Galactosemia Educational Symposium

April 28, 2020

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Disclaimer

This Educational Symposium will discuss an investigational drug in clinical development, AT-007. AT-007 is an investigational product and is not yet approved.

Faculty: Eva Morava-Kozicz, MD, PhD

Eva Morava-Kozicz, MD, PhD

is a Professor of Medical Genetics at the Mayo Clinic School of Medicine. She completed specialty trainings in pediatrics, genetics and metabolism. Dr. Morava clinically focuses on inborn errors of metabolism, and established a research laboratory on translational research in mitochondrial disorders and congenital disorders of glycosylation.

Dr. Morava is the editor in chief of the Journal of Inherited Metabolic Disease.

Disclosure: EMK is an employee of the Mayo Clinic Foundation

Faculty: Riccardo Perfetti, MD, PhD

Riccardo Perfetti, MD, PhD

is the Chief Medical Officer at Applied Therapeutics. A clinical endocrinologist by training, Dr. Perfetti focused on metabolic disease research at the NIH, and then practiced clinical endocrinology at Cedars Sinai.

After 20 years in clinical practice, Dr. Perfetti shifted his attention to drug development, holding various positions of leadership in drug development at Amgen and Sanofi, and now Applied Therapeutics.

Disclosure: RP is an Applied Therapeutics employee and shareholder

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Faculty: Shoshana Shendelman, PhD

Shoshana Shendelman, PhD

is the Founder and CEO of Applied Therapeutics. She is a neurobiologist by training and has led drug development for CNS diseases (including rare CNS diseases) for nearly 20 years.

Disclosure: SS is an Applied Therapeutics employee and shareholder

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Agenda

1:00-1:25	• Understanding the high unmet medical need in Galactosemia • Role of galactitol (a toxic metabolite of galactose) in Galactosemia complications • Rationale for aldose reductase inhibition as a therapeutic target for Galactosemia • Preclinical evidence for AT-007 – a highly selective, brain-penetrant aldose reductase inhibitor
1:25-1:50	• Design of the ACTION-Galactosemia study • ACTION-Galactosemia study results • AT-007 future development and next steps
1:50-2:00	• Moderated questions and answers from audience

Galactosemia Clinical Presentation

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Galactosemia:
Rare Genetic Metabolic Disease with High Unmet Medical Need

Pathogenesis of Disease

- Rare genetic metabolic disease caused by inability to break down galactose
- Galactose is a natural sugar formed by metabolism of lactose, but is also produced endogenously by the body
- **In patients with Galactosemia, Aldose Reductase converts galactose to galactitol, an aberrant toxic metabolite**

Standard of Care

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

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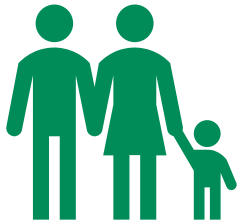
Galactosemia Clinical Presentation

Acute Newborn

- Hepatic and renal failure
- Brain swelling (edema; encephalopathy)
- Sepsis
- Potentially life threatening if not identified and managed immediately

Chronic/Long-Term



- CNS complications
  - Low IQ/ intellectual impairment
  - Motor skills
  - Speech/ language
  - Learning, behavioral, social impairments
  - Psychiatric problems (anxiety, depression)
- Primary ovarian insufficiency
- Cataracts

Galactosemia Effects ~2,800 Patients in the US and 3,500 Patients in EU

- **~2,800 living** US patients ; **~80 new births per year**
- **~3,500 living** EU patients; **~120 new births per year**
- Majority of patients are under the age of 40, as newborn screening was adopted in the 1980s and 1990s
- Potential regulatory pathway:
  - Galactosemia is a slowly progressive, low prevalence rare disease[1]
  - Under new FDA guidance, surrogate metabolic biomarkers may be acceptable for demonstration of therapeutic activity

1. Diseases with less than 5,000 living US patients are termed “low prevalence”

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Current Disease Management

- **Neonatal**
  - Lactose dietary restrictions (soy based or elemental formula)
  - Medical management of acute symptoms
- **Chronic**
  - Dietary management – restriction of lactose/ galactose intake
    - ***Dietary restriction does not block endogenous galactose production***
  - Appropriate cognitive, neurological and speech assessment evaluation and treatment
  - Symptomatic treatment for organ-specific issues

No currently approved drug therapies for acute or long-term treatment

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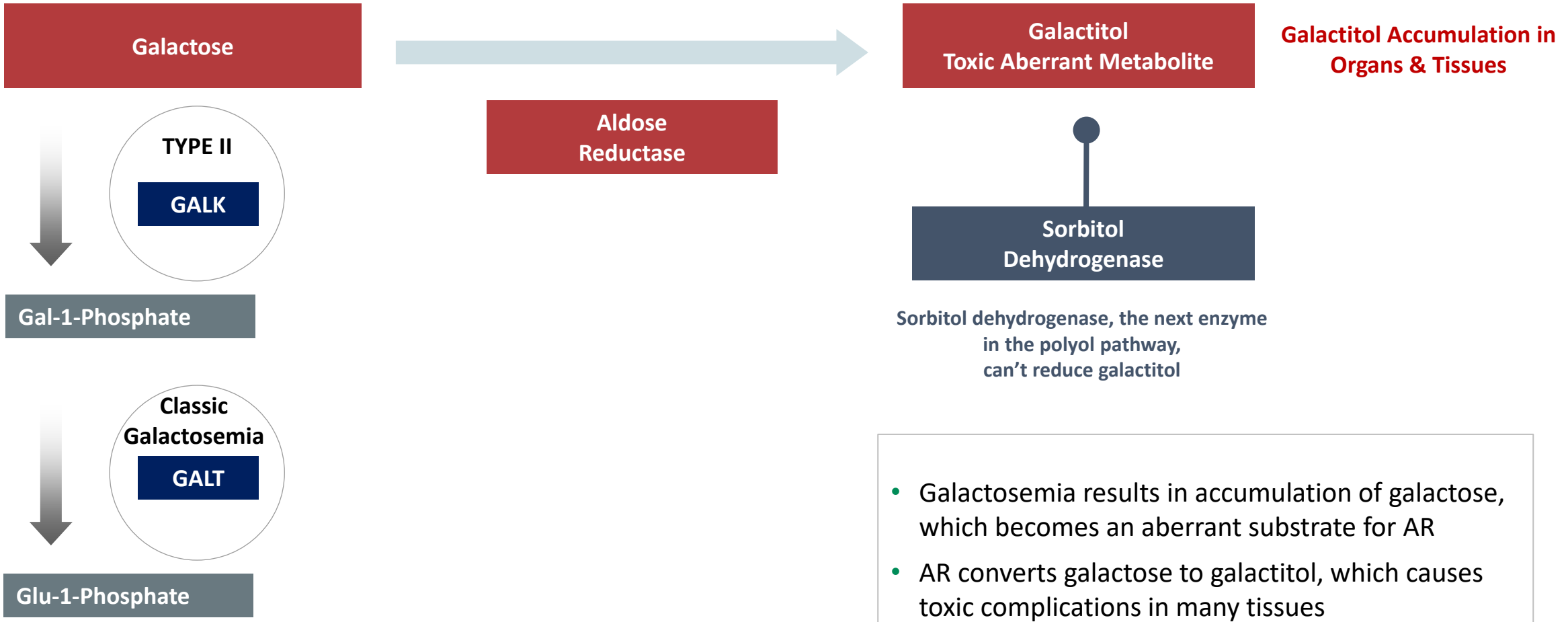
Role of Galactitol (a toxic metabolite of galactose) in Galactosemia Complications

Aldose Reductase Activity Causes Toxic Accumulation of Galactitol in Galactosemia



- Galactosemia results in accumulation of galactose, which becomes an aberrant substrate for AR
- AR converts galactose to galactitol, which causes toxic complications in many tissues

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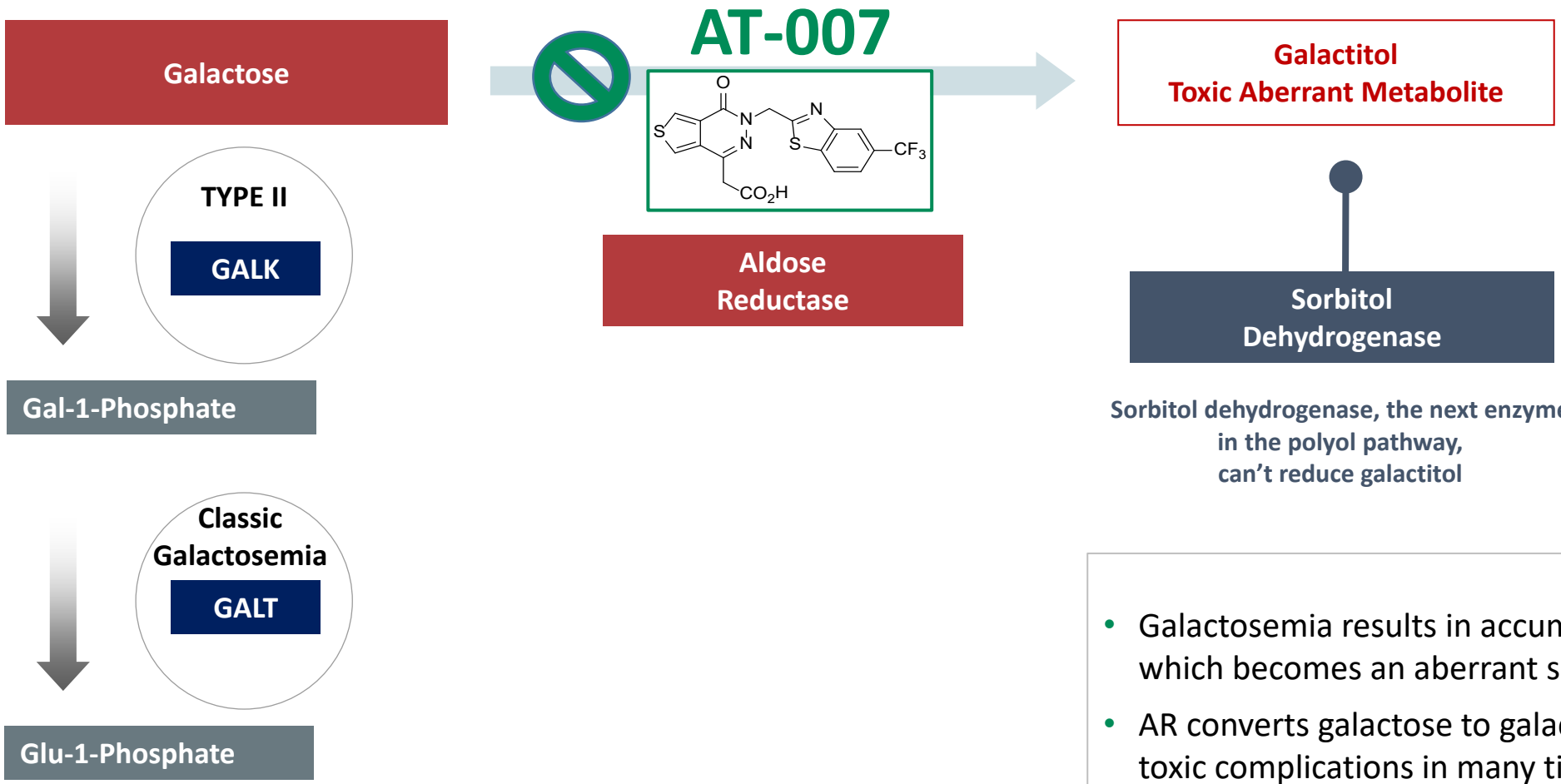
AT-007, a CNS-Penetrant Novel Aldose Reductase Inhibitor, Prevents Galactitol Formation and Accumulation



- Galactosemia results in accumulation of galactose, which becomes an aberrant substrate for AR
- AR converts galactose to galactitol, which causes toxic complications in many tissues

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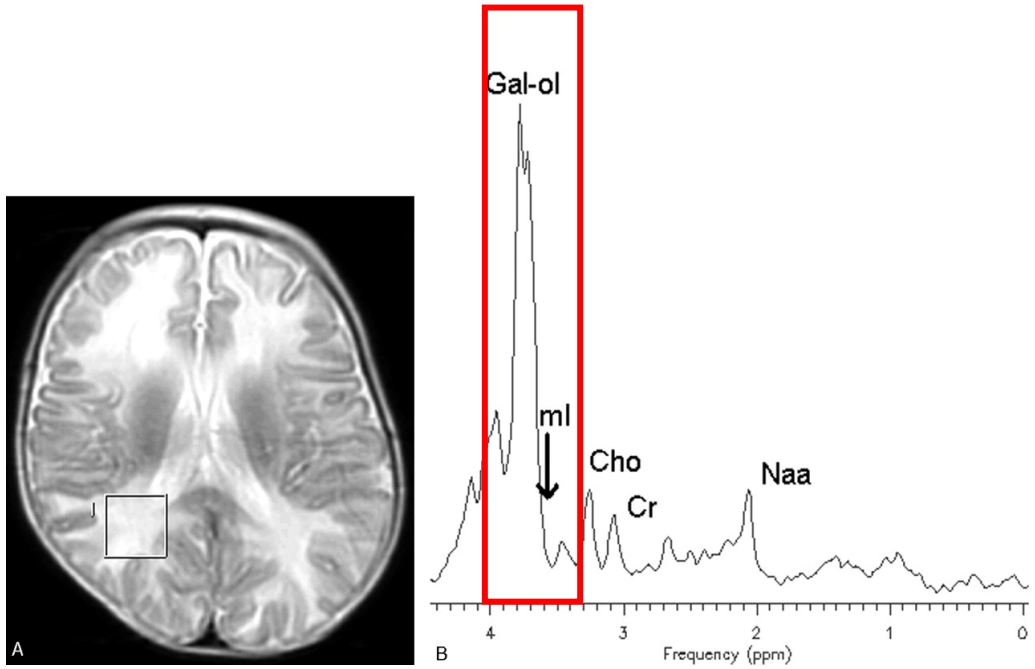
Galactitol Accumulates in Various Tissues Including the CNS

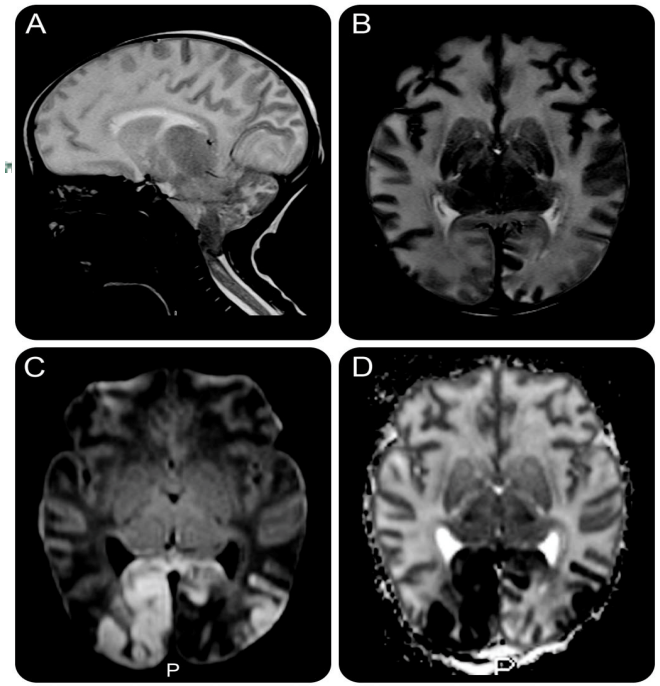
In vivo evidence of brain galactitol accumulation in an infant with Galactosemia and encephalopathy



Berry G et al *J of Pediatrics* 138(2):260-2, 2001

Otaduy MCG, et al American Journal of Neuroradiology 27 (1) 204-207, 2006

Galactitol peak and fatal cerebral edema in Classic Galactosemia



(A) Sagittal and (B) axial turbo-spin-echo T2-weighted images, (C) DWI, and (D) ADC. (A) Massive edema causes cerebellar tonsils to descend into the foramen magnum. (B) Brain and cerebellum appear diffusely swollen with reduced gray/white matter differentiation. (C) DWI and (D) ADC maps show large posterior areas of restricted diffusion consistent with cyto-toxic edema.

Martinelli D et al *Neurology* 86:e32-e33, 2016

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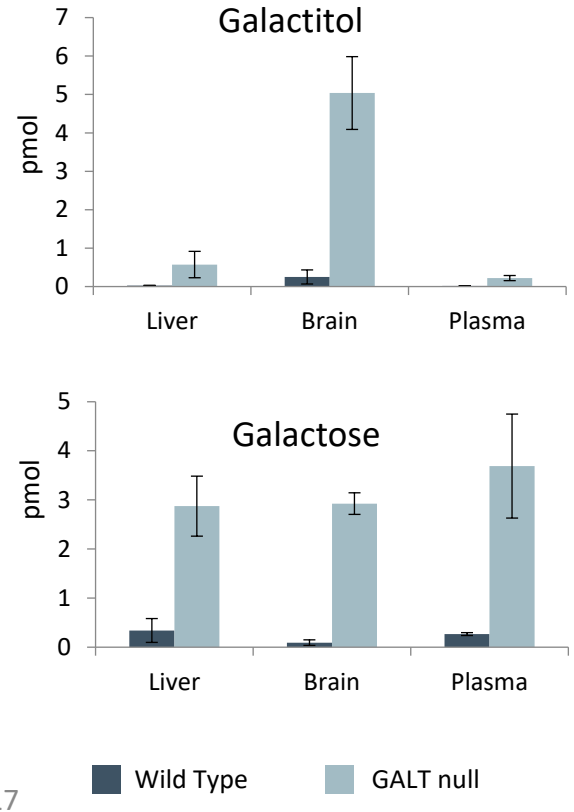
GALT Deficient Rat Model Closely Mirrors Human Disease

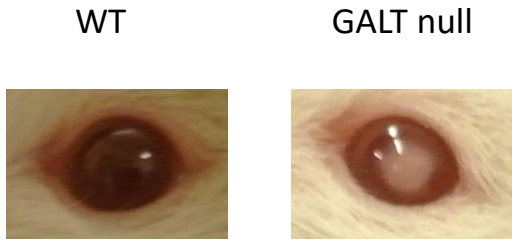
Biochemical Effects

GALT null rats have exponentially higher levels of galactose and galactitol, as well as Gal1p



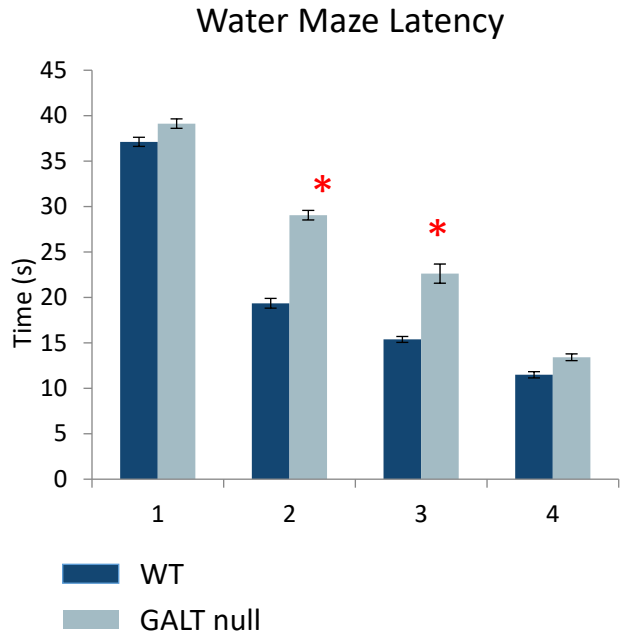
Tissue Deposition of Galactitol

All GALT null rats display cataracts (caused by galactitol deposition in the eye) vs. none of the WT rats



CNS Outcomes

GALT null rats display deficiencies in learning, cognition, and motor skills as measured by rotarod and water maze



Full animal model published by Fridovich-Keil and coworkers:
Rasmussen et al, J Inherit Metab Dis. 2019 Dec 17. doi: 10.1002/jimd.12205

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Aldose Reductase Inhibition as a Therapeutic Target for Galactosemia

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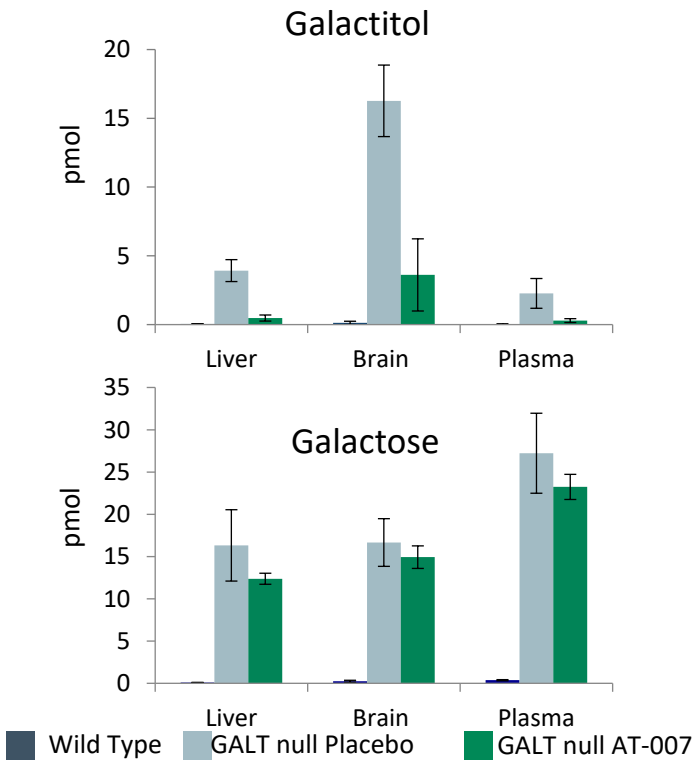
AT-007 Treatment Corrects All 3 Aspects of Disease in the Galactosemia Rat Model

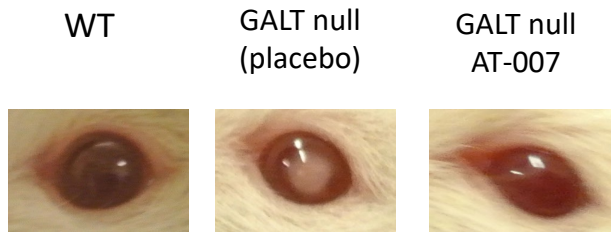
Biochemical Effects

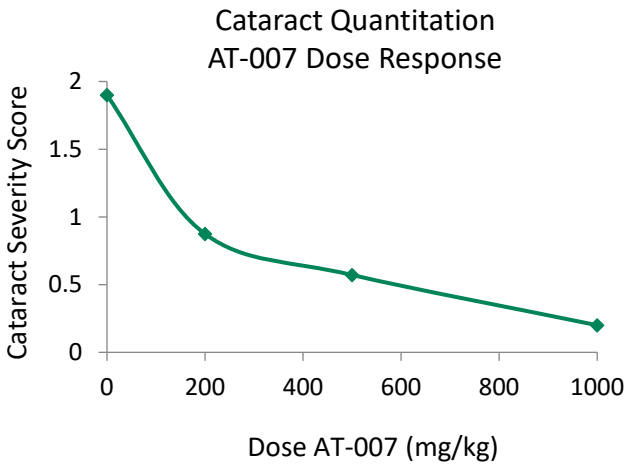
AT-007 treatment significantly reduced galactitol levels in all tissues without increasing galactose or Gal1p



Tissue Deposition of Galactitol

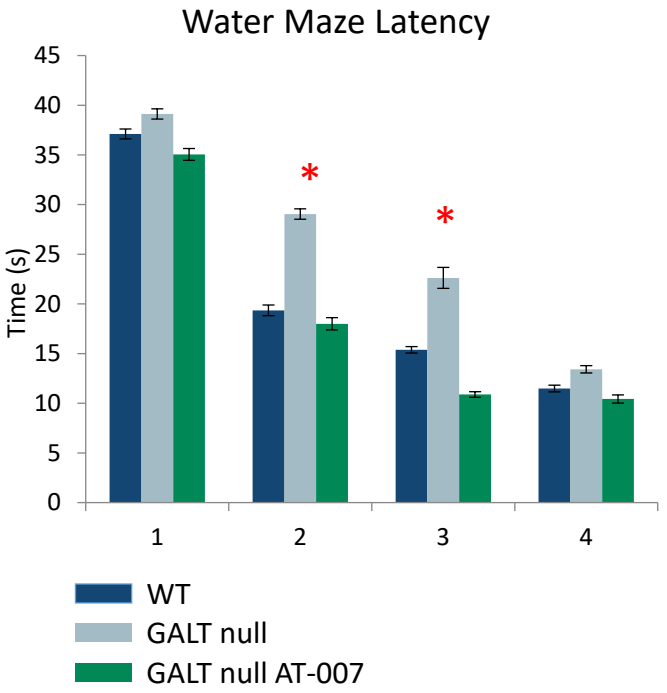
AT-007 treatment prevented galactitol accumulation in tissues, resulting in absence of cataracts





CNS Outcomes

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



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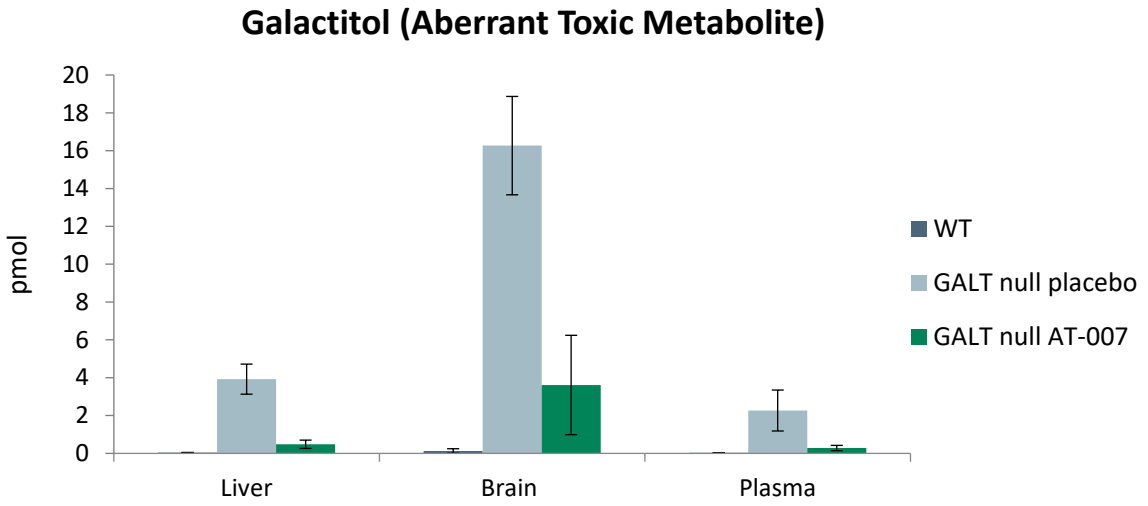
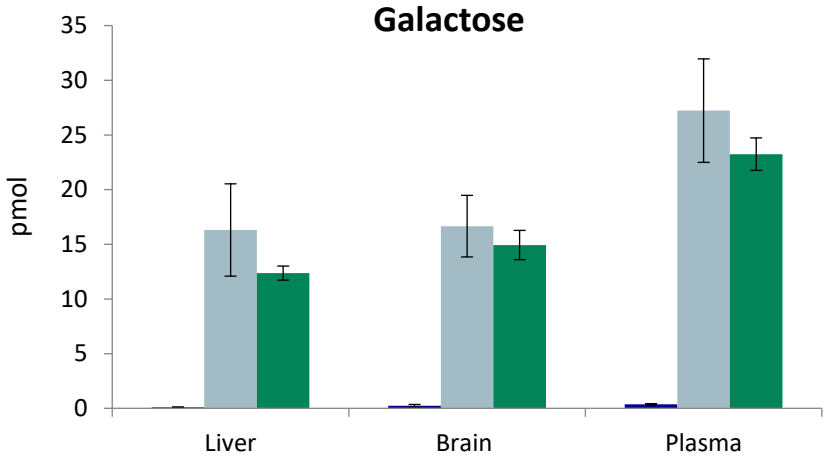
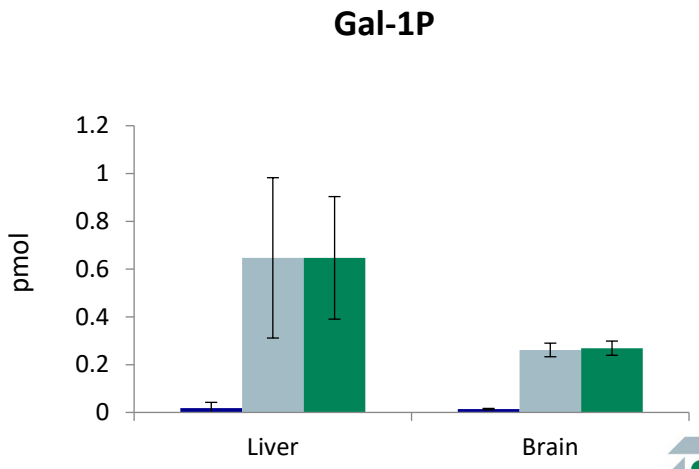
A Closer Look: AT-007 Significantly Reduces Galactitol Levels in all Target Tissues Without Increasing Galactose or Gal-1P



- 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 Gal1P levels; similar results seen at Day 22 and age 5 months





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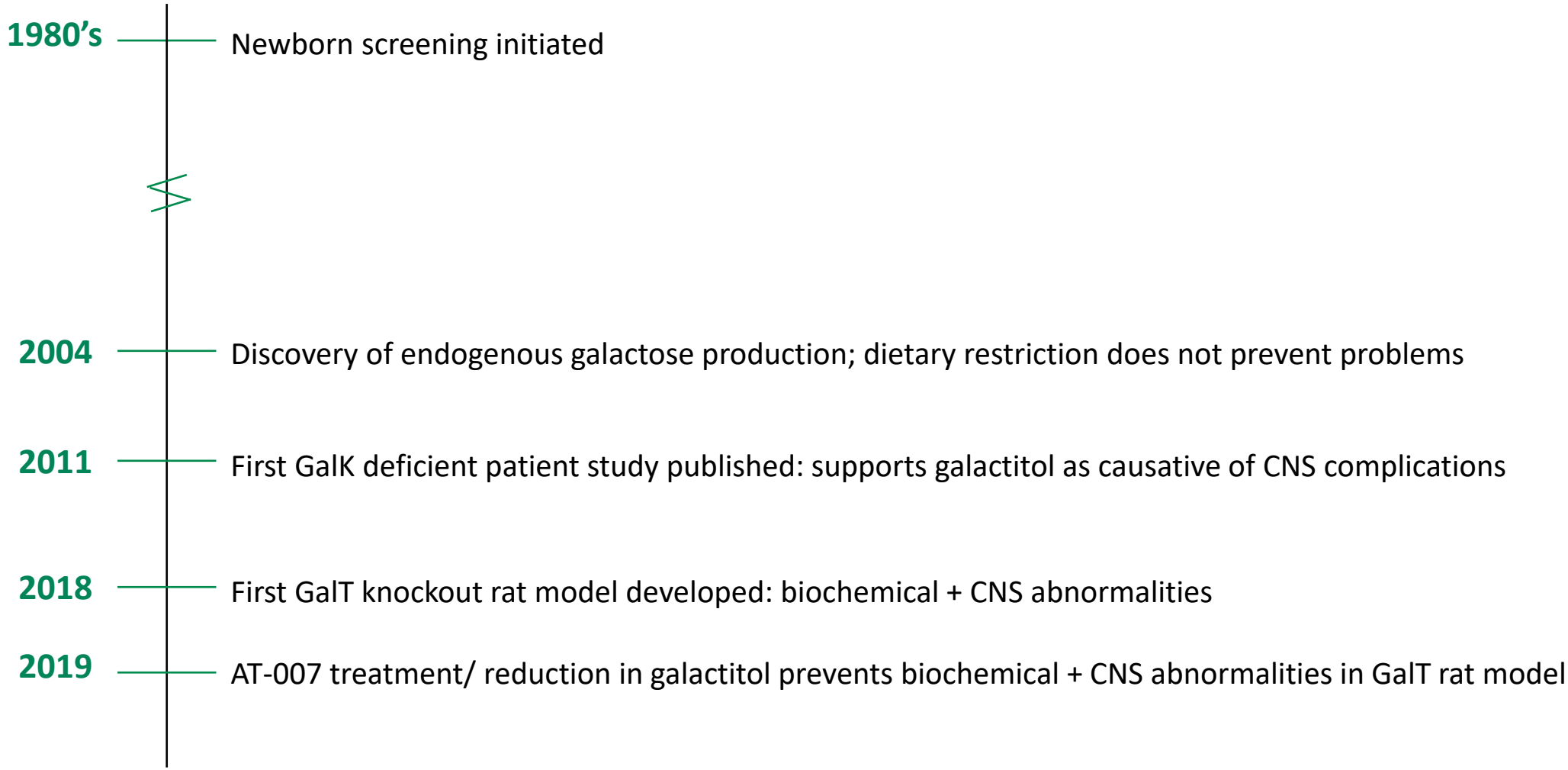
Galactosemia History Timeline



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Rational Drug Design Targeting Aldose Reductase: Improved Technology has Led to Improved Compounds

Technological Advancements

- Advanced crystallography provided novel understanding of structural changes within AR active site

Impact of Modified Structure

- Functional modifications improve compound's binding affinity and specificity
- High potency for Aldose Reductase inhibition
- No off-target Aldehyde Reductase inhibitory activity
- CNS penetrant

Preclinical Toxicology Supporting Human Clinical Trial Initiation

- AT-007 was safe and well tolerated in animals, with a broad dosing/ exposure window to humans
  - Rats, dogs, rabbits
  - Up to 9 months exposure (dogs); 6 months exposure (rats)
  - Includes developmental toxicology and juvenile toxicology studies

Summary

- 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
- Prevented clinical manifestations of disease in this model, including CNS abnormalities (learning, cognition, motor)
  - Also prevented cataract formation
- AT-007 was safe and well tolerated in animals, with a broad dosing/ exposure window to humans

Clinical Program: ACTION-Galactosemia Trial Design

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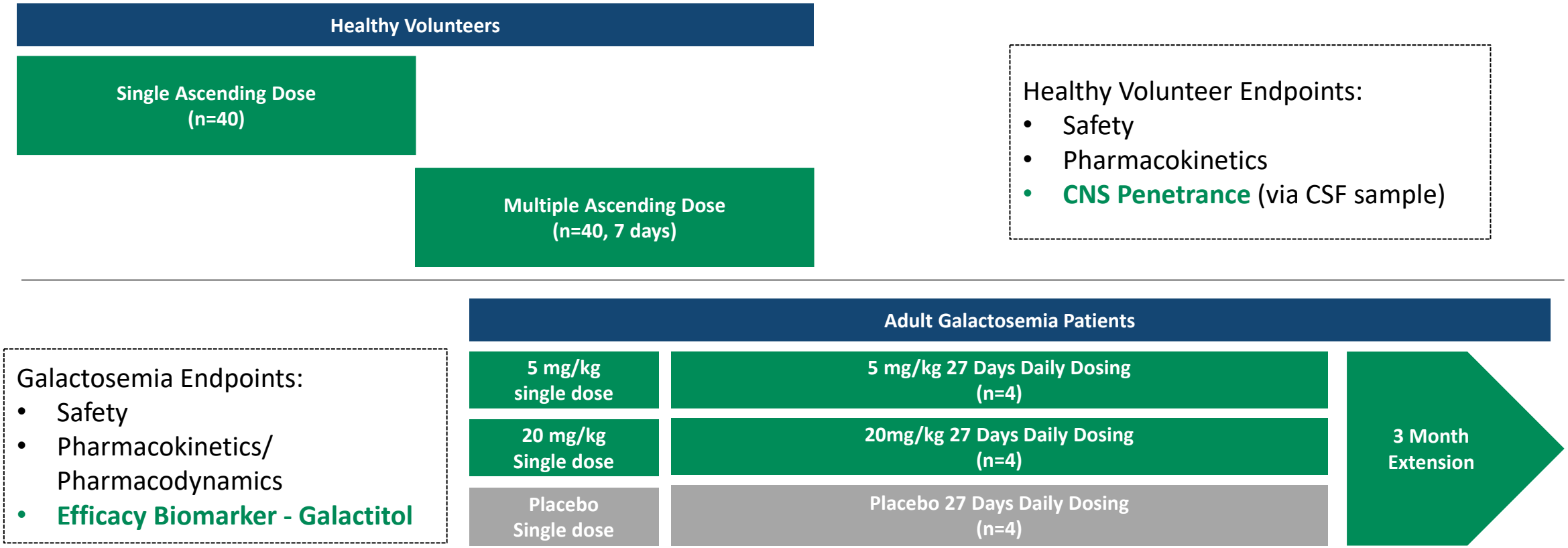
Galactosemia Phase 1/2 Registrational Study (ACTION-Galactosemia)

Multi-Center Placebo-Controlled Study in Healthy Volunteers & Adult Galactosemia Patients



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

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Clinical Program: ACTION-Galactosemia Trial Healthy Volunteer Data

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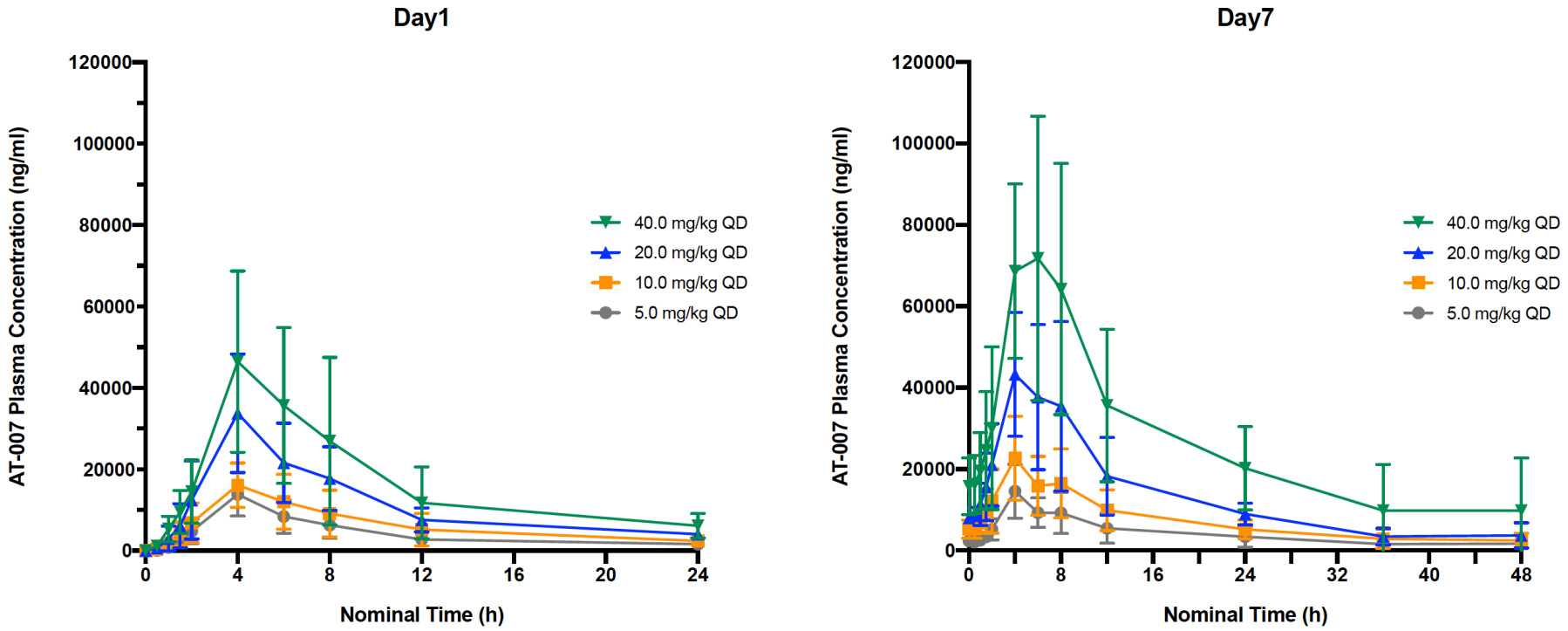
Healthy Volunteer Data
AT-007 Was Safe and Well Tolerated; PK Supportive of Once-Daily Dosing

- AT-007 was safe and well tolerated at all doses, including 40mg/kg
- No treatment-related discontinuations
- Dose-dependent increase in exposure
- PK results supportive of once daily oral dosing



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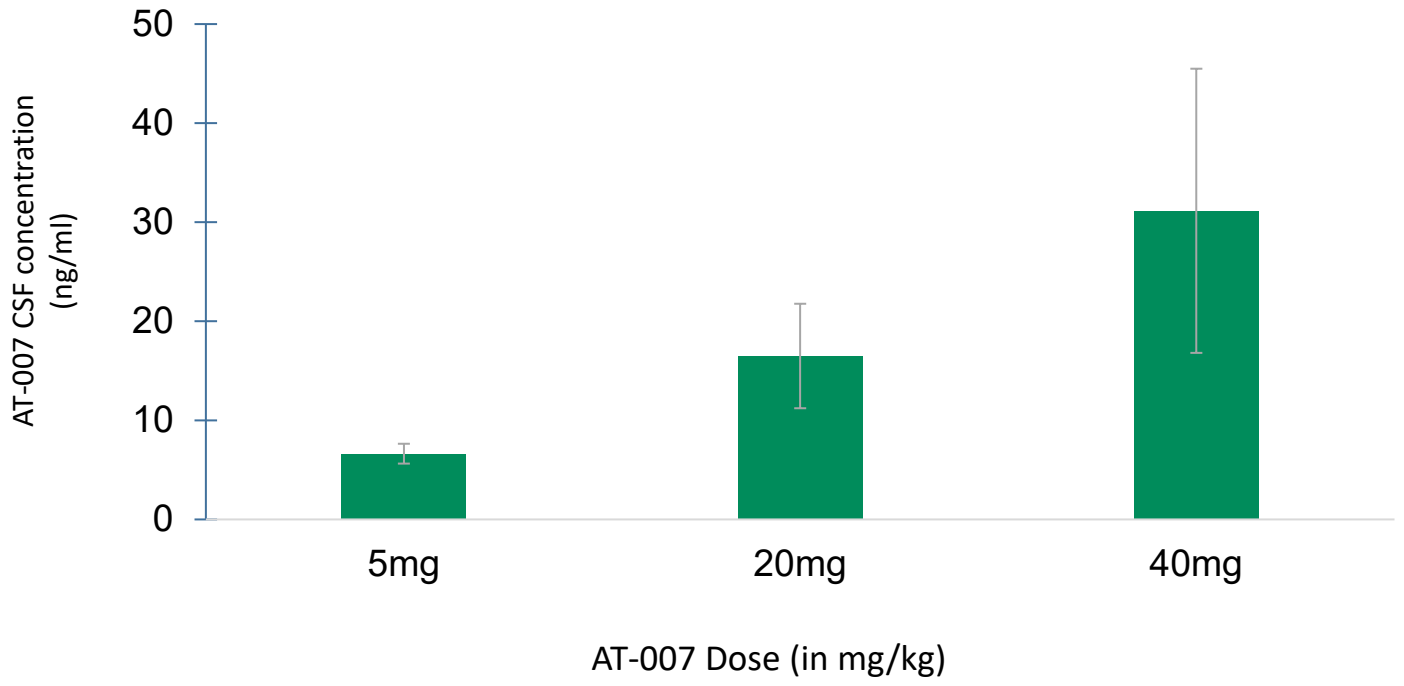
AT-007 is Brain Penetrant
Important in Galactosemia Given CNS Complications

Dose-Dependent Increase in CSF Concentration in Healthy Volunteers (via lumbar puncture)



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ACTION-Galactosemia Trial Data
Adult Galactosemia Patient Baseline Demographics

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Baseline Demographic and Diagnostic Characteristics (n=11*)
Broad Age Range, Multiple Genetic Mutations Represented

Subject	Age	Gender	Ethnicity	BMI	Gene mutation	Urine galactitol (mM/urine creatine mol/L) Baseline	Plasma galactitol (ng/ml) Baseline	GALT enzyme activity (Mmol/h/mg)
2003-101	33	M	Caucasian	24.3	Q188R/Q188R	**208**	2630	0
2003-102	51	M	Caucasian	21.7	Q188R/Q188R	**123**	2390	0
2003-104	19	M	Caucasian	21.6	Q188R/Q188R	**137**	2150	0
2003-105	22	F	Caucasian	22.7	Q188R/Q188R	**255**	2860	0
2004-001*	37	M	Caucasian	21.3	Q188R/Q188R	**152**	2700	0
2004-004	40	M	Caucasian	32.7	N314D/ c119-116 deletion	**102**	2500	0
2004-005	24	F	Caucasian	23.1	Q188R/Q188R	**142**	2210	0
2002-002	19	F	Caucasian	23.9	K285N/c119-116 deletion	**139**	2500	0
2004-007	19	F	Caucasian	21.4	Q188R/Q188R	**133**	2450	0
2004-008	22	M	Caucasian	17.4	Q188R/Q188R	**130**	1930	0
2004-009	28	M	Caucasian	20.5	Q188R/Q188R	**99**	2630	0
Summary	**28.55 ± 10.5**	**4F and 7M**	**Caucasian**	**22.78 ± 3.8**	**9 Q118R homozygous and 2 compound heterozygous**	**147.27 ± 45.8**	**2450 ± 268.7**	**0**

*One placebo patient in cohort 1 crossed over to active for total of n=12

Baseline Demographic and Diagnostic Characteristics
Cohorts Well Balanced

Subject	Age	Gender	BMI	Ethnicity	Gene mutation	Urine galactitol (mM/urine creatine mol/L)	Plasma galactitol (ng/ml)	GALT enzyme activity Mmol/h/mg
PLACEBO								
2004-001*	37	M	21.3	Caucasian	Q188R/Q188R	**152**	2700	0
2004-004	40	M	32.7	Caucasian	N314D/ c119-116 deletion	**102**	2500	0
2004-005	24	F	23.1	Caucasian	Q188R/Q188R	**142**	2210	0
2002-002	19	F	23.9	Caucasian	K285N/c119-116 deletion	**139**	2500	0
MEAN (SD)	30 (10.1)	2F/2M	25.3 (5.1)	4 Caucasians	2Q188R and 2 compound heterozygous	**134 (21.9)**	2478 (201.7)	0
5mg								
2003-101	33	M	24.3	Caucasian	Q188R/Q188R	**208**	2630	0
2003-102	51	M	21.7	Caucasian	Q188R/Q188R	**123**	2390	0
2003-104	19	M	21.6	Caucasian	Q188R/Q188R	**137**	2150	0
2003-105	22	F	22.7	Caucasian	Q188R/Q188R	**255**	2860	0
MEAN (SD)	31 (14.5)	1F/3M	22.6 (1.3)	4 Caucasians	4Q188R	**134 (21.9)**	2478 (201.7)	0
20mg								
2004-001*	37	M	21.3	Caucasian	Q188R/Q188R	**152**	2700	0
2004-007	19	F	21.4	Caucasian	Q188R/Q188R	**133**	2450	0
2004-008	22	M	17.4	Caucasian	Q188R/Q188R	**130**	1930	0
2004-009	28	M	20.5	Caucasian	Q188R/Q188R	**99**	2630	0
MEAN (SD)	26.5 (7.9)	1F/3M	20.2 (1.9)	4 Caucasian	4Q188R	**129 (21.9)**	2428 (348.0)	0
Overall Summary	**28.55 ± 10.5**	**4F and 7M**	**22.78 ± 3.8**	**Caucasian**	**9 Q118R homozygous and 2 compound heterozygous**	**147.27 ± 45.8**	**2450 ± 268.7**	**0**

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Galactosemia Patient Baseline Clinical & Descriptive Characteristics (n=11*)

Clinical Characteristics

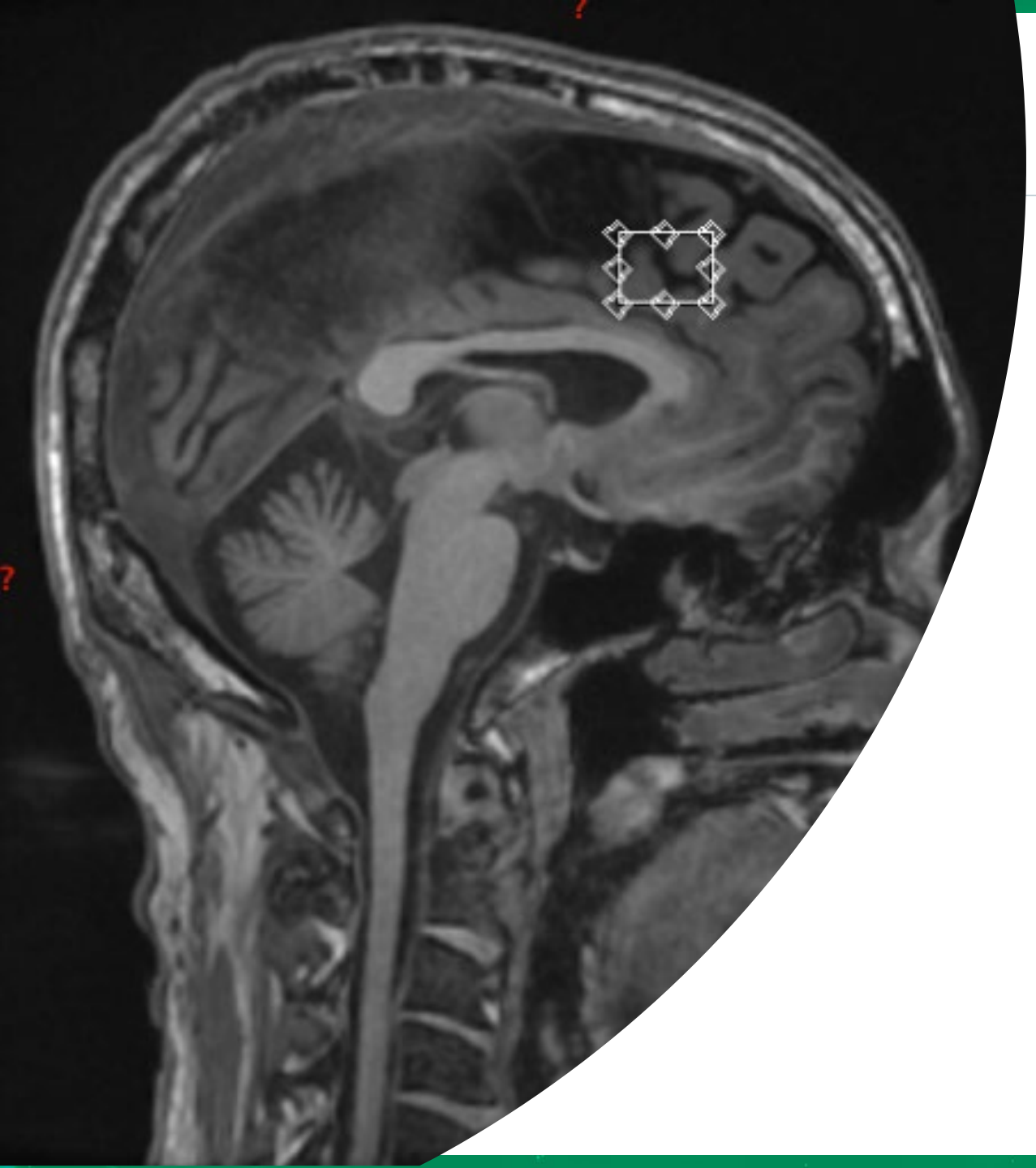
CNS Disorders	Psychiatric Disorders
Seizures (n=5)	Anxiety (n=4)
Dementia (n=1)	Depression (n=3)
Encephalopathy (n=1)	ADHD (n=3)
Tremor	

Endocrine Disorders	
Primary ovarian insufficiency (All Females)	Short stature (n=1)
Gynecomastia (n=1)	Osteopenia (n=2)
Erectile dysfunction (n=1)	Vitamin D deficiency (n=6)
Hypothyroidism (n=1)	

Descriptive Characteristics

Patient Quality of Life
Living with family members or proximity of caregiver (all, n=11)
Able to travel only with caregiver (n=9)
Unemployed and/or not in school (n=5)
Employed (primarily manual employment, unskilled labor n=6)
Secondary education (n=2)

*One placebo patient in cohort 1 crossed over to active for total of n=12



MRI/MRS Baseline Characteristics

- Brain morphology changes caused by galactitol-induced osmotic dysregulation (edema)
- Galactitol was present and quantifiable in the brain of all adult Galactosemia patients (absent in healthy adults)
- Galactitol levels in the brain correlated with galactitol levels in the blood
- N-acetyl-aspartate, a marker of neuronal health, was markedly decreased (-75%) in all Galactosemia patients

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ACTION-Galactosemia Trial Data

AT-007 Pharmacokinetics and Safety Data in Galactosemia Patients

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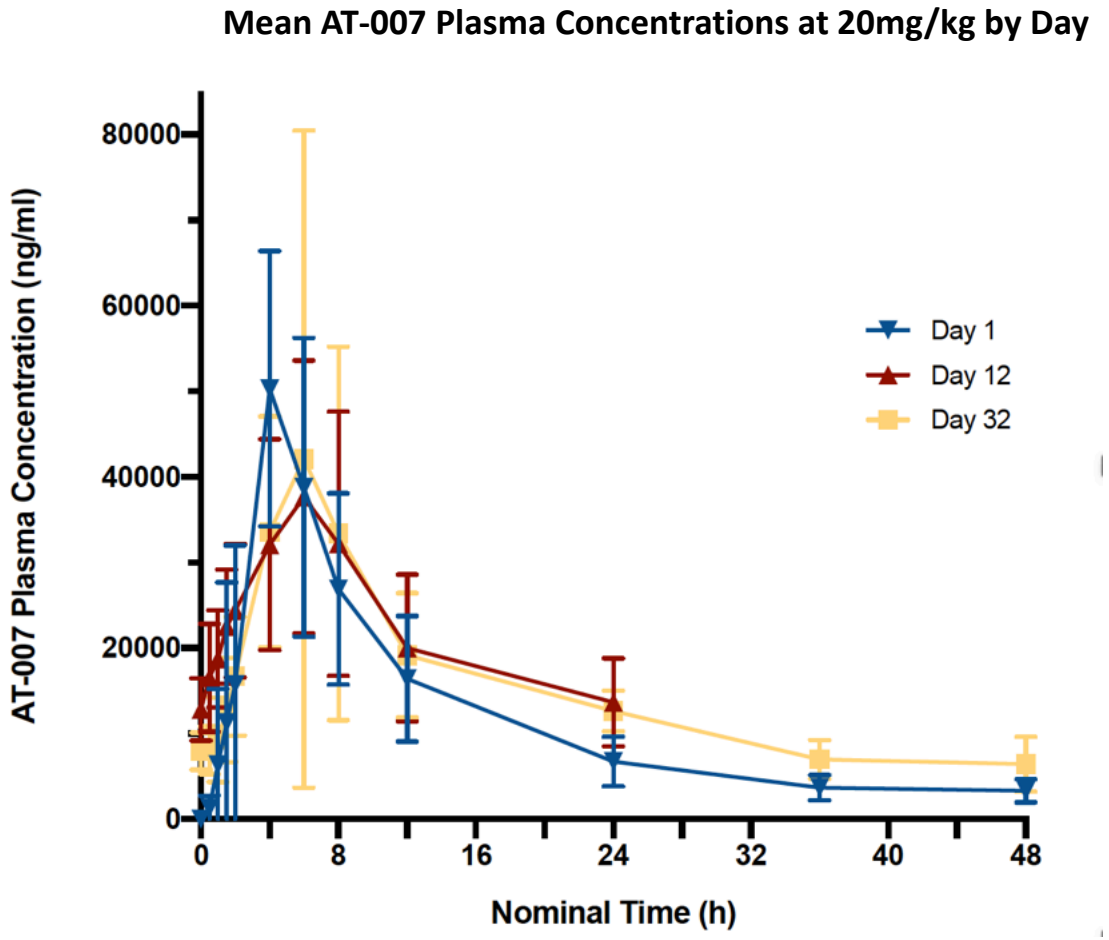
AT-007 Pharmacokinetic Results in Galactosemia Patients

- Plasma PK parameters potentially support once daily oral dosing
- PK profile in Galactosemia patients was similar to healthy volunteers, suggesting similar drug metabolism and clearance
- PK profile suggests no first pass clearance or other PK effects (de-sensitization or induction)



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Detailed Safety Findings

AT-007 Safe and Well-Tolerated: No Drug-Related Adverse Events

SYSTEM ORGAN CLASS PREFERRED TERM	NUMBER (%) OF PATIENTS, NUMBER OF EVENTS			
	Placebo N=4	AT-007 (5 mg/kg) N=4	AT-007 (20 mg/kg) N=4	Overall N=12*
Any Adverse Event	1 (25.0), 3	3 (75.0), 6	2 (50.0), 2	6 (50.0), 11
Cardiac Disorders	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1
Tachycardia	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1
Ear and Labyrinth Disorder	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1
Ear discomfort	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1
Gastrointestinal Disorders	1 (25.0), 1	1 (25.0), 1	0 (0.0), 0	2 (16.7), 2
Dyspepsia	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1
Abdominal Discomfort	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1
General Disorder and Administration site conditions	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1
Feeling hot	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1
Infections	0 (0.0), 0	2 (50.0) 2	0 (0.0), 0	2 (16.7) 2
Upper respiratory tract infection	0 (0.0), 0	2 (50%) 2	0 (0.0), 0	2 (17%) 2
Injury/ Procedural Complications	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1
Contusion	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1
Musculoskeletal and Connective Tissue Disorders	0 (0.0), 0	0 (0.0), 0	1 (25.0), 1	1 (8.3), 1
Mobility decreased	0 (0.0), 0	0 (0.0), 0	1 (25.0), 1	1 (8.3), 1
Psychiatric Disorder	0 (0.0), 0	0 (0.0), 0	1 (25.0), 1	1 (8.3), 1
Anxiety	0 (0.0), 0	0 (0.0), 0	1 (25.0), 1	1 (8.3), 1
Skin and Subcutaneous Tissue Disorders	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1
Pruritus	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1

APPLIED THERAPEUTICS

Detailed Laboratory Findings
No Drug-Related Changes in Hepatic or Renal Function

PARAMETER/VISIT	Placebo N=4	AT-007 5 mg/kg N=4	AT-007 20 mg/kg N=4
ALT (U/L) – Mean (SD)			
Baseline	21.50 (7.00)	17.75 (9.0)	18.25 (9.07)
Post-Dosing (Day 32)	23.00 (10.15)	14.5 (8.39)	22.00 (6.38)
AST (U/L) – Mean (SD)			
Baseline	22.00 (2.58)	19.25 (6.70)	21.75 (9.43)
Post-Dosing (Day 32)	21.33 (4.04)	17.25 (7.14)	23.33 (5.51)
Bilirubin (mg/dL) – Mean (SD)			
Baseline	0.44 (0.18)	0.51 (0.14)	0..38 (0.19)
Post-Dosing (Day 32)	0.38 (0.21)	0.44 (0.12)	0.5 (0.28)
GFR (mL/min/1.73/m^2) – Mean (SD)			
Baseline	116.50 (27.40)	98.75 (12.04)	109.75 (22.65)
Post – Dosing (Day 32)	108.67 (17.79)	88.50 (3.87)	115.25 (28.30)

APPLIED THERAPEUTICS

Safety and PK Summary in Galactosemia Patients

Pharmacokinetics

- PK potentially supports once-daily dosing
- Linear increase in AT-007 dose-dependent plasma concentration
- Similar exposure levels in Galactosemia patients and healthy volunteers

Safety

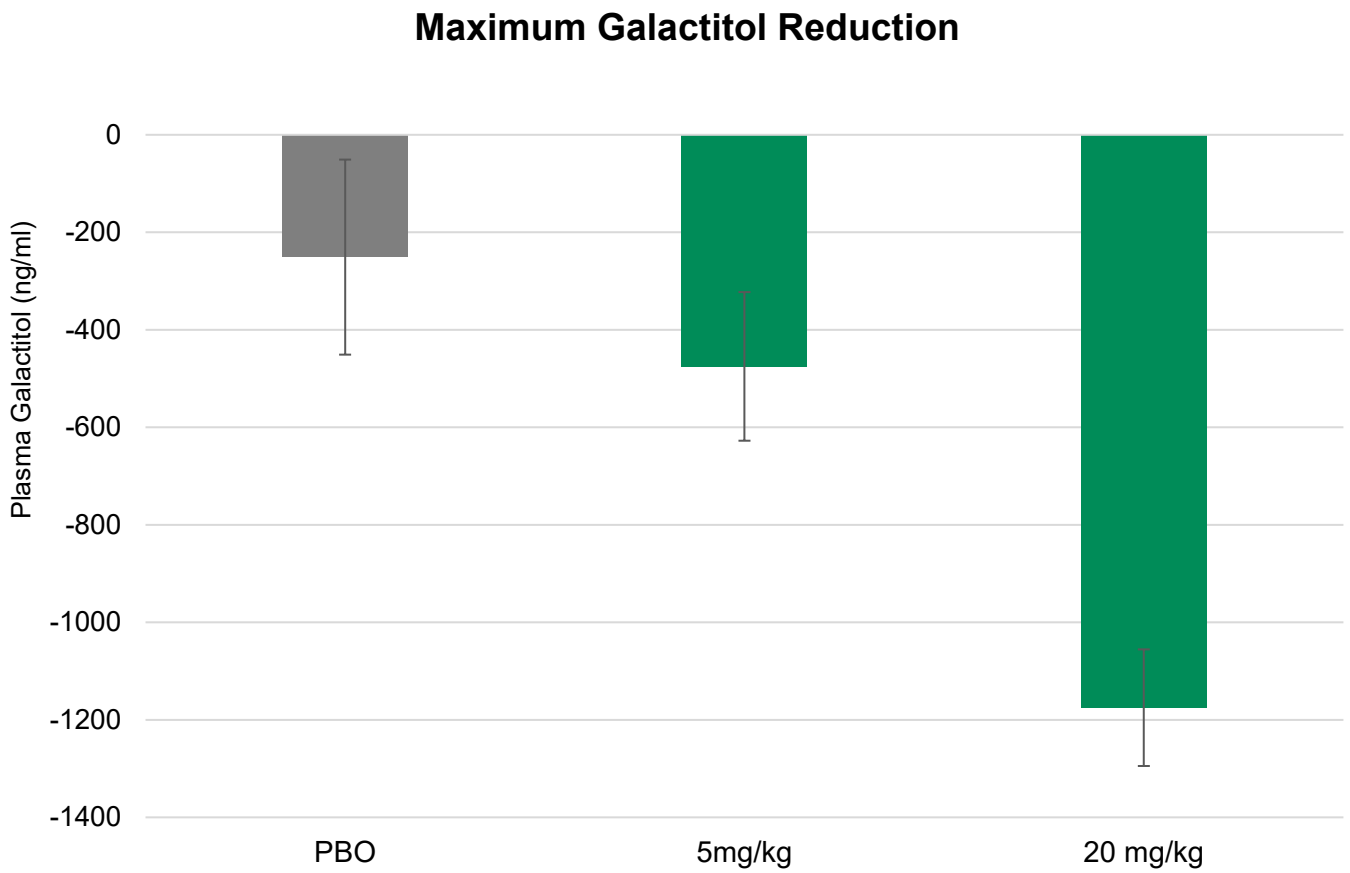
- AT-007 was safe and well-tolerated
- No treatment-related discontinuations
- No treatment-related Adverse Events
- No treatment-related lab abnormalities

ACTION-Galactosemia Trial Data

AT-007 Efficacy Biomarker Results in Galactosemia Patients

APPLIED THERAPEUTICS

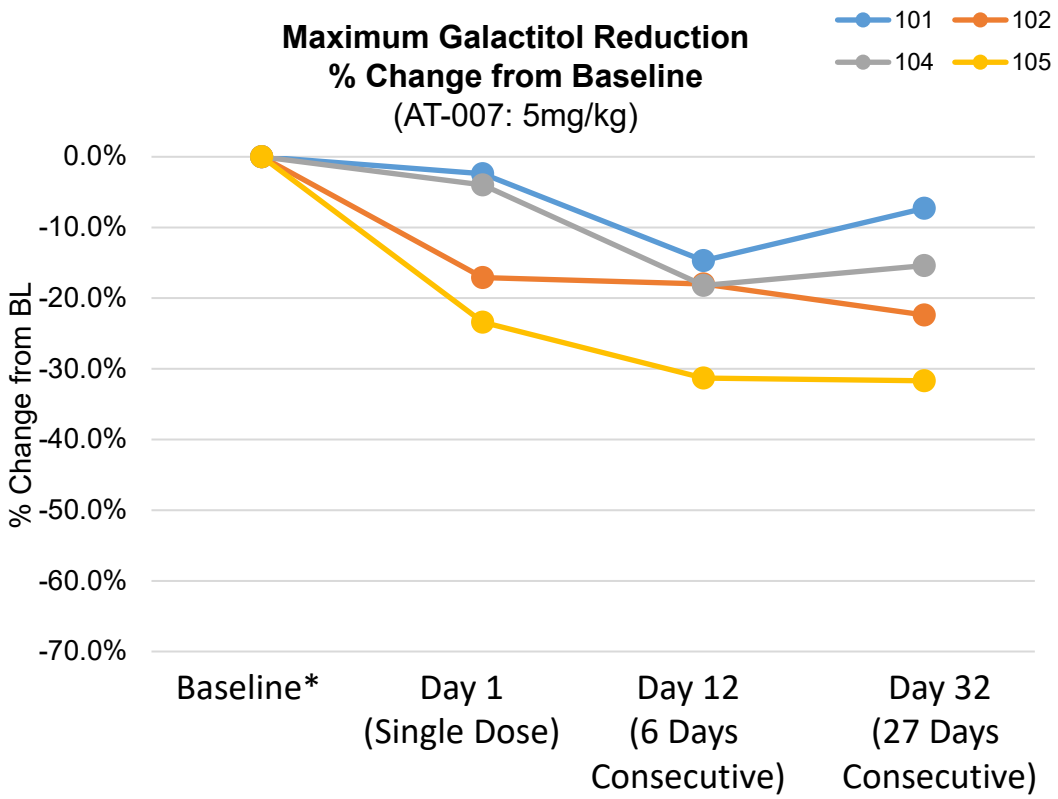
AT-007 Treatment Significantly Reduced Plasma Galactitol Levels in Adult Galactosemia Patients in a Dose-Dependent Fashion



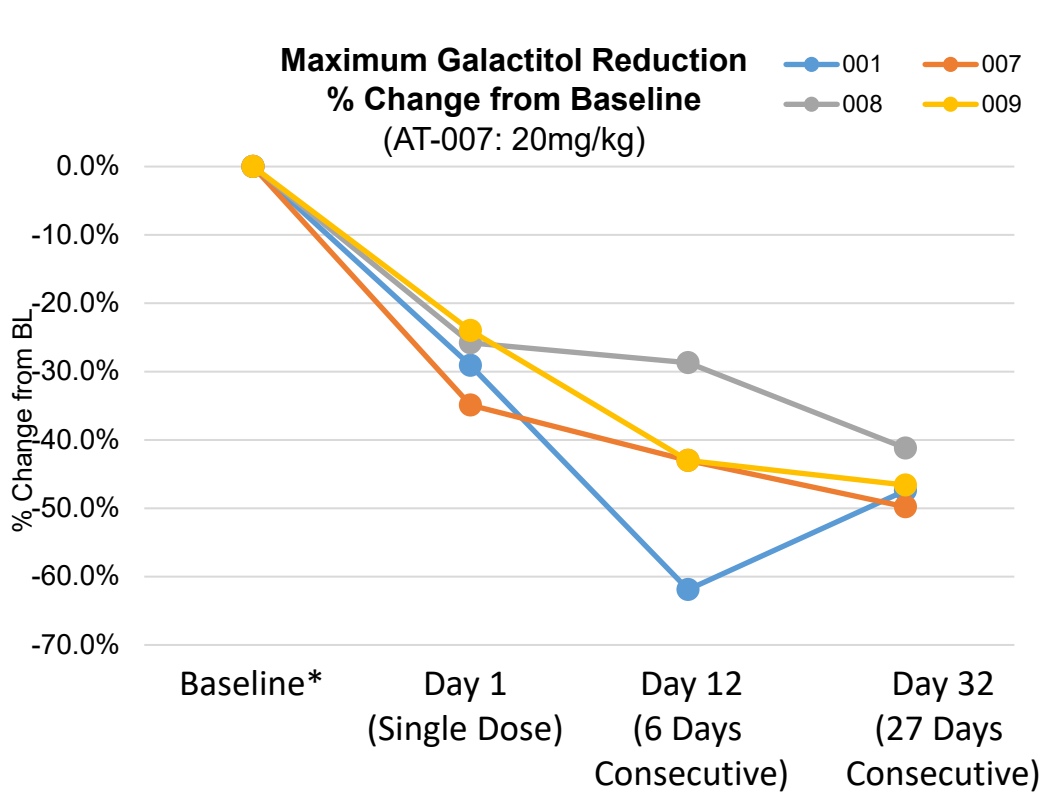
APPLIED THERAPEUTICS

AT-007 Decreased Galactitol Levels in All Treated Patients Galactitol Reduction Was Rapid and Sustained

Reduction in Galactitol at 5mg/kg ~20%



Reduction in Galactitol at 20mg/kg ~50%

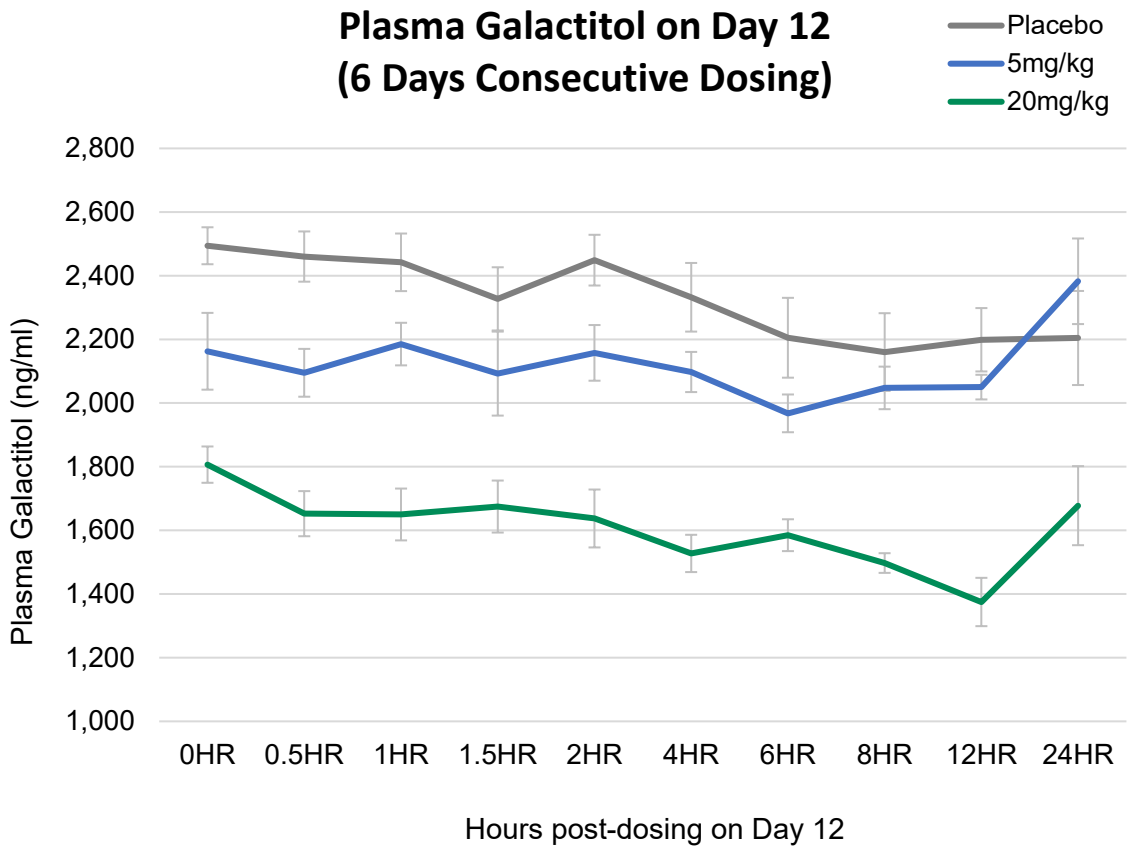


*Baseline is the mean value of Day -1 and Day 1 0hr timepoint

APPLIED THERAPEUTICS

AT-007 Reduction in Galactitol Was Maintained Throughout the 24-Hour Treatment Period

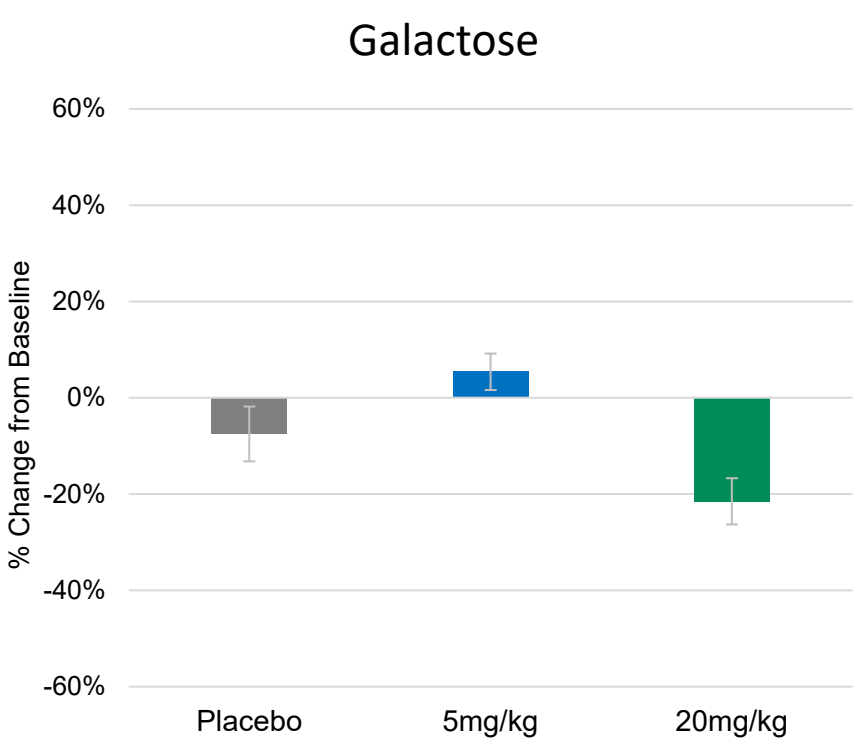
Reductions of ~20% at 5mg/kg and ~50% at 20mg/kg were stable throughout the 24-hour dosing period

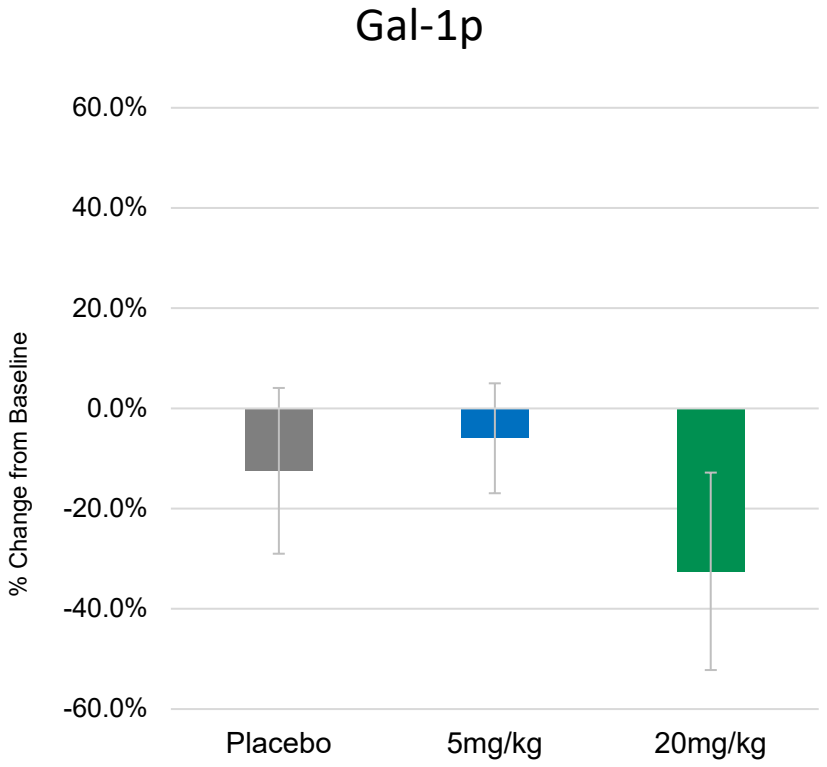


APPLIED THERAPEUTICS

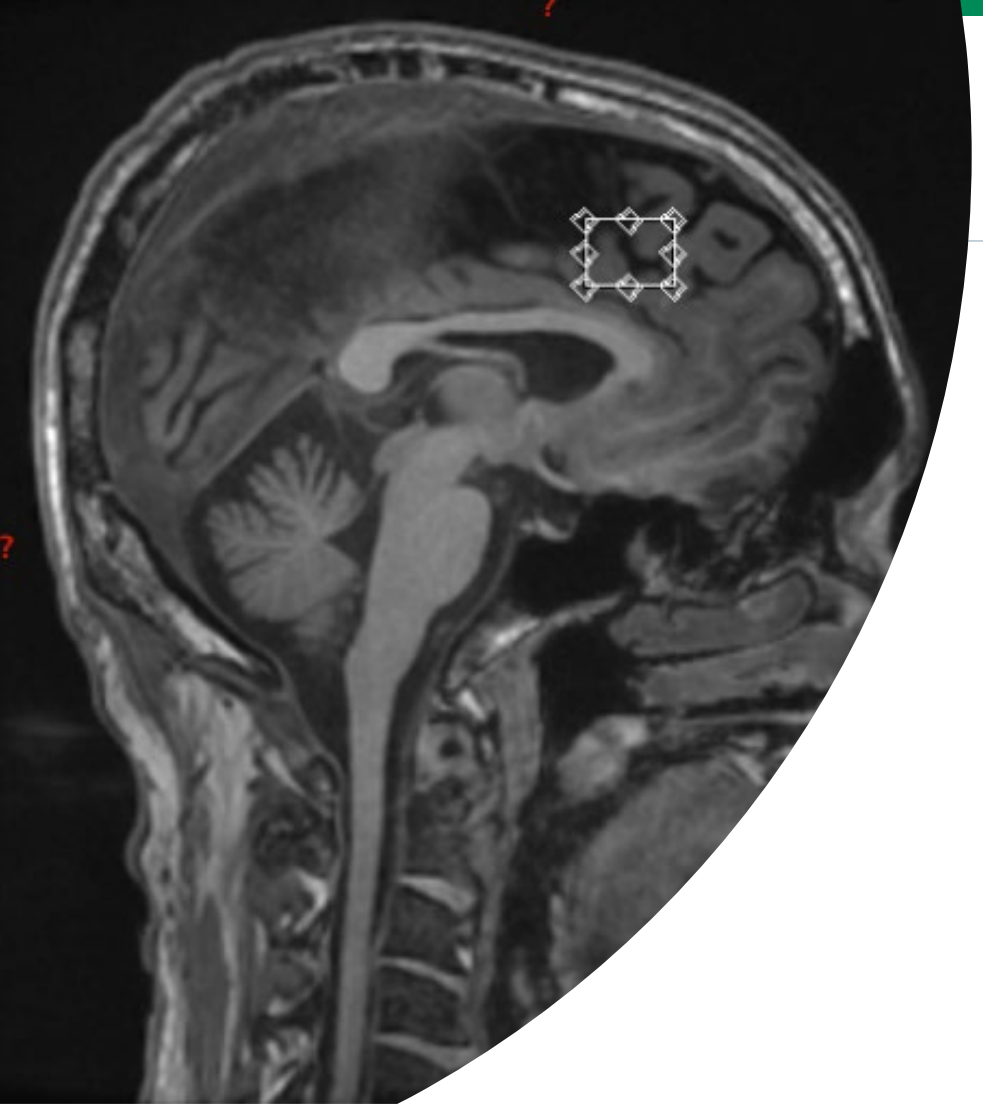
Treatment with AT-007 Decreases Galactitol and Does Not Increase Galactose or Gal-1p

No significant changes were seen in galactose or Gal-1p levels at steady state





APPLIED THERAPEUTICS



MRI/MRS Topline Results

MRI

- (3/3)* high dose patients demonstrated reduction in ventricular volume, a measure of brain edema
- (2/4) low dose patients demonstrated reduction in edema
- No placebo patients displayed significant changes on measures of brain edema

MRS

- Most patients demonstrated a decrease in brain galactitol with AT-007 treatment
- Magnitude of galactitol reduction in the brain correlated with reductions in the bloodstream

Additional MRI/MRS analyses underway; extension will also provide additional data on more patients

*MRI/MRS was limited by inability of some patients to withstand MRI (anxiety) and low-quality scans in others (due to tremor/ movement)

APPLIED THERAPEUTICS

A Closer Look at Seizures

Seizures

- 5 patients had a history of seizures (generalized onset)
- All 5 patients were maintained on antiepileptic medications
- 4 patients had < 1 seizure per year
- 1 patient had > 1 seizure per month
- No significant changes in seizure frequency during the ACTION-Galactosemia core study could be assessed due to the low frequency of seizures in the majority of patients

ACTION-Galactosemia Trial Data

AT-007 for Treatment of Galactosemia: Future Development Plans

APPLIED THERAPEUTICS

AT-007 Extension Study: Designed to Confirm Long-Term Safety

- 90 Day Safety Extension
- Open to those who participated in 28-day core study and new patients
- Safety monitoring & biomarker assessments (as conducted in core study)
- Revised to primarily at-home visits (limited to no travel required) to address burden of travel to sites/ impact on families and COVID-19 concerns
- Study remains on track despite COVID-19

Adult European Study Cohort to Recruit GALK-Deficient Patients

- Primarily designed to recruit GALK deficient patients
  - More prevalent in Europe, but still extremely rare
  - Display similar CNS complications to Classic Galactosemia (GALT-deficient) patients
- UK site
  - One cohort of patients (~6) planned at UK site, but large pool of patients exists (~70 at single site)

- Czech Republic
  - Population incidence in Romani/ Irish Traveler population

Proposed AT-007 Pediatric Study (Under Development)

Proposed Study Design

- 2-Part Multiple Dose Study
- Several age groups investigated
  - ≥ 2 – 6
  - ≥ 7 – 12
  - ≥ 13 <18
  - Children 2 months – 2 yrs may be added following initial safety data (newborns/ infants)

Proposed Study Objectives

- Safety
- Dose determination (via PK/PD)
- Efficacy biomarker effects (plasma galactitol)
- Exploratory: MRI/MRS effects
  - Galactitol quantitation
  - Brain morphometry
  - NAA concentration (neuronal health biomarker)

ACTION-Galactosemia Trial Data
Summary & Conclusions

APPLIED THERAPEUTICS

Summary: ACTION-Galactosemia Study Results

Safety/ PK/ PD

- AT-007 was safe and well-tolerated in the ACTION-Galactosemia study
- PK/PD data potentially supports once-daily oral dosing
- AT-007 is CNS penetrant – important in Galactosemia, which includes significant CNS clinical presentation

Efficacy in Galactosemia Patients

- AT-007 induced rapid and sustained reduction in plasma galactitol, an aberrant, toxic metabolite formed in Galactosemia patients
- 20mg/kg dosing resulted ~50% reduction in plasma galactitol ($p<0.01$ vs. placebo)
- AT-007 MRI/MRS impact

Thank you

APPLIED THERAPEUTICS