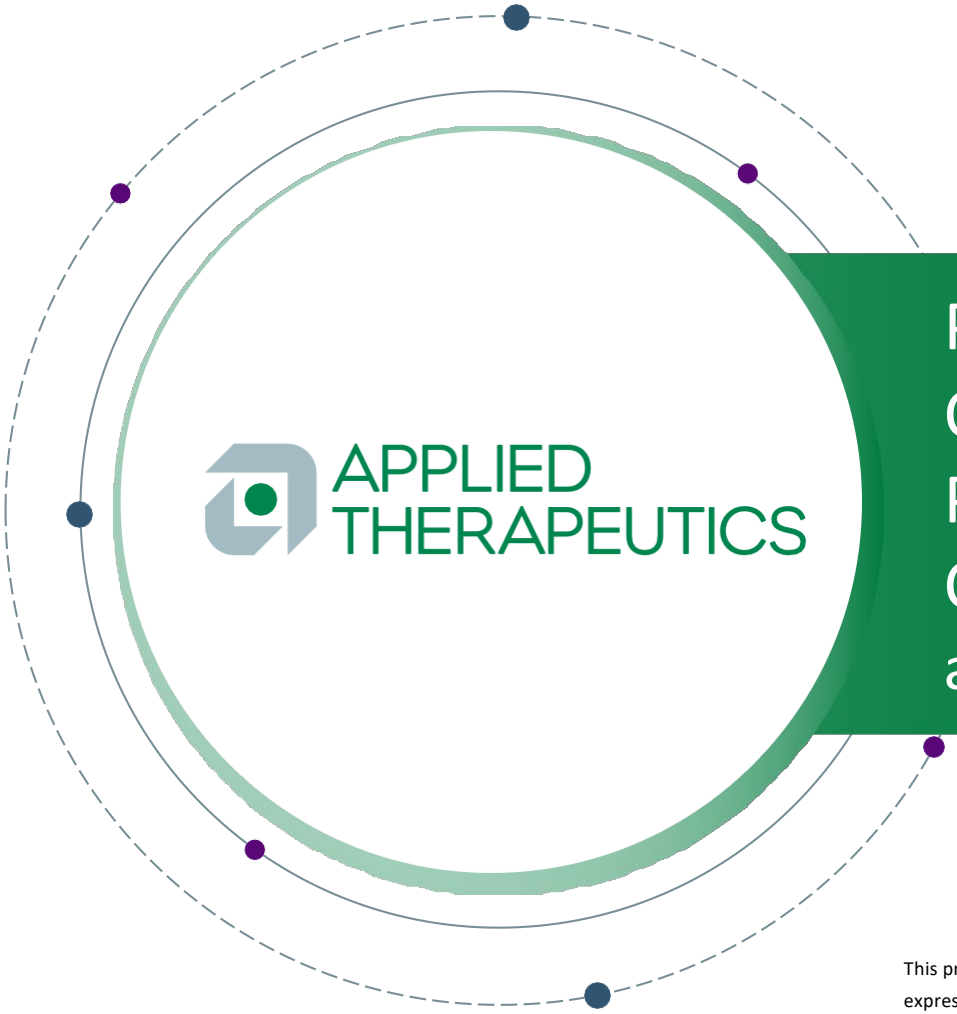

Progressive Worsening of Central Nervous System Phenotype in Children with Classic Galactosemia: a Cross-Sectional Analysis

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GALACTOSEMIA

Presented by

Dr. Riccardo Perfetti, MD, PhD

Chief Medical Officer, Applied Therapeutics

Progressive Worsening of Central Nervous System Phenotype in Children with Classic Galactosemia: a Cross-Sectional Analysis

Discuss disease manifestation in children with a specific focus on the CNS phenotype.

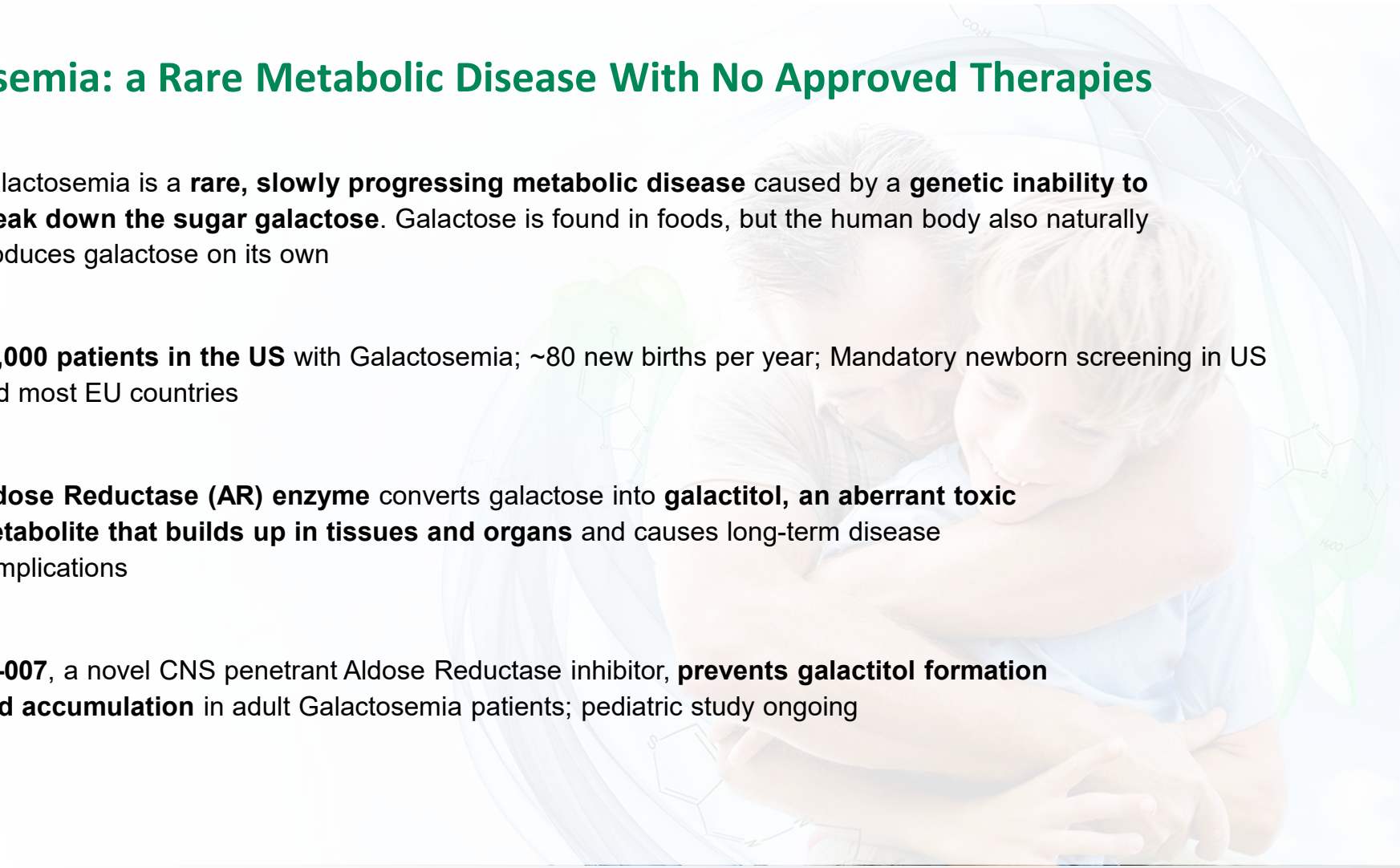
Review recent evidence demonstrating that Galactosemia is a progressive disease, significantly worsening with age.

Review current knowledge on disease pathogenesis and potential opportunities for intervention through clinical trials.

Disclaimer:
Riccardo Perfetti and Francesca Lawson are employees of Applied Therapeutics

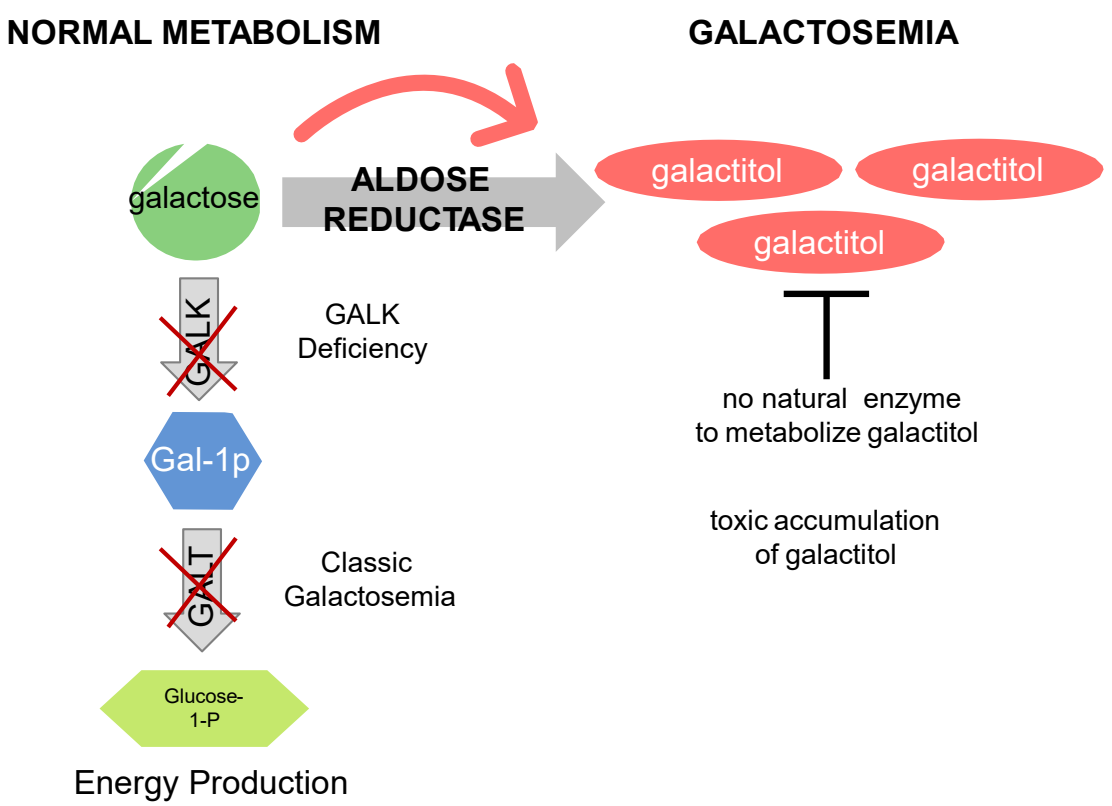
Galactosemia: a Rare Metabolic Disease With No Approved Therapies

- 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



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

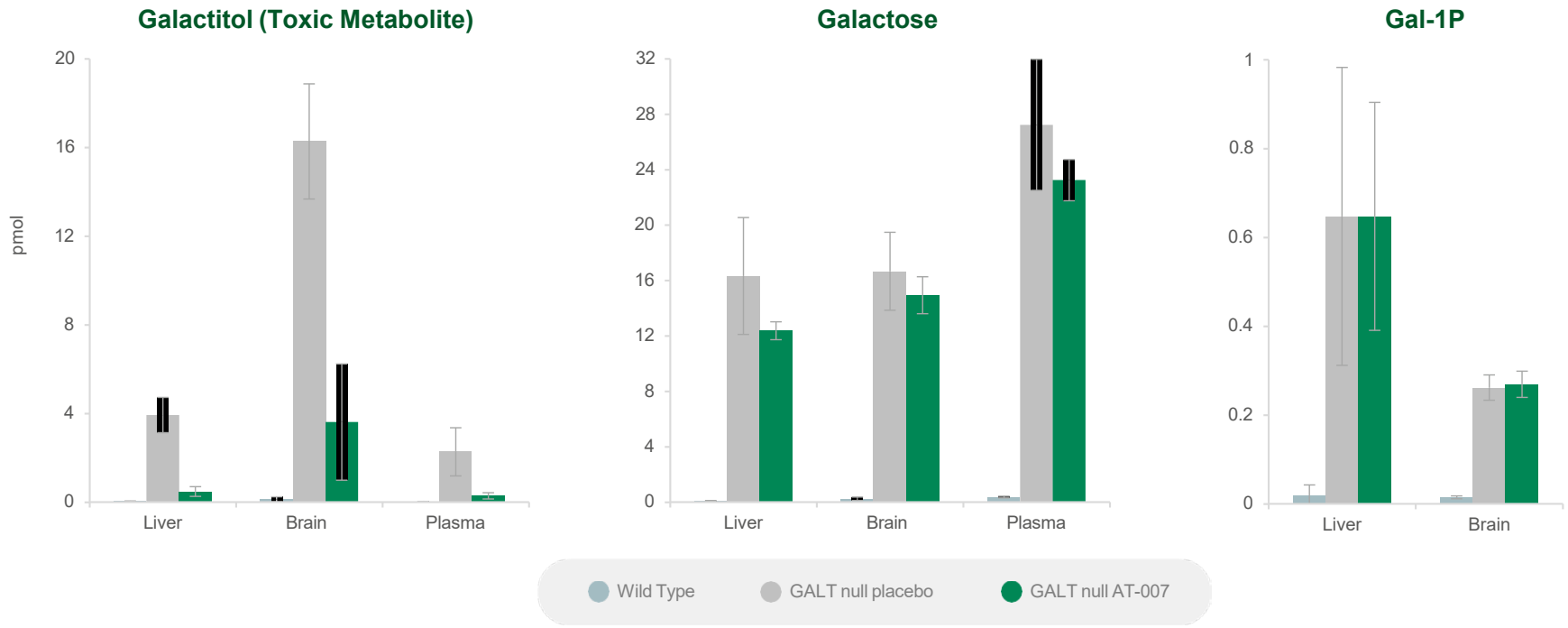
Aldose Reductase Converts Excess Galactose to Toxic Galactitol



AT-007 Blocks Aldose Reductase Conversion of Galactose to Galactitol Galactose is then shunted through a nontoxic pathway for metabolism and excretion

PRE-CLINICAL

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

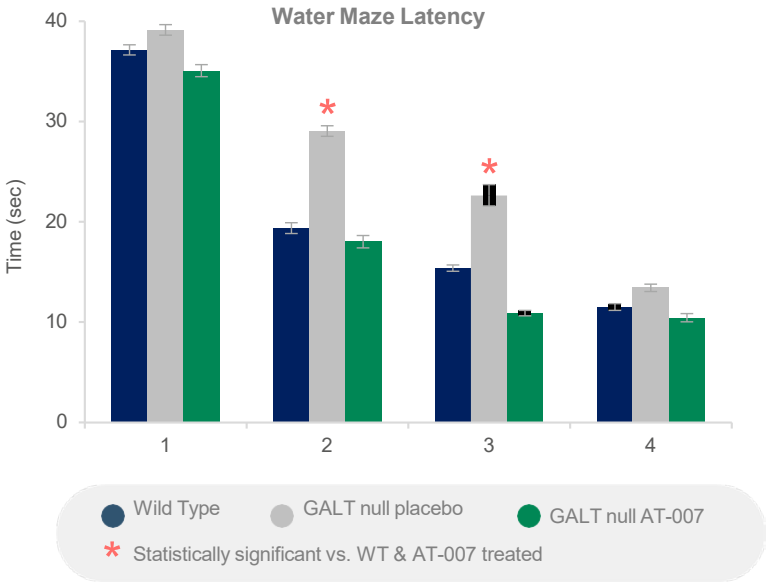


AT-007 treatment from neonatal Day 1 to Day 10 significantly reduced galactitol in liver, brain and plasma
AT-007 treatment did not increase galactose or Gal-1P levels; similar results seen at Day 22 and age 5 months

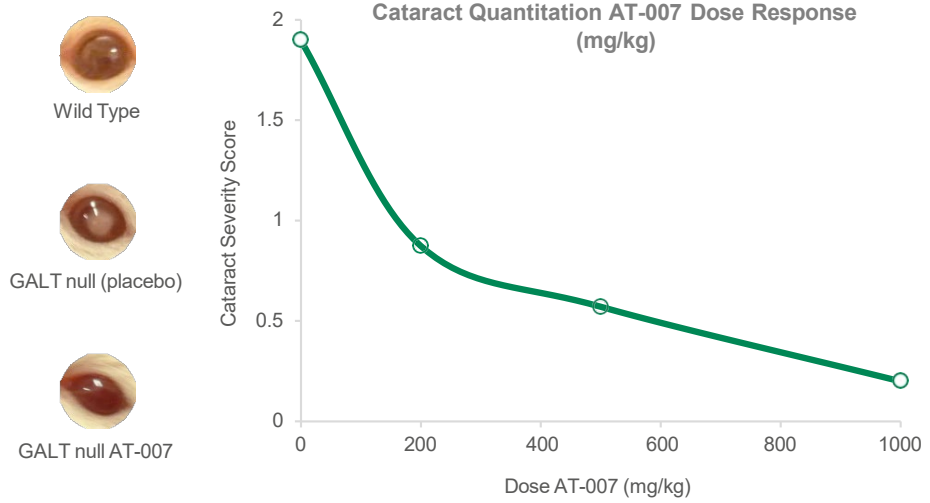
PRE-CLINICAL

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

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

- In a rat model of Galactosemia (GALT null), **reduction in galactitol** levels resulted in **normalization of CNS outcomes** of disease (learning, cognition, memory, motor skills) as measured by Water Maze and rotarod
- The GALT null mouse model **does not display elevated galactitol levels**, and these mice **do not have a CNS phenotype** of disease (because mice express low levels of Aldose Reductase as compared to rats and humans)
- **GALK deficient patients** are missing the GALK enzyme, and do not produce other galactose metabolites, such as Gal-1p; they **only have elevated galactitol levels**. These patients are rare, but they do **demonstrate a CNS phenotype similar to Classic Galactosemia**, including cognitive and intellectual deficiency, brain edema, and microcephaly
- A small number of **"biochemical variant"** Classic Galactosemia patients exist with a low level of residual GALT activity. These patients have **lower levels of galactitol** vs. typical Classic Galactosemia patients, and as a result have **less severe outcomes**.

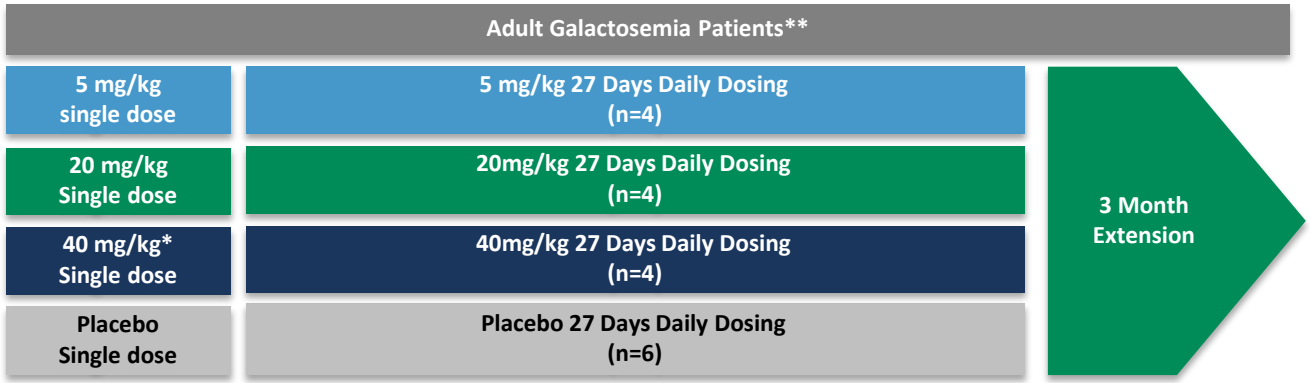
PHASE 1/2

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

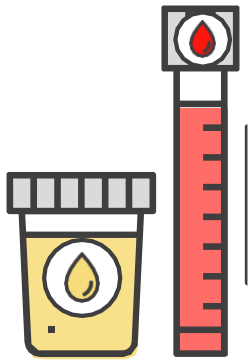
PHASE 1/2 – PHASE 1 HEALTHY VOLUNTEERS

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

Safety

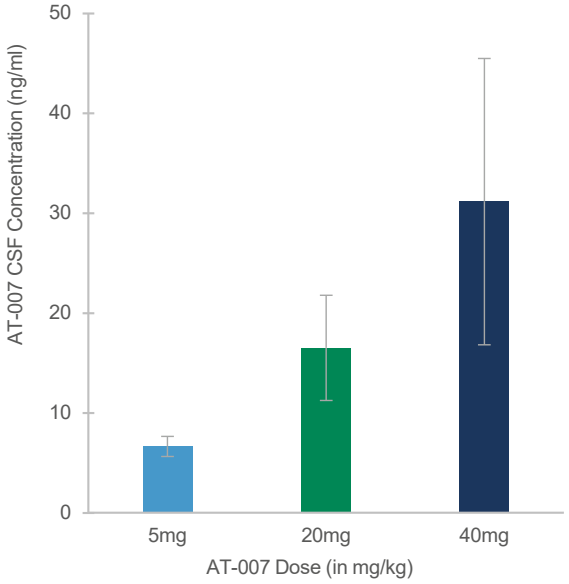
~80 healthy volunteers treated

AT-007 was safe and well tolerated at all doses



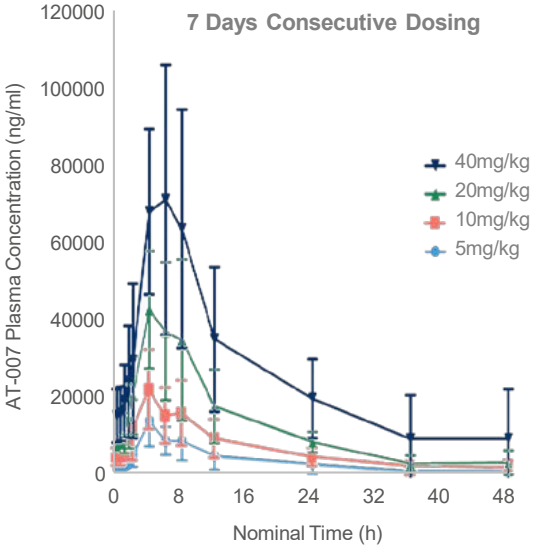
Brain Penetrance

Drug crosses into brain when dosed orally (CNS penetrant)



Pharmacokinetics

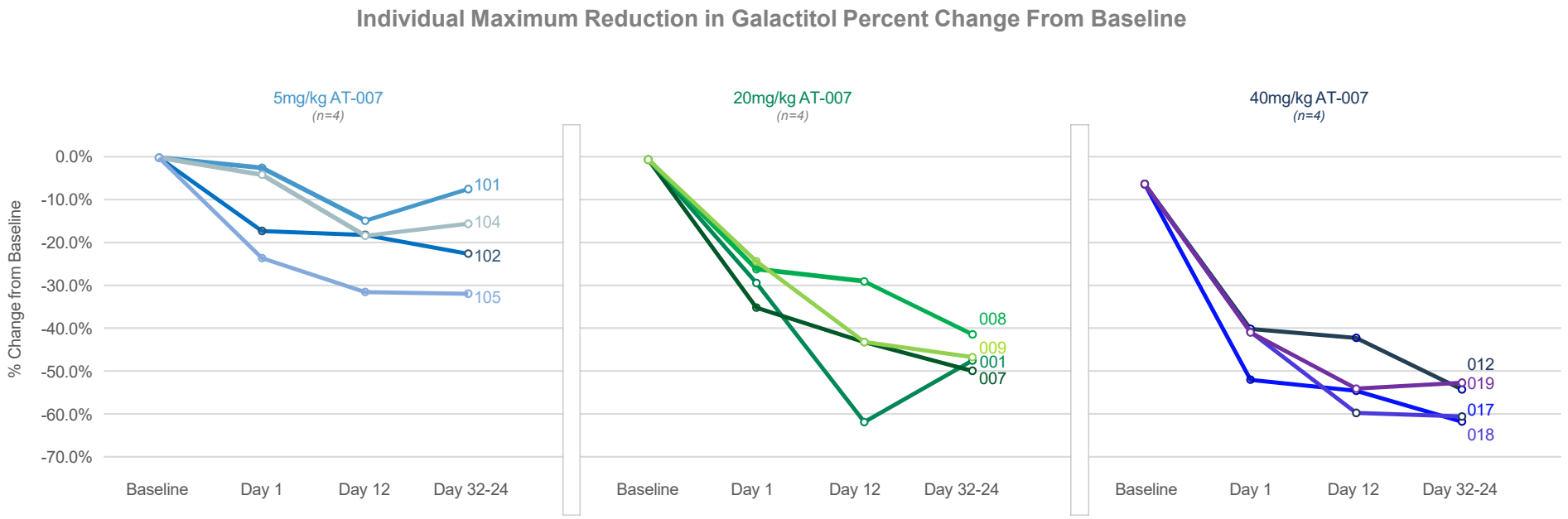
Dose-dependent increase in exposure; supportive of once daily oral dosing



PHASE 1/2 – PHASE 2 ADULT GALACTOSEMIA PATIENTS

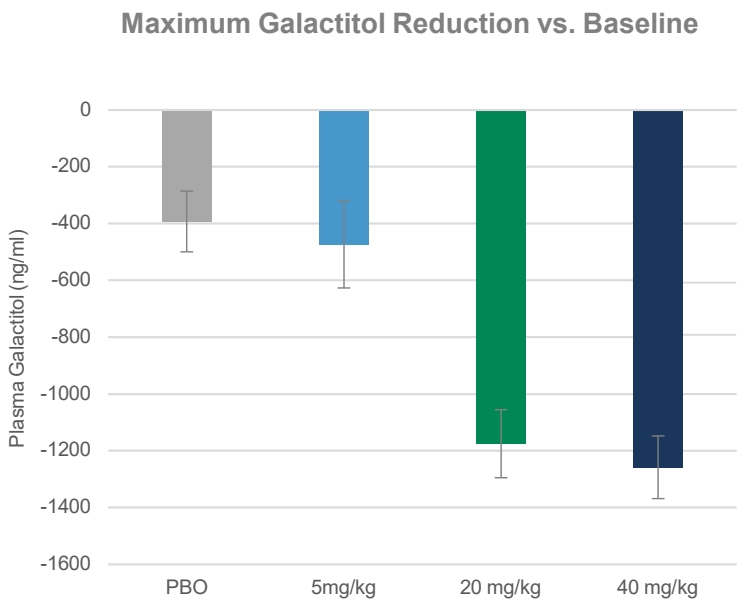
AT-007 Decreased Galactitol Levels in All Treated Patients

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 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)

GALACTOSEMIA PEDIATRIC PROGRAM

Presented by

Francesca Lawson, MD, FAHA

Head of Development, Applied Therapeutics

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

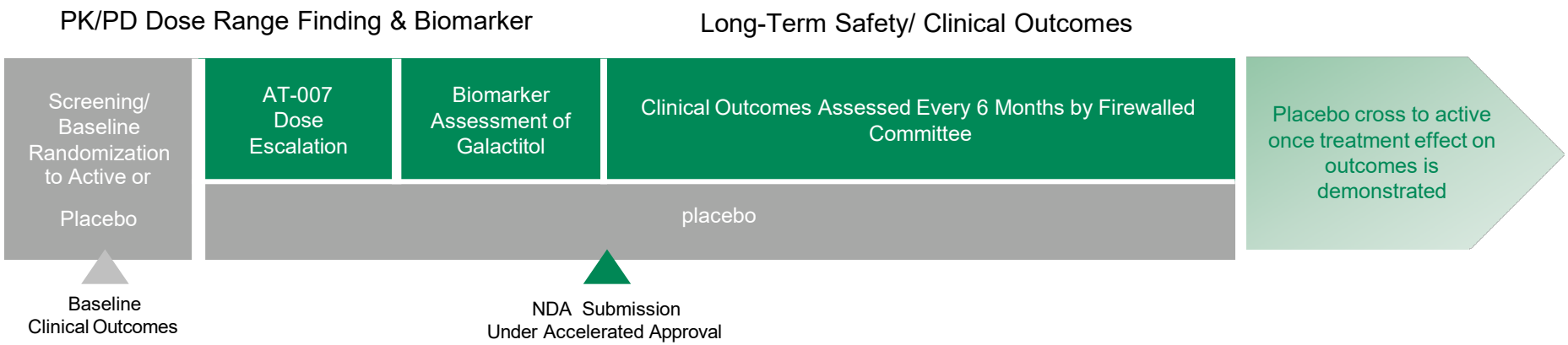
- Puberty and fertility problems (females)
- Growth delays
- Anxiety
- Social problems
- Learning difficulties
- Tremor

Adult

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

Pediatric Study

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

Galactosemia Outcomes Worsen Over Time

- **The Galactosemia population has not yet been studied prospectively in a longitudinal study** (same children progressing over time)
  - However, individual patients have been tracked over time, demonstrating progressively worsening symptoms
- **In the ACTION-GALACTOSEMIA Kids trial, a cross-sectional analysis of the first 19 pediatric patients at baseline** was performed to evaluate the effect of age on disease outcomes
  - This analysis provided baseline outcomes assessments on children age 3-15 across all 4 quadrants – speech, cognition, behavior motor skills
- **Disease severity increased with age, demonstrating that Galactosemia progressively worsens over time, impacting speech, cognition, behavior, motor skills**

Baseline Characteristics & Results Overview

Age & Gender

- 19 participants age 3 - 15
- 11 female and 8 male
- 7 patients 2-6yrs, 9 patients 7-12yrs, 3 patients 13-17yrs

Galactosemia characteristics

- 9 patients homozygous Q188R
- 1 patient homozygous K285N
- 9 patients compound heterozygous

Domain	% Patients with severe impairment (Standard Scores below 2 SD)		
	2-6 yr	7-12 yr	13-17 yr
Speech	0	33.3	66.7
Cognition	0	75.0	100.0
Adaptive Behavior	0	0	33.3
Motor	0	50.0	66.7

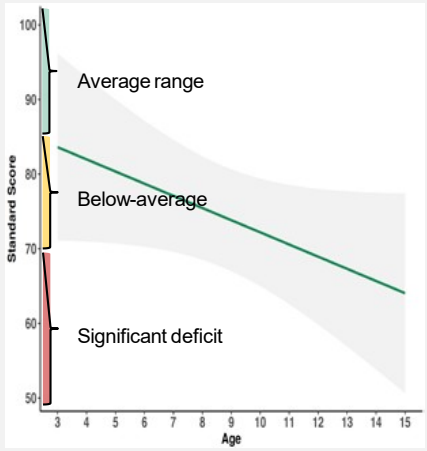
Baseline Characteristics

Age at entry (years)	Gender	Plasma galactitol (ng/mL)	GALT enzyme activity (nmol/h/mg)	Gene mutation
15	Female	2450	0.1	p.Q188R
14*	Female	233	0.4	p.K285N
13	Female	2530	0	p.Q188R
12	Male	1710	0	p.Q188R
12	Female	2530	0	p.Q188R, p.Q188P
12	Male	2010	0	p.Q188R, p.Y209C
11	Female	2720	0.1	p.Q188R
9	Male	2400	0.1	p.K285N/other
9	Male	2180	0	p.Q188R (Gin188Arg)
9	Female	2360	0	p.Q188R, p.Y209C
8	Male	2020	0.1	p.Q188R
7	Female	2200	0	p.Q188R
6	Male	2540	0	p.Q188R
5	Female	2060	0	p.Q188R, p.Q344K
4	Male	1470	0	p.Q188R, p.K285N
4	Female	2310	0	p.Q188R
4	Female	N/A	0	p.Q188R (Gin188Arg)
4	Female	1820	0	p.Q188R
3	Male	1880	0	p.L95P, p.Q188R

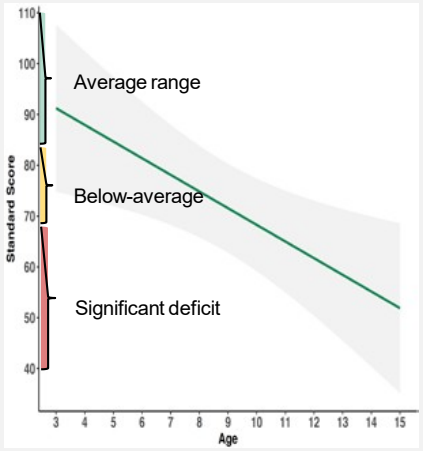
*This patient is believed to be a "biochemical variant" patient with remaining residual GALT enzyme activity.

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

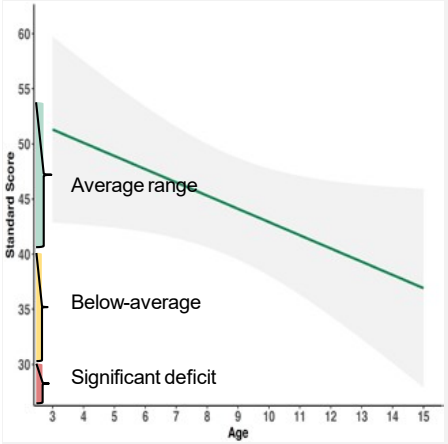
Speech



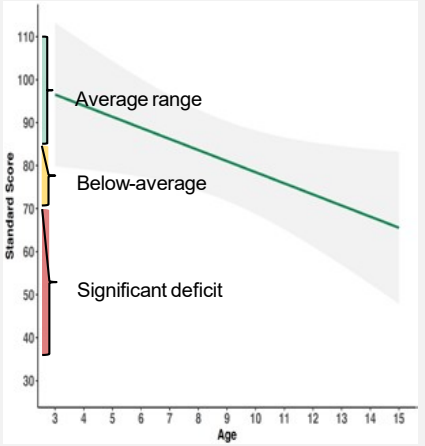
Cognition



Adaptive Behavior

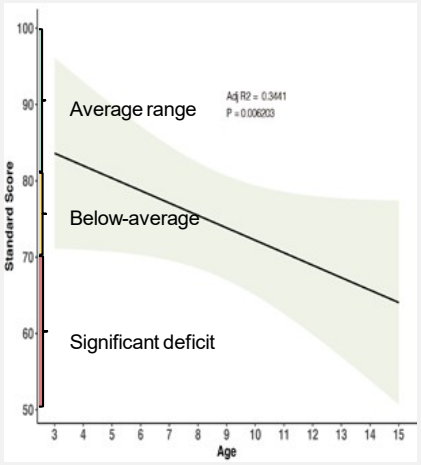


Motor Skills (Balance)

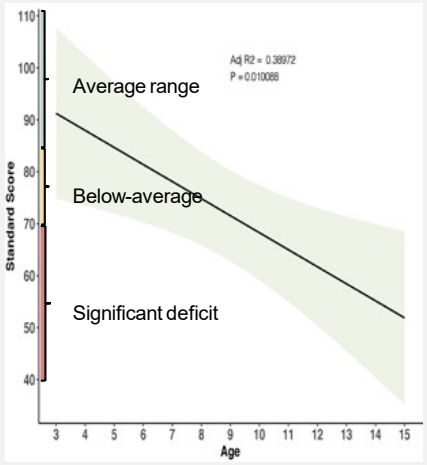


Cross Sectional Analysis of Outcomes in Children Age 3-15 Demonstrates Significant Progressive Worsening of Disease Over Time (Sensitivity Analysis)

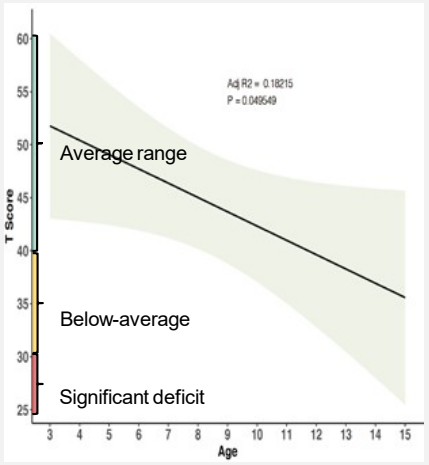
Speech



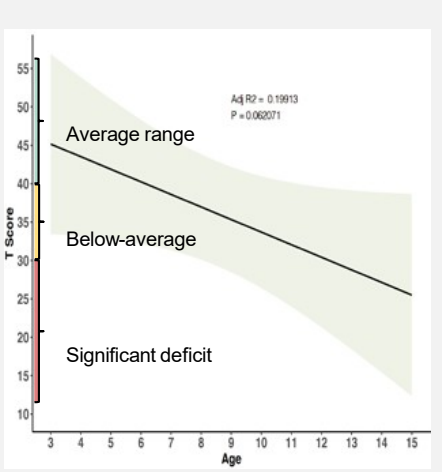
Cognition



Adaptive Behavior



Motor Skills (Balance)



Analysis excludes biochemical variant patient

Summary & Conclusions

- Galactosemia is a slowly progressive rare disease, which worsens over time with age
- Complications are caused by accumulation of the toxic aberrant metabolite, galactitol
  - Naturally produced by the human body despite galactose-free diet
- Galactitol reduction with AT-007 in a rat model of disease prevented CNS symptoms
- AT-007 treatment in adults with Galactosemia significantly reduced galactitol levels by ~50%
  - Similar degree of reduction shown to be effective in preclinical model
- A pediatric biomarker study is ongoing; patients seamlessly transition to the long-term part of the study, which will study clinical outcomes

Thank You

For additional information please visit
our website: AppliedTherapeutics.com

Or contact:
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