Applied Therapeutics

Corporate Presentation

January 2022

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

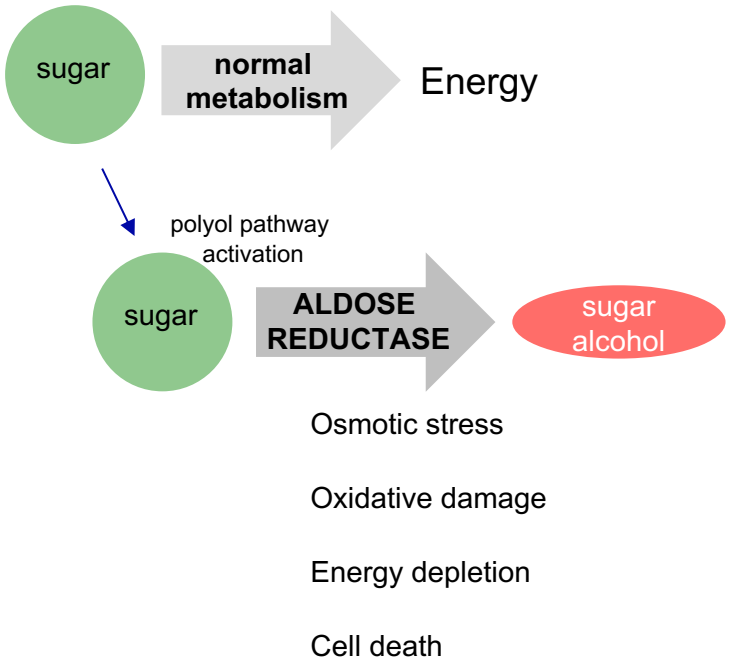
Limited / no competition

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				QD Oral	CNS	Positive adult and pediatric biomarker data; pediatric Phase 3 outcomes trial ongoing	
AT-007	SORD Deficiency				Oral	CNS	Positive pilot study data; Phase 3 registrational trial ongoing	
AT-007	PMM2-CDG				Oral	CNS	Phase 2 ready; Expanded Access open	
AT-001	Diabetic Cardiomyopathy				BID Oral	Systemic	Ph 3 registrational 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 2022	
PI3 KINASE FRANCHISE								
AT-104	PTCL, CTCL, TALL†				SC / Oral	Selective δ/γ inhibitor	Proof of concept preclinical	

†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

Applied Therapeutics' compounds are 1,000 X more potent than "old" ARIs and highly selective; no off-target inhibition of aldehyde reductase

AT-007: Late-Stage Programs in 2 Rare Diseases with High Unmet Need and No Approved Treatments

Galactosemia

- Positive adult and pediatric biomarker data
- Phase 3 pediatric outcomes study ongoing
- Orphan Drug Designation
- Pediatric Rare Disease Designation
- Fast-Track Designation

SORD Deficiency

- Positive pilot study results
- **Registrational Phase 2/3 study ongoing; biomarker data H2 2022**

- Significant unmet need in serious, debilitating diseases
- ~7,000 patients in US+EU in each indication – 13,000 patients total

AT-007

- Validated mechanism of action
- Patent exclusivity through 2037
- Convenient, once-daily oral dosing
- Favorable safety and tolerability profile
- Strong patient, caregiver, HCP interest
- Rare disease pricing potential
- Small commercial footprint needed

AT-001: Potential First Therapy in Diabetic Cardiomyopathy - Large Indication with Blockbuster Potential

Diabetic Cardiomyopathy

- Heart Failure affecting ~17-24% of diabetics
- Positive proof of concept in Phase 1/2
- ARISE-HF global Phase 3 trial ongoing; expected completion H1 2023
- No drugs approved - potential first approval in DbCM

Diabetic Peripheral Neuropathy

- Affects >30% of diabetics
- Proof of concept with ”old” ARIs
- Phase 2 sub-study embedded in ARISE-HF DbCM Phase 3
- Although pain drugs are approved for symptomatic treatment, no disease-modifying treatments exist; Potential first disease-modifying treatment in DPN

- DbCM potential market ~6M patients US; 5M EU5
- DPN potential market ~9M patients US; 7M EU5

AT-001

- Validated mechanism of action
- Demonstrated proof of concept
- Patent exclusivity through 2031
- Convenient, twice-daily oral dosing
- Favorable safety and tolerability profile
- Strong KOL support

AT-007
GALACTOSEMIA

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

Positive adult & pediatric biomarker data

Pediatric Ph 3 clinical outcomes study ongoing

APPLIED THERAPEUTICS

Galactosemia: a Rare Metabolic Disease With No Approved Therapies

- Galactosemia is an autosomal recessive progressive metabolic disease caused by a genetic inability to metabolize the sugar galactose
- Aldose Reductase (AR) enzyme converts galactose into galactitol, an aberrant toxic metabolite that accumulates in tissues and organs and causes long-term disease complications
- ~3,000 patients in the US & 3,500 in the EU with Galactosemia; ~200 new births per year; Mandatory newborn screening in US and most EU countries

1. Data on file: Decision Resources Group, Report Epidemiology of Galactosemia; 2020 June. 2. Phytila et al. *JIMD Rep*. 2015; 15: 79–93. 3. Burgard et al. *Report on the practices of newborn screening for rare disorders*. 2011. 4. Swaiman et al. *Pediatric Neurology*. 2018.

Galactosemia Results in Acute Life-Threatening Complications in the Newborn Phase Followed by Chronic Long-Term Complications

Acute Newborn Complications

- Liver failure
- Jaundice
- Kidney Failure
- Sepsis
- Brain edema, Pseudotumor cerebri
- Death

Chronic Long-Term Complications

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

Hawk Partners caregiver research, consistent with International Galactosemia treatment guidelines (Welling et al., 2017)

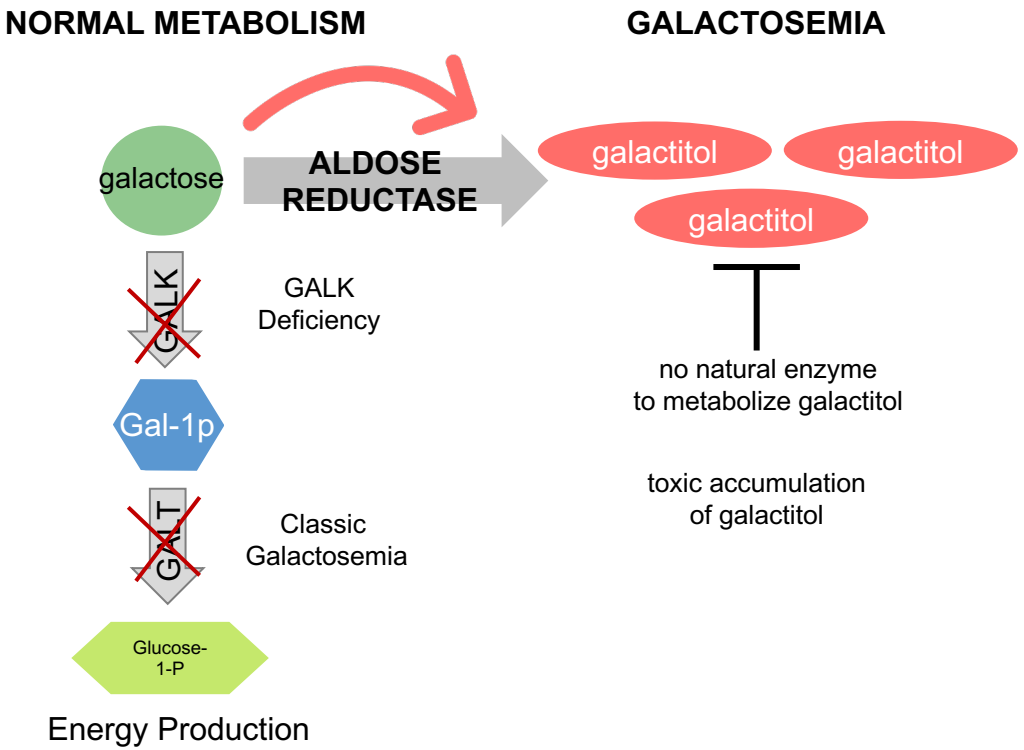
Galactose is a simple sugar found in foods and endogenously produced by the body

Following newborn screening, a Galactosemia diet is implemented in patients to limit external intake of galactose

- Restriction of high galactose/lactose products for life – includes restriction of breast milk and dairy products
- Galactose is also found at lower levels in foods required for nutritional support (fruits, vegetables, legumes) which can't be restricted

Despite dietary restriction, long-term complications develop due to endogenous synthesis of galactose by the body, which is 10X higher than intake from the Galactosemia diet

Mechanism of Disease: Deficiency in GALT or GALK Leads to Inability to Metabolize Galactose; Aldose Reductase Converts Excess Galactose to Toxic Galactitol



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

Galactosemia is a Debilitating Progressive CNS Disease

Children have normal CNS function early in life, **but progressive worsening with age results in significant deficits on 4 CNS Quadrants:**

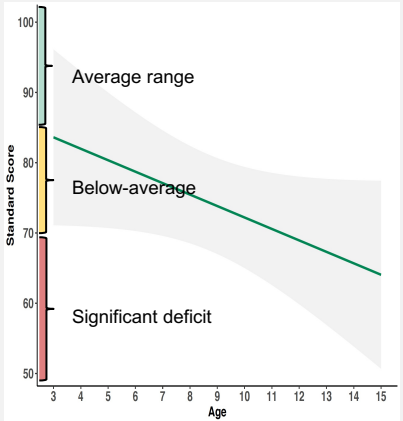
- Speech
- Cognition
- Behavior
- Motor Skills

Galactitol level correlates with severity of disease: patients with lower plasma galactitol levels have a less severe phenotype; patients with higher galactitol have a more severe phenotype

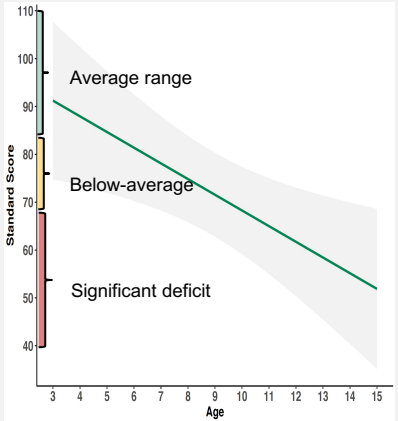
1. Data on file: Decision Resources Group, Report Epidemiology of Galactosemia; 2020 June. 2. Phytila et al. *JIMD Rep*. 2015; 15: 79–93. 3. Burgard et al. *Report on the practices of newborn screening for rare disorders*. 2011. 4. Swaiman et al. *Pediatric Neurology*. 2018.

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

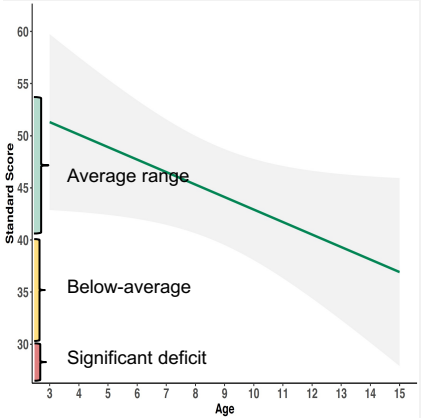
Speech



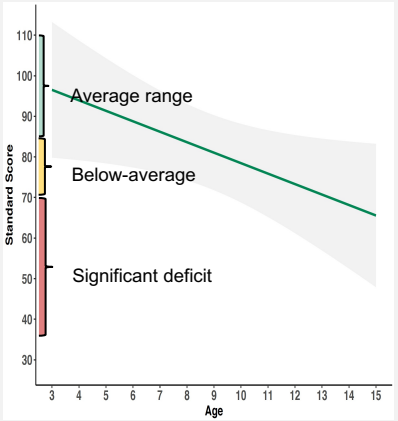
Cognition



Adaptive Behavior



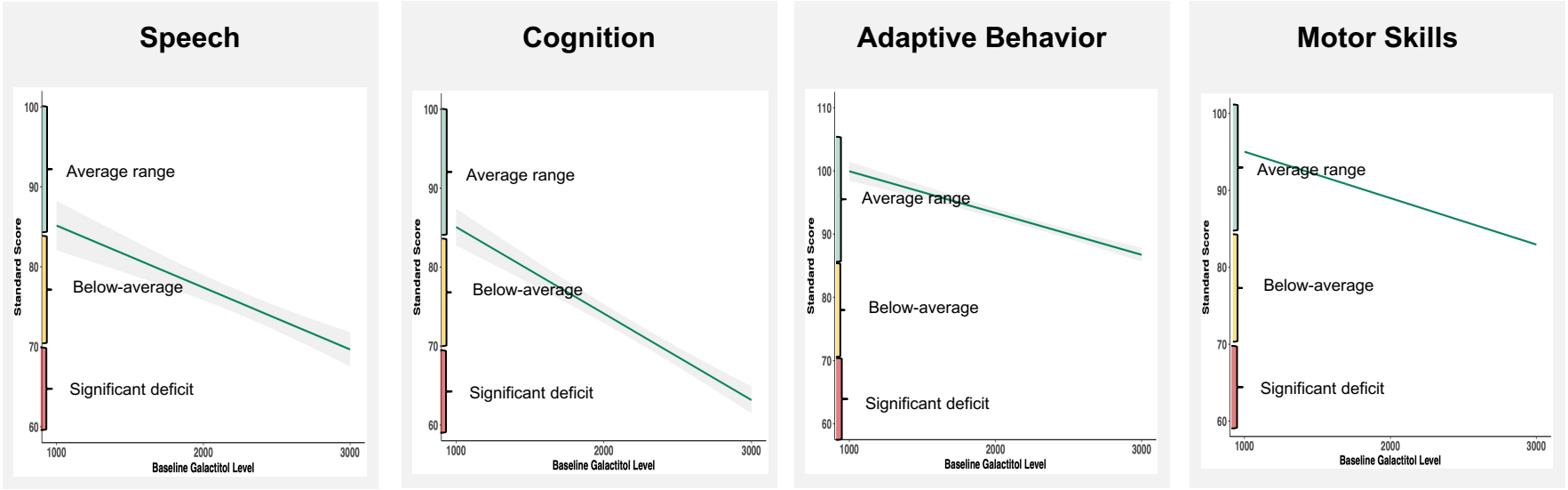
Motor Skills



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

Plasma Galactitol Level at Baseline Correlates with Severity of Disease

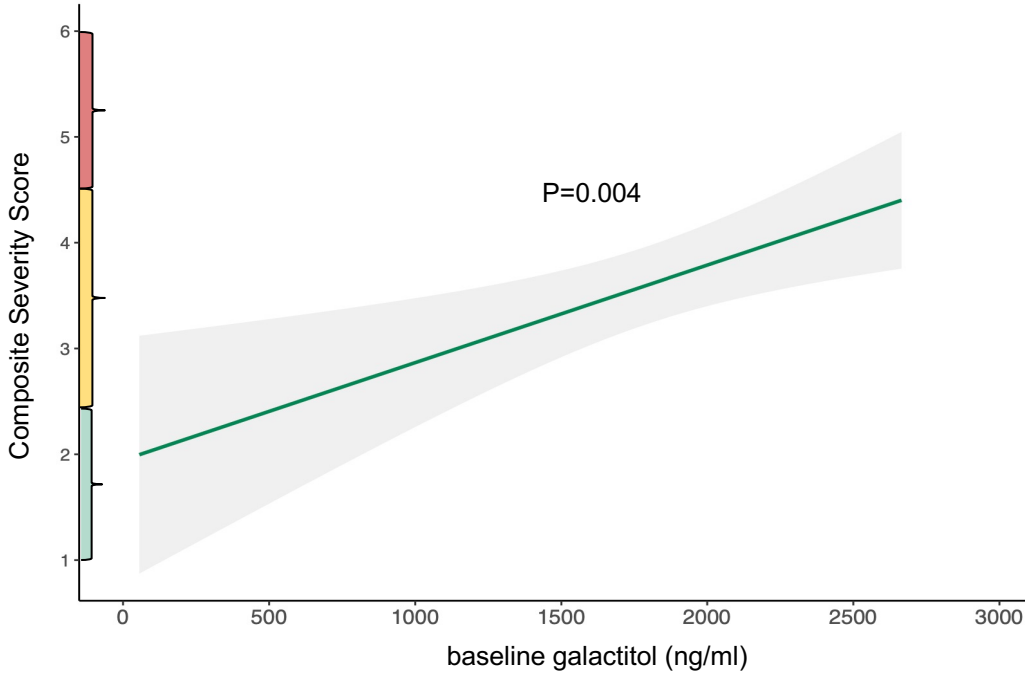
Analysis of the 47 children in the ACTION-Galactosemia Kids study demonstrated a correlation between baseline galactitol level and baseline clinical functional outcomes



- 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.

Perfetti R et al. Galactitol Level is a Predictor of Disease Severity in Children with Classic Galactosemia on Galactose Restricted Diet. Poster presented at: International Congress Inborn Errors of Metabolism Annual Meeting; November 21-23, 2021; Sydney, Australia.

Plasma Galactitol Level Correlates with Disease Severity



Composite score comprised of 4 CNS quadrants: speech, cognition, behavior, motor skills

- Correlation of galactitol with disease severity was highly statistically significant (p=0.004)
- As expected, Gal-1p did not correlate with disease severity

shaded area = 95% confidence interval
highest galactitol value for patient with full composite score available = 2,600ng/ml

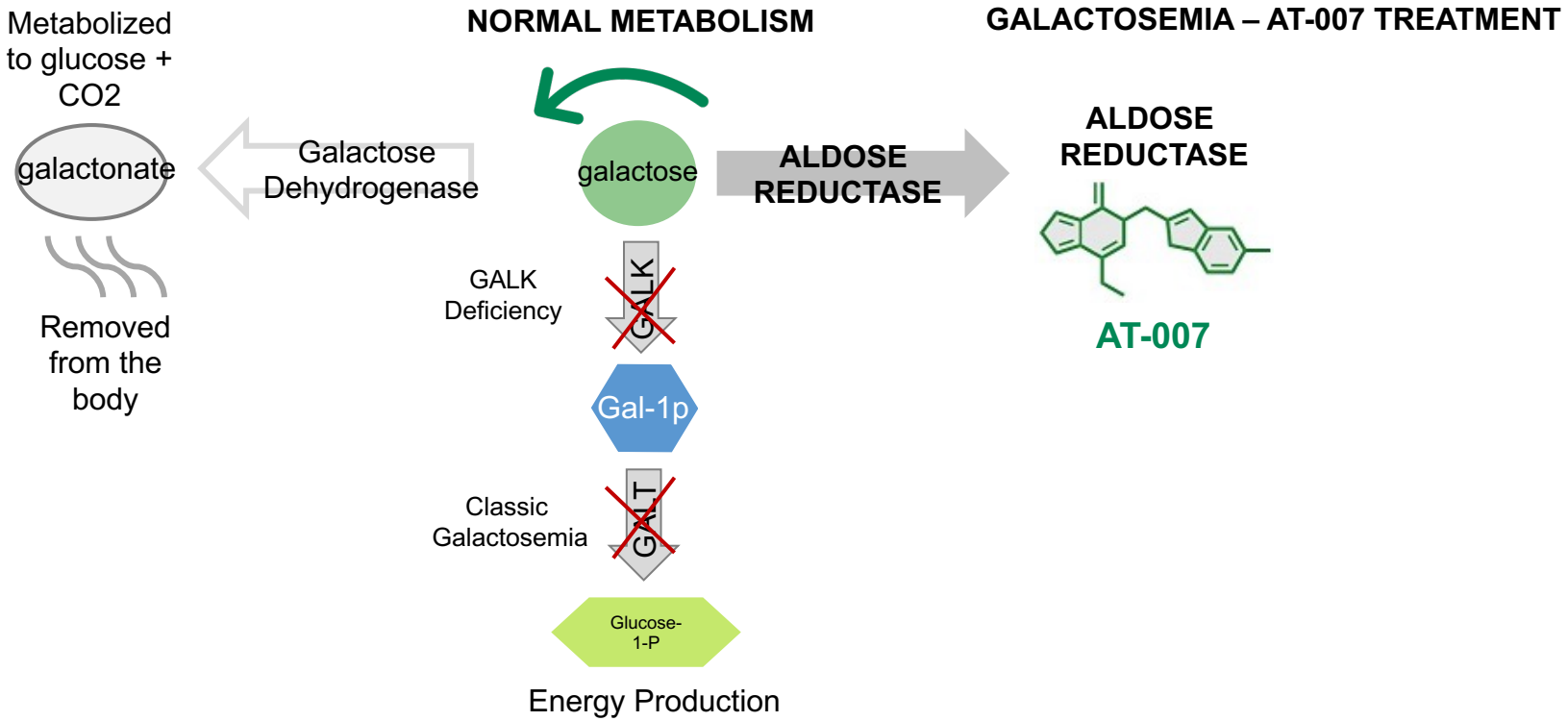
Perfetti R et al. Galactitol Level is a Predictor of Disease Severity in Children with Classic Galactosemia on Galactose Restricted Diet. Poster presented at: International Congress Inborn Errors of Metabolism Annual Meeting; November 21-23, 2021; Sydney, Australia.

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

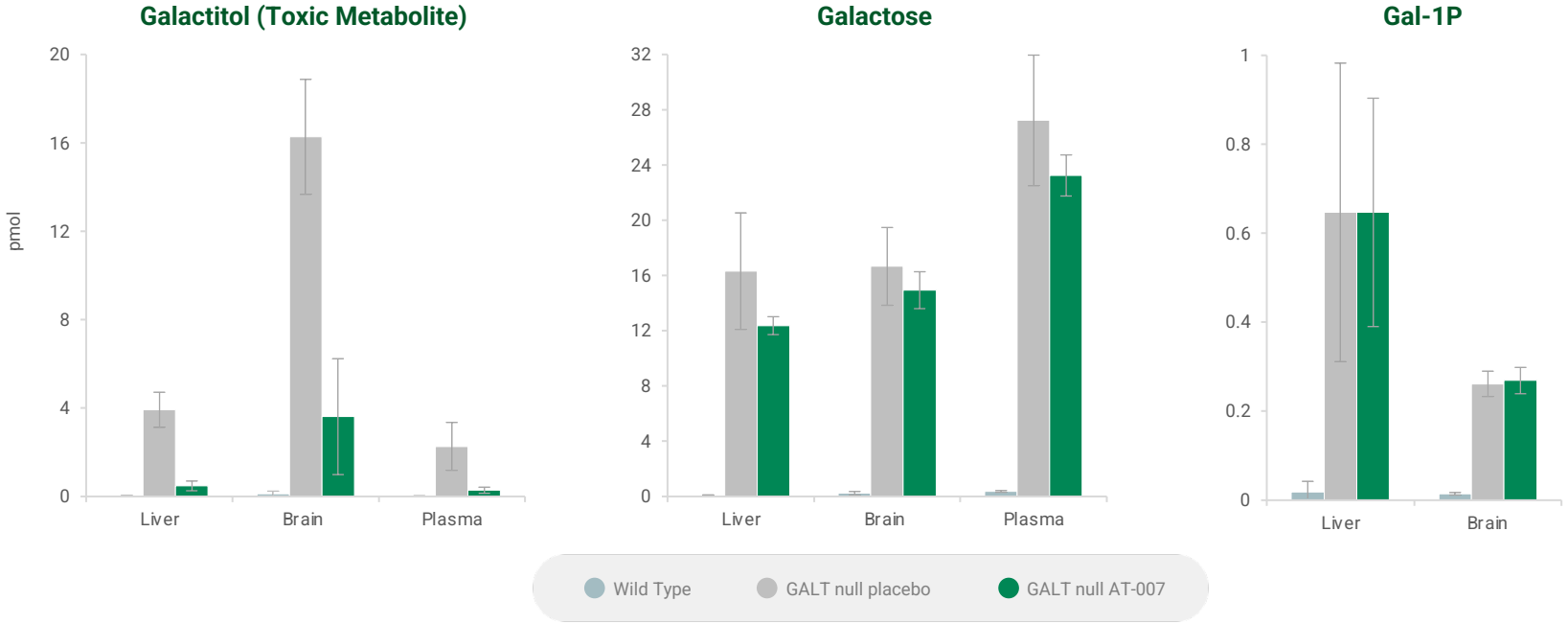
- **Preclinical Efficacy:** Reduced galactitol levels in a rat model of Galactosemia and prevented the disease phenotype (CNS symptoms & cataracts)
- **Clinical Efficacy**: Reduced galactitol levels in both adults & children with Galactosemia
  ~50% from baseline in adults
  ~40% from baseline in children age 2-17
- **Clinical Safety:** Safe and well tolerated in both children and adults
- **Dosing:** Once daily oral suspension

1. Data on file: Decision Resources Group, Report Epidemiology of Galactosemia; 2020 June. 2. Phytila et al. *JIMD Rep*. 2015; 15: 79–93. 3. Burgard et al. *Report on the practices of newborn screening for rare disorders*. 2011. 4. Swaiman et al. *Pediatric Neurology*. 2018.

AT-007 Blocks Aldose Reductase Conversion of Galactose to Galactitol; Galactose is Then Shunted Through a Nontoxic Pathway for Metabolism and Excretion



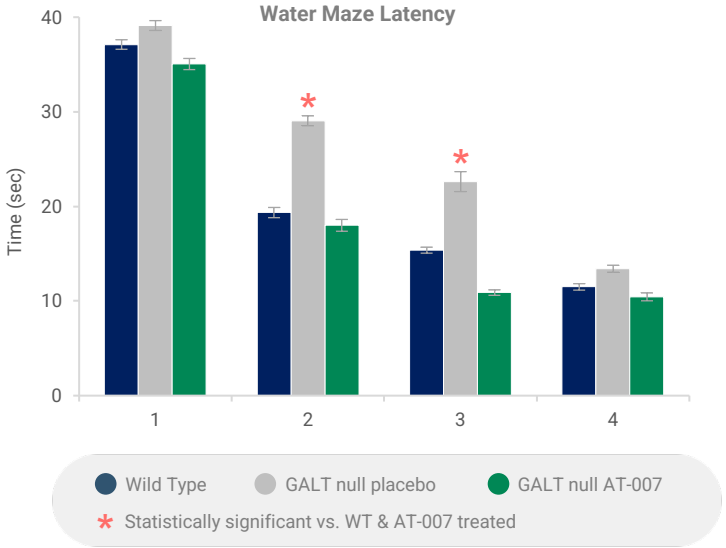
In a Rat Model of Galactosemia, AT-007 Significantly Reduced Toxic Galactitol Levels in All Target Tissues Without Increasing Galactose or Gal-1P



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

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

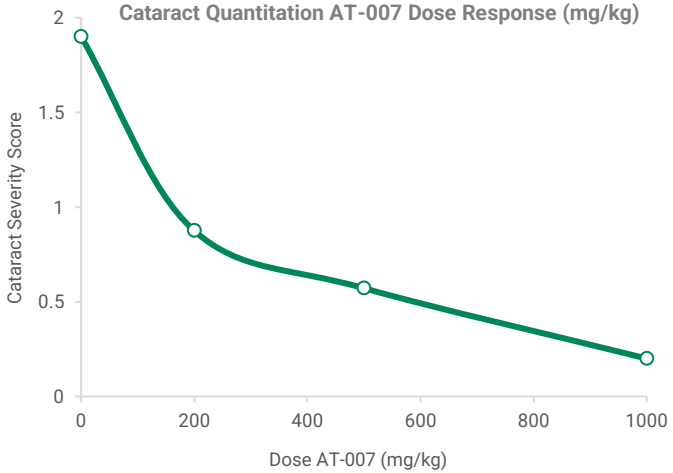


AT-007 treatment prevented galactitol accumulation in tissues, resulting in absence of cataracts


Wild Type


GALT null (placebo)


GALT null AT-007



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)

Long-term Extension

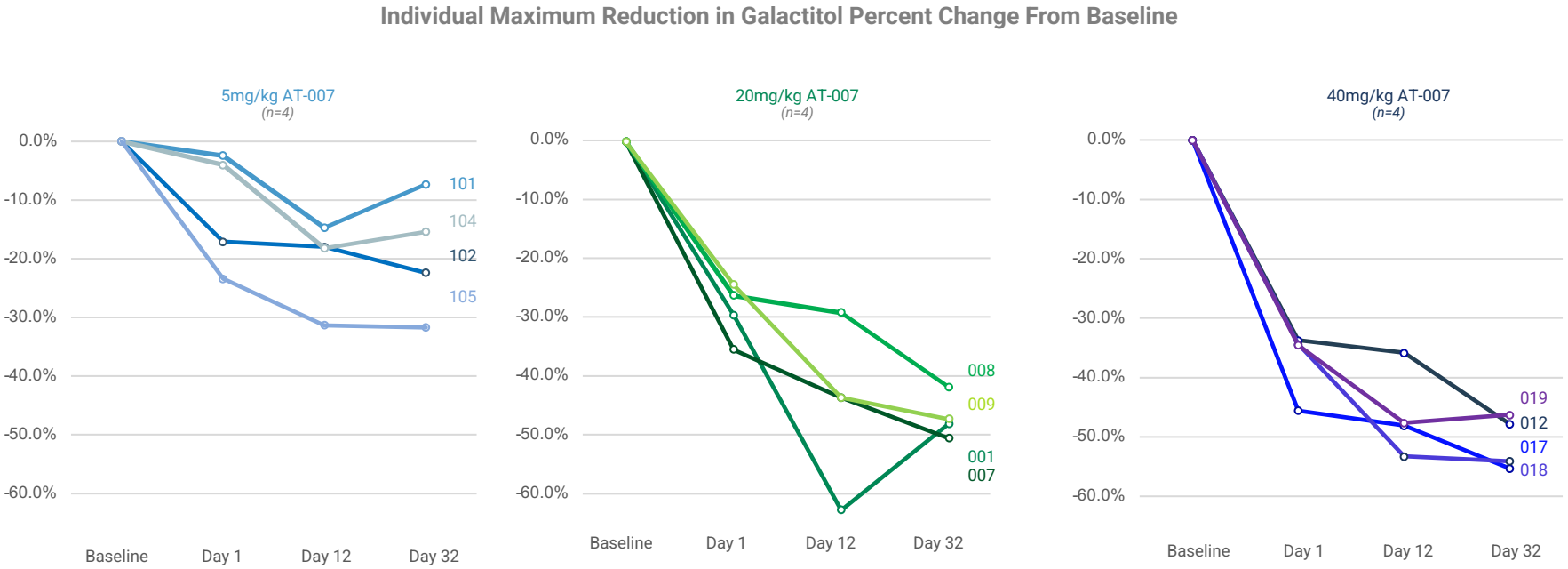
*Based on initial topline data from Jan 2020, the study was expanded to include a 40mg/kg dose in healthy volunteers and then Galactosemia patients. This cohort also included 2 additional placebo patients

**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

AT-007 Decreased Galactitol Levels in All Treated Patients

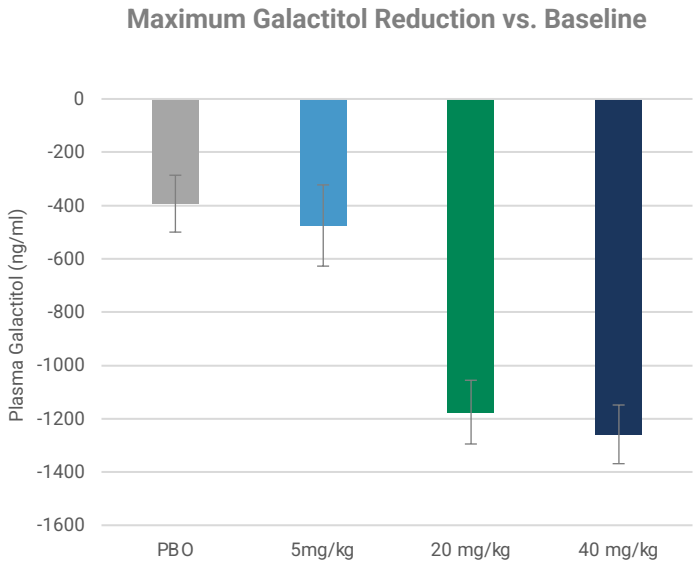
Decrease was dose-dependent, rapid and sustained; statistically significant at 20 & 40mg/kg



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

Data on file, Applied Therapeutics, Inc, New York, NY

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

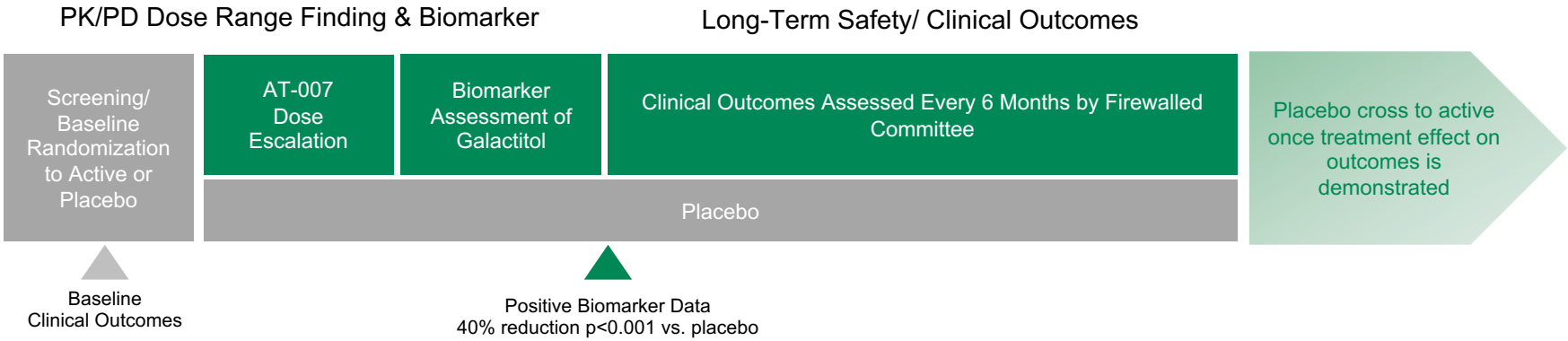
- Favorable safety and tolerability in core study and 3-month extension

Pharmacokinetics/ Pharmacodynamics

- PK supports once-daily dosing
- Rapid and sustained reduction in plasma galactitol
- Galactitol reduction in the brain demonstrated by MR Spectroscopy
- No compensatory increase in galactose or Gal-1p

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

ACTION-Galactosemia Kids Pediatric Registrational Clinical Study (Children 2-17 years old)



- Dose range finding PK/PD study to determine optimal dose in children and biomarker-based assessment of galactitol reduction
- Long-term clinical outcomes to assess impact on how patients feel and function
- First outcomes assessment in Q1 2022 and every 6 months thereafter

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

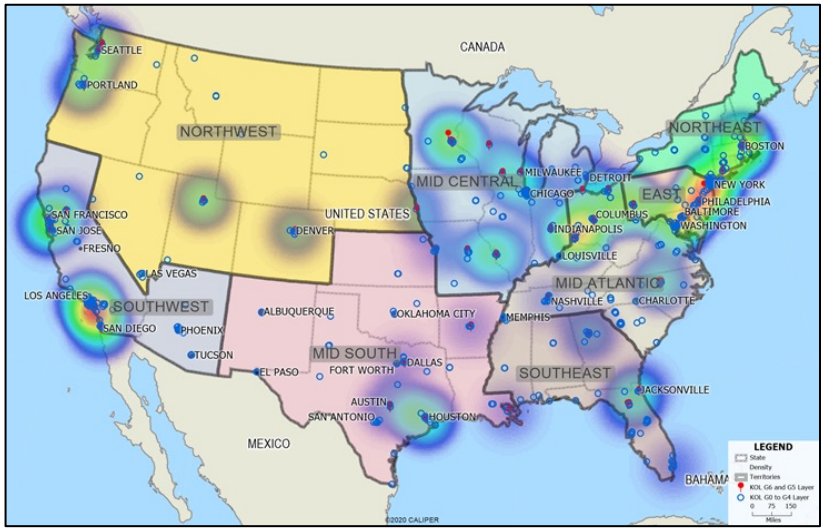
AT-007 Demonstrates Substantial and Statistically Significant Reduction in Plasma Galactitol in Children in ACTION-Galactosemia Kids

Weight Group	AT-007 Dose	% Reduction From Baseline
>40kg	15mg/kg	38.29%
20-40kg	20mg/kg	41.43%
<20kg	30mg/kg	39.83%
All groups combined	**15-30mg/kg**	**40.19% (p<0.001)**

Safe and well-tolerated; no compensatory increase in galactose or Gal-1p

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

Preliminary U.S. Sales Territory Heat Map



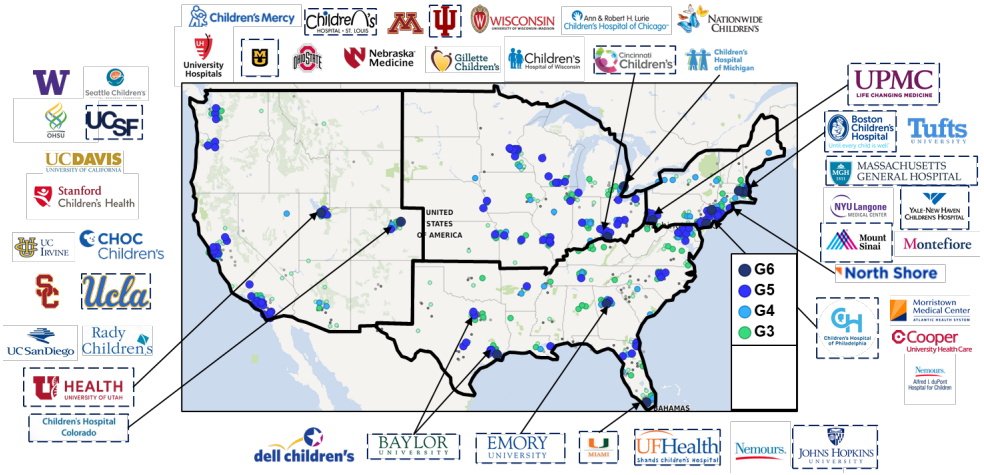
Commercialization Plan Linked to Opportunity:

- 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

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**
- 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

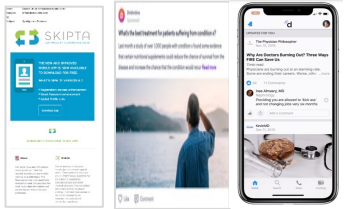
HCP

MEDIA

Web Health Network

Medscape

SOCIAL



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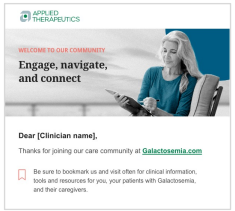
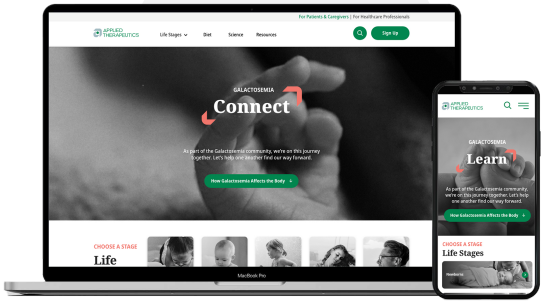


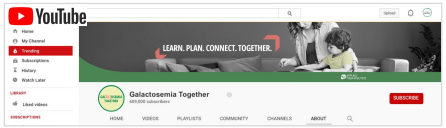
3D MOD VIDEO

HCP & PATIENT / CAREGIVER

WWW.GALACTOSEMIA.COM



YOUTUBE



SEARCH

Google Microsoft Bing

PATIENT / CAREGIVER

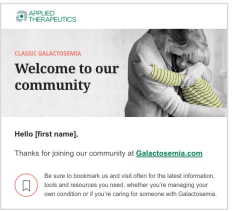
MEDIA

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

SORD DEFICIENCY

Preclinical proof of concept demonstrated

Positive pilot study completed

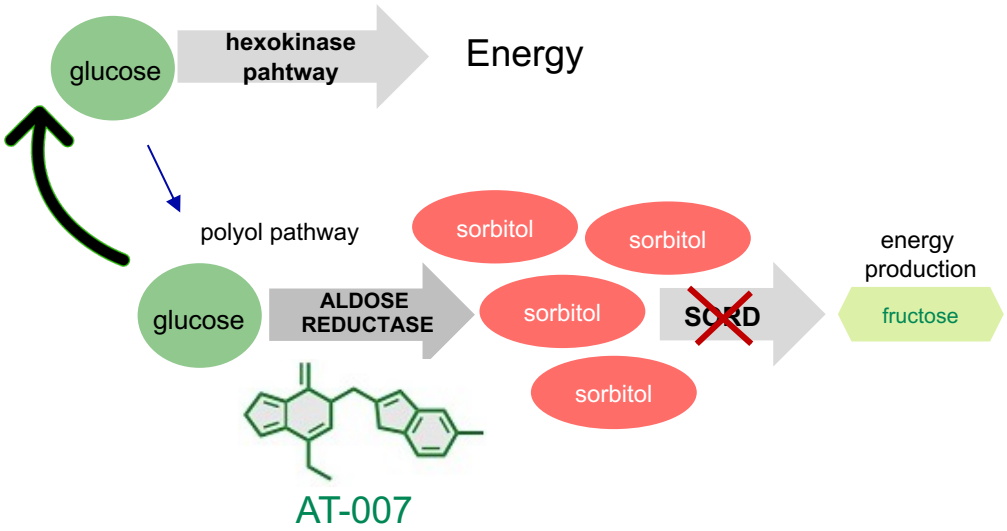
Registrational Phase 2/3 study ongoing

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
- Caused by mutations in the SORD gene resulting in **loss of enzyme Sorbitol Dehydrogenase (SORD) function** and consequent **intracellular toxic sorbitol accumulation**
- Previously, these patients were diagnosed symptomatically as 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); average age of onset is 17 years old
- 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 Neuropathy by Preventing Conversion of Glucose to Sorbitol

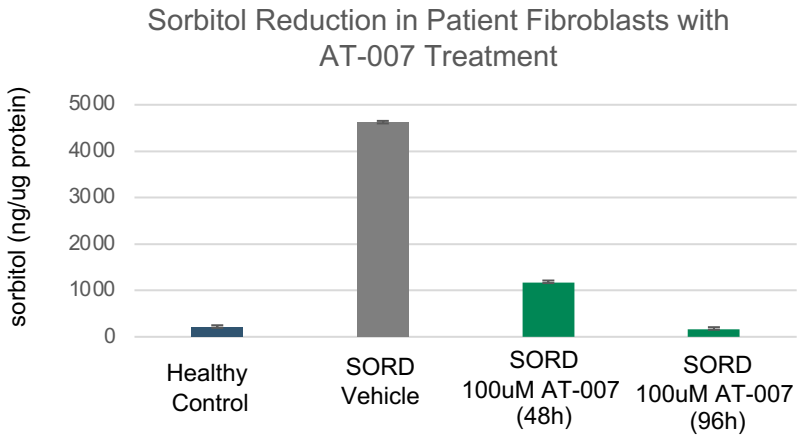


- In non-diabetic patients only 1-3% of glucose is metabolized through the polyol pathway, with the large majority of glucose being metabolized through other energy-efficient pathways
- Patients with SORD Deficiency are missing the SORD enzyme, which follows Aldose Reductase in the polyol pathway, and as a result are unable to metabolize sorbitol
- Patients with SORD Deficiency accumulate very high levels of sorbitol in their blood, cells and tissues
- High toxic sorbitol levels result in cell death and tissue degeneration, such as neuropathy.

Applied Therapeutics, data on file; pilot study

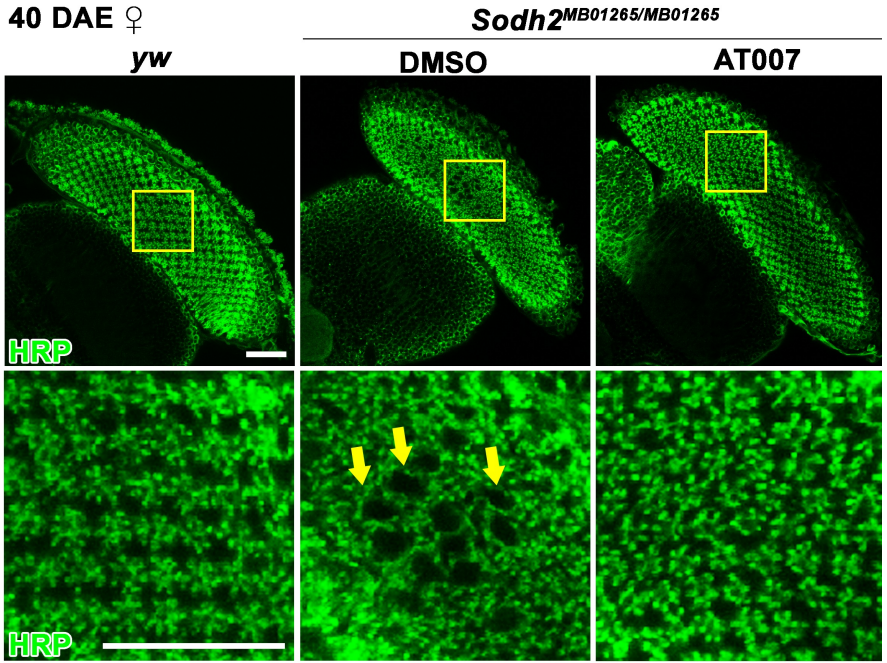
AT-007 Treatment Reduces Sorbitol Levels in Cultured Fibroblasts from SORD Deficient Patients

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

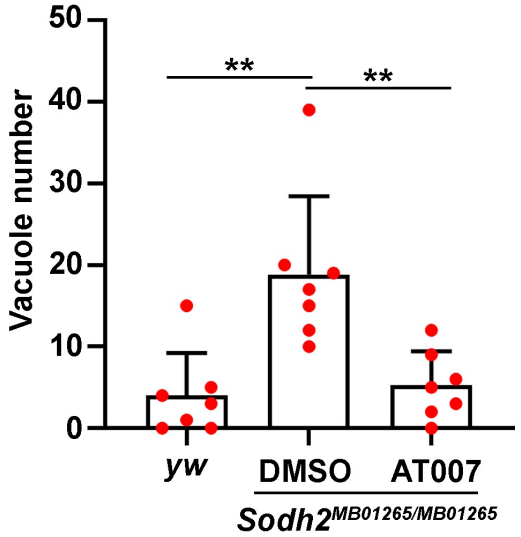


Applied Therapeutics, data on file; pilot study

AT-007 Ameliorates the SORD Disease Phenotype in Drosophila



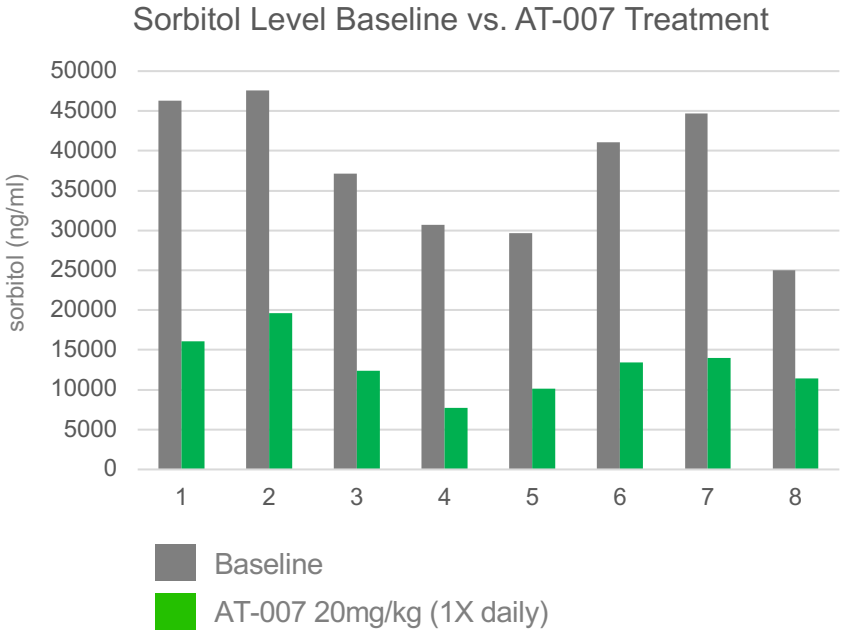
Neuronal Degeneration Assessed by Presence of Vacuoles

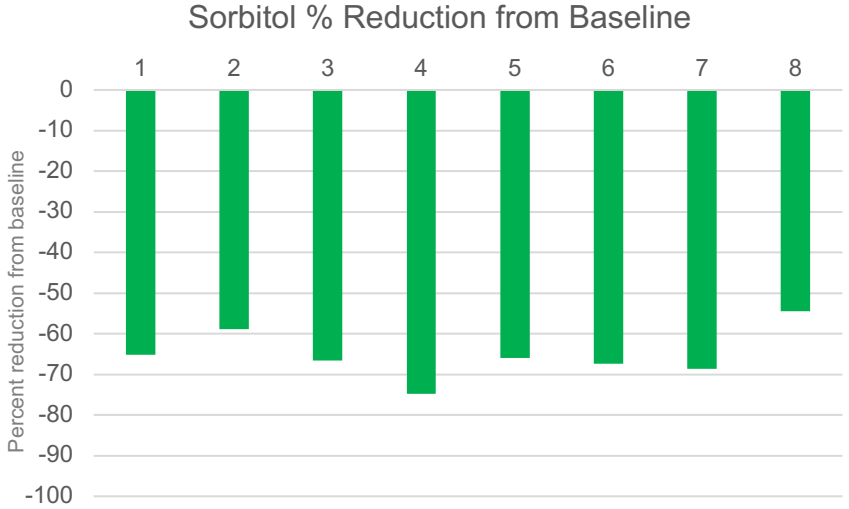


SORD mutant flies were treated with vehicle (DMSO) or 20ug/ml AT-007 in food for 40 days after eclosion (DAE) AT-007 treatment completely prevented neuronal degeneration in SORD mutant flies, as visualized by the presence vacuolar structures.

AT-007 Substantially Reduced Sorbitol in Patients with SORD Deficiency in 30-Day Open-Label Pilot Trial

Pilot open-label study data in 8 SORD patients demonstrated mean reduction from baseline of 66% (range 54%-75%)

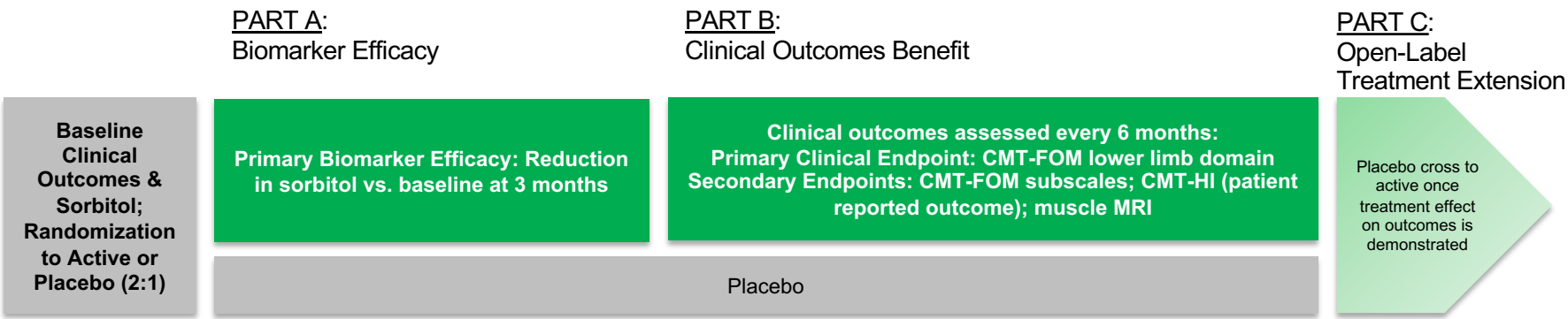




Mean baseline sorbitol level was ~38,000ng/ml

SORD Neuropathy Phase 2/3 Registrational Study (INSPIRE)

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

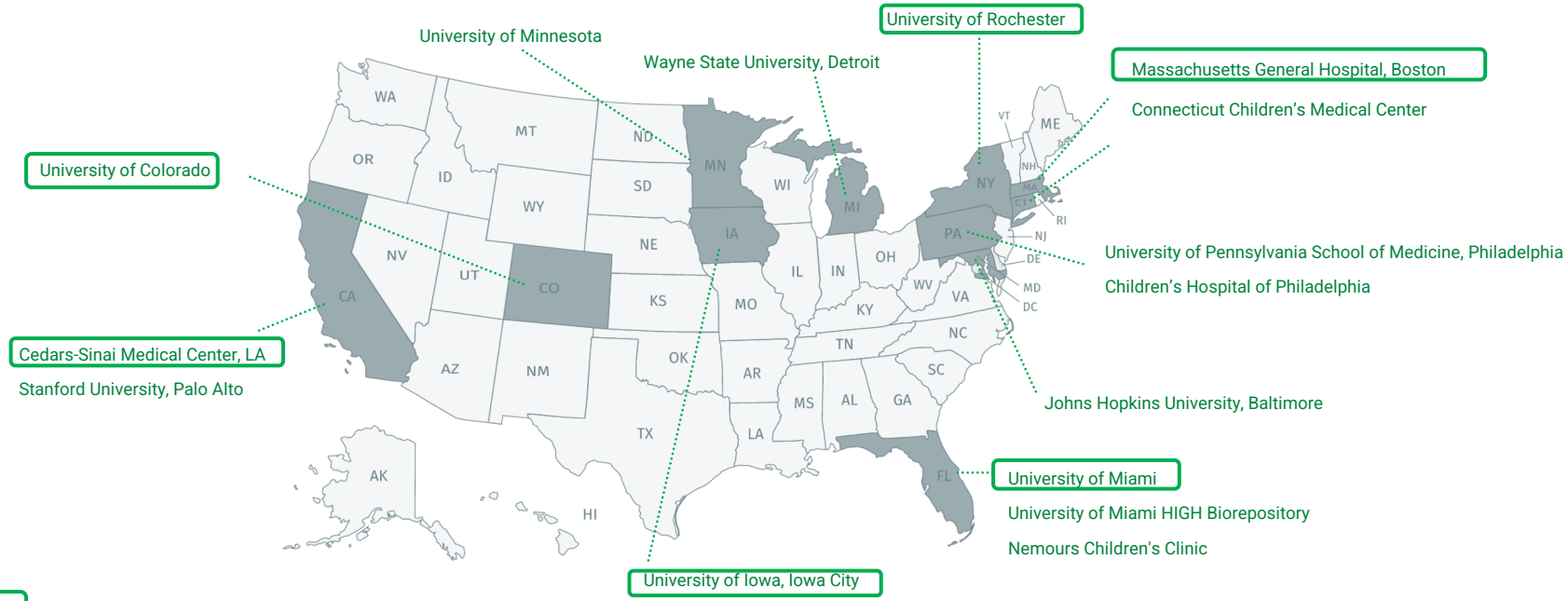


Global clinical sites: US, EU, UK

Sequential Design: In Part B, interim analyses of the primary endpoint will be performed at Month 6 and every 6 months subsequently.

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

Inherited Neuropathy Consortium Centers of Excellence and Global CMT Registries Exist to Support Trial Enrollment & SORD Patient Treatment



Available from: https://www.rarediseasesnetwork.org/cms/inc/centers#CSMC.

AT-007: Potential First Therapy for SORD Deficiency

High Unmet Need in SORD

- No approved therapies
- No other products currently in development for SORD Deficiency
- 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
- Potential for Accelerated Approval based on reduction in sorbitol
- Registrational study 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

Expanded Access program open

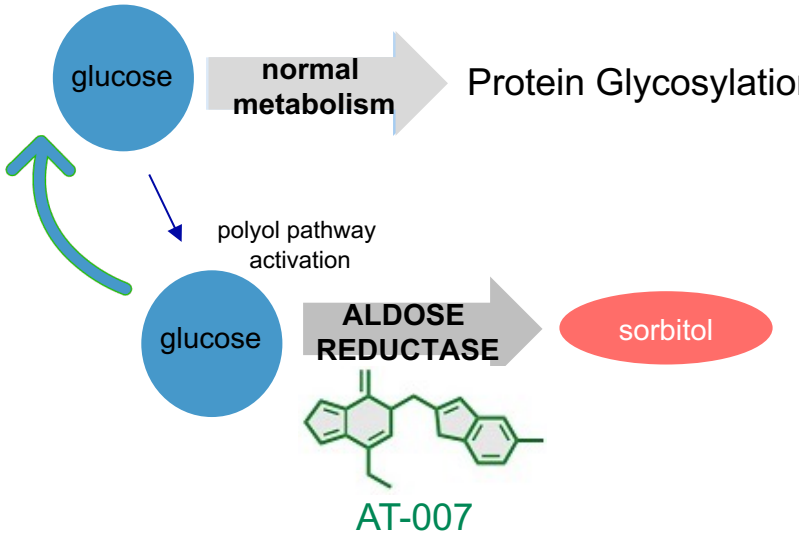
APPLIED THERAPEUTICS

What is PMM2-CDG?

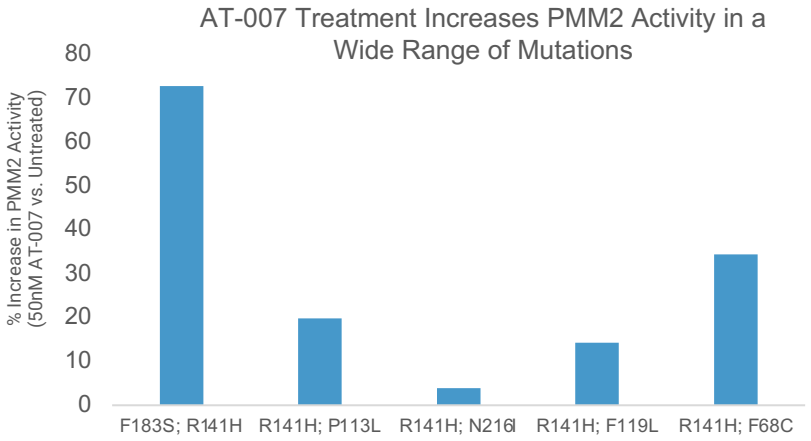
- **Glycosylation** is a process by which sugars are chemically attached to proteins to form glycoproteins, which are required by crucial functions within the human body
- **PMM2-CDG**†, is an ultra-rare mutation of the PMM2 gene (phosphomannomutase) which **results in loss of PMM2 protein function and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



- 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
- 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-001

DIABETIC CARDIOMYOPATHY

Positive proof of concept Ph 1/2 data

Ph 3 initiated in Q3 2019

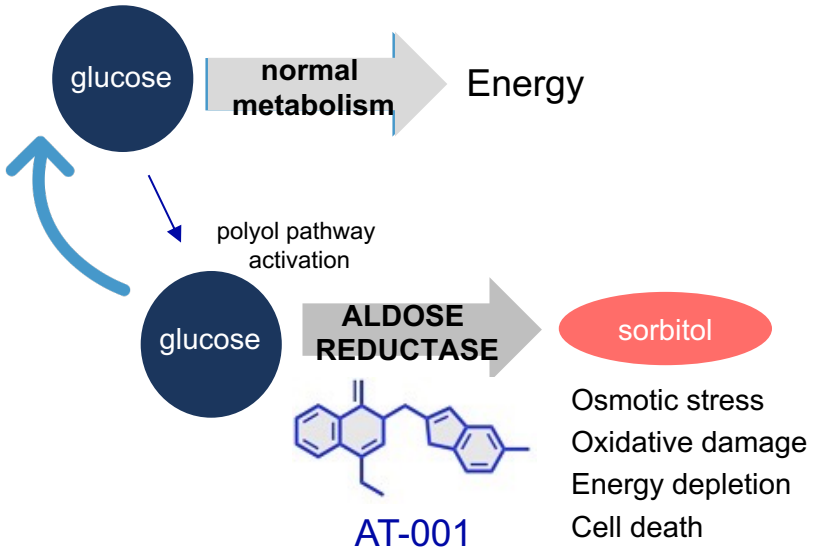
Data read-out expected 1H ‘23

APPLIED THERAPEUTICS

What is Diabetic Cardiomyopathy (DbCM)?

- DbCM is a **form of heart failure (Stage B)**, diagnosed by echocardiogram or cardiac biomarkers, 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 ~17-24% 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

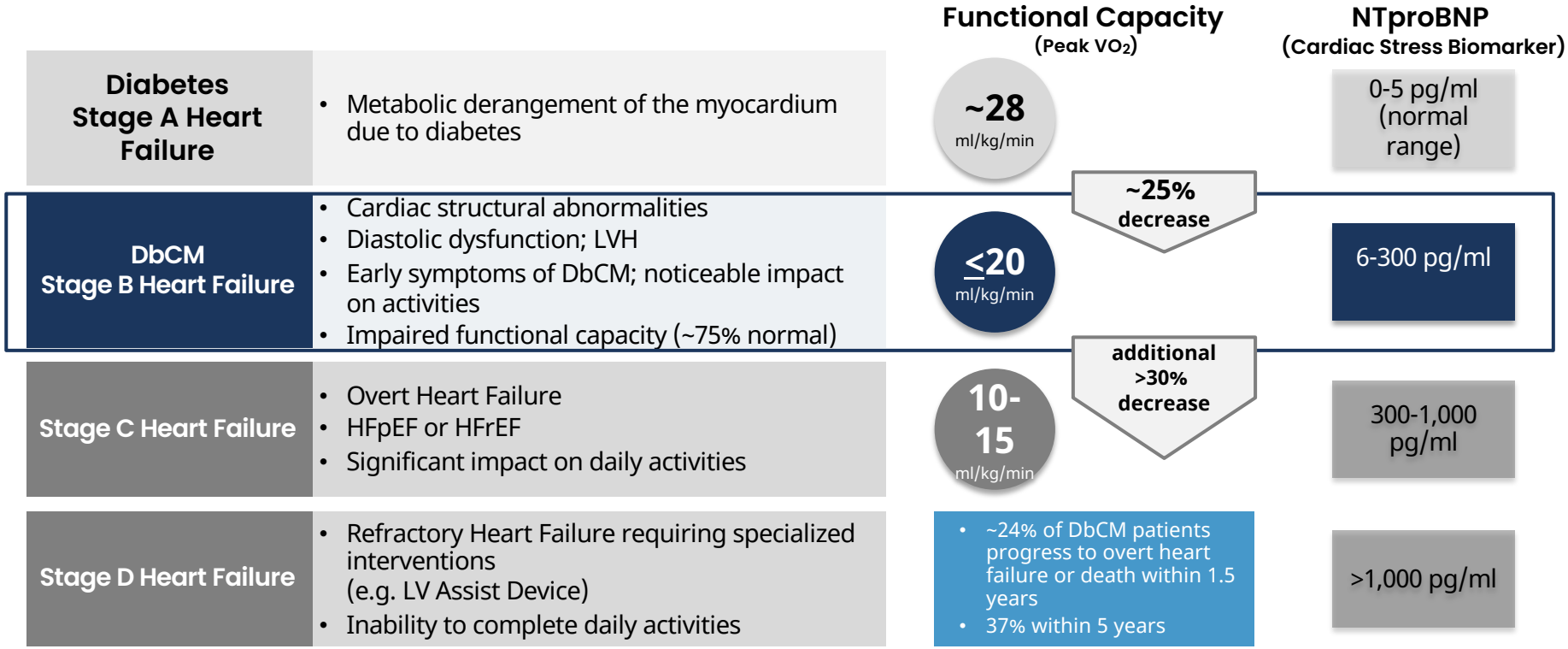
Aldose Reductase (the first and rate limiting enzyme in the polyol pathway) converts this glucose into **sorbitol** and eventually **fructose**

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



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)*

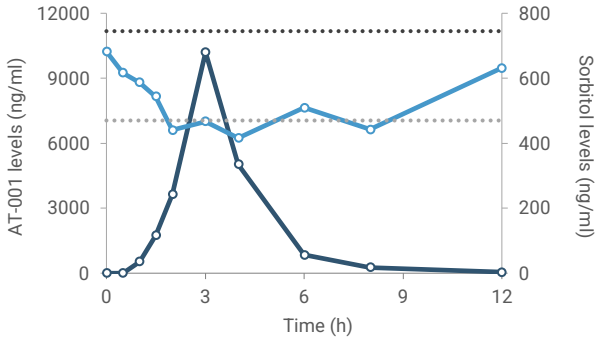
1,000mg TID Dosing *(n=10)*

Placebo *(n=6)*

†All participants remained on concomitant medications

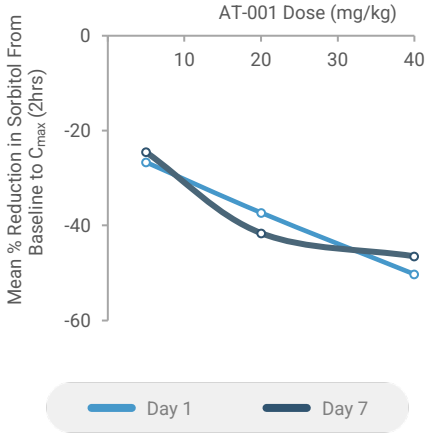
AT-001 Normalizes Sorbitol, a Biomarker of AR Activity, in Diabetic Patients

Proof of Biological Activity



AT-001 normalized sorbitol in diabetics to healthy volunteer levels

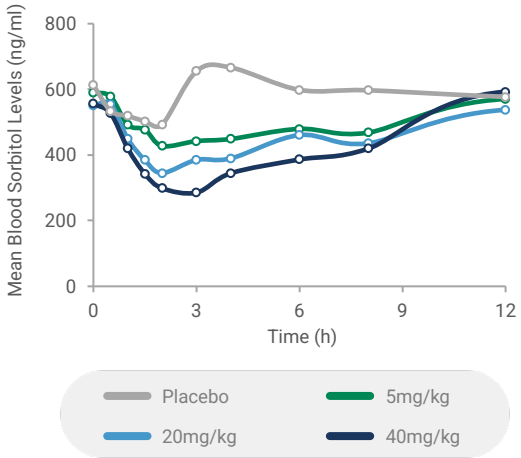
Sorbitol Reduction by Dose



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

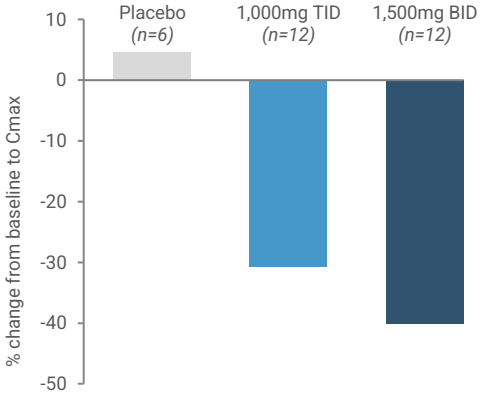


Rapid release capsule provides sorbitol normalization effects (PD biomarker) through **10-12hrs post-dose** at >10mg/kg

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

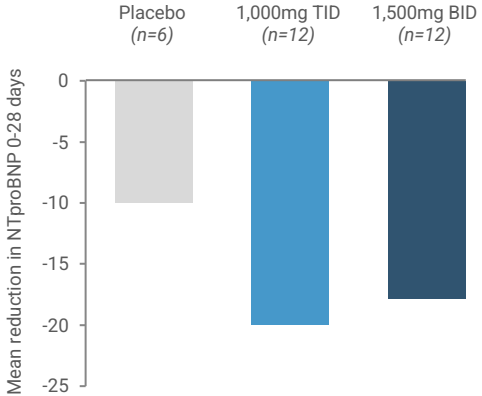
Sorbitol Normalization



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

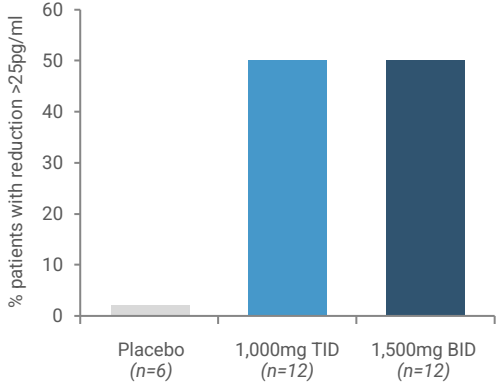
Mean Reduction in NTproBNP



Mean reduction in NTproBNP seen over 28 days vs. placebo

Mean baseline NTproBNP was 65pg/ml

Clinical Responder Analysis

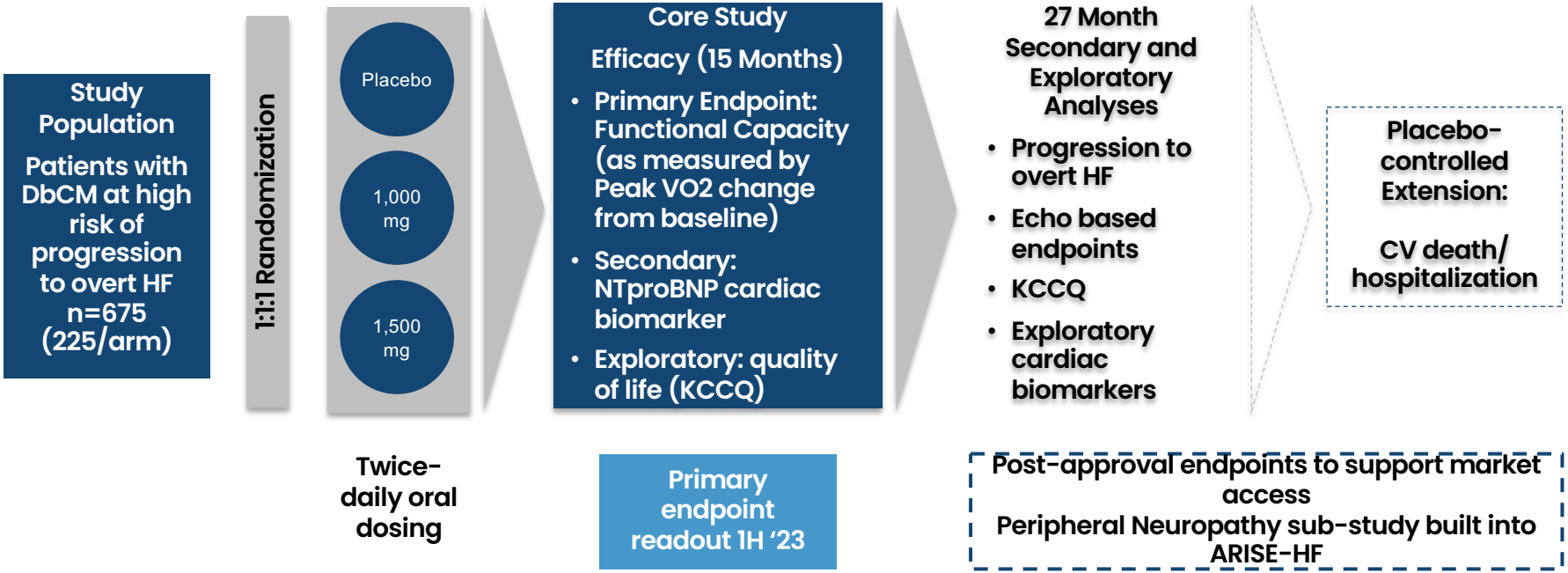


~50% AT-001 treated patients demonstrated a clinically meaningful reduction in NTproBNP over 28 days

>25pg/ml reduction from baseline

DbCM Phase 3 Registrational Study (ARISE-HF)

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



AT-001 Has Potential to be First Product to Treat DbCM, a Form of Heart Failure Affecting 1 in 5 People with Diabetes

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

Significant unmet need with no approved treatment

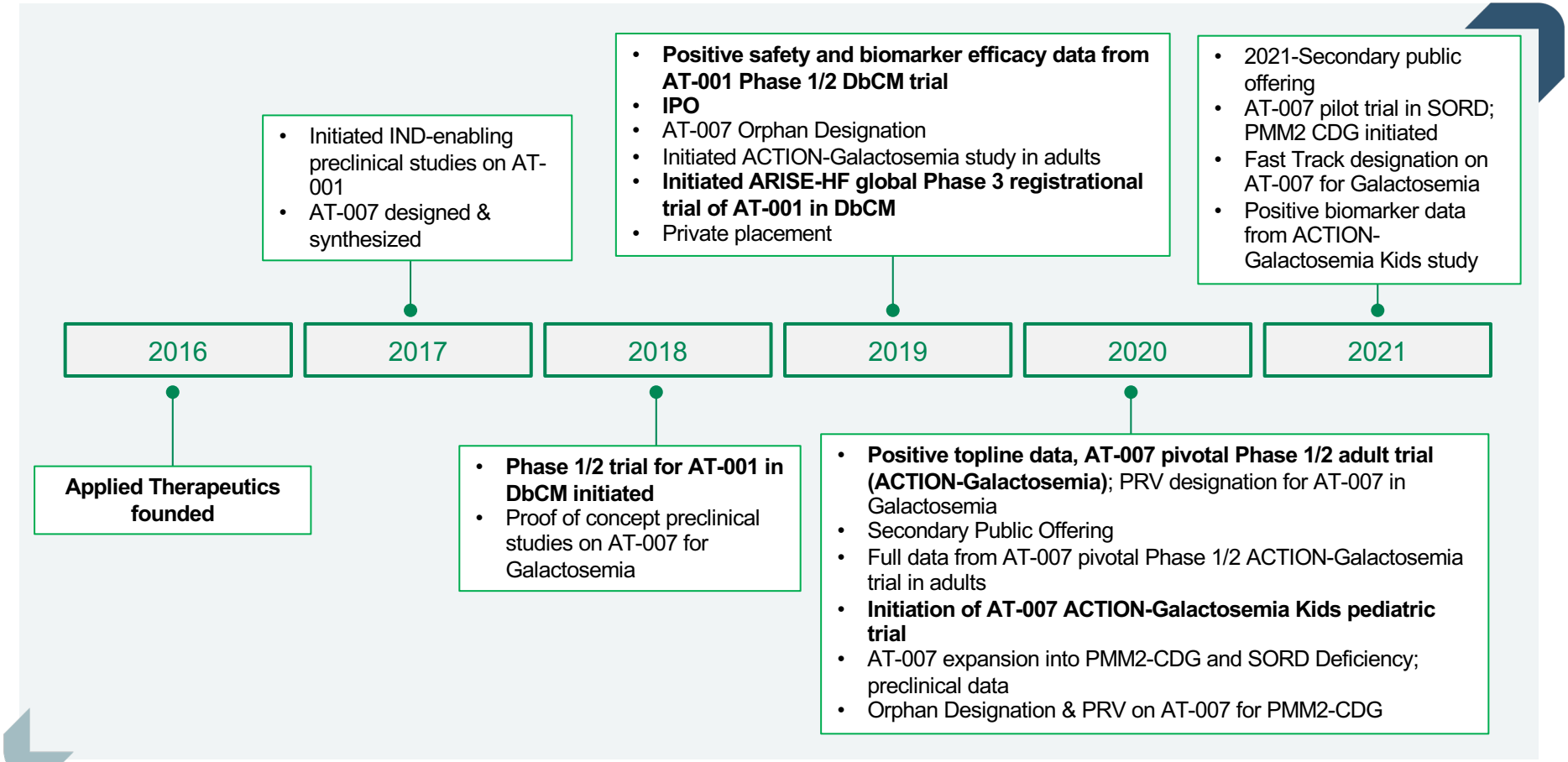
Potential for pricing in-line with SGLT2s and Entresto

Diagnosis confirmed by echocardiogram or cardiac biomarker

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

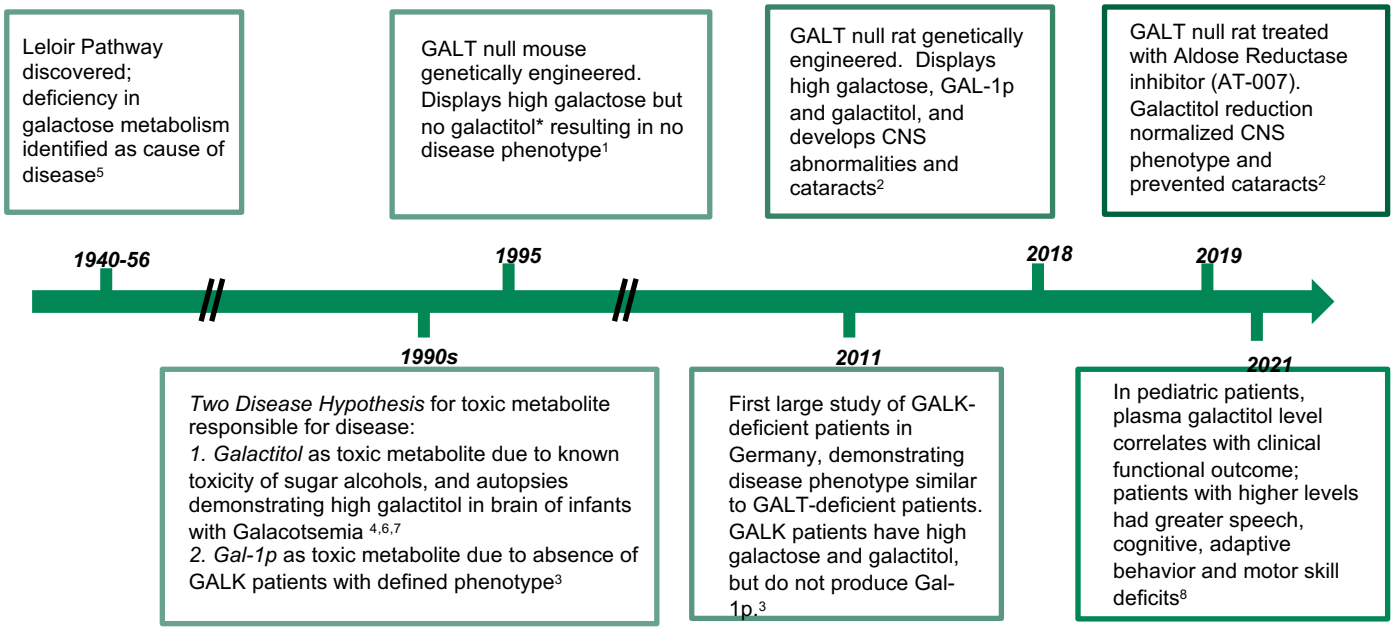
In-licensed composition of matter patents that cover AT-001 and related compounds (US, EP, JP, CA and AU)

- 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

70+ Years of Evolving Evidence Demonstrates that Galactitol is the Toxic Metabolite in Galactosemia



Gal1-p= galactose-1phosphate; GALK=galactokinase; GALT= galactose-1-phosphate uridylyltransferase
*mice do not express aldose reductase

1.Leslie ND. Insights into the pathogenesis of galactosemia. Annu Rev Nutr. 2003;23(1):59-80. 2. Rasmussen SA, Daenzer JMI, MacWilliams JA, et al. A galactose-1-phosphateuridylyltransferase-null rat model of classic galactosemia mimics relevant patient outcomes and reveals tissue-specific and longitudinal differences in galactose metabolism. J Inherit Metab Dis. 2020;43(3):518-528. 3. Hennermann JB, Schadewaldt P, Vetter B, Shin YS, Mönch E, Klein J. Features and outcome of galactokinase deficiency in children diagnosed by newborn screening. J Inherit Metab Dis. 2011;34(2):399-407. 4. Berry, G.T. (2008), *Galactosemia and Amenorrhea in the Adolescent*. Annals of the New York Academy of Sciences, 1135: 112-117. 5. Didem Demirbas, Xiaoping Huang, Vikram Daesety, et al. The ability of an LC-MS/MS-based erythrocyte GALT enzyme assay to predict the phenotype in subjects with GALT deficiency, Molecular Genetics and Metabolism, 2019;126(4):368-376. 6.M.C.G. Otaduy, C.C. Leite, M.T.C. Lacerda et al. Proton MR Spectroscopy and Imaging of a Galactosemic Patient before and after Dietary treatment. AJNR Am J Neuroradiol 2006;27:204-207. 7. Diego Martinelli, Bruno Baernardi, Anotnio Napolitano, et al. Teaching NeuroImages: Galactitol peak and fatal cerebral edema in classic galactosemia. American Academy of Neurology. 2016;96:e32-e33. 8. Pediatric Study AT-007-1002.

How Do We Know Galactitol is Responsible for Long-Term CNS Complications in Galactosemia?

- GALK deficient patients do not produce Gal-1p, yet still suffer acute infantile symptoms and chronic CNS complications[1]
- Aldose reductase and production of galactitol are necessary for galactosemia phenotype in animal models[2,3]
- In animal models, galactitol reduction prevents CNS complications[4]
- Patients with higher galactitol levels have more severe disease[5]

1. Hennermann JB, Schadewaldt P, Vetter B, Shin YS, Mönch E, Klein J. Features and outcome of galactokinase deficiency in children diagnosed by newborn screening. J Inherit Metab Dis. 2011;34(2):399-407 ; 2. Leslie ND. Insights into the pathogenesis of galactosemia. Annu Rev Nutr. 2003;23(1):59-80. 3. Rasmussen SA, Daenzer JMI, MacWilliams JA, et al. A galactose-1-phosphateuridylyltransferase-null rat model of classic galactosemia mimics relevant patient outcomes and reveals tissue-specific and longitudinal differences in galactose metabolism. J Inherit Metab Dis. 2020;43(3):518-528. 4. Poster 2020-A-1958-"Post-natal galactitol reduction is associated with normalization of CNS phenotype in an animal model of Galactosemia" ASHG 2020 Virtual Meeting held October 27-30, 2020 5. Perfetti R et al. Galactitol Level is a Predictor of Disease Severity in Children with Classic Galactosemia on Galactose Restricted Diet. Poster presented at: International Congress Inborn Errors of Metabolism Annual Meeting; November 21-23, 2021; Sydney, Australia.