ACTION-Galactosemia Kids: Pediatric Study of AT-007 in Children with Galactosemia

Galactosemia Foundation Conference

July 17-19, 2020

Shoshana Shendelman, PhD, CEO and Founder

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AT-007 is an investigational drug being studied in patients with Classic Galactosemia. It has not been approved by the FDA.

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

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Agenda

This Presentation

- Overview of Galactosemia- Stages of Disease
- Mechanism of Disease
- AT-007 Preclinical (animal) Data
- AT-007 Clinical (human) Data
- AT-007 Pediatric Study Design

Other Presentations at the Galactosemia Foundation 2020 Conference

(Archived - please see recorded presentations)

- AT-007: Development of an Oral Treatment for Patients with Galactosemia; Saturday, July 18 10:00 – 11:00 a.m. ET
- ACTION-Galactosemia: Clinical Experience with Adult Galactosemia Patients and Path Forward; Saturday, July 18 4:15 – 5:00 p.m. ET

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Overview of Galactosemia & Stages of Disease

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Galactosemia Overview

Rare metabolic disease affecting ~2,800 patients in the US; ~80 new births per year

Caused by enzyme deficiency and inability to metabolize the simple sugar galactose

Galactose is formed by metabolism of external lactose, but **Galactose is also produced naturally by the body** (endogenously)

No approved therapies; mandatory newborn screening and initiation of dairy free diet; Dietary restriction prevents fatalities, but **does not prevent long term consequences of disease**

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Symptoms of Galactosemia in Newborns

Newborns are screened for Galactosemia, but sometimes symptoms can develop before the results are available. Complications may be serious, requiring intensive care or even causing death.

Acute Symptoms

- Liver failure
- Jaundice
- Kidney problems
- Sepsis
- Swelling of brain (edema)
- Pressure around brain that causes neurological problems (pseudotumor cerebri)

Chronic Symptoms

- Feeding difficulties
- Growth problems
- Cataracts

Monitoring

- Newborns are monitored at least every 3 months for the first year

Sources: Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, et al, eds. *GeneReviews®*. University of Washington: Seattle, WA: 993-2020; Berry GT, et al. *Lancet*. 1995;346(8982):1073-1074; Coelho A, et al. *J Inherit Metab Dis*. 2017;40(3):325-342; Rubio-Gozalbo ME, et al. *Orphanet J Rare Dis*. 2019;14(1):86; Welling L, et al. *J Inherit Metab Dis*. 2017;40(2):171-176.

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Symptoms of Galactosemia in Infants and Toddlers

At this stage, there may be early signs of developmental delays and speech problems.

Symptoms

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

Monitoring

- **7 to 12 months:** Begin testing for speech/language delays
- **2 to 3 years:** Begin assessments of early speech/language and motor development

Sources: Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, et al, eds. *GeneReviews®*. University of Washington: Seattle, WA: 993-2020; Berry GT, et al. *Lancet*. 1995;346(8982):1073-1074; Coelho A, et al. *J Inherit Metab Dis*. 2017;40(3):325-342; Rubio-Gozalbo ME, et al. *Orphanet J Rare Dis*. 2019;14(1):86; Welling L, et al. *J Inherit Metab Dis*. 2017;40(2):171-176.

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Symptoms of Galactosemia in Primary School Children

Developmental delays may become more noticeable during this stage as children go to school.

Symptoms

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

Monitoring

- **4 to 5 years:** Begin neuropsychological tests, evaluations of school readiness, and early educational support
- **8 to 10 years:** Begin assessment of cognitive development
- Regular neurological and psychological evaluations, bone density screening, eye tests, and dietary monitoring throughout this stage

Sources: Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, et al, eds. *GeneReviews®*. University of Washington: Seattle, WA: 993-2020; Berry GT, et al. *Lancet*. 1995;346(8982):1073-1074; Coelho A, et al. *J Inherit Metab Dis*. 2017;40(3):325-342; Rubio-Gozalbo ME, et al. *Orphanet J Rare Dis*. 2019;14(1):86; Welling L, et al. *J Inherit Metab Dis*. 2017;40(2):171-176.

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Symptoms of Galactosemia in Teens

Teens with Galactosemia can struggle with social problems as a result of behavioral, cognitive, or developmental issues they experience.

Symptoms

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

Monitoring

- **12 to 14 years:** Begin neuropsychological assessment for executive function
- Bone density screening and additional psychological, cognitive, and endocrine/hormone testing (for girls) throughout this stage

Sources: Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, et al, eds. *GeneReviews®*. University of Washington: Seattle, WA: 993-2020; Berry GT, et al. *Lancet*. 1995;346(8982):1073-1074; Coelho A, et al. *J Inherit Metab Dis*. 2017;40(3):325-342; Rubio-Gozalbo ME, et al. *Orphanet J Rare Dis*. 2019;14(1):86; Welling L, et al. *J Inherit Metab Dis*. 2017;40(2):171-176.

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Symptoms of Galactosemia in Adults

Some symptoms that begin earlier in life may continue into adulthood. Because of long-term health issues, it may be difficult for adults with Galactosemia to become independent.

Symptoms

- Anxiety
- Depression
- Attention deficit hyperactivity disorder (ADHD)
- Tremor
- Seizures
- Cataracts

Sources: Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, et al, eds. *GeneReviews®*. University of Washington: Seattle, WA: 993-2020; Berry GT, et al. *Lancet*. 1995;346(8982):1073-1074; Coelho A, et al. *J Inherit Metab Dis*. 2017;40(3):325-342; Rubio-Gozalbo ME, et al. *Orphanet J Rare Dis*. 2019;14(1):86; Welling L, et al. *J Inherit Metab Dis*. 2017;40(2):171-176.

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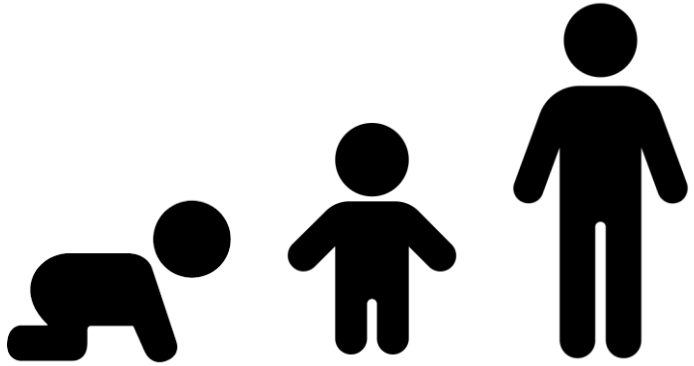
Mechanism of Disease

Dietary Restriction and Endogenous Galactose Production

Diet Can Reduce Exposure to Galactose From Lactose-Containing Foods

- Acute complications in the newborn period may be caused by external galactose (breast milk or dairy formula)
- Dietary restriction of lactose is important to prevent acute disease and death in infancy

However, the Body Produces Galactose On Its Own, Even With Diet



- Every cell in the human body makes galactose on its own (“endogenous”)
- Long-term complications of Galactosemia are caused by endogenous production of galactose, not by lack of dietary control

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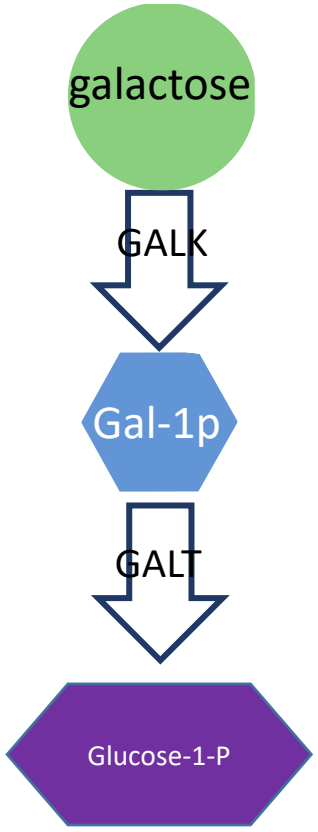
Galactosemia:

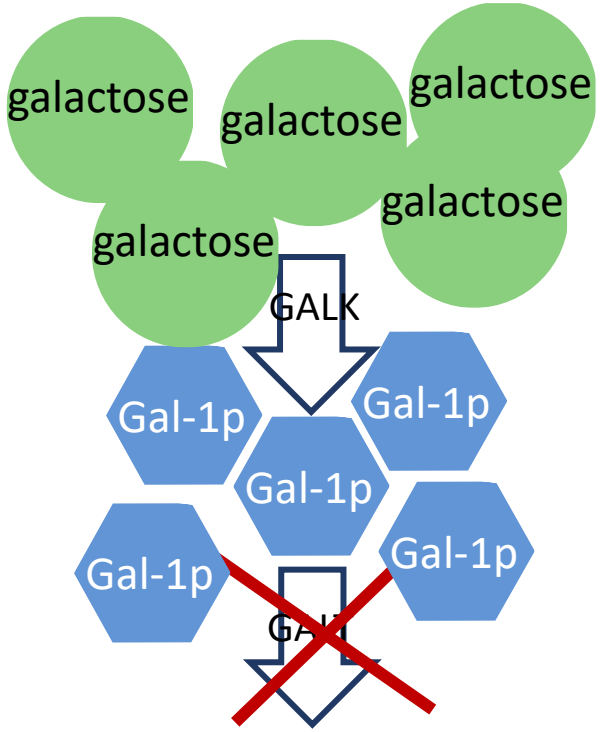
Enzyme Deficiency in GALT or GALK Leads to Inability to Metabolize Galactose

Galactose Metabolism



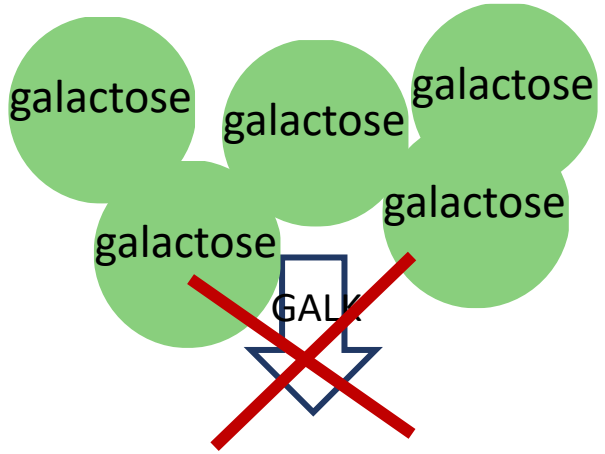
Energy Production

Classic Galactosemia



GALT Enzyme Deficiency

Galactokinase Deficiency



GALK Enzyme Deficiency

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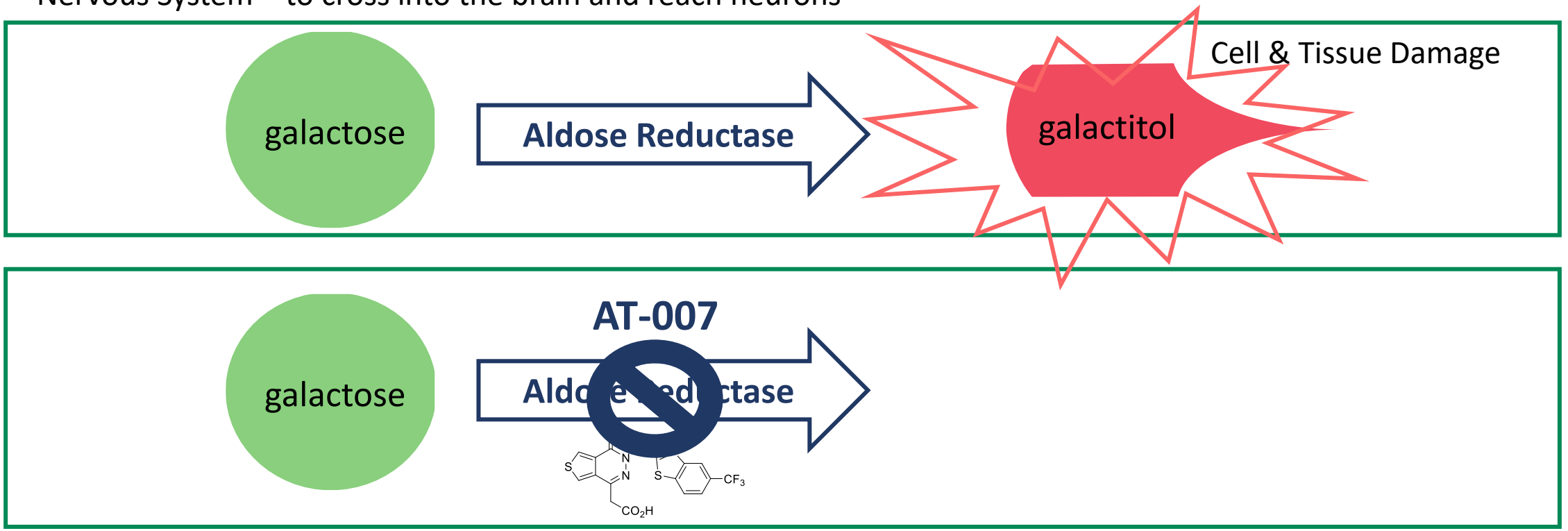
The Role of Aldose Reductase in Galactosemia

- When galactose levels are abnormally high in blood and tissues, the enzyme Aldose Reductase can convert galactose to galactitol
- This does not happen in healthy people, and galactitol is a toxic, abnormal metabolite
- AT-007 is a potent and selective Aldose Reductase inhibitor, which was specifically designed to penetrate the Central Nervous System – to cross into the brain and reach neurons



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AT-007 Development

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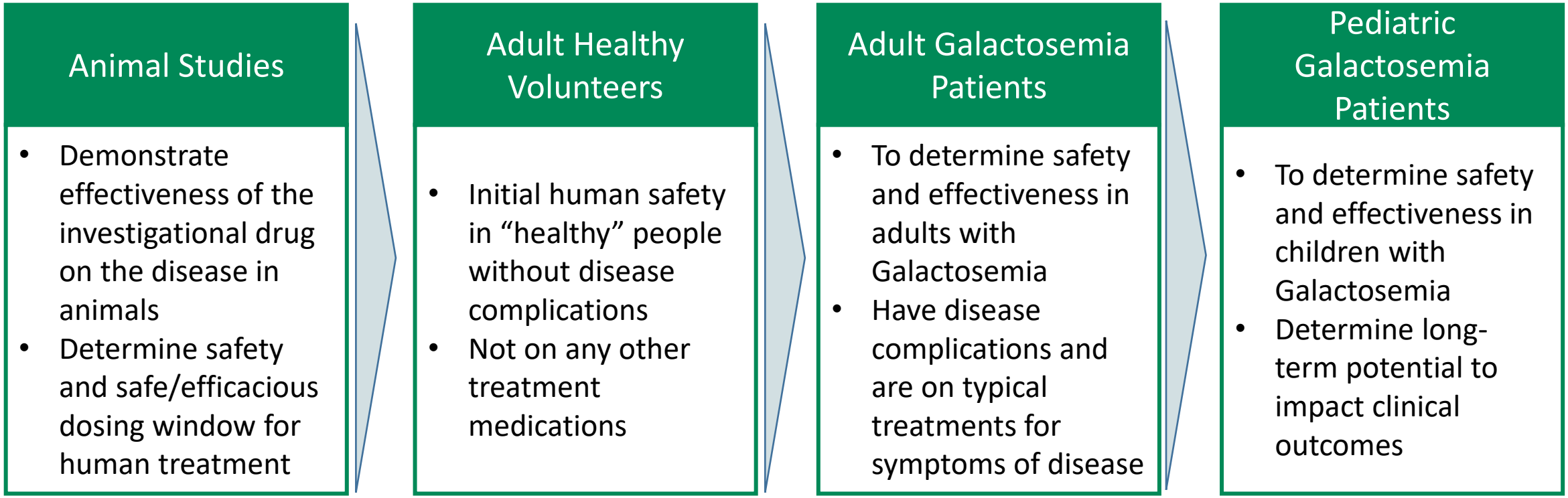
Stages of Preclinical and Clinical Development



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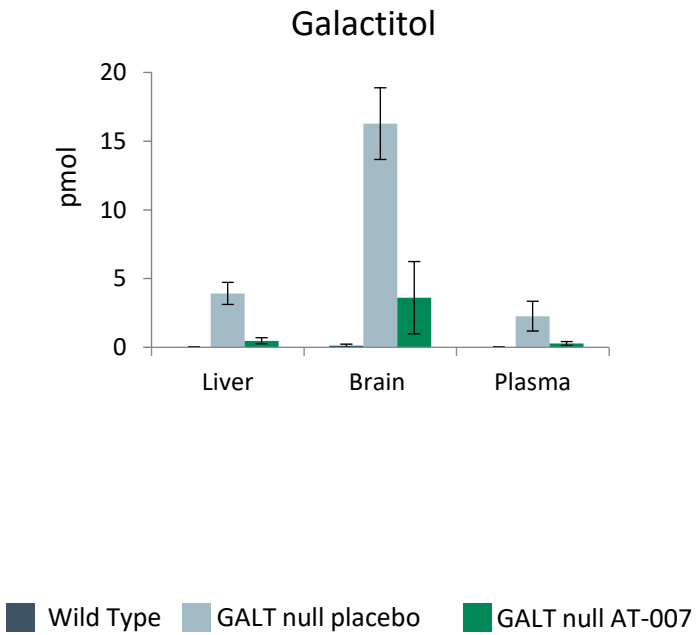
AT-007 Preclinical (Animal) Data

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

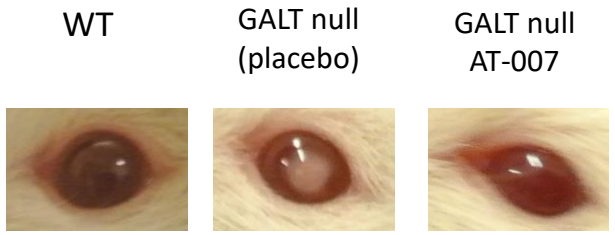
Biochemical Effects

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



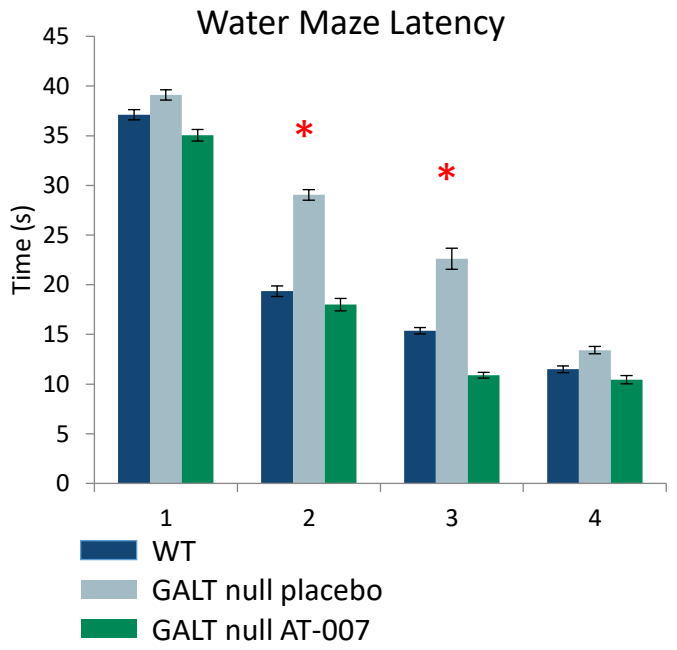
Tissue Deposition of Galactitol

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



CNS Outcomes

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



* Statistically significant vs. WT & AT-007 treated

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

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Extensive Preclinical Toxicology / Safety Studies Completed to Date

Chronic Toxicology

- 1-Month Treatment (in rats)
- 1-Month Treatment (in canines)
- 3-Month Treatment (in rats)
- 3-Month Treatment (in canines)
- 6-Month Treatment (in rats)
- 9-Month Treatment (in canines)

Specialized Studies

- Juvenile Toxicology (newborn to adult rats)
- Developmental/ Reproductive Toxicology (in rats & rabbits)
- Enzyme Inhibition / Drug Metabolism Studies
- Drug Transporter Studies (to predict potential drug-drug interactions)

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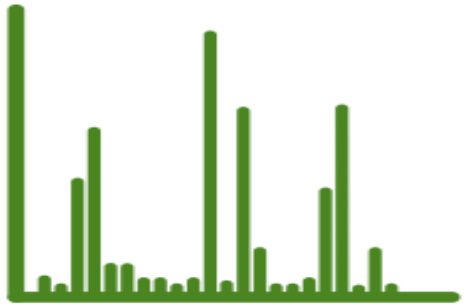
Summary: AT-007 Preclinical (Animal) Studies

Safety & PK/PD

AT-007 was safe and well tolerated in animals, with a broad dosing/ exposure window to humans

Biochemical Manifestations



In an animal model of Galactosemia, AT-007 prevented biochemical manifestations of disease; prevented production of toxic galactitol in blood and tissues, without adversely impacting galactose or Gal-1p

Clinical Manifestations

Prevented clinical manifestations of disease in animals including CNS abnormalities (learning, cognition, motor)

AT-007 Clinical (Human) Data

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Summary: ACTION-Galactosemia Adult Study Results

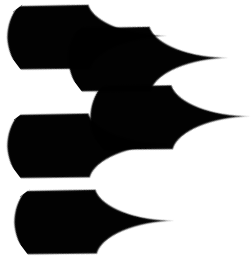
AT-007 was safe & well-tolerated in the ACTION-Galactosemia adult study

- Includes 80 healthy volunteers and 14 Classic Galactosemia patients

AT-007 was shown to be CNS penetrant

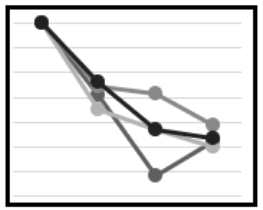
- Important in Galactosemia, which includes significant CNS clinical presentation
- Supports once-daily oral dosing

Galactitol is a toxic metabolite formed in Galactosemia patients



- Not formed in healthy people
- Detectable in blood and tissues, including the brain

AT-007 induced rapid and sustained reduction in plasma galactitol



- 20 and 40mg/kg dosing resulted in significant reduction in plasma galactitol ($p<0.01$ vs. placebo)
- No significant change in galactose or Gal-1p

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AT-007 Pediatric Study: ACTION-Galactosemia Kids

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Separating Myths from Truths Regarding Galactosemia Treatment

Myth	Galactosemia is an acute disease caused by damage at birth, prior to starting a restricted diet.
Truth	In rare cases, permanent damage may occur as a result of acute lactose exposure in newborns. Most newborns' symptoms due to acute lactose exposure resolve completely once put on a lactose-free diet. Disease complications manifest in later infancy and early childhood, with chronic progression throughout adulthood.
How Do We Know?	Newborns with a Galactosemia sibling are typically started on soy formula immediately at birth and not exposed to external lactose. These children generally display the same disease progression as children who had acute lactose exposure prior to diagnosis. Restriction of milk to mother's during pregnancy did not affect long-term outcomes in children[1].

Ref: 1. Berry GT. Classic Galactosemia and Clinical Variant Galactosemia. 2000 Feb 4 [Updated 2017 Mar 9]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.

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Separating Myths from Truths Regarding Galactosemia Treatment

Myth	Tissue damage in Galactosemia happens prenatally, so a treatment taken after birth cannot help
Truth	There is no evidence that any damage occurs prenatally.[1]
How Do We Know?	In an animal model of Galactosemia, treatment after birth with AT-007 prevented clinical disease. Treatment with AT-007 in the pediatric phase of disease prevented cognitive, learning, memory and fine motor skills problems, and prevented cataracts.[2] Treatment would be unlikely to effect disease progression had the damage happened prior to birth.

Ref: 1. Berry GT. Classic Galactosemia and Clinical Variant Galactosemia. 2000 Feb 4 [Updated 2017 Mar 9]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. 2. Perfetti, R et al. (2020) Post-Natal Galactitol Reduction is Associated with Normalization of CNS Phenotype in an Animal Model of Galactosemia ASHG Abstract October 27-31 2019

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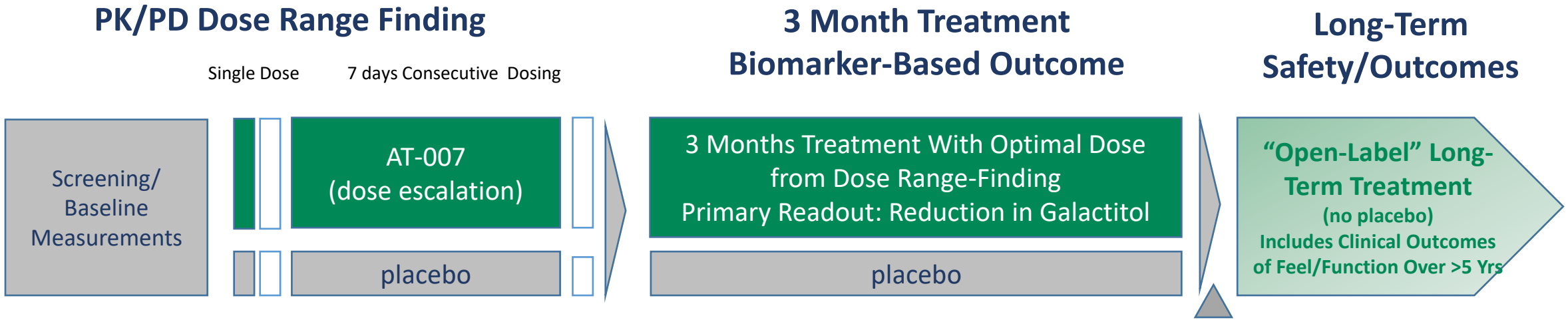
ACTION-Galactosemia Kids Pediatric Registrational Clinical Study Underway



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

▲ Planned NDA submission

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ACTION-Galactosemia Kids Study Overview

About Clinical Studies

- A clinical study (also called a clinical trial) is a scientific research program designed to learn more about diseases and potential ways to prevent, diagnose or safely treat them
- Clinical studies are required for a medicine to be approved by the Food and Drug Administration (FDA)
- In a rare disease like Galactosemia, it's important that as many families as possible participate in the clinical studies because the condition is so rare, and there are so few patients available

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ACTION-Galactosemia Kids Study Overview

Study Objectives and Design

- Designed to evaluate the safety and effectiveness of AT-007 (novel investigational drug) in children with Classic Galactosemia
- In the first part of the study, participants are randomly assigned to AT-007 or placebo
  - In the Dose Range Finding part of the study, out of every 3 children, 2 are assigned to AT-007 and 1 to placebo
  - In the 3 Month Treatment part of the study out of every 4 children, 3 are assigned to AT-007 and 1 to placebo
- Both placebo and AT-007 are taken once daily by mouth
- In the second part of the study (known as the open-label extension), all participants receive AT-007

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ACTION-Galactosemia Kids Study Overview

Why Do We Use Placebo?

- A placebo looks just like the drug being studied but doesn't contain any active medication
- A placebo is used to better understand if potential changes in participants' health are from the investigational drug and not by chance

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ACTION-Galactosemia Kids Study Overview

Screening

- Goal: to make sure potential participants are eligible to participate in the study

Dose Finding (Summer 2020)

- To help find the optimal dose for safety and effectiveness in children 2 to 17 years old

3 Month Treatment (Fall 2020)

- Goal: to test the safety and effectiveness of AT-007 compared to placebo
- Some receive AT-007 and others receive placebo (2:1)
- Visits at start and end of 3-month treatment period and monthly health checks; may be at clinic or home health visits

Open Label Extension (2021 and beyond)

- Goal: to evaluate long-term safety and effectiveness
- Will enroll additional participants
- All receive AT-007
- Health checks every 6 months for first 2 years and annually after that

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Clinical Outcomes of “Feel and Function” to Be Studied Long-Term in Children in the Open-Label Extension

Cognition & Learning

- Cognitive and intellectual development
- Attention
- Executive Function
- Memory (episodic and working memory)
- Processing speed

Speech

- Articulation
- Expressive language
- Communication skills

Motor Skills

- Dexterity
- Strength
- Balance

Growth & Physical Development

- Bone density (DEXA scan)
- Ovarian function & hormonal levels (in girls)

Behavioral / Psychosocial

- Anxiety
- Depression
- Adaptive/ social skills

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Thank You to Our Medical Heroes, Including the Tanella Family!

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More Information About the Pediatric Trial

- AT-007 is administered as either a capsule, or a strawberry-flavored liquid suspension (both taken by mouth)
- Home health visits instituted to limit travel, impact of study participation on families, and potential exposure to COVID-19
- Study site located in Atlanta, GA

For more information please visit our virtual booth or email galactosemia@appliedtherapeutics.com

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Thank You

Thank you to all of the families who are participating in the ACTION-Galactosemia program

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