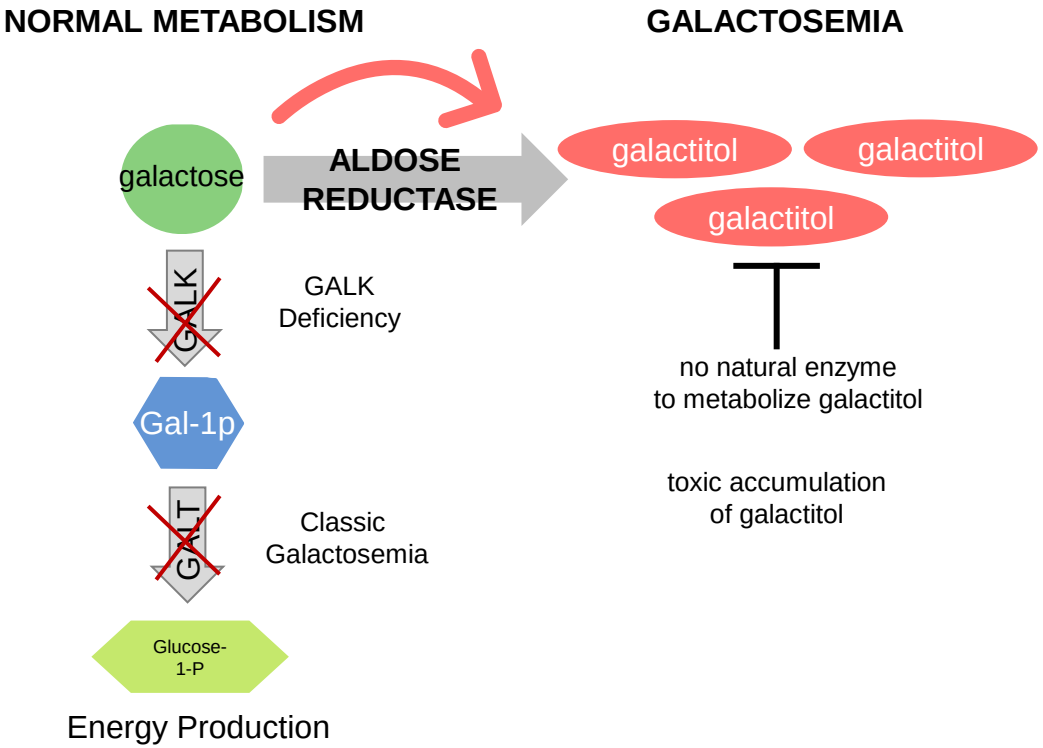
Abstract eP011: Progressive Worsening of Central Nervous System Phenotype in Children with Classic Galactosemia: a Cross-Sectional Analysis;; ACMG 2021 conference

Behavior Assessment Scales for Children (BASC) utilized for adaptive behavior

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

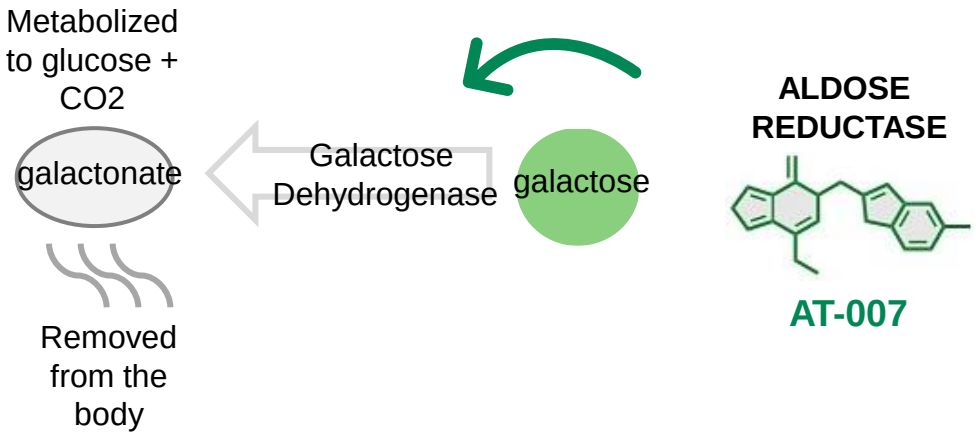
Aldose Reductase Converts Excess Galactose to Toxic Galactitol

- Galactitol is an aberrant metabolite
- Healthy people (without Galactosemia) do not have measurable levels of galactitol in blood or tissues
- Mean plasma galactitol level for adults with Galactosemia on a restricted diet in ACTION-Galactosemia study was ~2,500ng/mL
- Mean plasma galactitol level for children with Galactosemia on a restricted diet in ACTION-Galactosemia-Kids was ~2,000ng/mL

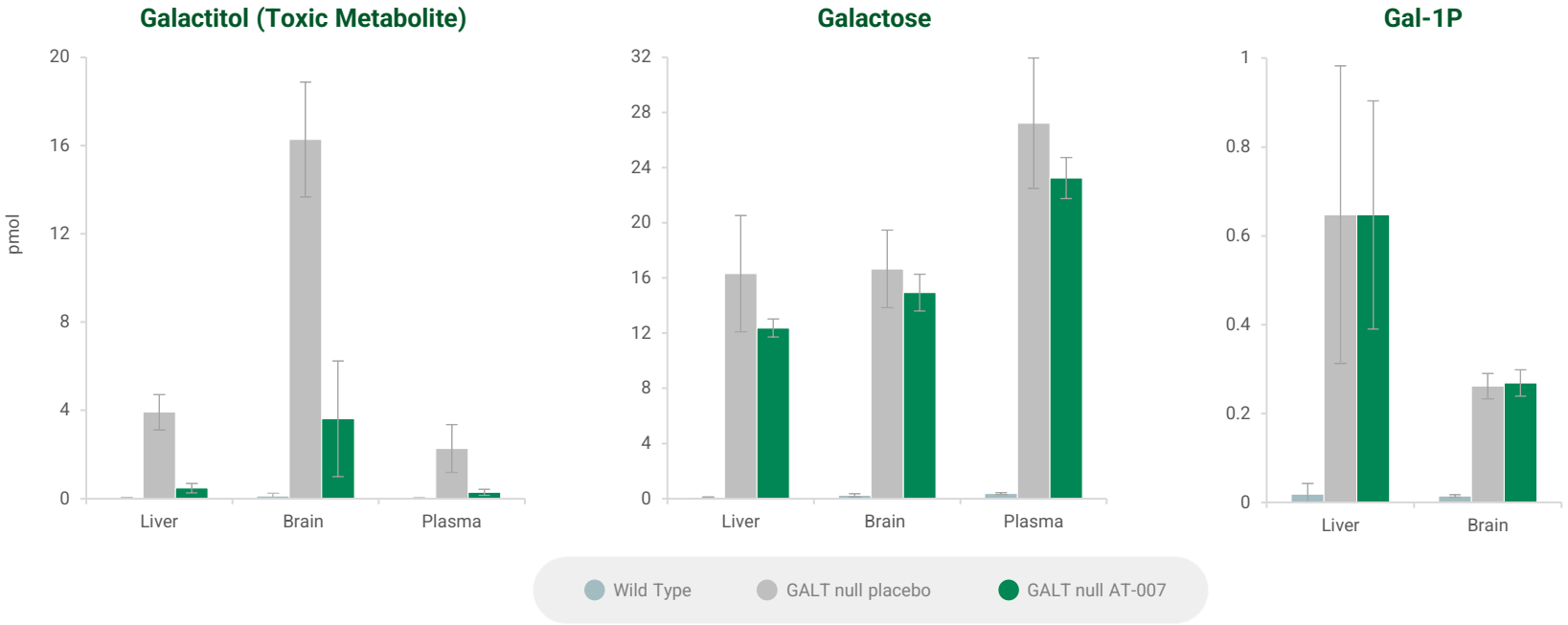


AT-007 Blocks Aldose Reductase Conversion of Galactose to Galactitol

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



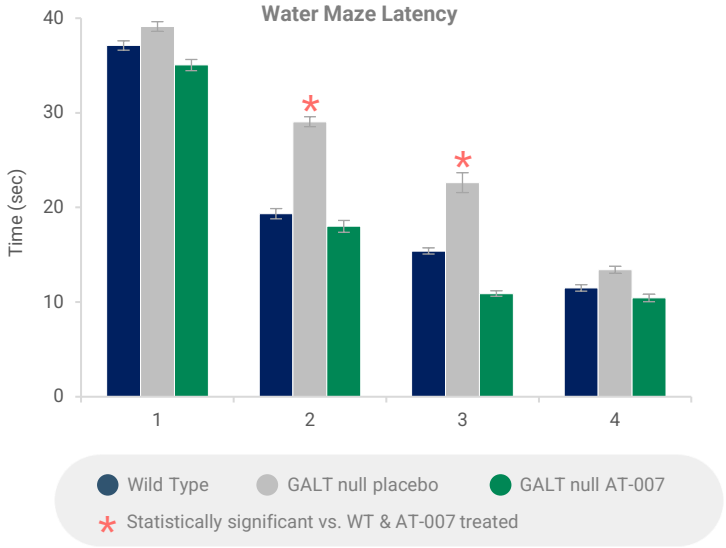
AT-007 Significantly Reduces Toxic Galactitol Levels in All Target Tissues Without Increasing Galactose or Gal-1P



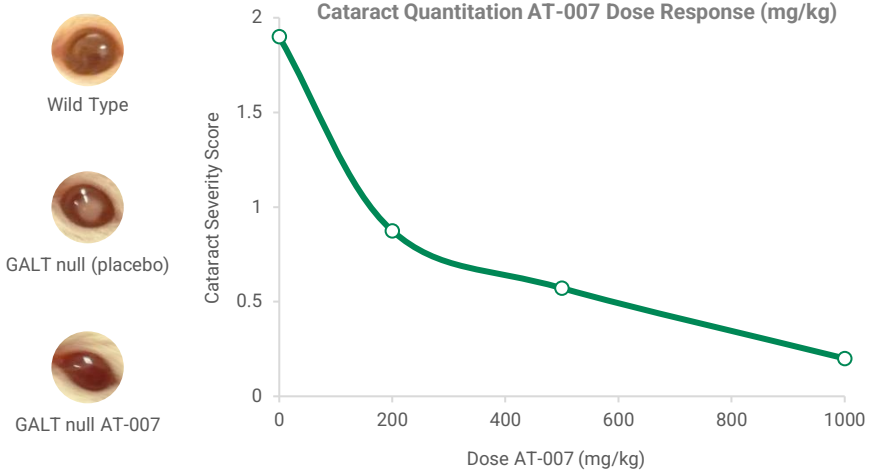
AT-007 treatment from neonatal Day 1 to Day 10 significantly reduced galactitol in liver, brain and plasma
AT-007 treatment did not increase galactose or Gal-1P levels; similar results seen at Day 22 and age 5 months

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



In contrast, GALT null mouse did not display a phenotype – GALT null mice display high galactose + Gal1-p but not galactitol (mice don't express AR)

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

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)**

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

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)
40 mg/kg* Single dose	40mg/kg 27 Days Daily Dosing (n=4)
Placebo Single dose	Placebo 27 Days Daily Dosing (n=6)

3 Month Extension

*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

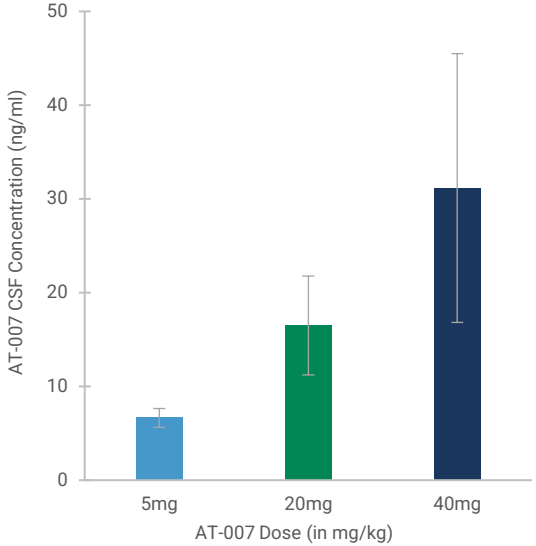
Safety

~80 healthy volunteers treated

AT-007 was safe and well tolerated at all doses

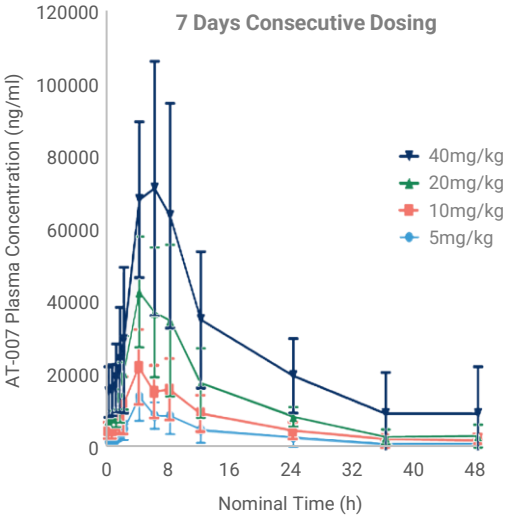
Brain Penetrance

Drug crosses into brain when dosed orally (CNS penetrant)



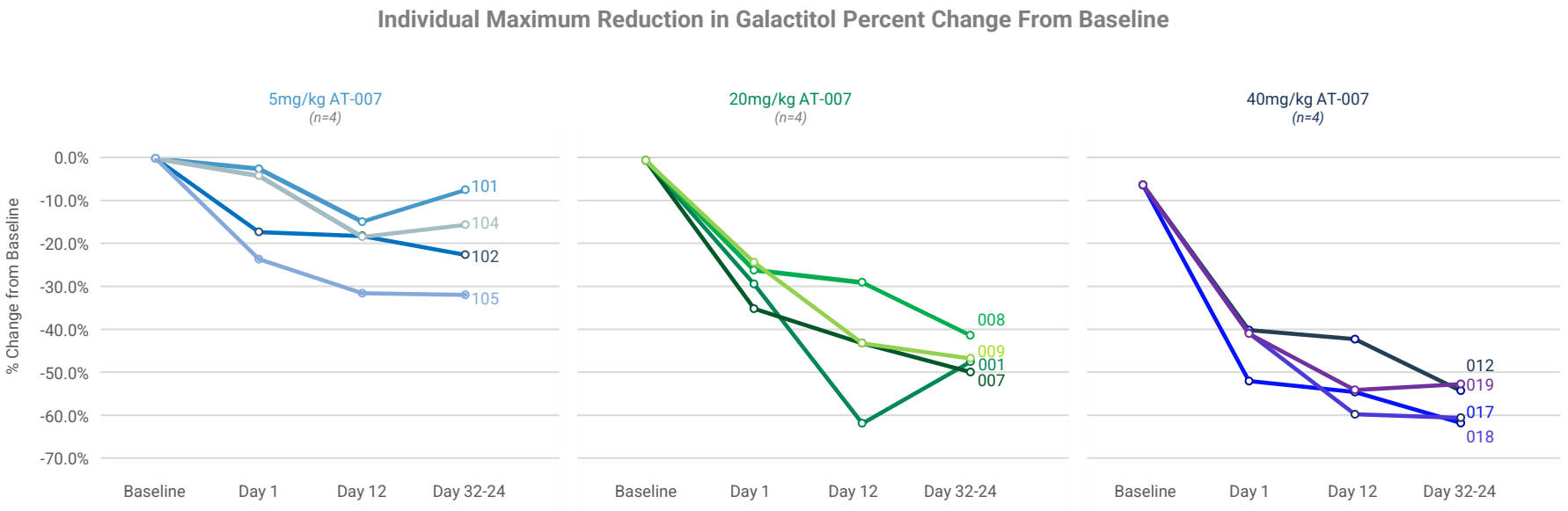
Pharmacokinetics

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



AT-007 Decreased Galactitol Levels in All Treated Patients

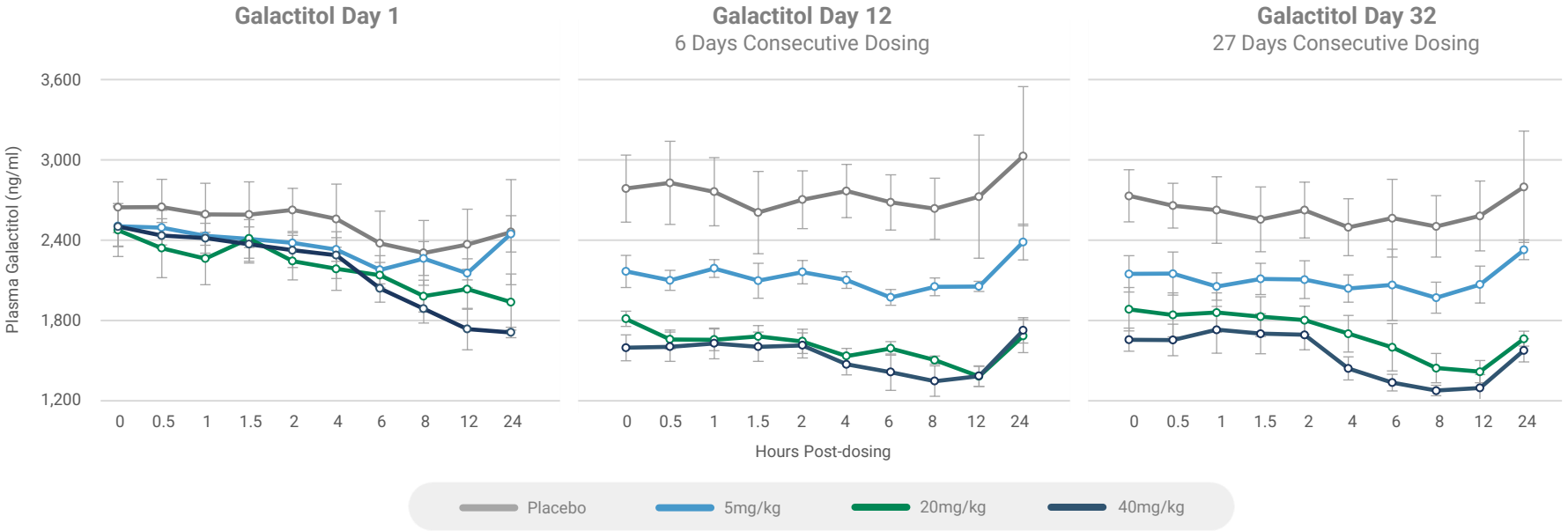
Decrease was dose-dependent, rapid and sustained; statistically significant at 20 & 40mg/kg



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

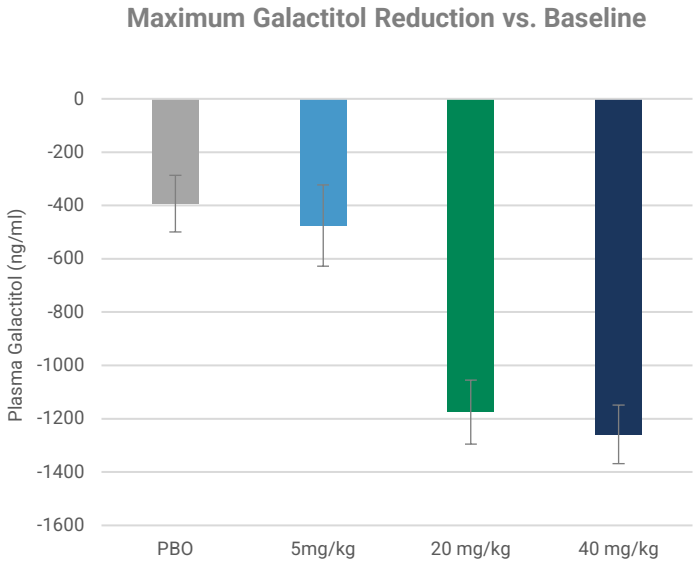
AT-007 Galactitol Reduction is Rapid and Sustained, Beginning on 1st Day of Treatment and Sustained Over 1 Month of Treatment

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

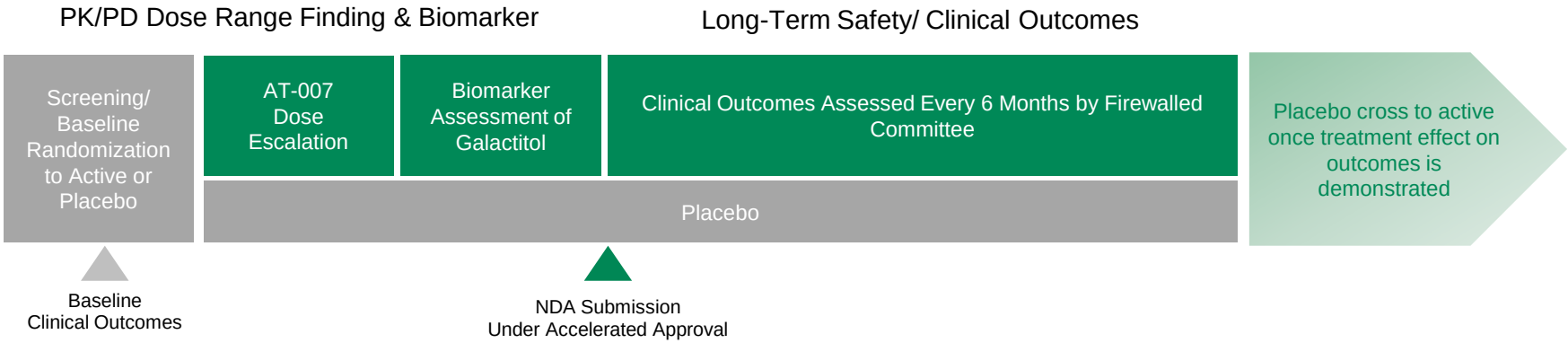
- Favorable safety and tolerability in core study and 3-month extension

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 Battey: 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

Baseline Characteristics of Children Enrolled in ACTION-Galactosemia Kids

AGE	GENDER	RACE	Allele 1	Allele 2
16	Female	White	Q188R	other
16	Female	White	Q188R	other
13	Male	White	Q188R	Y209C
13	Male	White	K285N	K285N
14	Female	White	Q188R	other
15	Male	White	in process	in process
13	Female	White	in process	in process
16	Female	White	in process	in process
13	Male	White	in process	in process
13	Female	White	in process	in process
16	Male	White	Q188R	Q188R
16	Female	White	Q188R	other
10	Female	Hispanic	Q188R	Q188R
10	Male	White	Q188R	Q188R
10	Male	White	Q188R	N314D
12	Male	White	Q188R	Q188R
10	Female	White	Q188R	Y209C
7	Male	White	Q188R	Q188R
2	Male	White	Q188R	other
13	Female	White	Q188R	Q188R
7	Male	White	Q188R	M142K
5	Male	White	Q188R	K285N
6	Female	White	Q188R	K285N
4	Female	White	in process	in process

AGE	GENDER	RACE	Allele 1	Allele 2
12	Female	White	Q188R	other
11	Female	White	Q188R	other
9	Female	White	Q188R	L195P
9	Male	White	Q188R	other
12	Male	White	K285N	other
10	Male	White	K285N	other
9	Male	White	K285N	other
7	Male	White	other	other
12	Female	White	S135L	other
8	Female	White	Q188R	Deletion 5kb
8	Female	White	Q188R	Q188R
7	Male	White	in process	in process
4	Female	White	Q188R	other
4	Female	White	Q188R	Q188R
3	Female	White	Q188R	Q188R
5	Male	White	Q188R	K285N
6	Male	White	N314D	Y209C
5	Female	White	K285N	other
3	Male	White	K285N	other
4	Male	White	Q188R	L195P
3	Female	White	Q188R	Q188R
6	Female	White	Q188R	Q334K
2	Male	White	in process	in process

Summary Baseline Characteristics

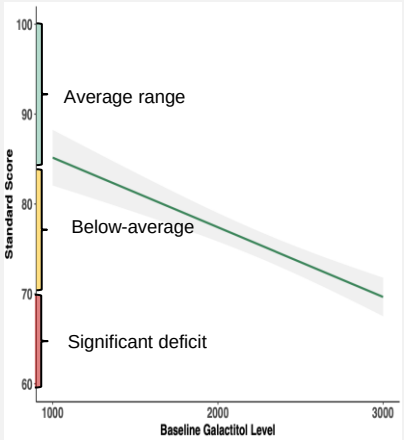
Mean Age	Gender	Race	Genetics*
9	24 Female	46 White	homozygous Q188R (10); homozygous K285N (1); compound heterozygous (28); in process (8)
	23 Male	1 Hispanic	

*Genetic mutational analysis still pending for some patients

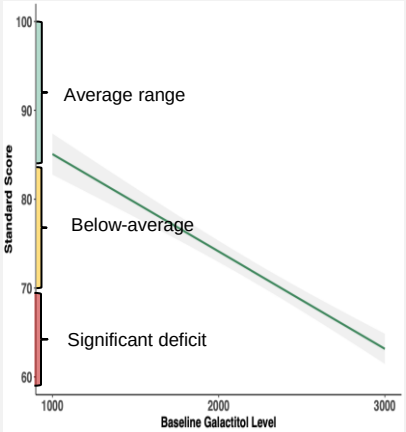
Plasma Galactitol Level at Baseline Correlates with Severity of Disease

Analysis of the 47 children in the ACTION-Galactosemia Kids study demonstrated a correlation between baseline galactitol level and baseline clinical functional outcomes

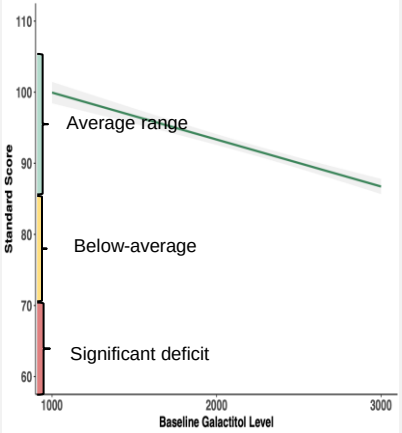
Speech



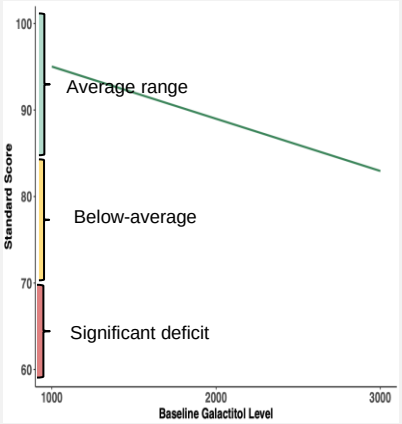
Cognition



Adaptive Behavior



Motor Skills



- Broad range of GALT mutations captured in the large number of children studied in ACTION-Galactosemia Kids permitted an analysis of a wide range of baseline galactitol with severity of disease.
- This data is the first demonstration of correlation of a biochemical biomarker with severity of disease in Galactosemia patients. Full data will be presented at a future medical conference.

Vineland Adaptive Behavior Scales utilized for adaptive behavior

Initial Pediatric Biomarker Data Demonstrates Substantial and Statistically Significant Reduction in Plasma Galactitol at Day 30

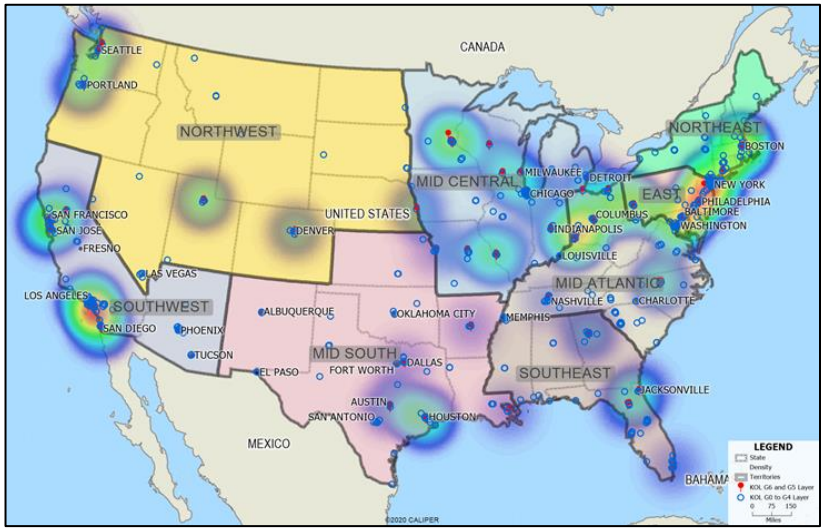
Opportunity for Increased Dose in Children with Low Body Weight to Optimize Exposure

- AT-007 treatment at the current doses resulted in 35% reduction in plasma galactitol at Day 30 ($p<0.001$ vs. placebo)
- AT-007 was safe and well tolerated in children of all ages (2-17)
- Pharmacokinetic analysis of drug exposure levels performed in parallel demonstrated that a dose adjustment may optimize exposure in children with low body weight
- Biomarker data will be re-analyzed once Day 30 is completed in children who received a dose adjustment

Age Group	% Reduction from baseline	Statistics
13-17	29.4%	$p<0.05$
7-12	39.2%	$p=0.001$
2-6	35.5%	$p<0.001$
All ages combined (2-17)	**35%**	**$p<0.001$**

Commercial Strategy:
Potential U.S. Launch Will Focus on Medical Geneticists

Preliminary U.S. Sales Territory Heat Map



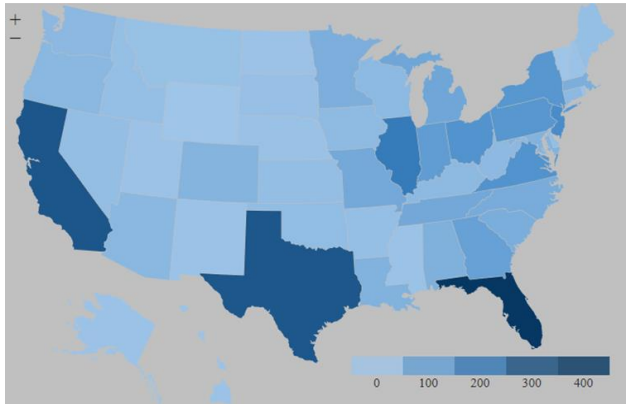
Commercialization Plan Linked to Opportunity:

- Small specialty sales force focused on high-volume providers @ COEs
- Efficient digital marketing to educate lower volume specialists and facilitate non-personal promotion
- Robust patient services program to support patient on-boarding, compliance and persistence
- Pricing expected to be in-line with similar rare disease therapies for conditions of high unmet need
- U.S. Galactosemia patients have largely Commercial or Government coverage

KOL Mapping Analysis, MD Details, April 2020

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)

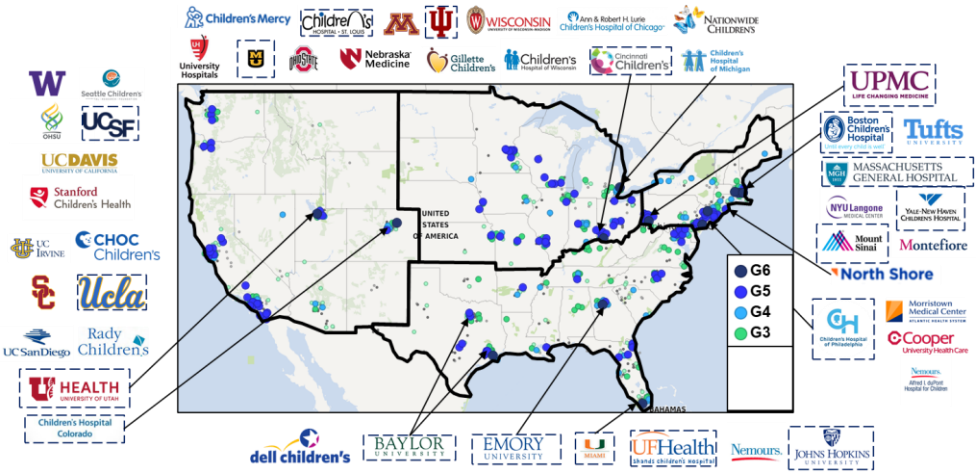
Age Group	Female	Male	Grand Total
<2	313	264	577
2-6	456	543	999
7-12	210	204	414
13-18	155	138	294
19-34	219	192	410
35-54	112	82	194
55-64	43	38	81
65+	60	54	114
Grand Total	1568	1515	3083

Decision Resources Group, Galactosemia Claims Data Report, June 3, 2020.

Galactosemia KOL Mapping Analysis:

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

MD Details Galactosemia KOL Mapping Report, 2020

Market Research Indicates High Patient and HCP Interest in New Treatment; Payers Anticipate Covering Similar to Other Rare Disease Products

HCP Market Research[1]

- **100% responded 'yes' when asked if they would Rx** for their patients
- Most want to see long-term clinical outcomes, but are **willing to use upon biomarker approval if safe and well tolerated**

"It's hard - no matter how strict, how compliant, they are still going to get long term complications, even those we identify early on. It's frustrating. So variable. Even if you have siblings, even if you have the same mutation."

"I can save their lives, but I'm not saving their brains... that's disappointing."

Patient Market Research[1]

- Families are **very excited** about the prospect of a treatment; **100% responded 'yes' when asked if they would ask for this Tx / give to their child**
- Willing to use if proven "safe," even if efficacy data is not long-term
- **Sense of urgency to use as early as possible**, to prevent issues before they begin
- Families with school-age children and those who are severely affected are **very attuned to developmental delays and concerned about CNS symptoms that develop later, like seizures**

U.S. Payer Market Research[2]

- Payers liked the **fast onset and sustained reduction in galactitol, no concerns with safety profile, reacted favorably to QD dosing and ability to penetrate CNS**
- Noted **similarity to other orphan drugs with only biomarker efficacy** at launch and later long-term outcomes; **will cover if approved with only biomarker-based endpoint**
- Payers expect AT-007 to be **managed similarly to other rare metabolic therapies,** covered on specialty tier, with PA to trial criteria and re-authorization based on patient biomarker response to therapy

1. Galactosemia HCP & Patient Journey Market Research, June 3, 2020 2. Trinity Partners Payer Insights Report, July 14 2020. Market Research included 5 US Payers. US screening criteria limited to Pharmacy Directors at larger national or regional plans that cover > 5M lives, familiar with rare metabolic disorders and currently vote on P&T Committee for rare metabolic disorders

Award-Winning Disease State Awareness Campaign Effectively Engaging with and Educating the Galactosemia Community Prior to Launch

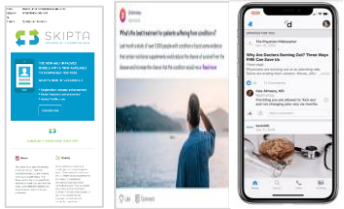
HCP

MEDIA

Web Health Network

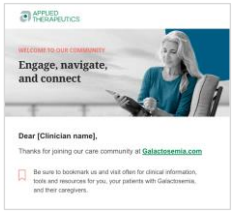
Medscape

SOCIAL



SKIPTA sermo doximity

EMAIL

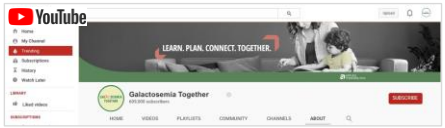


3D MOD VIDEO

HCP & PATIENT / CAREGIVER

WWW.GALACTOSEMIA.COM

YOUTUBE



SEARCH

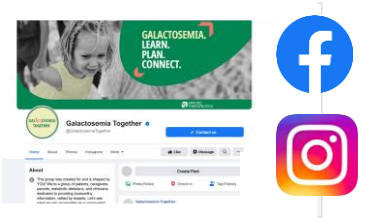
Google Microsoft Bing

PATIENT / CAREGIVER

MEDIA

WebMD

SOCIAL



2D MOD VIDEO

EMAIL

PM360 "Top 2020 DSA Campaign;" Fierce Pharma "Best Websites for Consumers;" DTC National "Best Disease Education Websites."

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

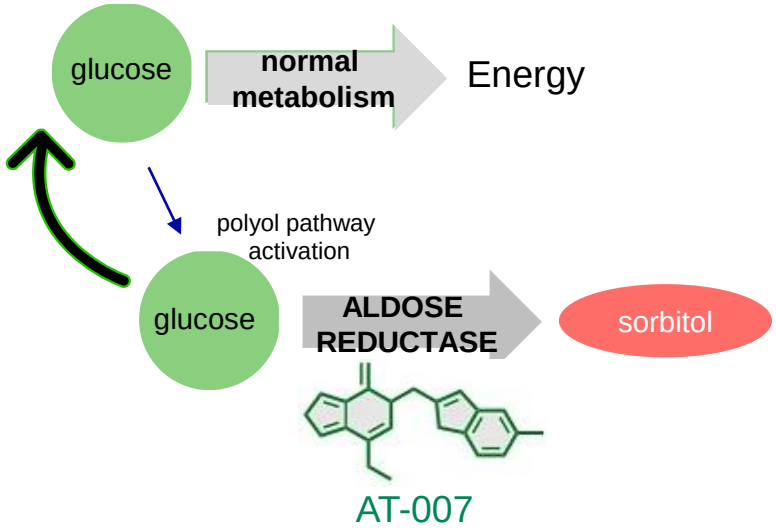
Pilot study ongoing; Registrational study expected Q4 2021

APPLIED THERAPEUTICS

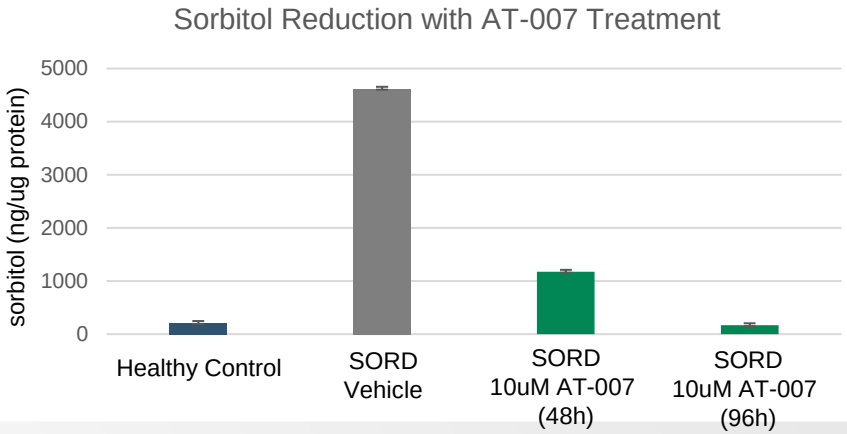
SORD Deficiency is One of the Most Common Recessive Causes of Hereditary Neuropathy, Impacting ~3,000 US Patients

- **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
- Pilot trial ongoing 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

- Orphan Drug Designation
- Pediatric Rare Disease Designation (PRV)

Preclinical proof of concept

Phase 2 ready- clinical study start 2021

Expanded Access program open

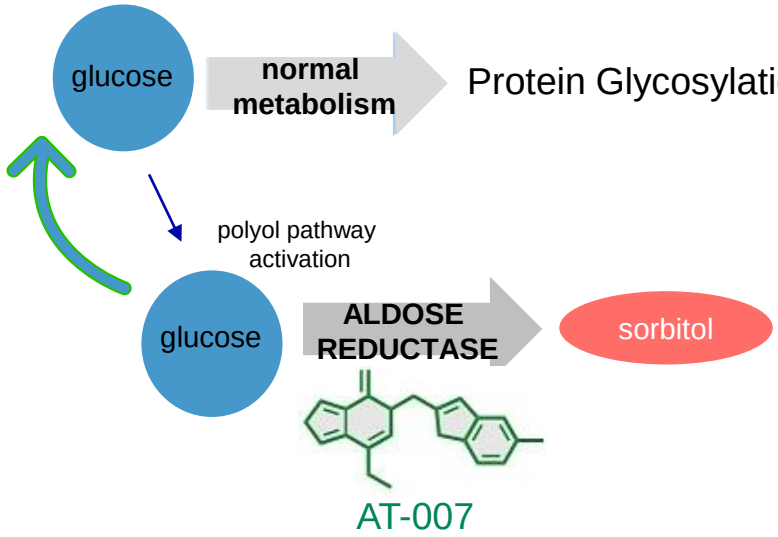
APPLIED THERAPEUTICS

What is PMM2-CDG?

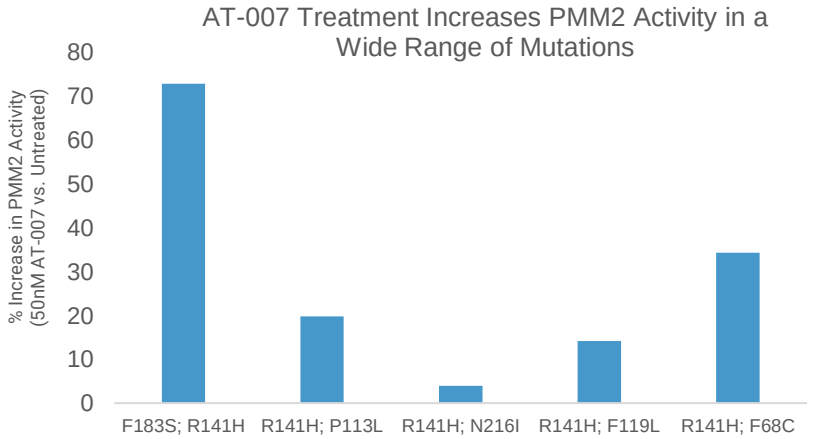
- **Glycosylation** is a process by which sugars are chemically attached to proteins to form glycoproteins, which are required by crucial functions within the human body
- **PMM2-CDG†**, is an ultra-rare mutation of the PMM2 gene (phosphomannomutase) which **results in loss of PMM2 protein function and 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-CDG[1-3]



- 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

Clinicians and regulators are working together to develop a robust study
Urgent cases considered under expanded access program

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

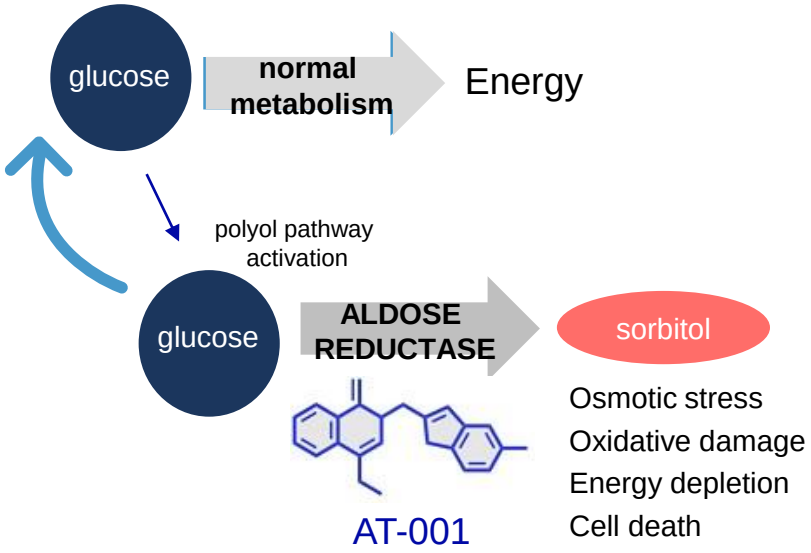
Data read-out expected 1H ‘23

APPLIED THERAPEUTICS

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

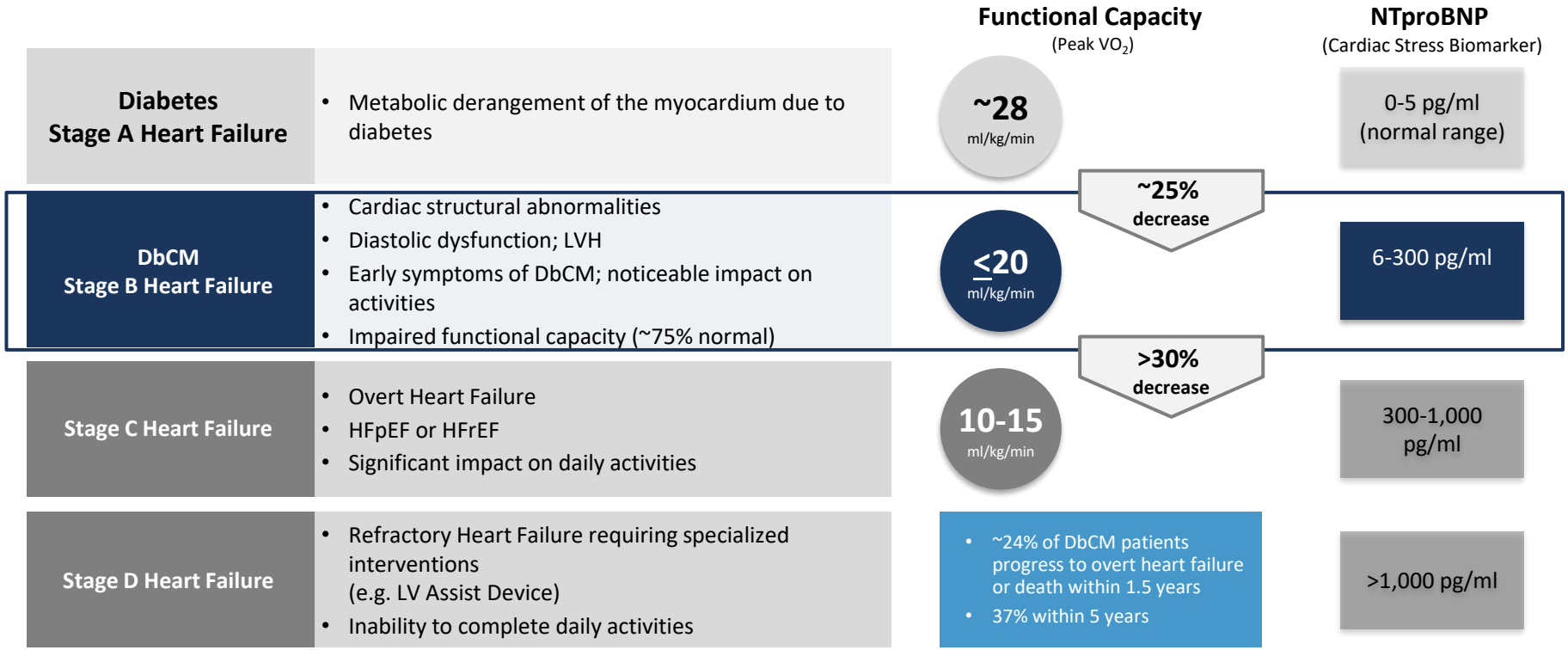
Aldose Reductase (the first and rate limiting enzyme in the polyol pathway) converts this glucose into **sorbitol** and eventually **fructose**

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)*

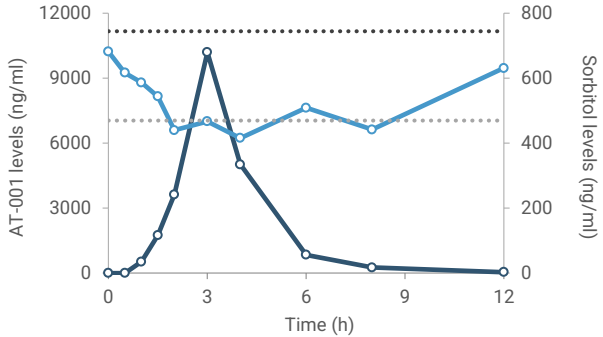
1,000mg TID Dosing *(n=10)*

Placebo *(n=6)*

†All participants remained on concomitant medications

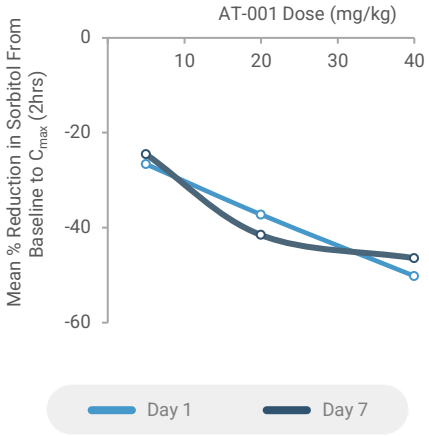
AT-001 Normalizes Sorbitol, a Biomarker of AR Activity, in Diabetic Patients

Proof of Biological Activity



AT-001 normalized sorbitol in diabetics to healthy volunteer levels

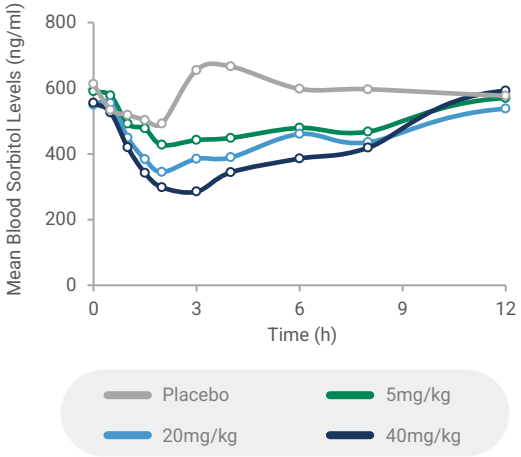
Sorbitol Reduction by Dose



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 Normalization Over Time

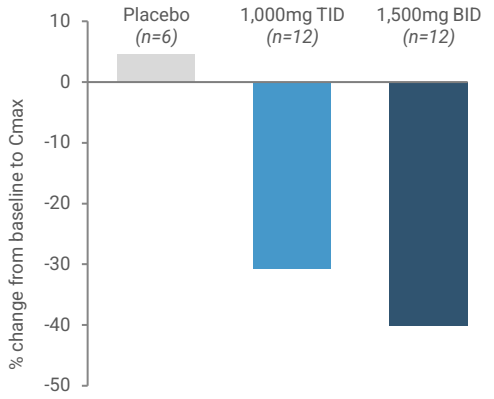


Rapid release capsule provides sorbitol normalization effects (PD biomarker) through **10-12hrs post-dose** at >10mg/kg

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

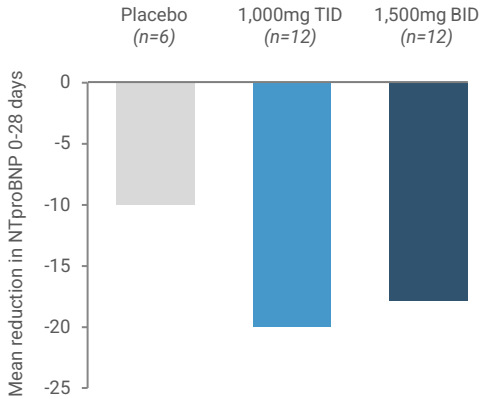
Sorbitol Normalization



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

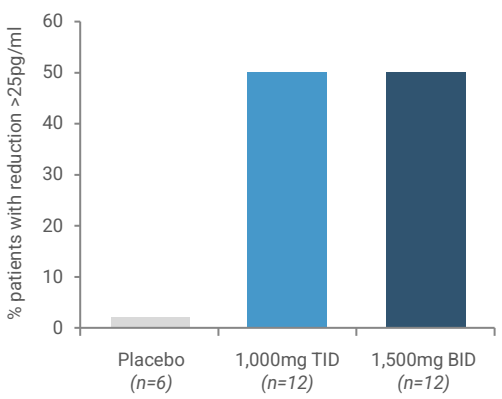
Mean Reduction in NTproBNP



Mean reduction in NTproBNP seen over 28 days vs. placebo

Mean baseline NTproBNP was 65pg/ml

Clinical Responder Analysis

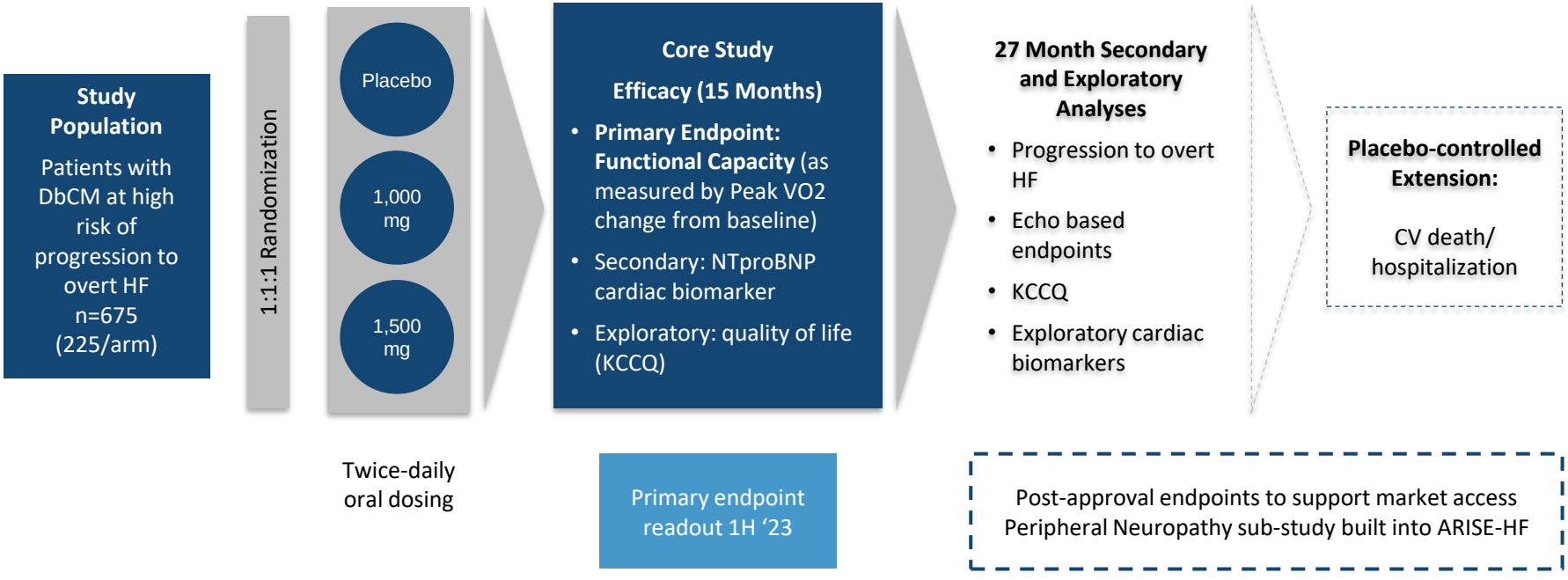


~50% AT-001 treated patients demonstrated a clinically meaningful reduction in NTproBNP over 28 days

>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)

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

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

Significant unmet need with no approved treatment

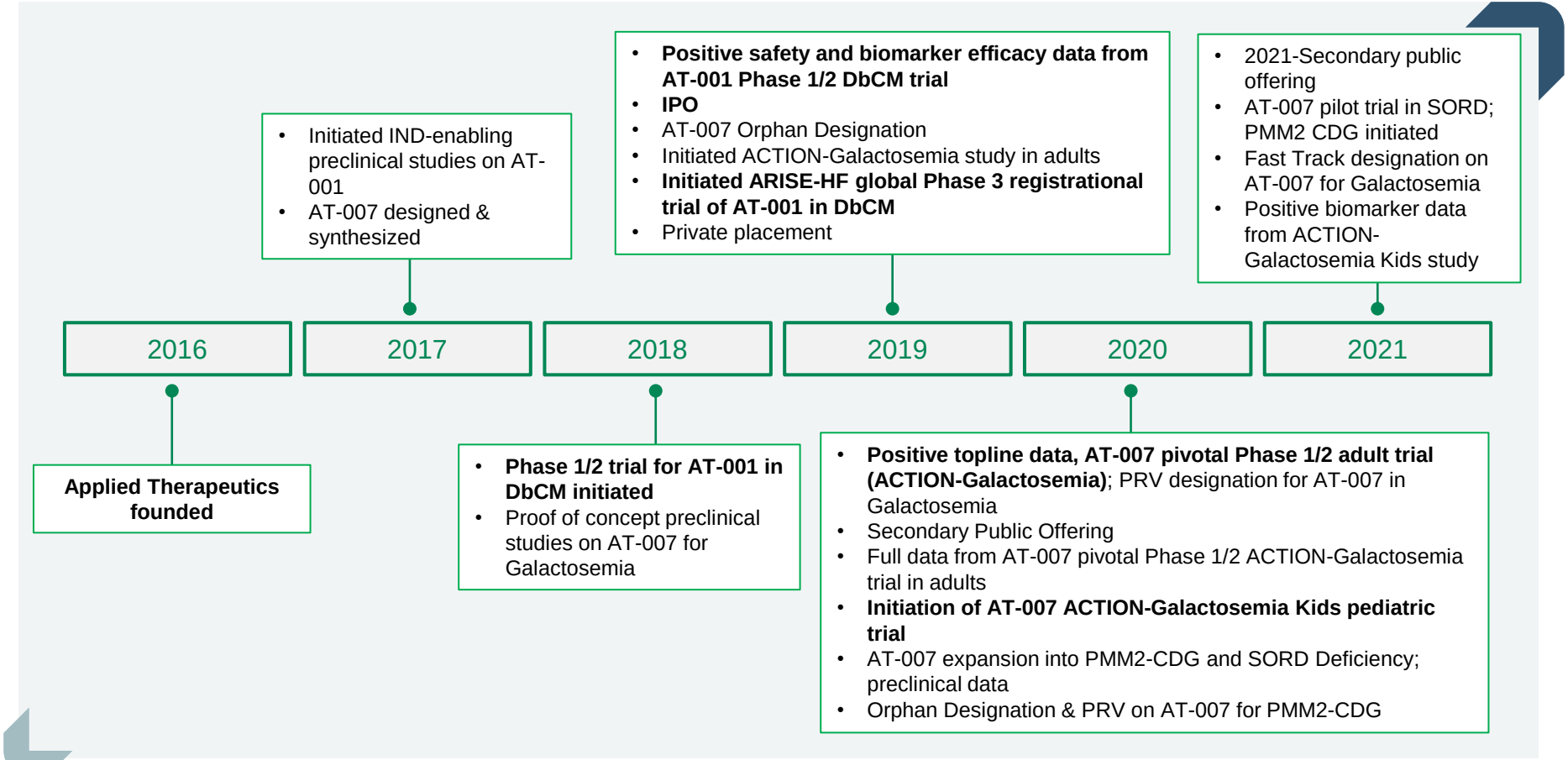
Potential for pricing in-line with SGLT2s and Entresto

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 Five 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