ACTION-GALACTOSEMIA: April 2020 Trial Results

Development of AT-007 for the Treatment of Galactosemia

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Summary: ACTION-Galactosemia Study Results

Safety/ PK/ PD

- AT-007 was safe and well-tolerated
- PK/PD data 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)
- Positive AT-007 MRI/MRS impact

Overview of Galactosemia

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AT-007 for Treatment of Galactosemia

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

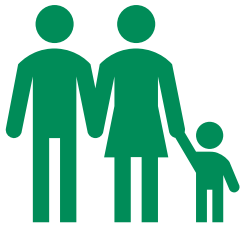
- Mandatory newborn screening and initiation of dairy free diet
- Dietary restriction prevents fatalities, but **does not prevent long term consequences of disease**
- No approved therapies

Galactosemia Clinical Presentation

Acute Newborn

- Hepatic and renal failure
- Brain swelling (edema; encephalopathy)
- 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

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Galactosemia Effects ~2,800 Patients in the US; Potential for Abbreviated Regulatory Approval & Low Burden of Development

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

Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Result From Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Rm. 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

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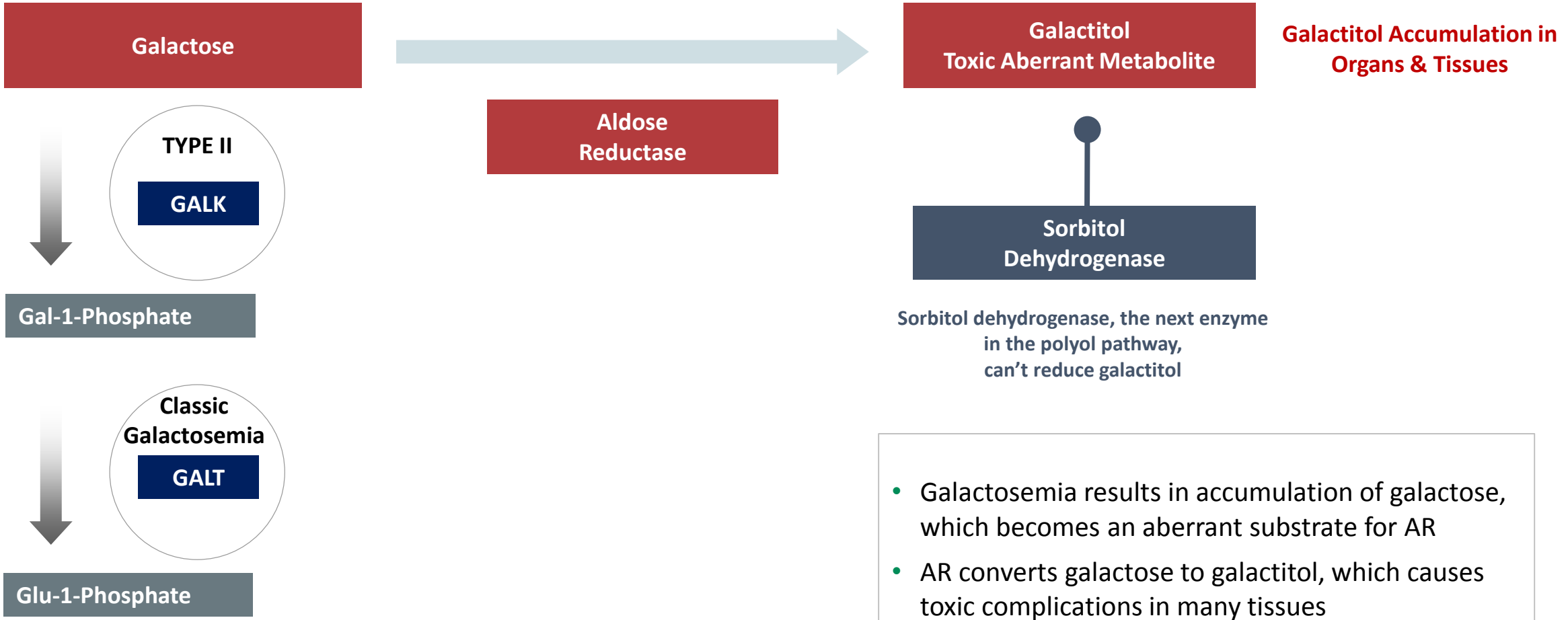
Aldose Reductase Activity Causes Toxic Accumulation of Galactitol in Galactosemia



- 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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Galactosemia Preclinical Data

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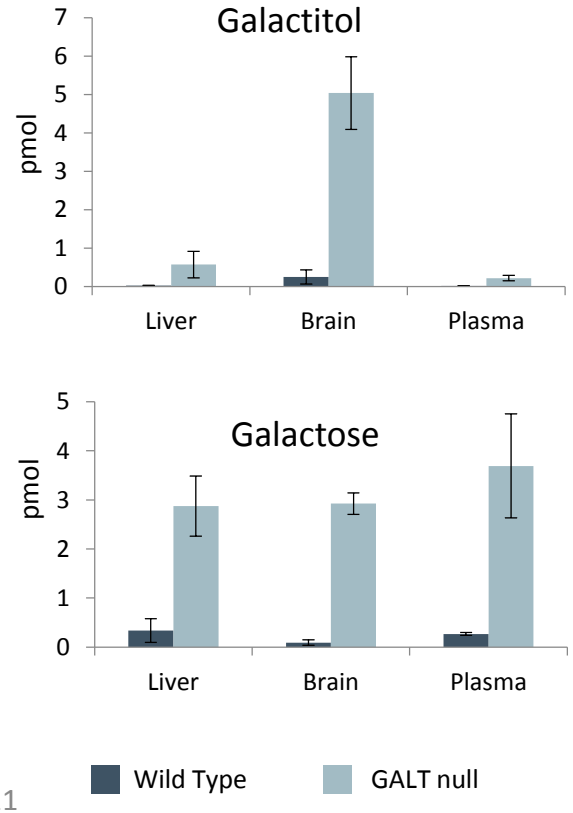
GALT Deficient Rat Model Closely Mirrors Human Disease

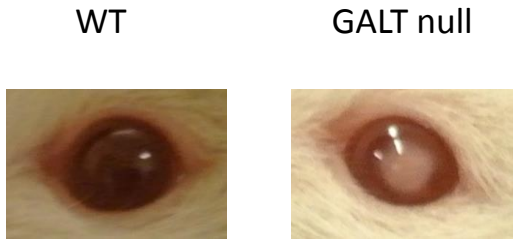
Biochemical Effects

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



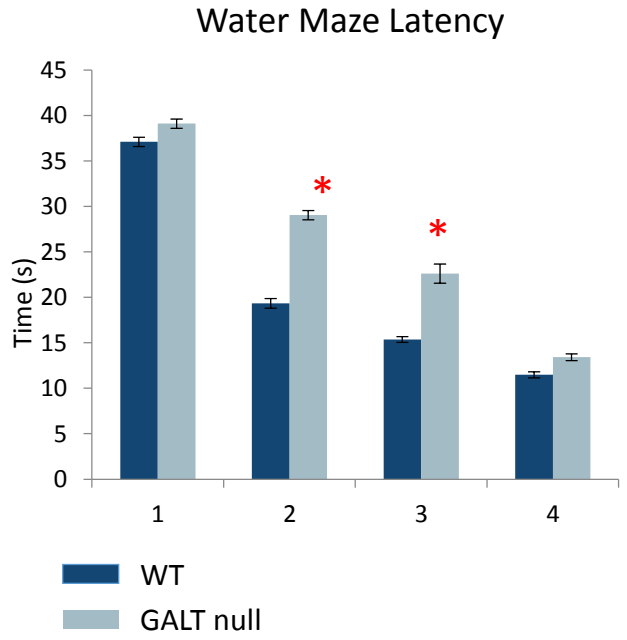
Tissue Deposition of Galactitol

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



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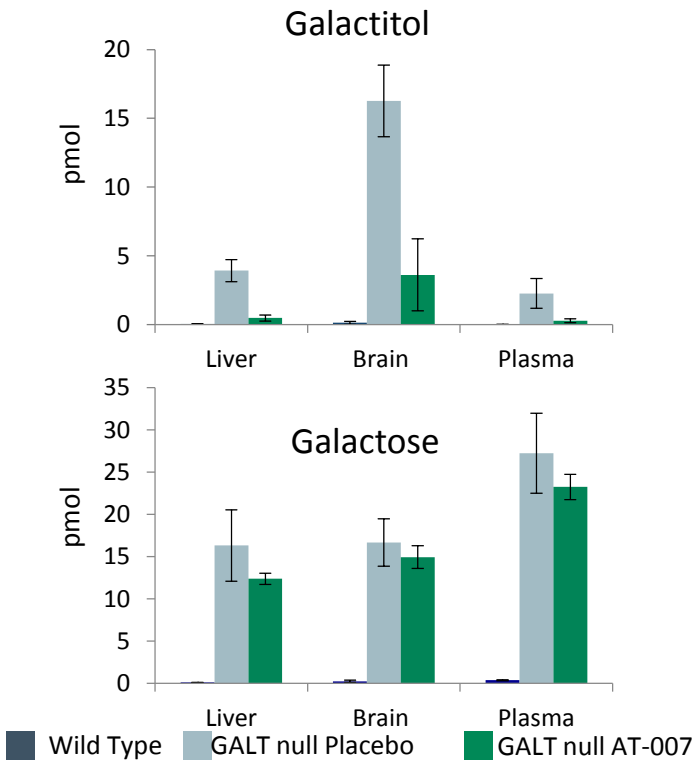
AT-007 Treatment Corrects All 3 Aspects of Disease in the Galactosemia Rat Model

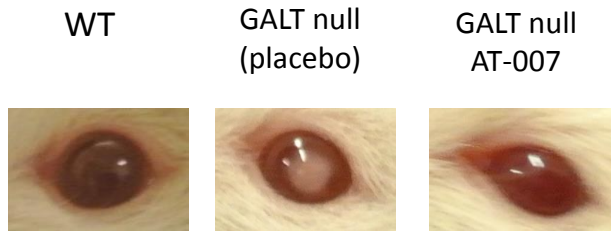
Biochemical Effects

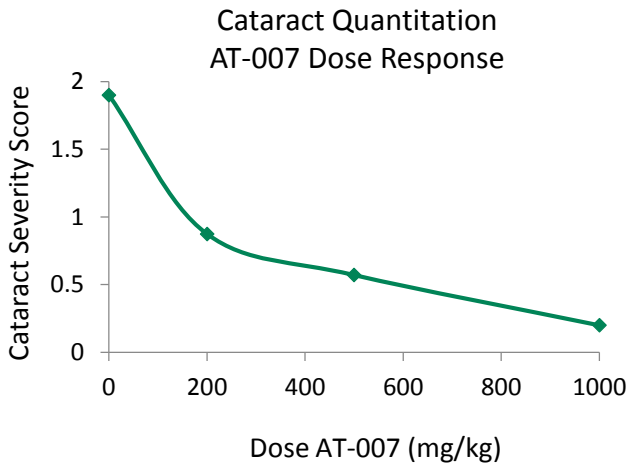
AT-007 treatment significantly reduced galactitol levels in all tissues without increasing galactose or Gal1p



Tissue Deposition of Galactitol

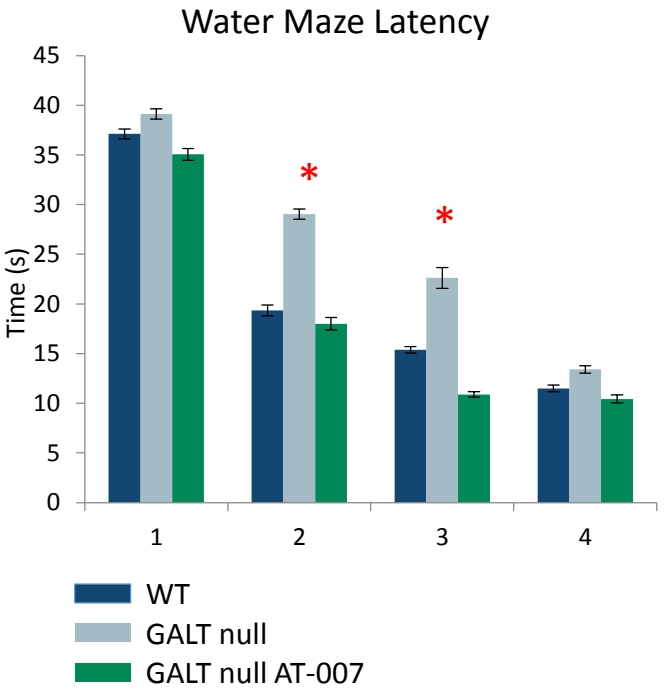
AT-007 treatment prevented galactitol accumulation in tissues, resulting in absence of cataracts





CNS Outcomes

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



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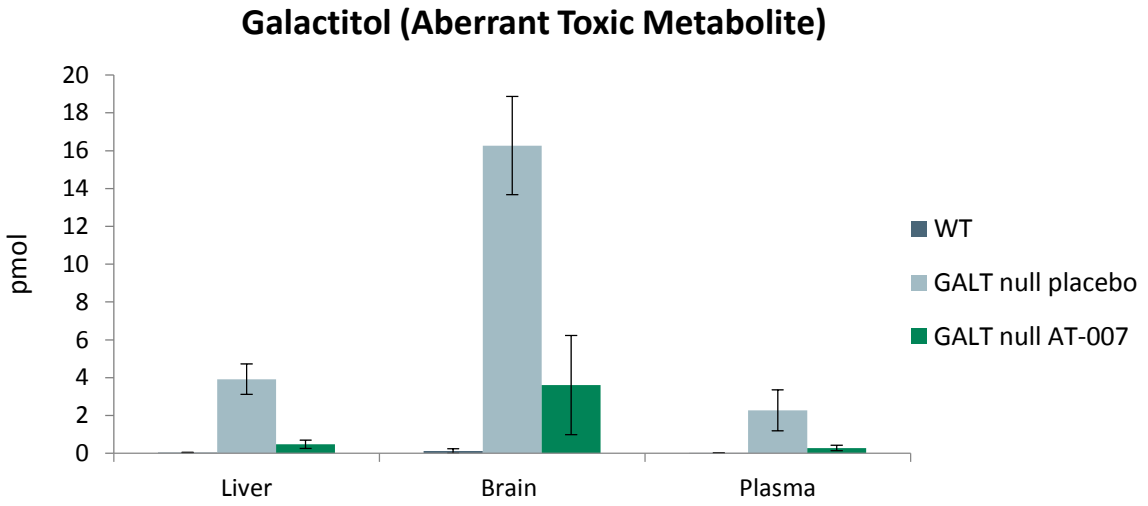
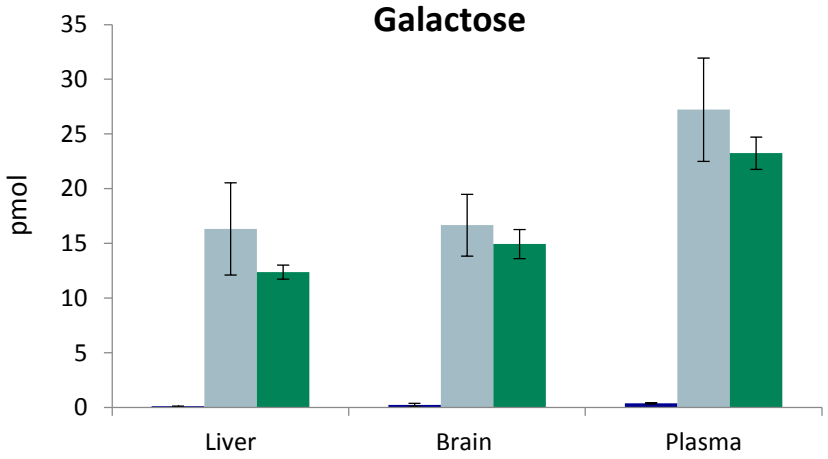
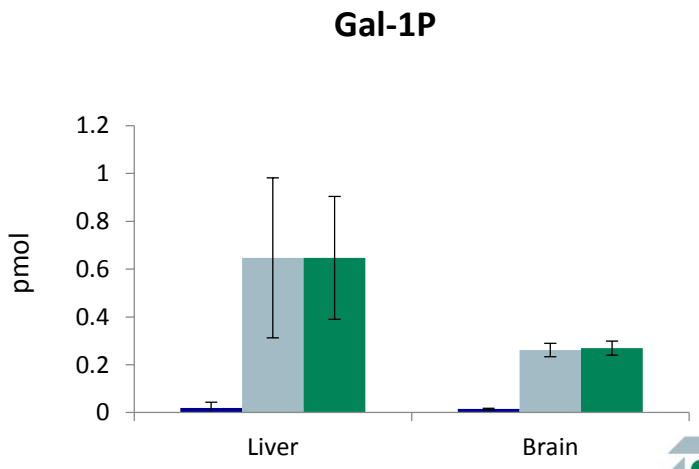
A Closer Look: AT-007 Significantly Reduces Galactitol Levels in all Target Tissues Without Increasing Galactose or Gal-1P



- 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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Clinical Program: ACTION-Galactosemia Trial

April 2020 Data

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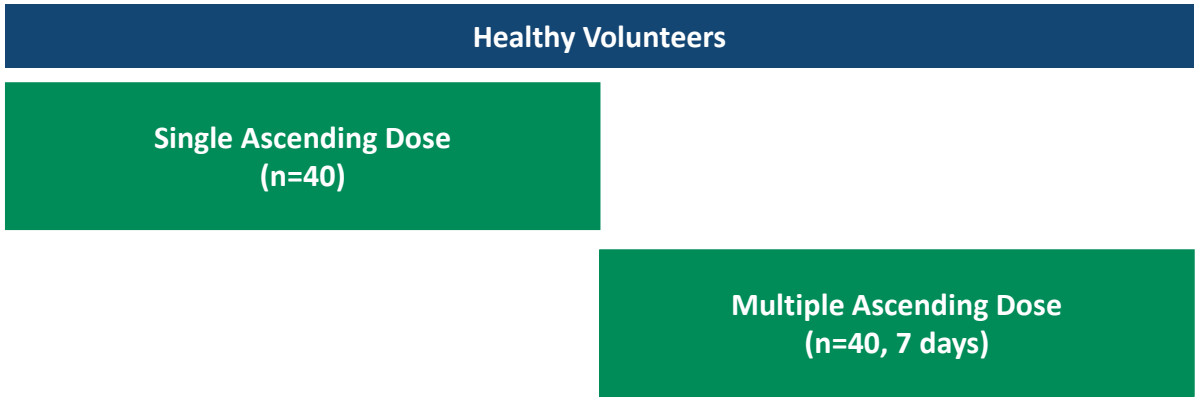
Galactosemia Phase 1/2 Registrational Study (ACTION-Galactosemia)

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

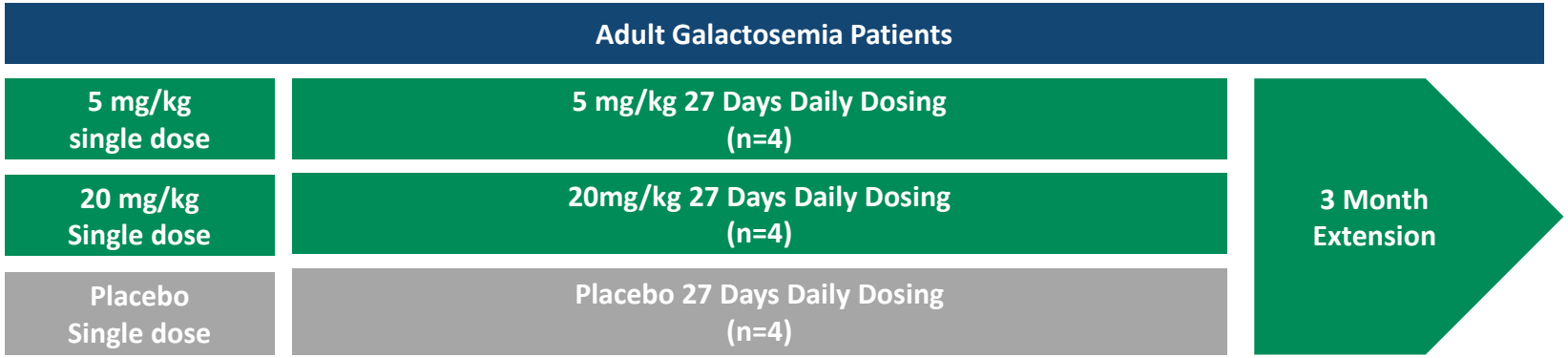


Healthy Volunteer Endpoints:

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

Galactosemia 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

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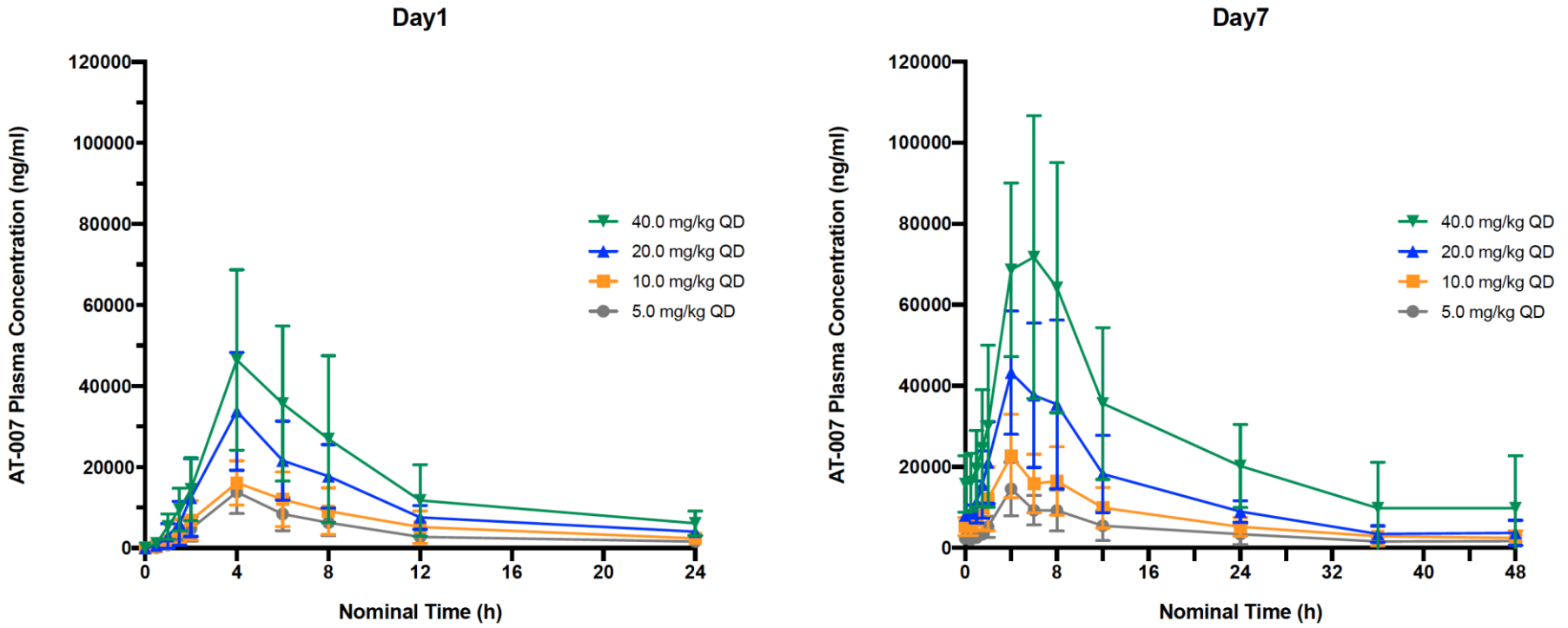
Healthy Volunteer Data
AT-007 Was Safe and Well Tolerated; PK Supports Once-Daily Dosing

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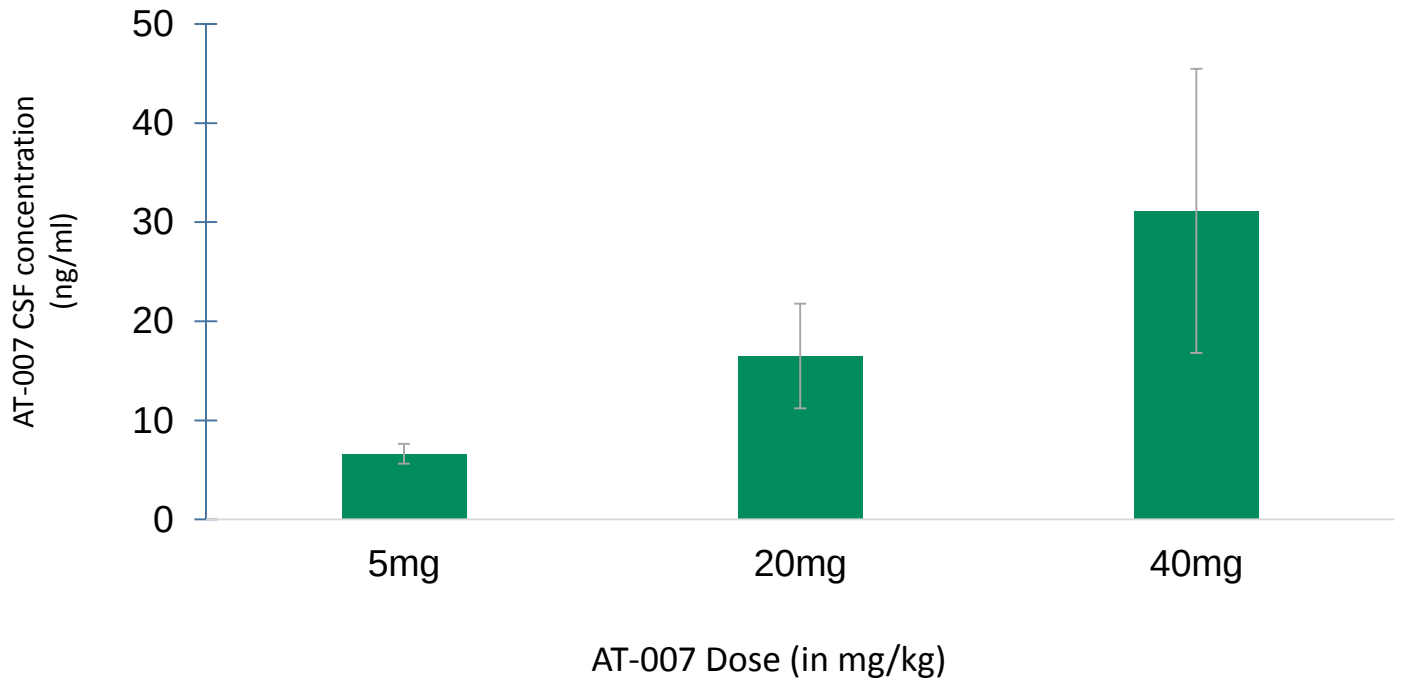
AT-007 is Brain Penetrant
Important in Galactosemia Given CNS Complications

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

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

Clinical Characteristics

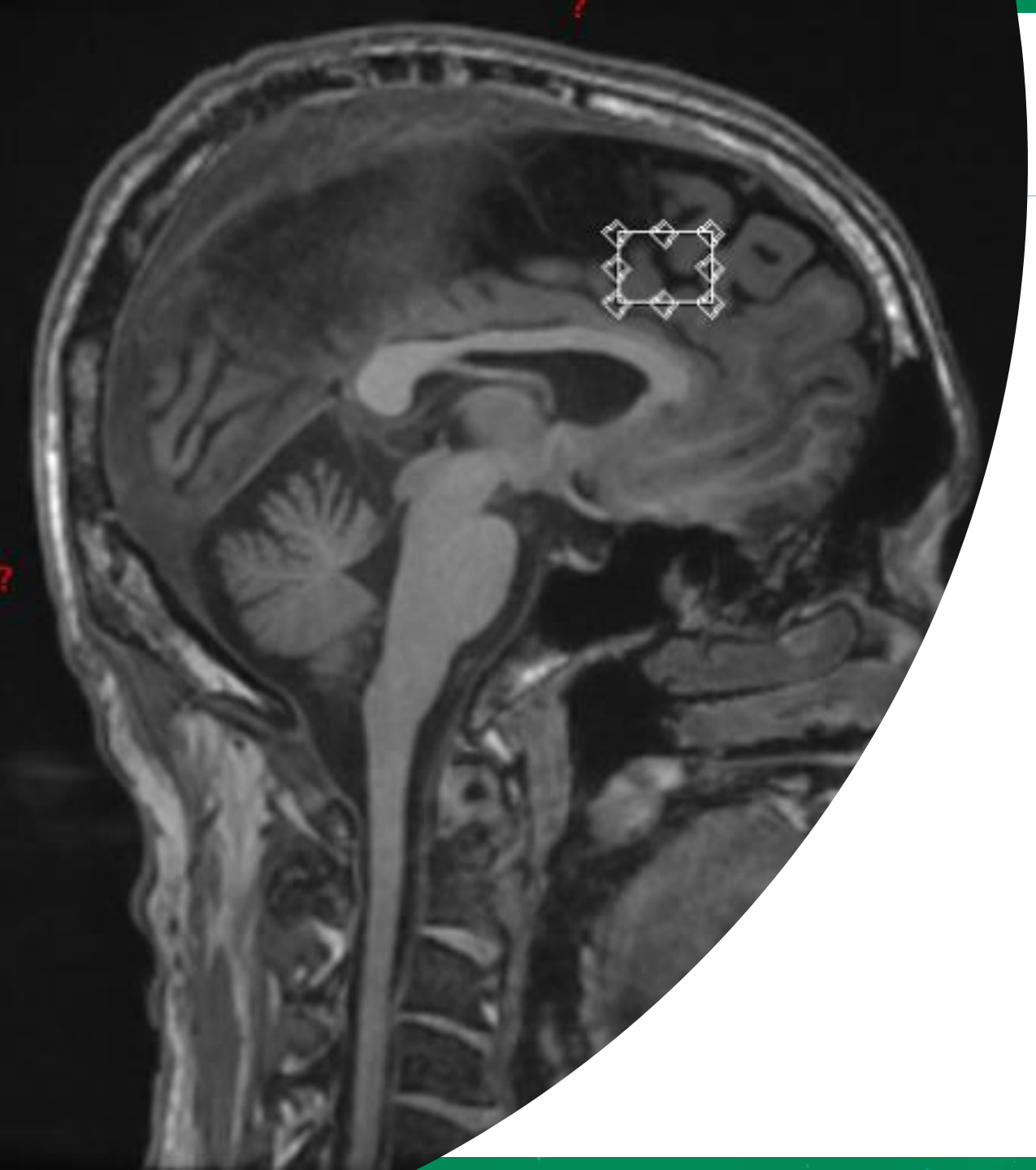
CNS Disorders	Psychiatric Disorders
Seizures (n=5)	Anxiety (n=4)
Dementia (n=1)	Depression (n=3)
Encephalopathy (n=1)	ADHD (n=3)
Tremor	

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
- Galactitol was present and quantifiable in the brain of all adult Galactosemia patients (absent in healthy adults)
- 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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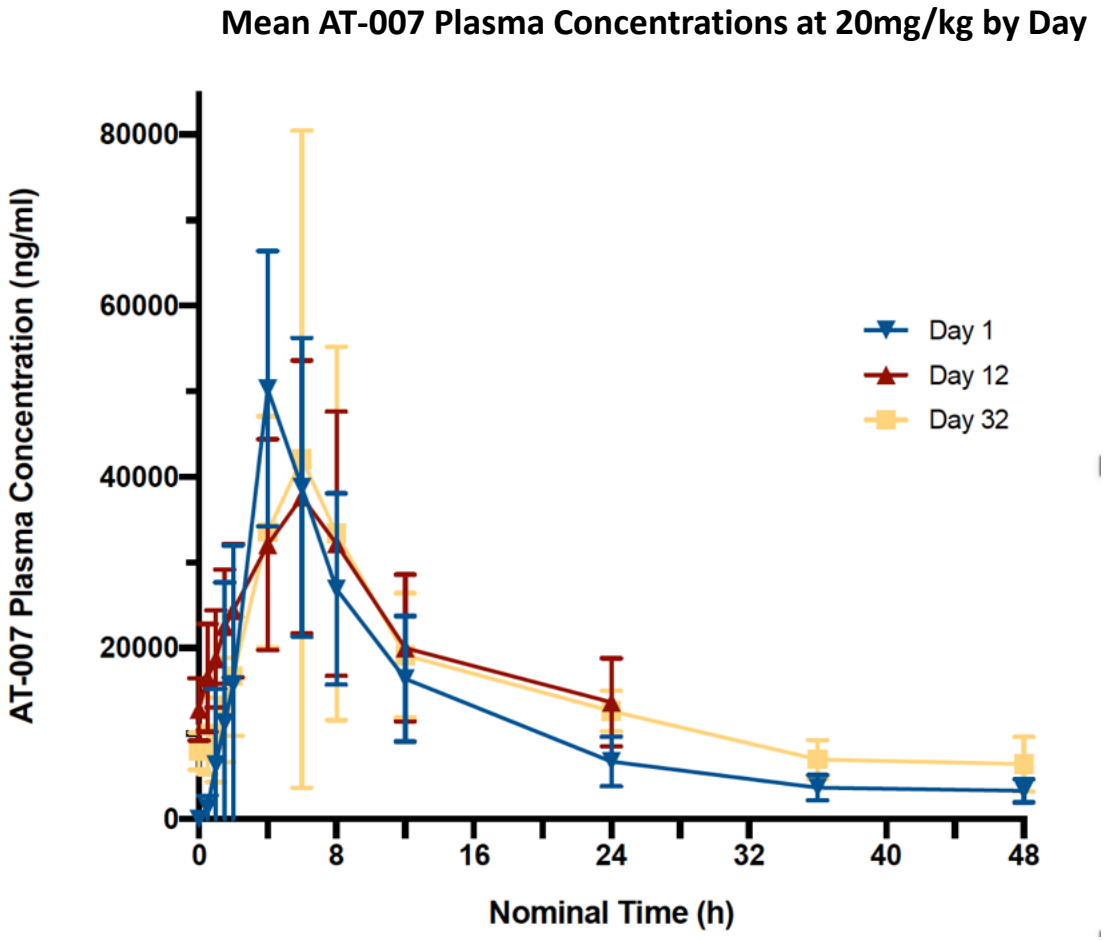
Pharmacokinetic Results Support Once Daily Dosing in Galactosemia Patients

- Plasma PK parameters of AT-007 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)



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*	Significance
Any Adverse Event	1 (25.0), 3	3 (75.0), 6	2 (50.0), 2	6 (50.0), 11	Not Significant
Cardiac Disorders	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1	Not Significant
Tachycardia	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1	Not Significant
Ear and Labyrinth Disorder	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1	Not Significant
Ear discomfort	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1	Not Significant
Gastrointestinal Disorders	1 (25.0), 1	1 (25.0), 1	0 (0.0), 0	2 (16.7), 2	Not Significant
Dyspepsia	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1	Not Significant
Abdominal Discomfort	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1	Not Significant
General Disorder and Administration site conditions	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1	Not Significant
Feeling hot	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1	Not Significant
Infections	0 (0.0), 0	2 (50.0) 2	0 (0.0), 0	2 (16.7) 2	Not Significant
Upper respiratory tract infection	0 (0.0), 0	2 (50%) 2	0 (0.0), 0	2 (17%) 2	Not Significant
Injury/ Procedural Complications	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1	Not Significant
Contusion	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1	Not Significant
Musculoskeletal and Connective Tissue Disorders	0 (0.0), 0	0 (0.0), 0	1 (25.0), 1	1 (8.3), 1	Not Significant
Mobility decreased	0 (0.0), 0	0 (0.0), 0	1 (25.0), 1	1 (8.3), 1	Not Significant
Psychiatric Disorder	0 (0.0), 0	0 (0.0), 0	1 (25.0), 1	1 (8.3), 1	Not Significant
Anxiety	0 (0.0), 0	0 (0.0), 0	1 (25.0), 1	1 (8.3), 1	Not Significant
Skin and Subcutaneous Tissue Disorders	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1	Not Significant
Pruritus	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1	Not Significant

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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	Significance
ALT (U/L) – Mean (SD)				
Baseline	21.50 (7.00)	17.75 (9.0)	18.25 (9.07)	Not Significant
Post-Dosing (Day 32)	23.00 (10.15)	14.5 (8.39)	22.00 (6.38)	Not Significant
AST (U/L) – Mean (SD)				
Baseline	22.00 (2.58)	19.25 (6.70)	21.75 (9.43)	Not Significant
Post-Dosing (Day 32)	21.33 (4.04)	17.25 (7.14)	23.33 (5.51)	Not Significant
Bilirubin (mg/dL) – Mean (SD)				
Baseline	0.44 (0.18)	0.51 (0.14)	0..38 (0.19)	Not Significant
Post-Dosing (Day 32)	0.38 (0.21)	0.44 (0.12)	0.5 (0.28)	Not Significant
GFR (mL/min/1.73/m^2) – Mean (SD)				
Baseline	116.50 (27.40)	98.75 (12.04)	109.75 (22.65)	Not Significant
Post – Dosing (Day 32)	108.67 (17.79)	88.50 (3.87)	115.25 (28.30)	Not Significant

Safety and PK Summary in Galactosemia Patients

Pharmacokinetics

- PK 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 Results in Galactosemia Patients

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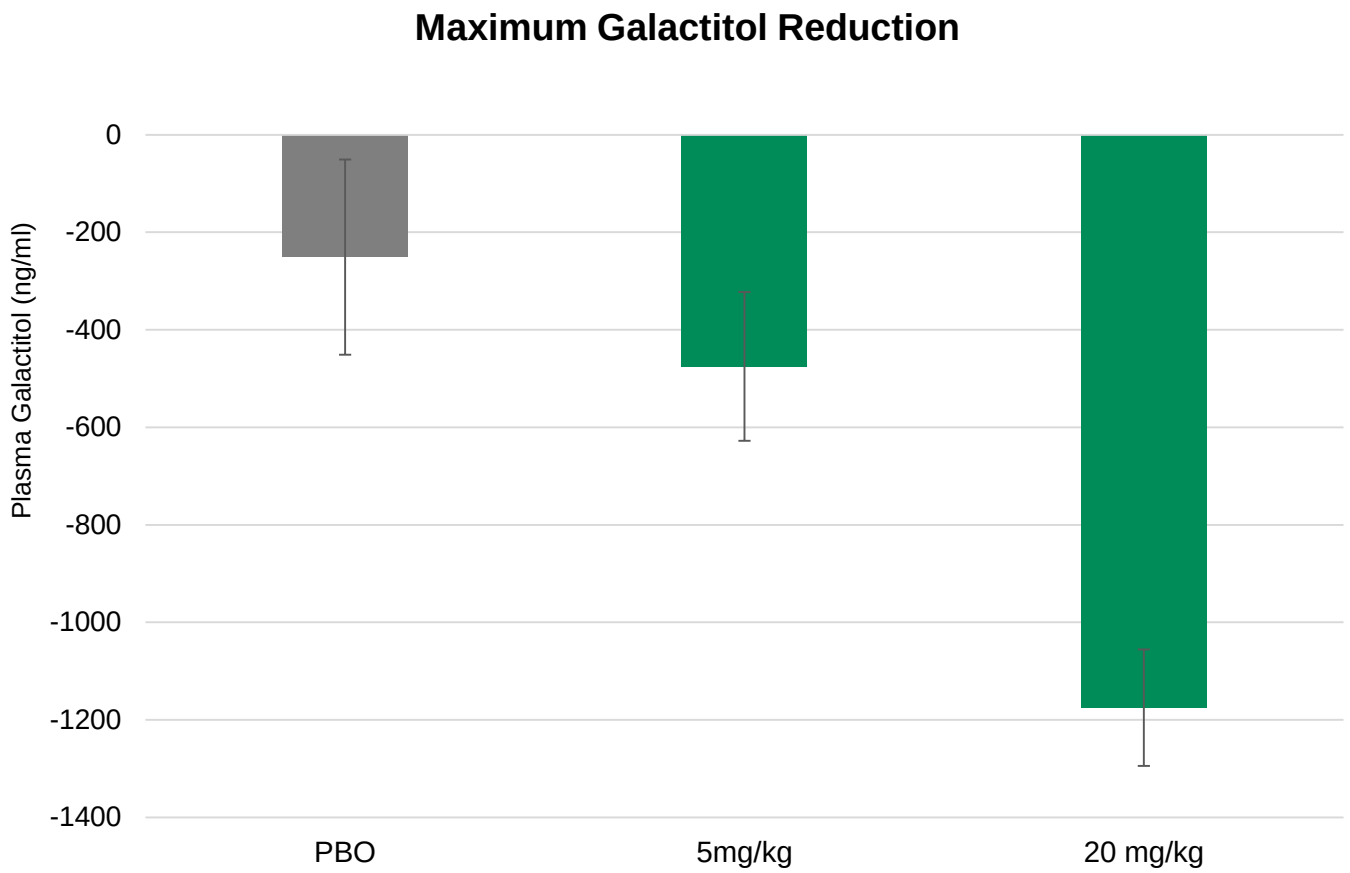
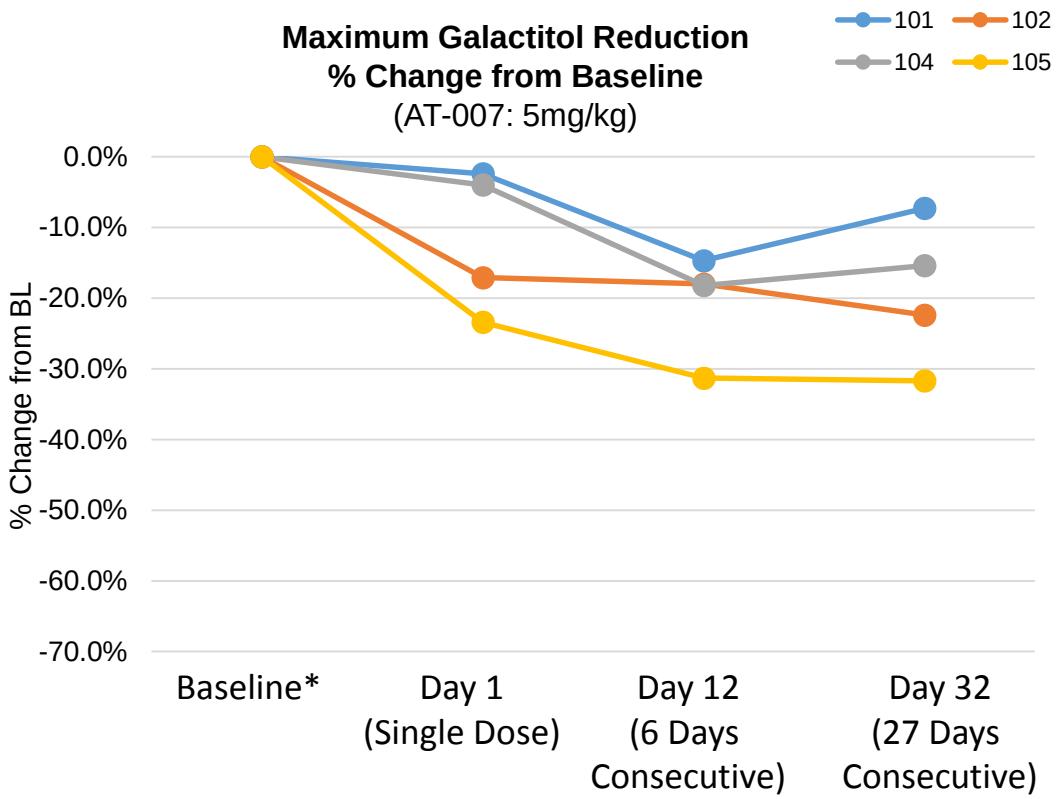
AT-007 Treatment Significantly Reduced Plasma Galactitol Levels in Adult Galactosemia Patients in a Dose-Dependent Fashion

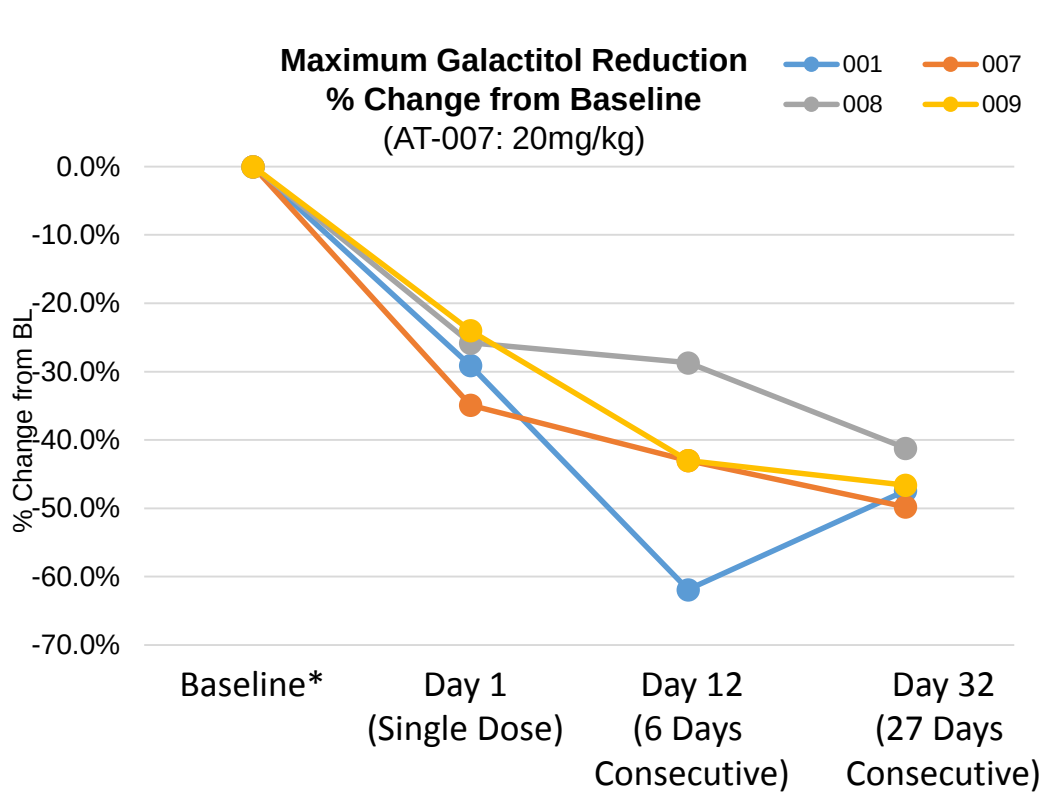


AT-007 Decreased Galactitol Levels in All Treated Patients
Galactitol Reduction Was Rapid and Sustained

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

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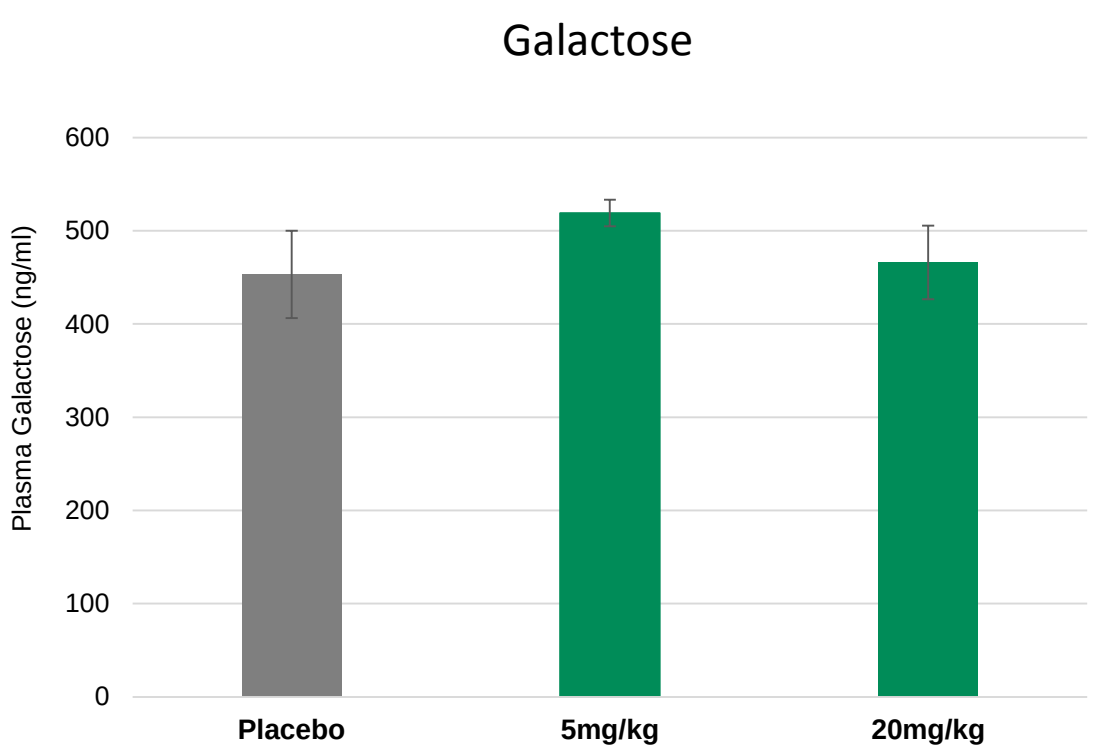
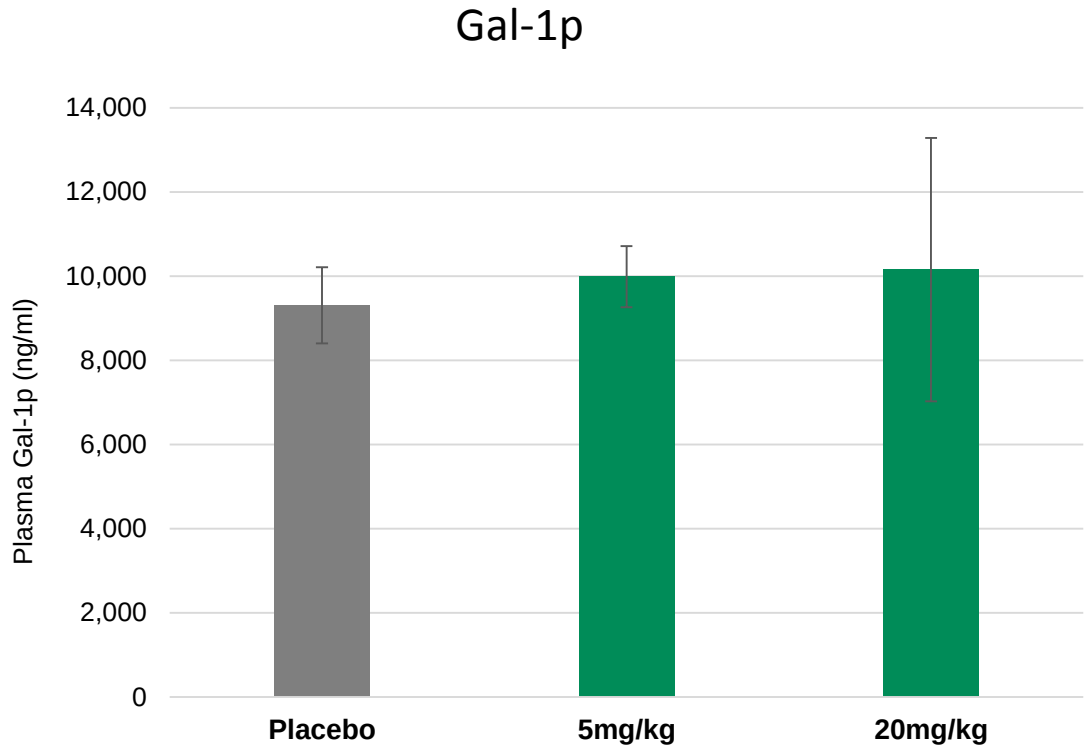
Treatment with AT-007 Does Not Significantly Increase Galactose or Gal-1p
No Derangement of Galactose Pathway Metabolites

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





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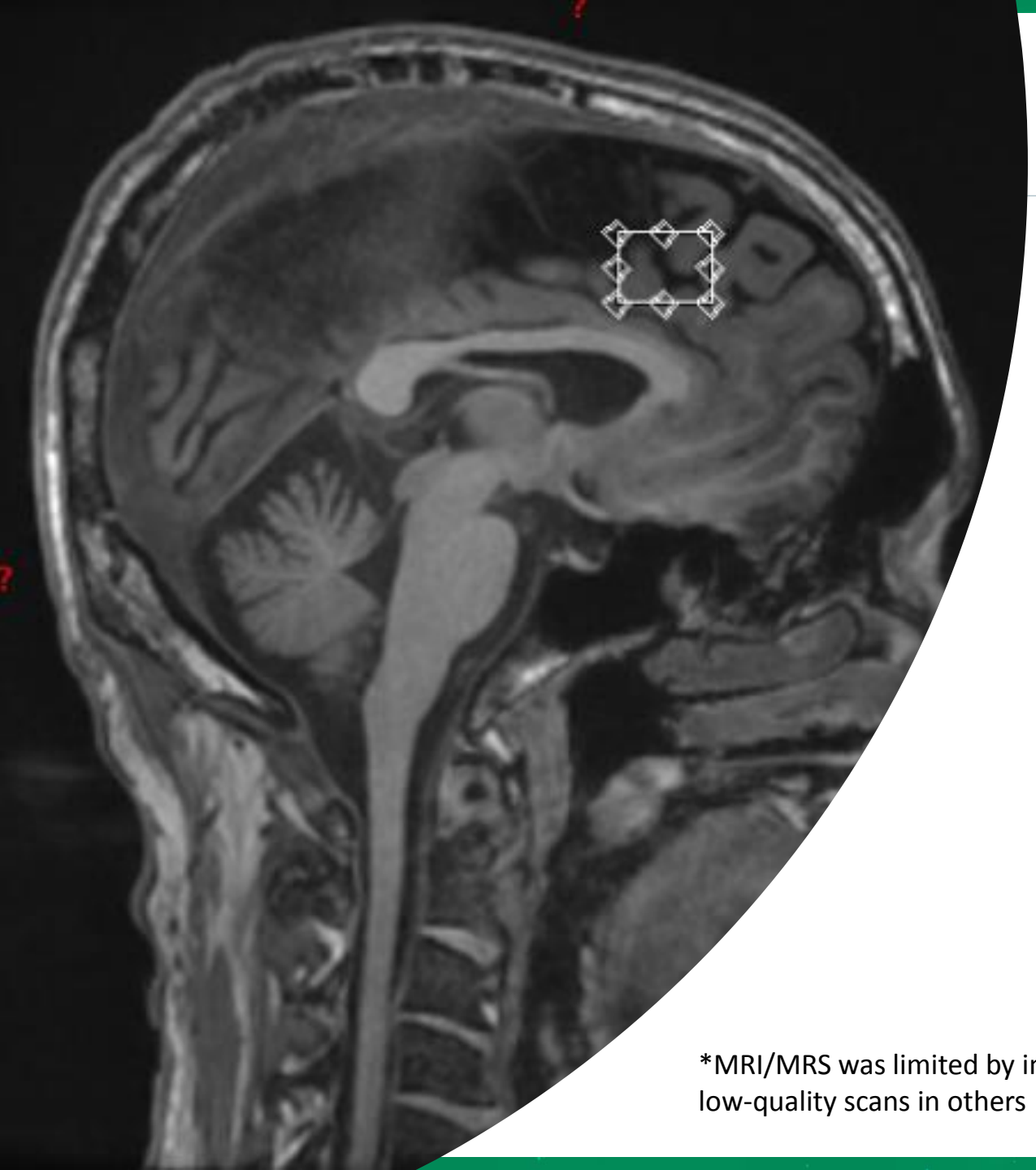

MRI/MRS Results

MRI

- AT-007 treated patients demonstrated a trend towards decreased ventricular volume, a measure of edema (brain swelling)

MRS

- AT-007 treated patients (4 out 6)* demonstrated decreased galactitol levels in the brain
- AT-007 treated patients (4 out of 6) demonstrated an improvement in N-acetyl-aspartate (NAA, a marker of neuronal health)

*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
- Due to the low frequency of seizures in the majority of patients, no significant changes in seizure frequency during the ACTION-Galactosemia core study (1 month treatment) could be assessed

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 and Support EU Approval

- 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
- Secondary objective to include European patients to support EU approval
- UK site (University College London)
  - One cohort of patients (~6) planned at UK site, but large pool of patients exists (~70 at single site)

- Czech Republic alternative site for GALK deficient patients (given incidence in Romani/ Irish Traveler population)

Proposed AT-007 Pediatric Study (Under Discussion with FDA)

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)

Study Objectives

- Safety
- Dose determination (via PK/PD)
- Efficacy biomarker effects (plasma galactitol)
- Exploratory: MRI/MRS effects
  - Galactitol quantitation
  - Brain morphometry & cerebral edema
  - 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
- PK/PD data 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)
- Positive AT-007 MRI/MRS impact

Thank you

APPLIED THERAPEUTICS