



AT-007: Development of an Oral Treatment for Patients with Galactosemia

Galactosemia Foundation Conference

July 17-19, 2020

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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

Agenda

This presentation

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

Other Presentations at the Galactosemia Foundation 2020 Conference

- ACTION-Galactosemia: Clinical Experience with Adult Galactosemia Patients and Path Forward; 4:15pm – 5:00pm (Eastern)
- ACTION-Galactosemia Kids: Pediatric Study of AT-007 in Children with Galactosemia; 5:30pm – 6:15pm (Eastern)

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



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



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



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**

Galactosemia Clinical Presentation

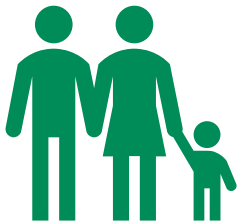
Acute Newborn



Life threatening if not identified and managed immediately:

- **Hepatic and Renal Failure**
- **Brain Swelling** (Edema/ Encephalopathy/ Pseudotumor Cerebri)
- **Sepsis**

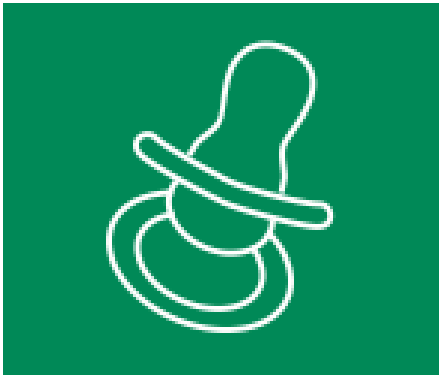
Chronic/Long-Term



- **CNS Complications**
 - Low IQ / intellectual deficits
 - Motor skills / coordination
 - Seizures
 - Tremors
 - Speech/ language
 - Learning, behavioral, social impairments
 - Psychiatric problems (anxiety, depression)
- **Primary Ovarian Insufficiency**
- **Cataracts**

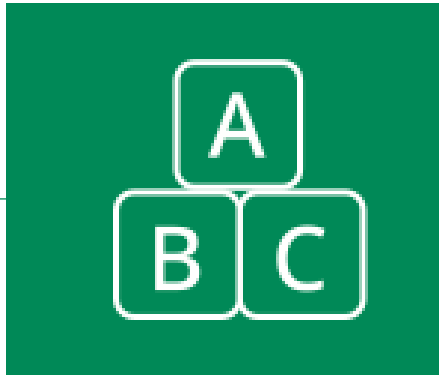
Galactosemia: Disease at Different Stages of Life

Newborns



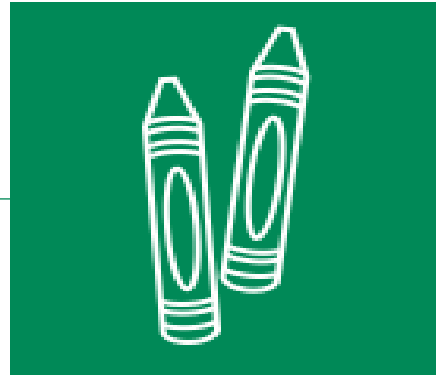
Newborns are screened for Galactosemia, but sometimes symptoms can develop before the results are available; **acute complications may be serious**, requiring intensive care or even causing death

Infants & Toddlers



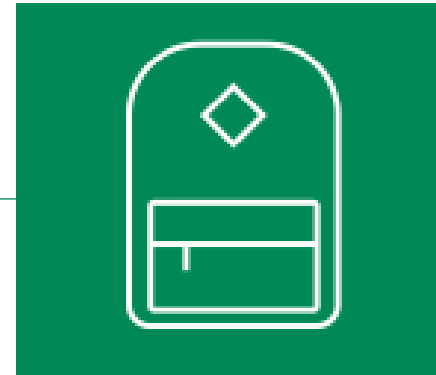
Toddlers may develop early signs of **developmental delays including growth and coordination, as well as speech problems**

Primary School Children



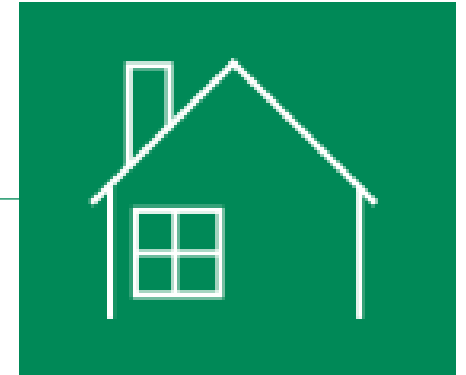
Developmental delays, learning, motor skill, behavioral and emotional problems may become more noticeable during this stage as children go to school

Teens



Teens with Galactosemia can struggle as a result of **behavioral, cognitive, or developmental issues, including puberty delays (& fertility issues in females)**

Adults



Because of long-term health issues, including **seizures, tremors or cataracts**, it may be **difficult for adults with Galactosemia to become independent**

Everyone with Galactosemia will experience disease differently, but this slide includes some common health issues that can occur at different stages of life

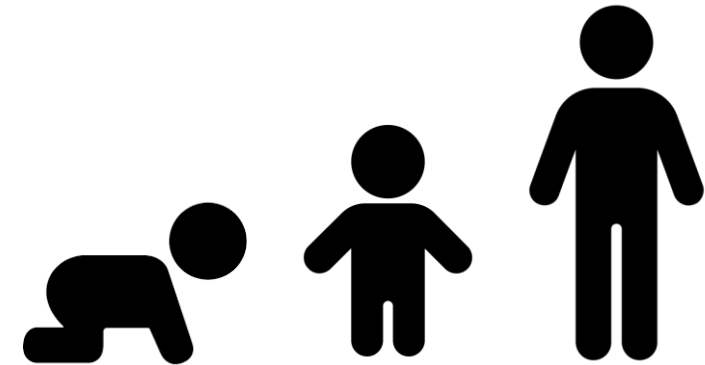
Dietary Restriction and Endogenous Galactose Production

Diet Can Reduce Exposure to Galactose From Lactose-Containing Foods



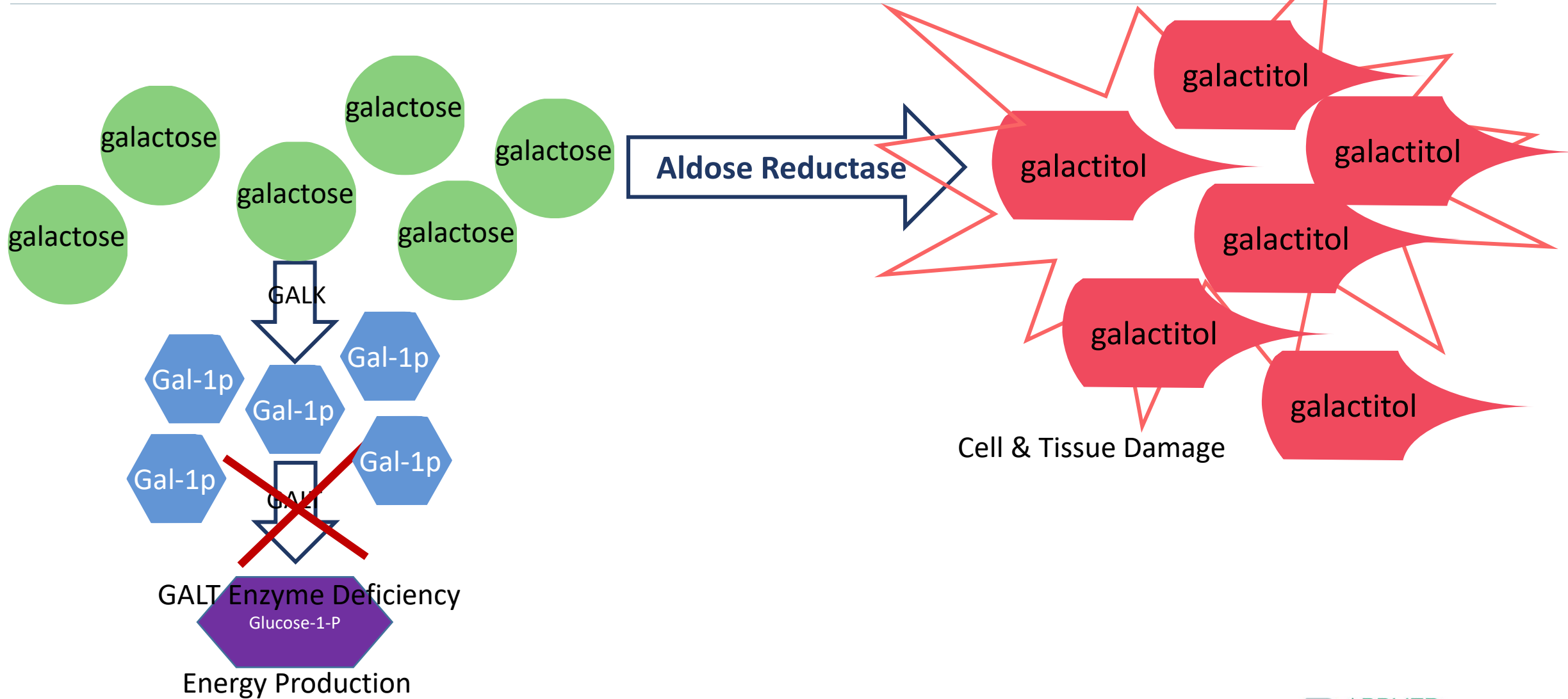
- Acute complications in the newborn period may be caused by external galactose (breast milk or dairy formula)
- Dietary restriction of lactose is important to prevent acute disease and death in infancy

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

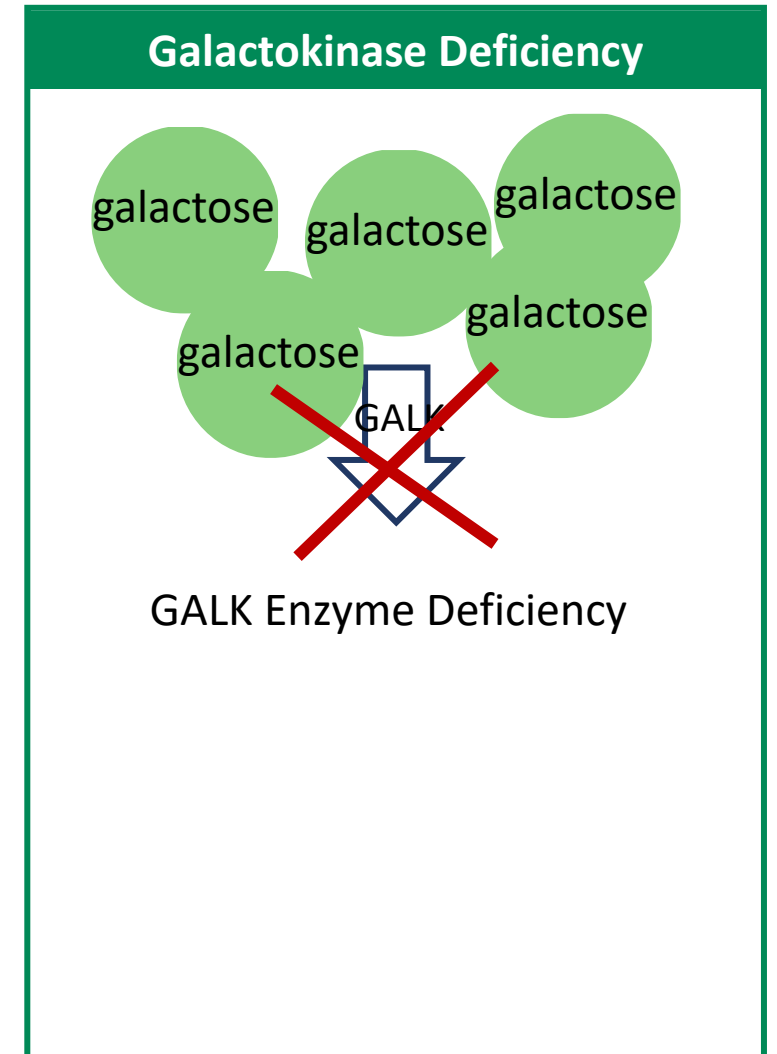
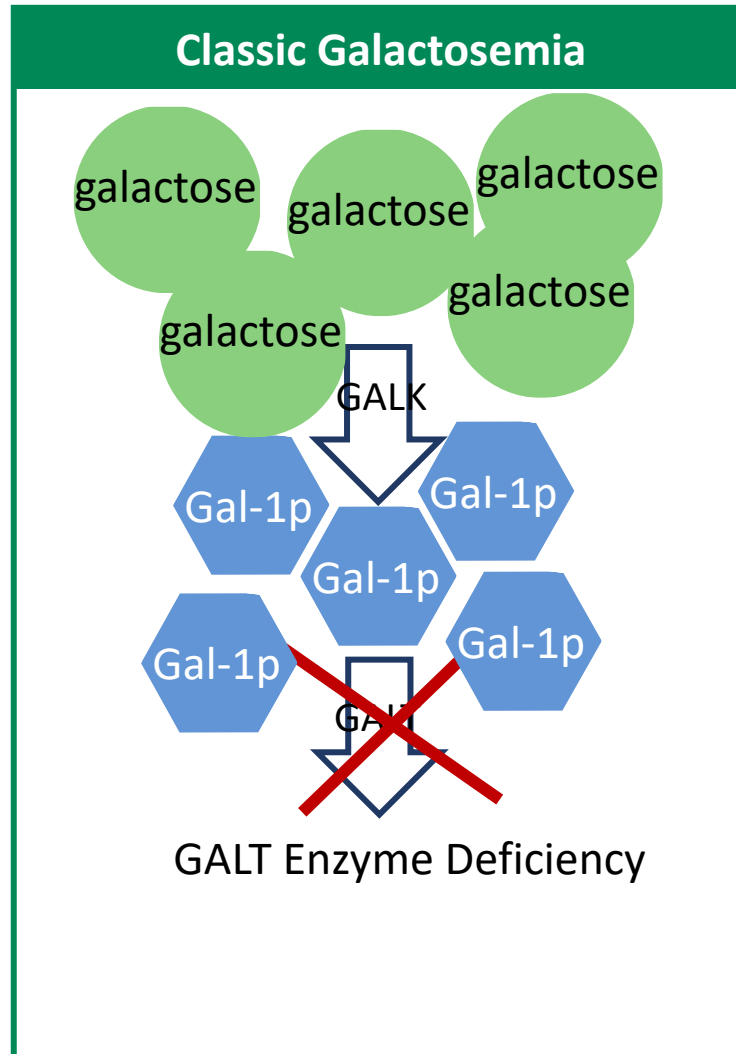
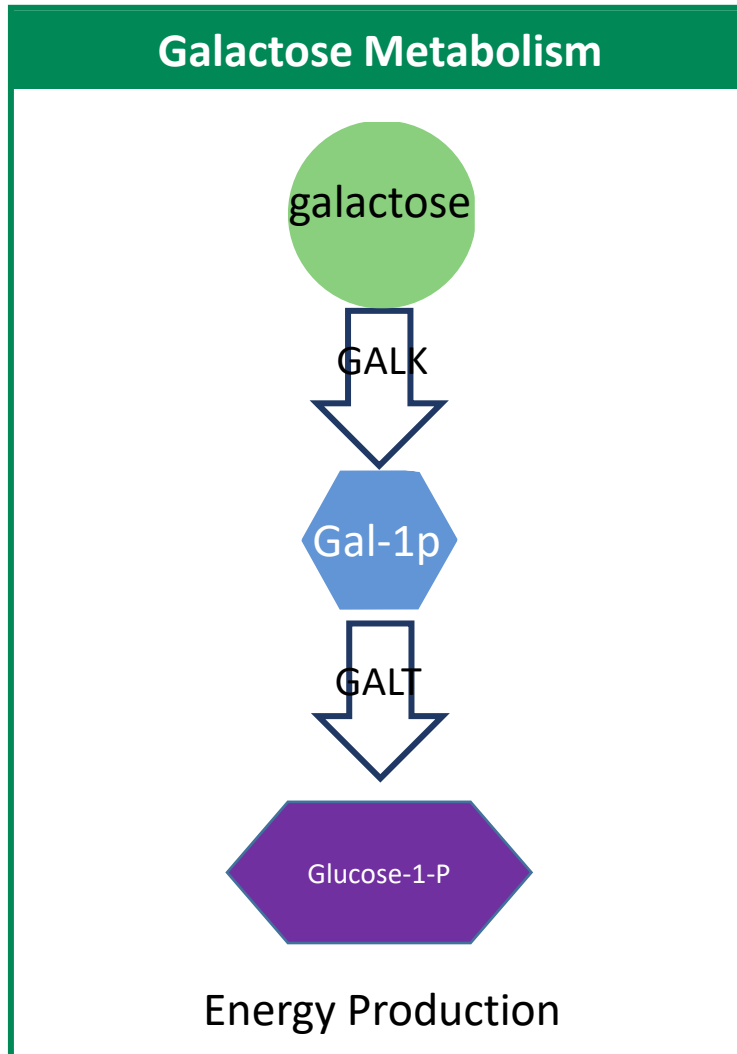
The Role of Aldose Reductase in Galactosemia



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Galactosemia:

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



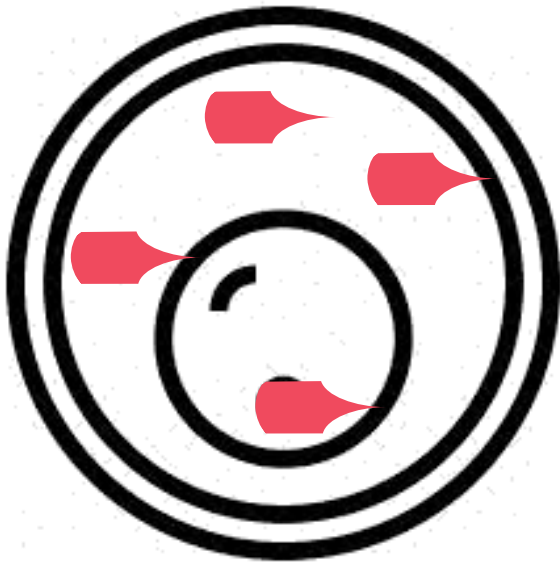
The Role of Aldose Reductase in Galactosemia

- 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



Galactitol is Toxic to Cells and May Cause Complications in Galactosemia

Ovarian Cells



Ovarian Insufficiency

Neurons



Tremor, Neuropathy

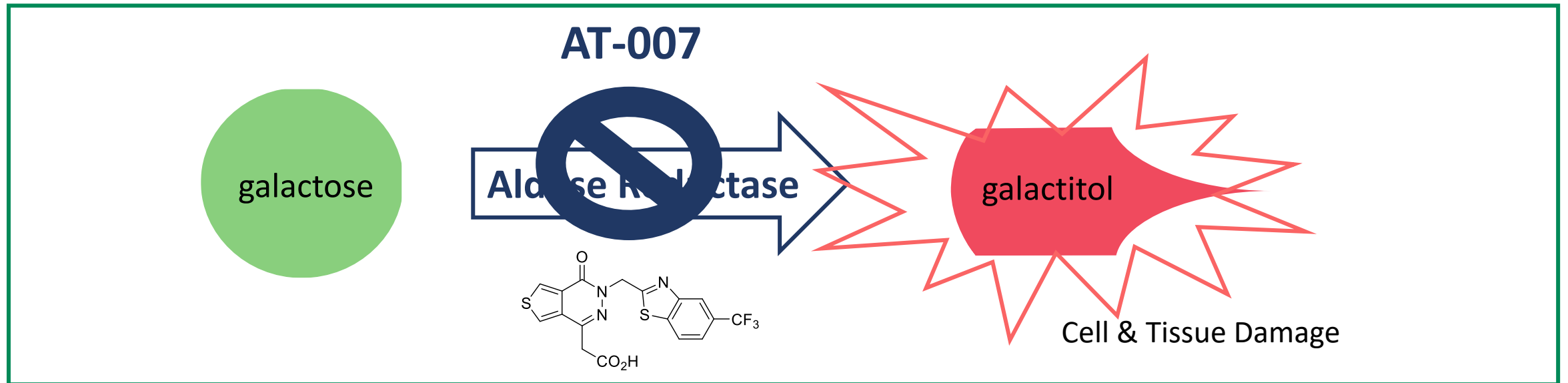
Brain



Speech, Motor, Developmental Delay,
Cognition, Memory, Seizures

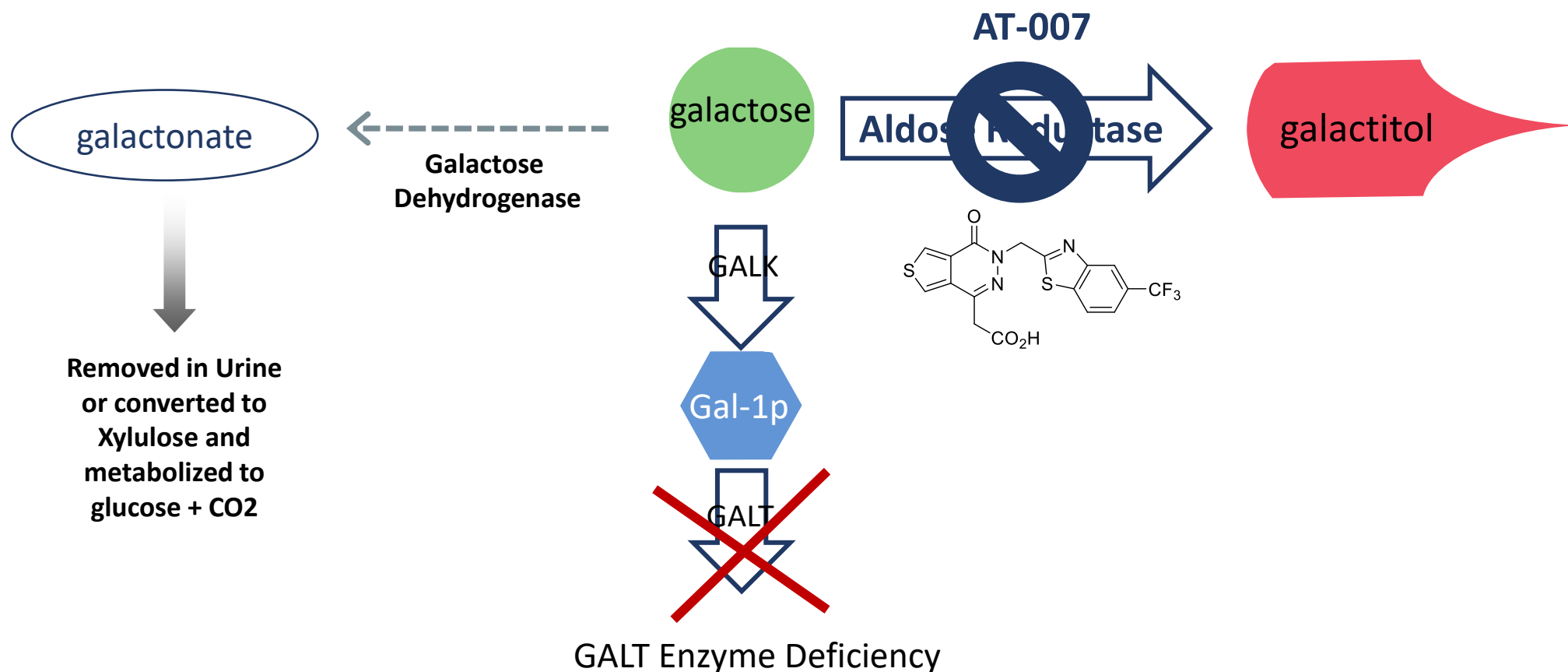
AT-007 is an Investigational Drug That Blocks Aldose Reductase Activity and Stops Conversion of Galactose to Galactitol

- AT-007 was specifically designed to penetrate the Central Nervous System – to cross into the brain and reach neurons
- In clinical trials, AT-007 is dosed orally once daily as a capsule or as a liquid suspension for children



If Blocking AR Doesn't Increase Galactose or Gal-1p..... Where Does the Extra Substrate Go?

Galactose can also be converted to a non-toxic intermediary called galactonate, which can then be metabolized by the body



What Evidence is There That Galactitol is Toxic?

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3 Lines of Evidence Support Galactitol as the Toxic Metabolite Responsible for Galactosemia Complications

1. Human genetic and clinical data^{1,2,3}

- GALK deficient patients demonstrate similar developmental abnormalities to GALT deficient patients
- GALK deficient patients don't produce Gal-1p; they only have elevated galactose and galactitol (because GALK is the enzyme that converts galactose to Gal-1p)
- Galactitol accumulation in the brain causes cerebral edema and seizures in both GALT (Classic Galactosemia) and GALK patients

2. Aldose Reductase expression is necessary to produce a disease phenotype in animal models^{4,5}

- Mice deficient for GALT show no disease phenotype (they are normal)
- Mice express extremely low levels of AR and therefore do not produce high levels of galactitol as humans do
- Rats produce near-human levels of AR, and do produce galactitol when GALT is knocked out
- The Rat GALT knock-out model shows a phenotype of disease similar to that in humans (cataracts plus developmental deficiencies)

3. When galactitol is reduced via AR inhibition, the disease phenotype is prevented^{6,7}

- In the GALT null rat, AT-007 treatment reduced galactitol levels (but not galactose or Gal-1p) and prevented cataracts and CNS abnormalities
- Galactose-induced ovarian insufficiency in rats is prevented by ARI treatment

1. Hennerman, J et al, J Inher Metab Dis 34:399–407, 2011; 2. Litman, N et al (1975) *Galactokinase deficiency presenting as pseudotumor cerebri*. J Peds V86, Issue 3, P410-412

3. Berry, G et al. (2001) In vivo evidence of brain galactitol accumulation in an infant with galactosemia and encephalopathy. J Pediatr 2001;138:260-2; 4. A Mouse Model of Galactose-1-Phosphate Uridyl Transferase Deficiency Leslie N. D. (2003). Insights into the pathogenesis of galactosemia. Annu. Rev. Nutr. 23, 59-80; 5. Rasmussen S, J Fridovich-Keil A (2019) *Galactose-1-phosphate Uridyltransferase-Null Rat Model of Classic Galactosemia Mimics Relevant Patient Outcomes and Reveals Tissue-Specific and Longitudinal Differences in Galactose Metabolism* J Inher Metab Dis 43(3):518-528, 2019; 6. 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; 7. Meyer, W et al (1992) Aldose Reductase inhibition prevents galactose-induced ovarian dysfunction in the Sprague-Dawley Rat. J Obs Gyn V167; Issue 6, P1837-1843

Human Genetic and Clinical Data

GALK Patients Do Not Produce Gal-1P, But Have Similar Clinical Presentation and Long-Term Complications to Those With Classic Galactosemia¹

- GALK-deficient patients do not produce Gal-1P (as the GALK enzyme is necessary to convert Galactose into Gal-1P)¹
- Clinical symptoms observed in GALK-deficient children include mental retardation, microcephaly, failure to thrive, seizures, deafness, hepatomegaly¹
- Suggests galactitol (not Gal-1p) is responsible for chronic complications, such as learning, cognition and growth deficiencies¹

	Number	Percentage
Number of patients	18	100
Cataract	9/18	50
Hypoglycemia	6/18	33
Microcephaly	6/18	33
Mental retardation	5/16 ^a	31
Failure to thrive	4/18	22
Hepatosplenomegaly	1/18 ^b	6
Seizures	1/18	6
Bilateral deafness	1/18	6
Pseudotumor cerebri	0/18	0
Hypercholesterolemia	4/13	31

n.d. Not determined

Clinical Features in GALK Deficiency (Berlin Group shown¹)

1. Hennerman, J et al, J Inherit Metab Dis 34:399–407, 2011

Human Genetic and Clinical Data

GALK Patients Develop Acute CNS Complications, Such as Seizures, Pseudotumor Cerebri and Edema in the Brain, Just Like GALT (Classic) Patients

- GALK-deficient and GALT-deficient patients both develop similar CNS (brain) complications
 - Edema (swelling of the brain)
 - Pseudotumor Cerebri (pressure around the brain)
 - Seizures
 - Galactitol can be measured in the brain at high concentration by MRI/MRS or autopsy of brain tissue
- “The same mechanism of intracellular solute accumulation which causes cataract formation in both transferase [GALT] and kinase [GALK] deficiencies appears also to affect the brain resulting in pseudotumor cerebri, seizures, and possible mental retardation in each of the enzyme defects.”¹
 - “In a newborn infant with galactose-1-phosphate uridylyltransferase [GALT] deficiency and encephalopathy, brain magnetic resonance imaging revealed cytotoxic edema in white matter. Using in vivo proton magnetic resonance spectroscopy, **we detected approximately 8 mmol galactitol per kilogram of brain tissue, an amount potentially relevant to the pathogenesis of brain edema.**”²
 - “Increased activity of the alternate galactose pathway enzyme, aldose reductase, catalyzes the conversion of galactose to galactitol. It has been speculated that brain edema, as well as cataract formation, is secondary to galactitol accumulation. **Indeed, galactitol had been reported to be markedly increased in the brain, the highest of the examined tissues obtained at autopsy from an infant with brain edema**”²

Refs: 1. Litman, N et al (1975) *Galactokinase deficiency presenting as pseudotumor cerebri*. J Peds V86, Issue 3, P410-412. 2. Berry, G et al.(2001) In vivo evidence of brain galactitol accumulation in an infant with galactosemia and encephalopathy. J Pediatr 2001;138:260-2

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Animal Data

Aldose Reductase Expression is Necessary to Produce a Disease Phenotype in Animal Models; Mouse GALT Knock-Out (No Elevated Galactitol) is Normal

- Mice express very low levels of Aldose Reductase (unlike humans)
- When a GALT knock-out mouse was created, the mice had high galactose and Gal-1p levels, but *not* high galactitol levels (only a “trace”)
- These mice were normal and healthy

“...mice that have no detectable GALT activity **accumulate large amounts of** galactose as well as **galactose-1-phosphate but still appear healthy**”

“This study suggests that alternative routes of galactose metabolism are important in the pathogenesis of galactosemia.....**Galactitol, on the other hand, may assume a more important role in future studies of pathophysiology**”

Ref: A Mouse Model of Galactose-1-Phosphate Uridyl Transferase Deficiency Leslie N. D. (2003). Insights into the pathogenesis of galactosemia. Annu. Rev. Nutr. 23, 59-80

Animal Data

Aldose Reductase Expression is Necessary to Produce a Disease Phenotype in Animal Models; Rat GALT Model Has Elevated Galactitol & Human Disease Characteristics

- Rats express human levels of Aldose Reductase
- GALT rat model has elevated galactose, Gal-1p and galactitol – just like humans with Classic Galactosemia
- Rat model displays human-like disease complications, including cognitive, learning, motor and growth deficiencies

“Here we introduce a new GALT-null rat model of CG and demonstrate that **these rats display** cataracts, cognitive, motor, and growth **phenotypes reminiscent of patients outcomes.**”

“With regard to mechanism, the results presented here provide a foundation for questioning the relative roles of different galactose metabolites as likely contributors to pathophysiology in CG...**Our results raise serious concern about using RBC Gal-1P as a biomarker for disease, and suggest that plasma galactose or galactitol, and by extension perhaps urinary galactitol, may provide a more meaningful proxy**”

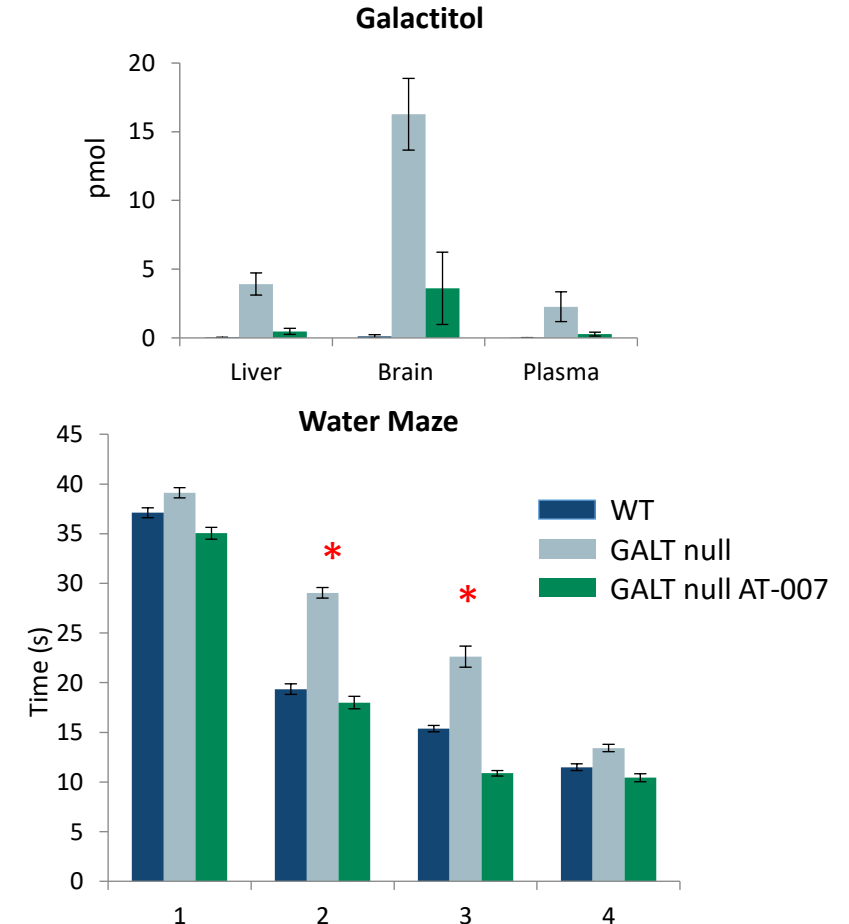
Ref: Rasmussen S, J Fridovich-Keil A (2019) *Galactose-1-phosphate Uridyltransferase-Null Rat Model of Classic Galactosemia Mimics Relevant Patient Outcomes and Reveals Tissue-Specific and Longitudinal Differences in Galactose Metabolism* J Inherit Metab Dis 43(3):518-528, 2019

Animal Data

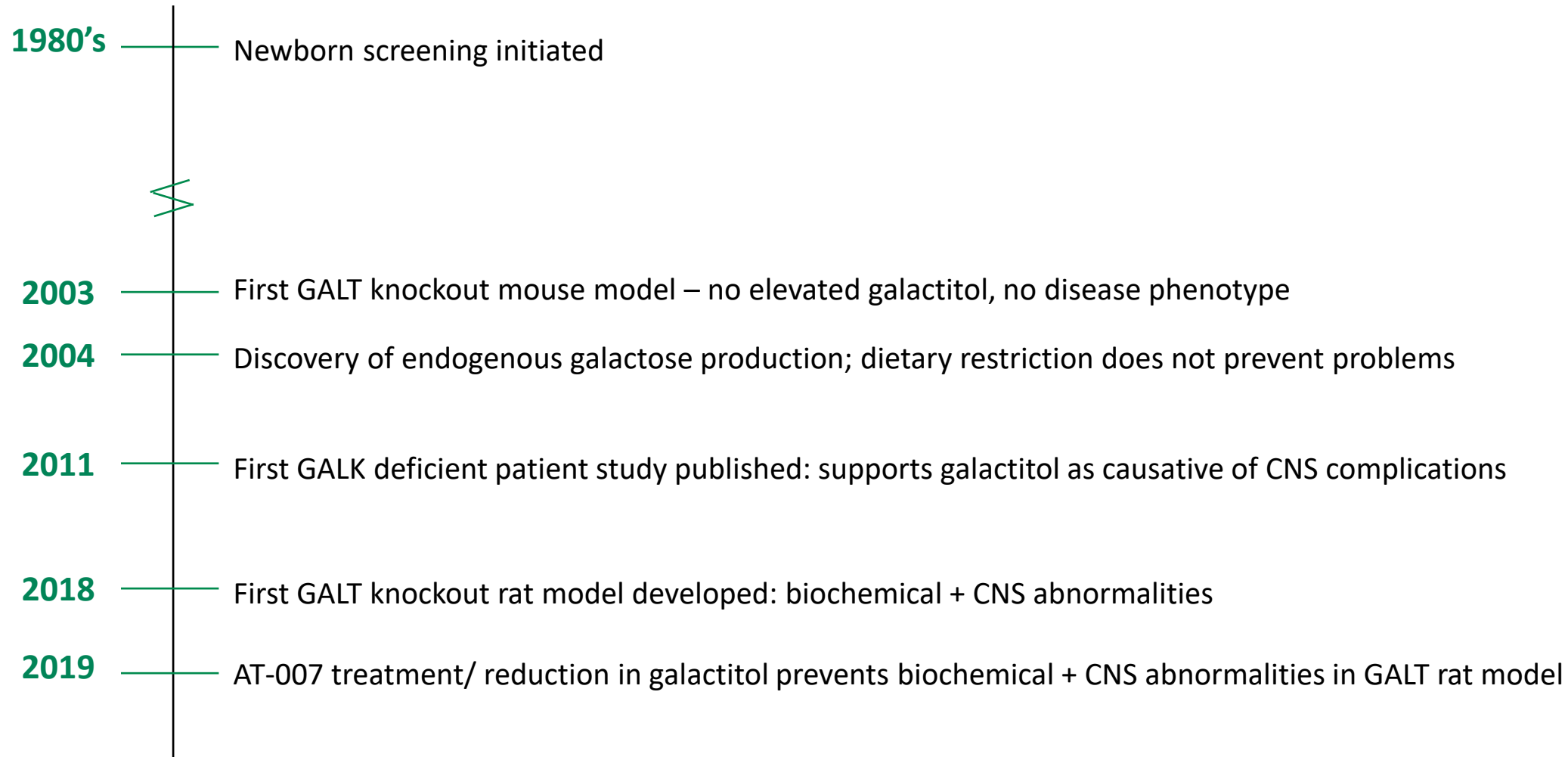
Reduction of Galactitol Prevents Complications of Disease in Animal Models

- Reducing galactitol levels in rats improves CNS outcomes and prevents ovarian insufficiency^{1,2}
- GALT null rats treated with AT-007 demonstrate reduced galactitol and improved CNS outcomes¹
 - Water maze and rotarod
- Normal rats treated with high galactose to induce high galactitol levels have ovarian insufficiency
- Reduction in galactitol with an “old” AR inhibitor prevents ovarian insufficiency²

Ref: 1. 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; 2. Meyer, W et al (1992) Aldose Reductase inhibition prevents galactose-induced ovarian dysfunction in the Sprague-Dawley Rat. *J Obs Gyn* V167; Issue 6, P1837-1843



Galactosemia History Timeline

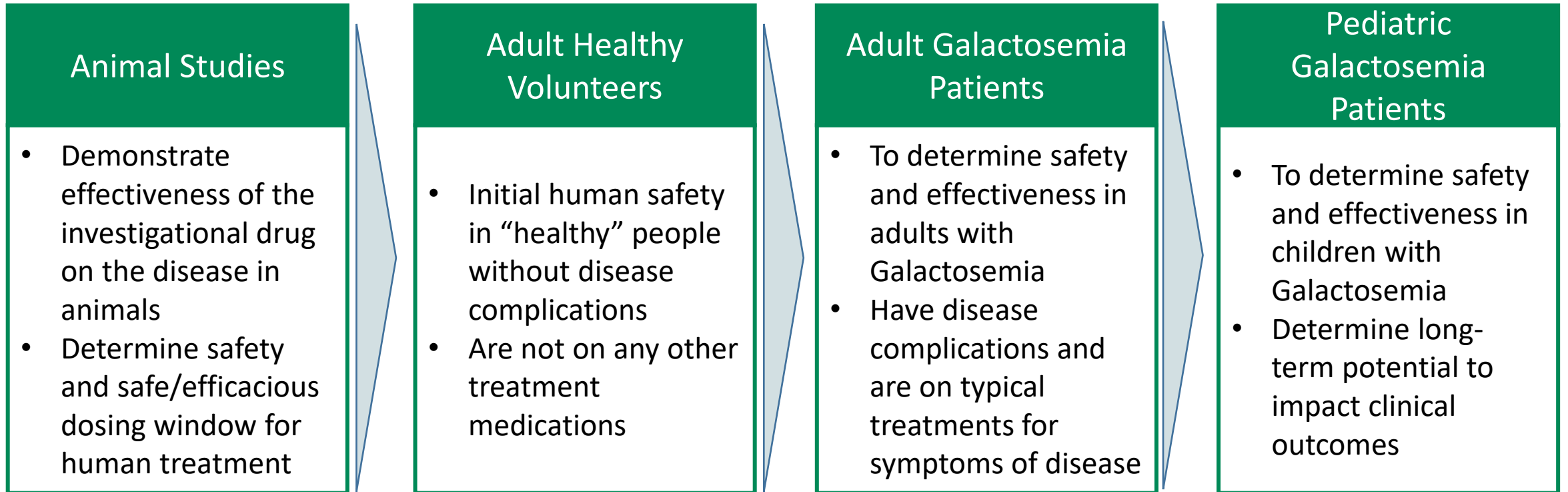


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AT-007 - an Investigational Drug in Development for Galactosemia

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Stages of Preclinical and Clinical Development



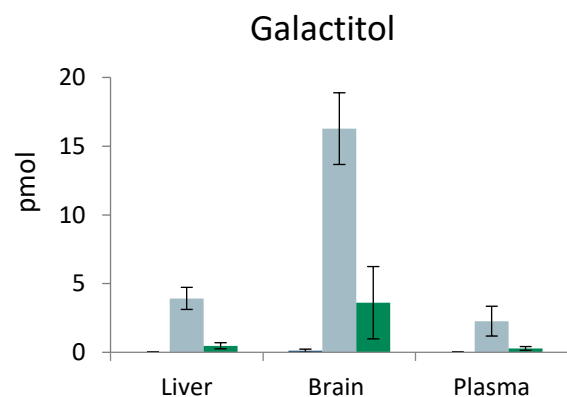
AT-007 Preclinical (Animal) Data

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

Biochemical Effects

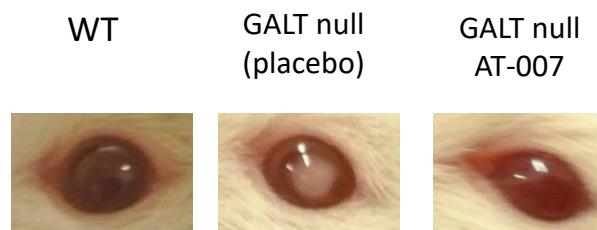
AT-007 treatment significantly reduced galactitol levels in all tissues without increasing galactose or Gal1p



■ Wild Type ■ GALT null placebo ■ GALT null AT-007

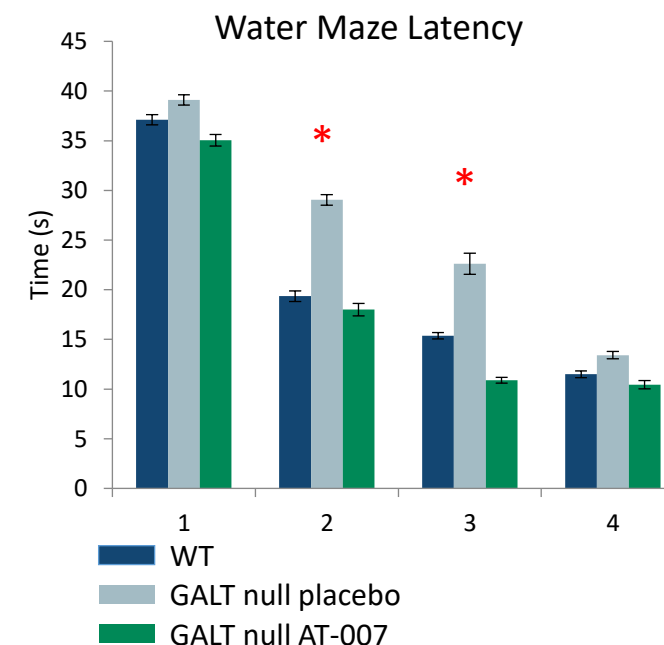
Tissue Deposition of Galactitol

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

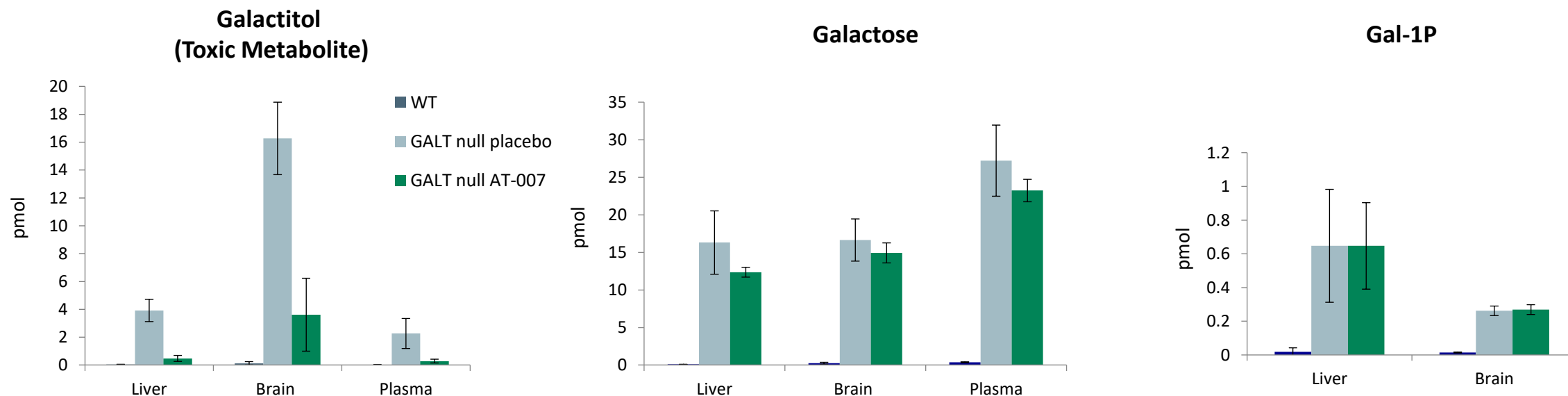


* Statistically significant vs. WT & AT-007 treated

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

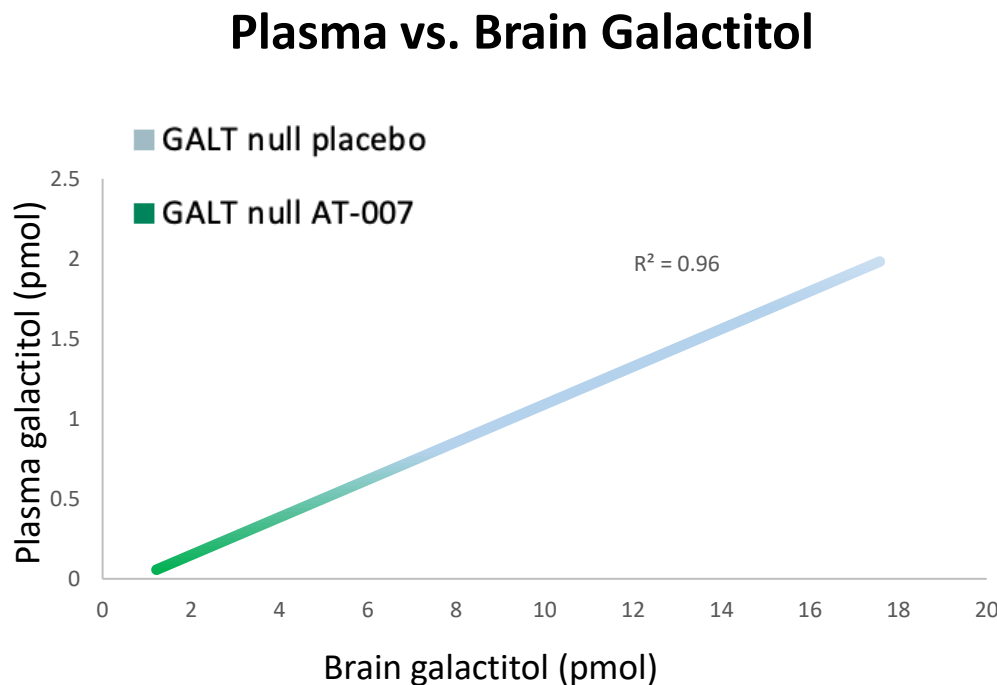
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A Closer Look: AT-007 Significantly Reduces Galactitol Levels in all Target Tissues Without Increasing Galactose or Gal-1P



- 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

Reduction in Plasma (Blood) Galactitol Correlates With Reduction in the Brain



- Levels of galactitol in plasma and brain correlated in individual animals
- Reduction in galactitol induced by AT-007 treatment correlated in plasma and brain

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)

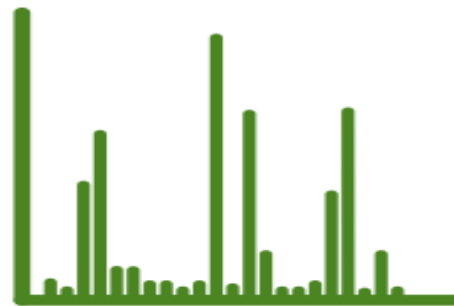
Summary: AT-007 Preclinical (Animal) Studies

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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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)

Healthy Volunteer Endpoints:

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

Galactosemia 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)

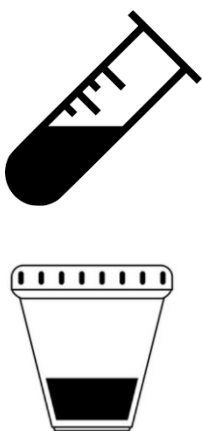
Patients were on lactose-restricted diet prior to enrollment and throughout study

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Summary: Healthy Volunteer Data

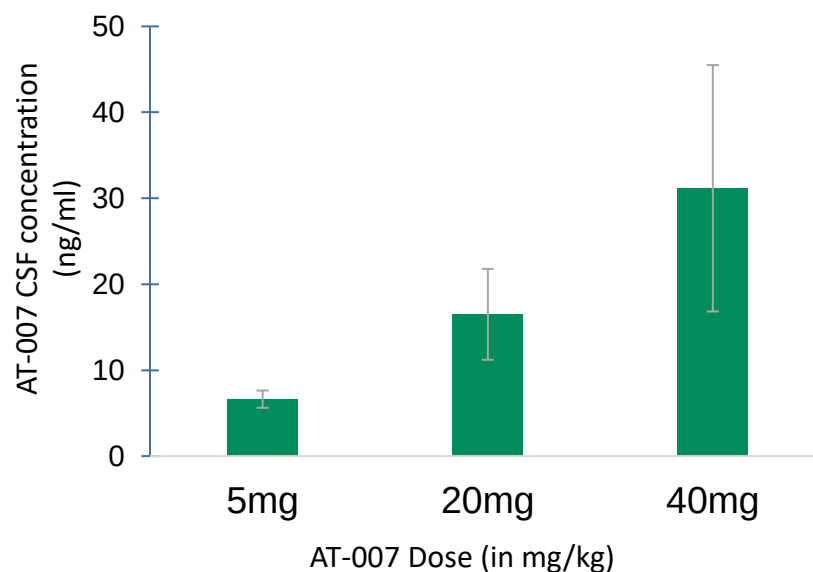
AT-007 Was Safe and Well Tolerated; PK Supportive of Once-Daily Dosing

Safety



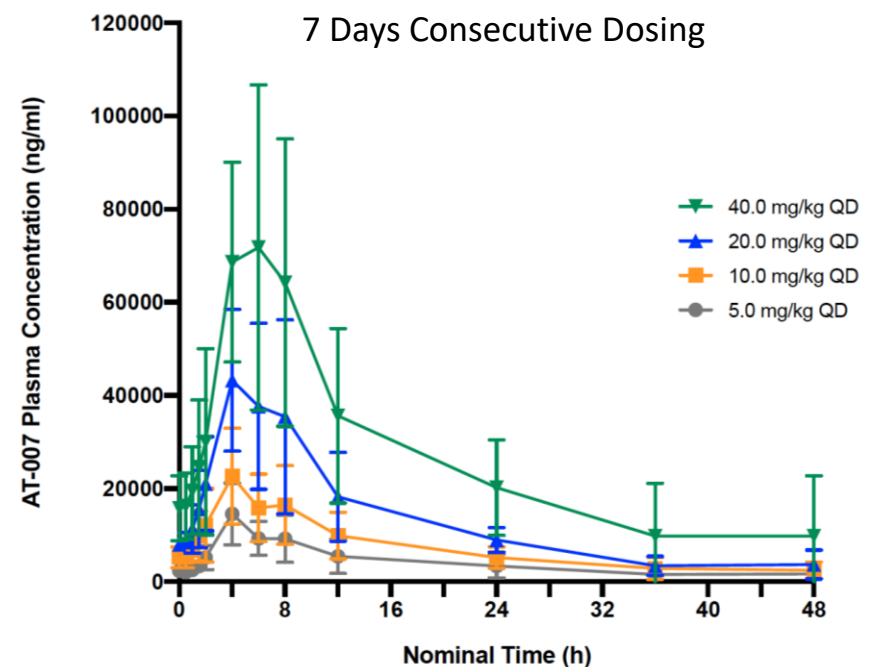
~80 healthy volunteers treated; AT-007 was safe and well tolerated at all doses

Brain Penetrance



Drug crosses into brain when dosed orally (CNS penetrant)

Pharmacokinetics



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

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Galactosemia 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)

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

AT-007 Safety in Adult Galactosemia Patients

AT-007 Was Safe and Well Tolerated at All Doses Tested



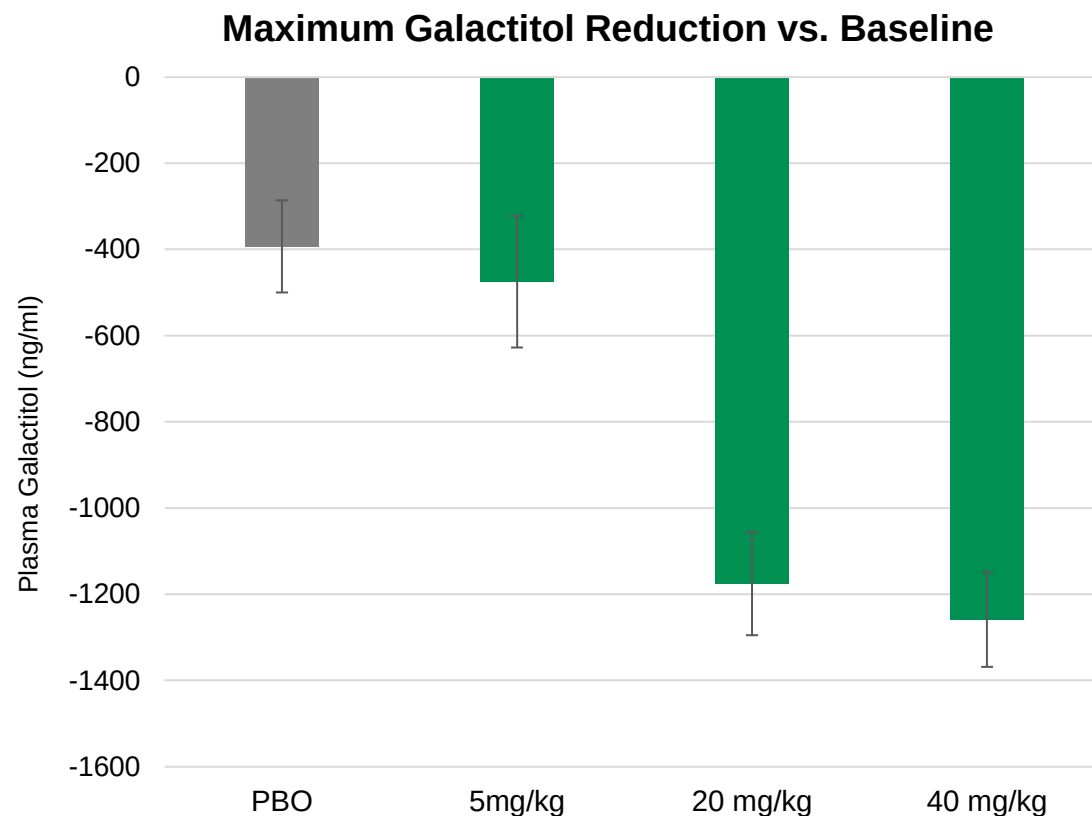
Laboratory & clinical assessments demonstrated safety and tolerability



Pharmacokinetics (drug levels over time) supports once-daily dosing

Biomarker Results

AT-007 Significantly Decreased Galactitol Levels in Plasma at 20 and 40mg/kg



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

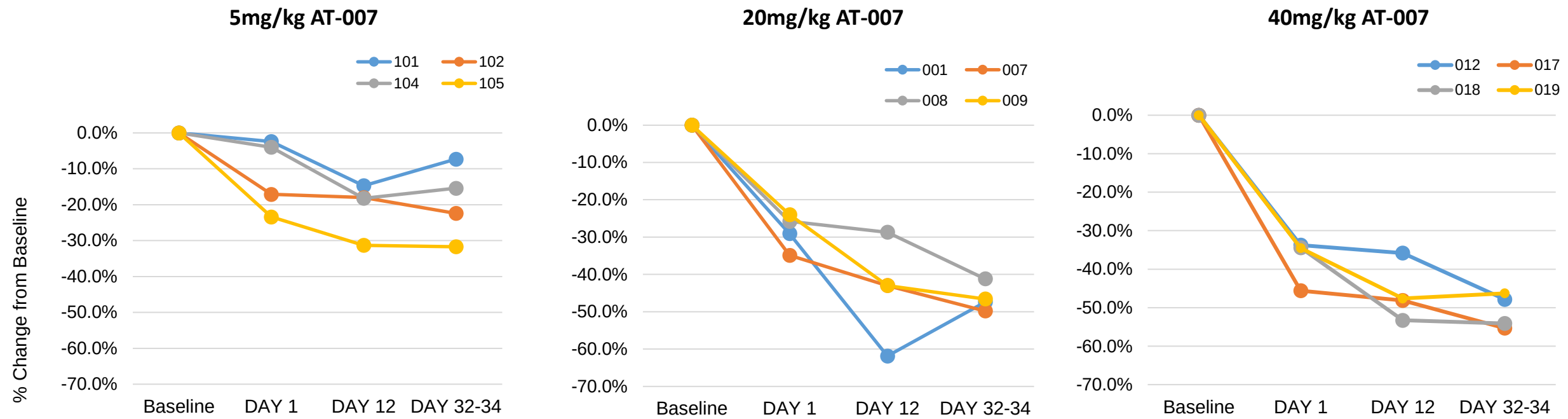
All biomarker assays were developed, validated, and performed by Icon Labs Whitesboro, NY (independent 3rd party lab)

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

AT-007 Decreased Galactitol Levels in All Treated Patients

Decrease was Dose-Dependent, Rapid and Sustained; Statistically Significant at 20 & 40mg/kg

Individual Maximum Reduction in Galactitol Percent Change From Baseline

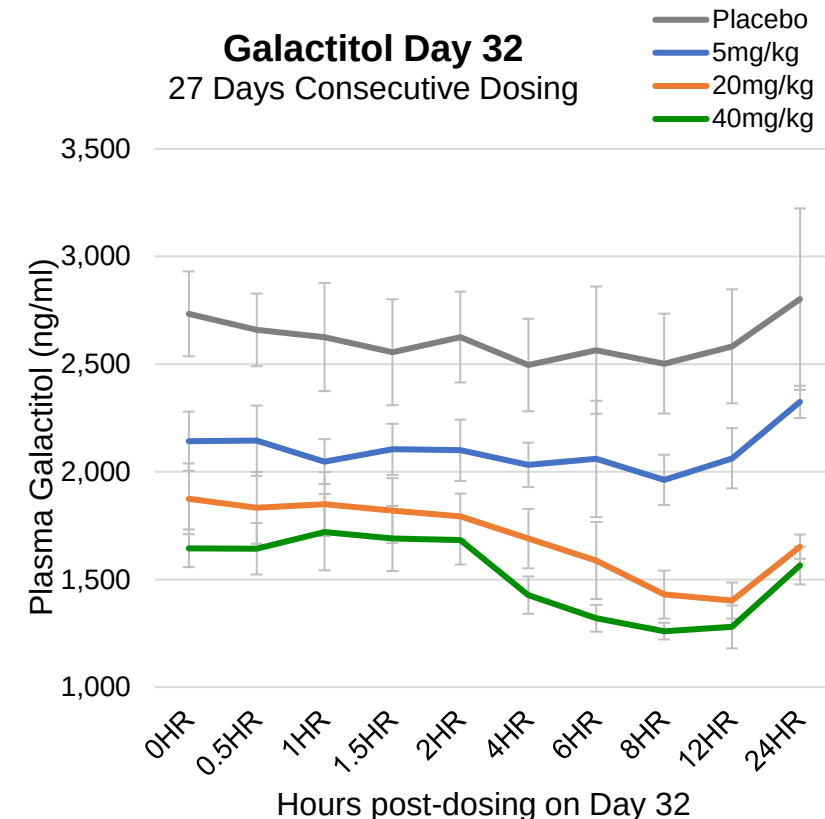
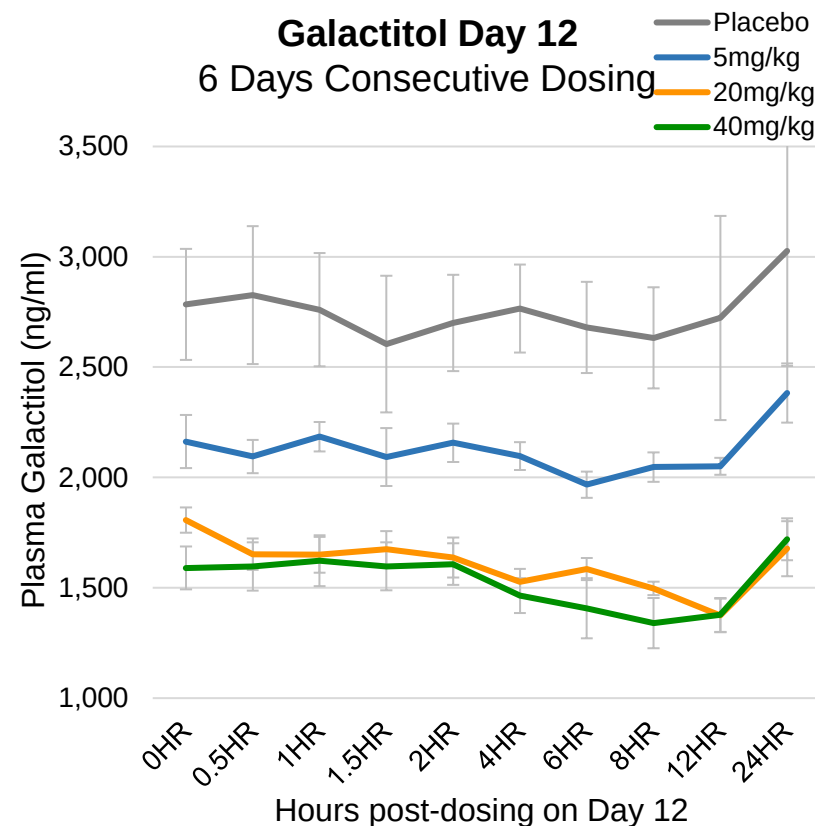
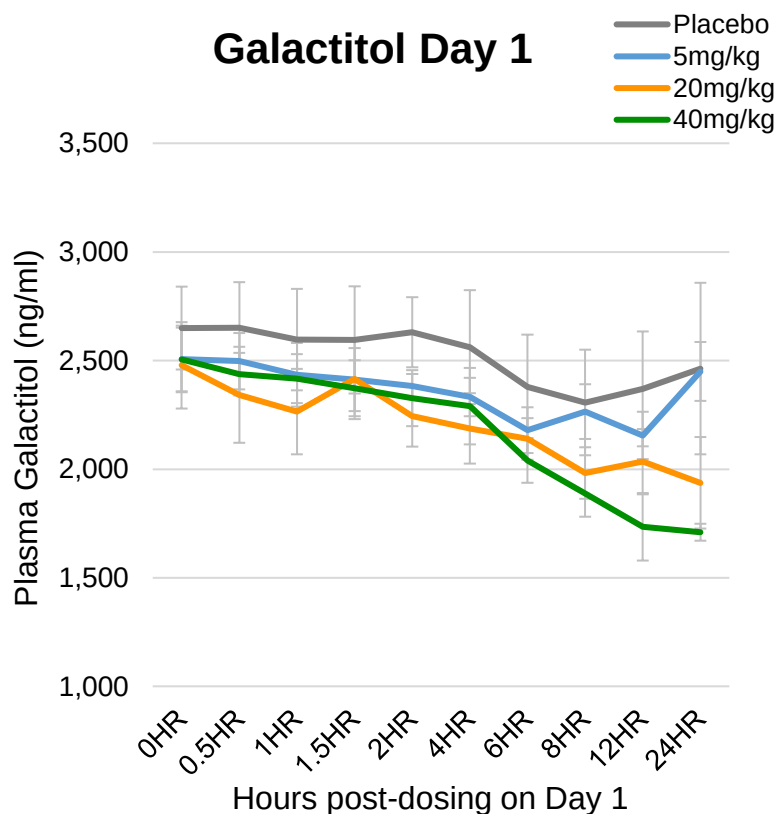


Further Characterization of AT-007 in adult Galactosemia patients in ongoing long-term safety study

AT-007 Galactitol Reduction is Rapid and Sustained

Reduction Begins on 1st Day of Treatment and is Sustained Over 1 Month of Treatment

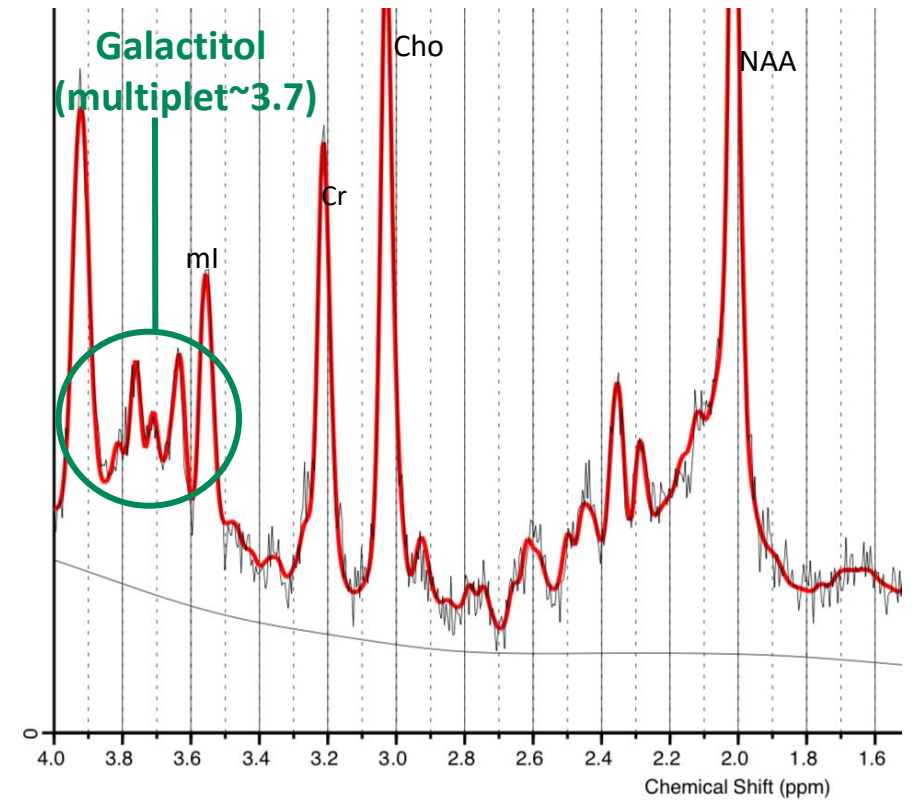
Galactitol Reduction is Sustained Over the 24hr Dosing Period at Steady State (Day 12 and Day 32), Supporting Once Daily Oral Dosing



Data for each cohort is shown as mean $\pm$ SEM; Baseline mean galactitol was not statistically different between cohorts

Galactitol Can be Measured in the Brain

- Galactitol can be quantitatively assessed in the brain by MR Spectroscopy
- Galactitol is not present in the brain of healthy volunteers and is only present in Galactosemia patients
- In “old” studies with low power magnets, the abnormal galactitol peak was only visible in patients who were not on a compliant diet
- Higher power 3T MRI/MRS now allows detection and quantitation of galactitol in the brain of patients on a galactose-free diet, representing galactitol in the brain formed by endogenous galactose production



Representative baseline MRS of adult Galactosemia patient from ACTION-Galactosemia study
(on galactose-free diet; 3T MRI)
ml=myoinositol; Cr=creatine; Cho=choline; NAA=N-acetyl aspartate

Effects of AT-007 on brain galactitol will be presented at upcoming conference

Summary: ACTION-Galactosemia Adult Study Results

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



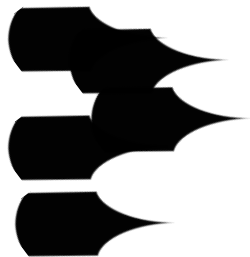
- Includes 80 healthy volunteers and 14 Classic Galactosemia patients

AT-007 was shown to be CNS penetrant



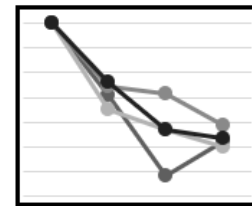
- Important in Galactosemia, which includes significant CNS clinical presentation
- Supports once-daily oral dosing

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

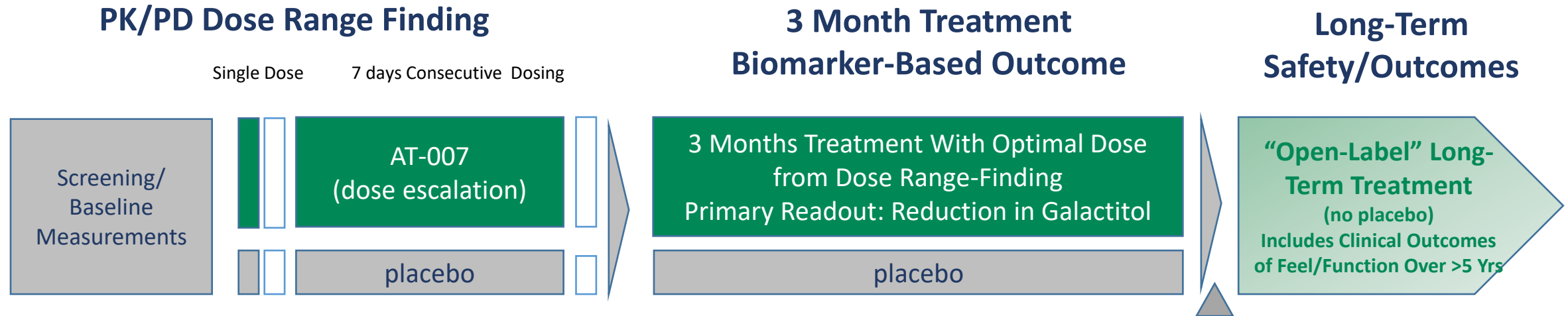


- 20 and 40mg/kg dosing resulted in significant reduction in plasma galactitol ($p < 0.01$ vs. placebo)
- No significant change in galactose or Gal-1p

AT-007 Pediatric Study: ACTION-Galactosemia Kids

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

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

For more details please see pediatric study presentation, today at 5:30pm – 6:15pm

Thank You

Thank you to all of the families who participated in the ACTION-Galactosemia study and help make this development program possible



Applied Therapeutics @ GLOW for Galactosemia March 2020 in Nashville, TN

Thank you to the Galactosemia community for welcoming us!