Disclosure Slide

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Post-Natal Galactitol Reduction is Associated with Normalization of CNS Phenotype in Animal Model of Galactosemia

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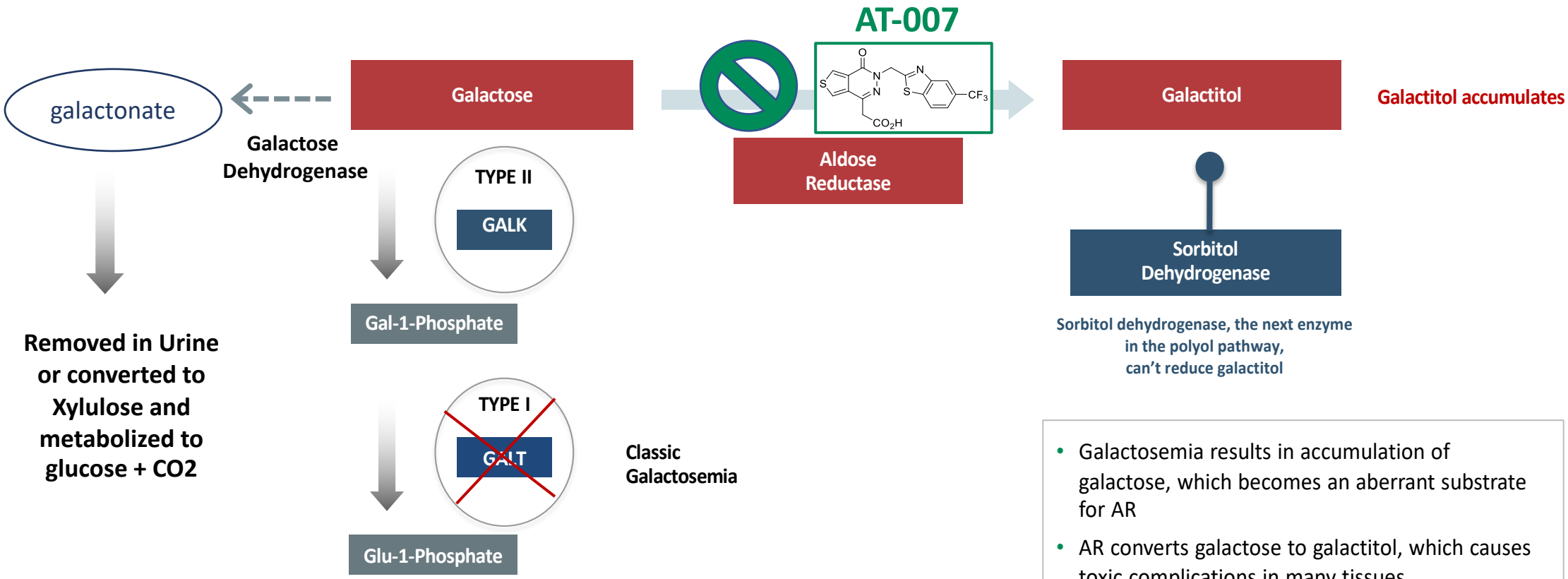
Background

- Galactosemia is an inherited rare metabolic disease, estimated to impact ~3,000 individuals in the US
- Life threatening if not identified and managed immediately at birth
- Long-term consequences of disease include: significant motor, speech, cognitive, and psychiatric impairments, tremor, seizers, frequent pre-senile cataracts, and ovarian insufficiency
- Even with strict dietary restriction of galactose-containing food, endogenous galactose production by the body leads to toxic build-up of galactitol and consequent tissue damage and long-term complications
- No pharmacologic treatments for Galactosemia are currently approved. Standard of care is strict dietary restriction of galactose, which does not prevent long term consequences of disease.

AT-007, a Novel CNS Penetrant Aldose Reductase Inhibitor, Blocks the Production of Galactitol, a Toxic Metabolite of Galactose

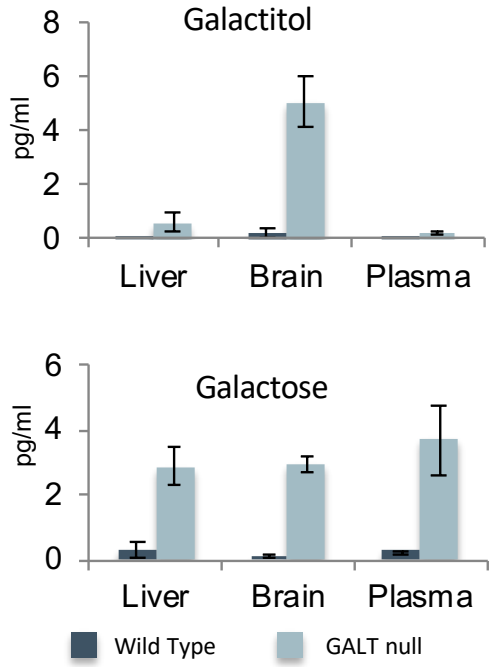


- Galactosemia results in accumulation of galactose, which becomes an aberrant substrate for AR
- AR converts galactose to galactitol, which causes toxic complications in many tissues

Galt-Null Rats Closely Reproduce the Clinical and Biochemical Characteristics of Galactosemia in Humans

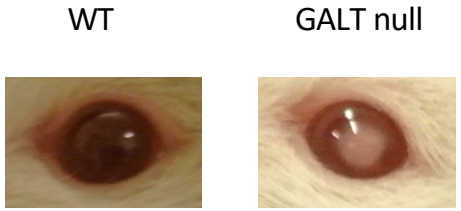
Biochemical Effects

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



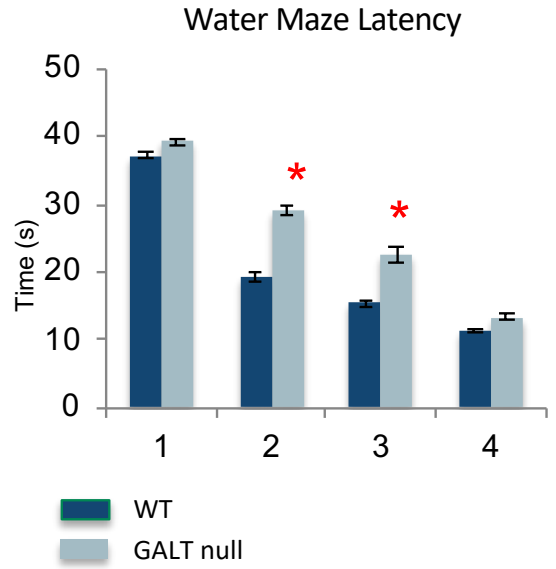
Tissue Deposition of Galactitol

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

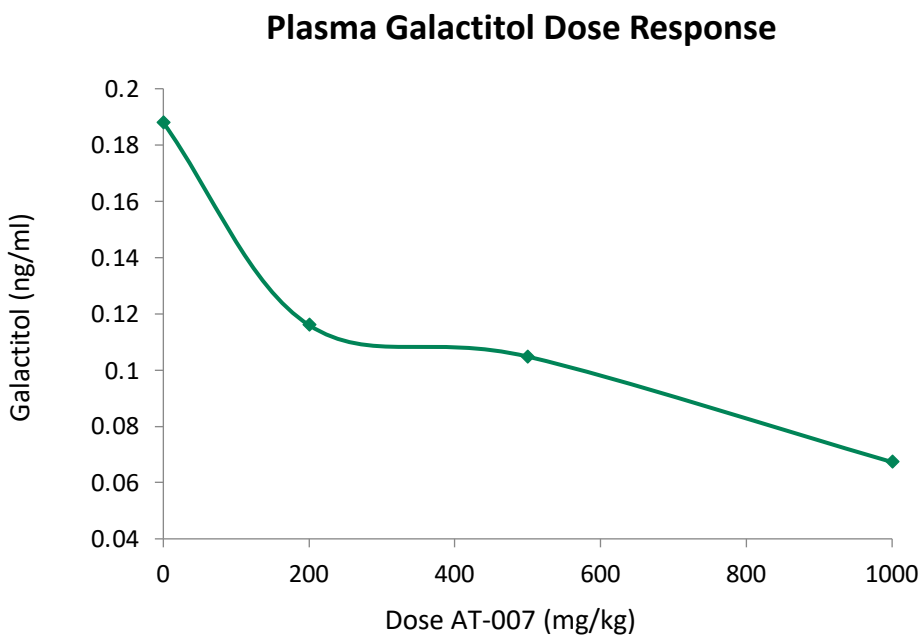


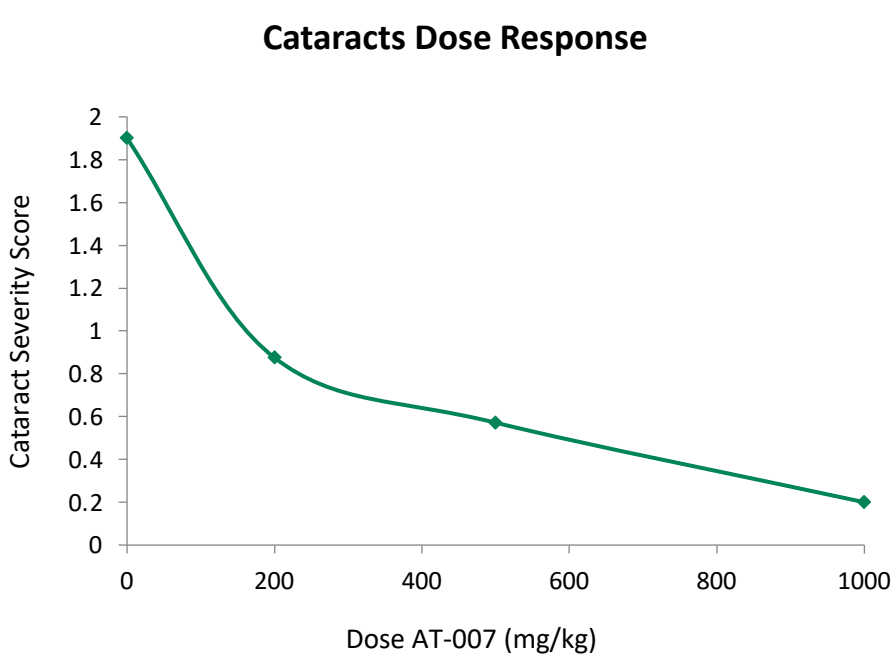
CNS Outcomes

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



Dose-Dependent Reduction in Plasma Galactitol Correlates with Improvement Clinical Outcomes



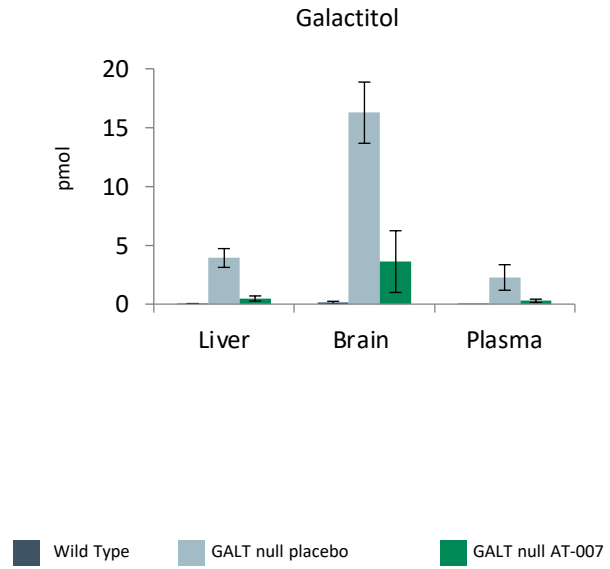


No cataracts in WT or AT-007 treated GALT null rats, but visible cataracts in all GALT null placebo rats at Neonatal Day 22

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

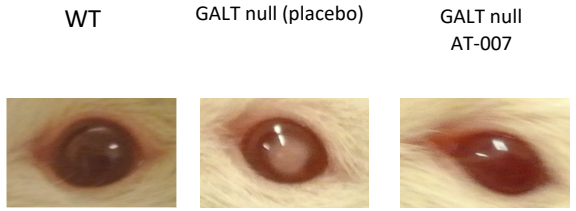
Biochemical Effects

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



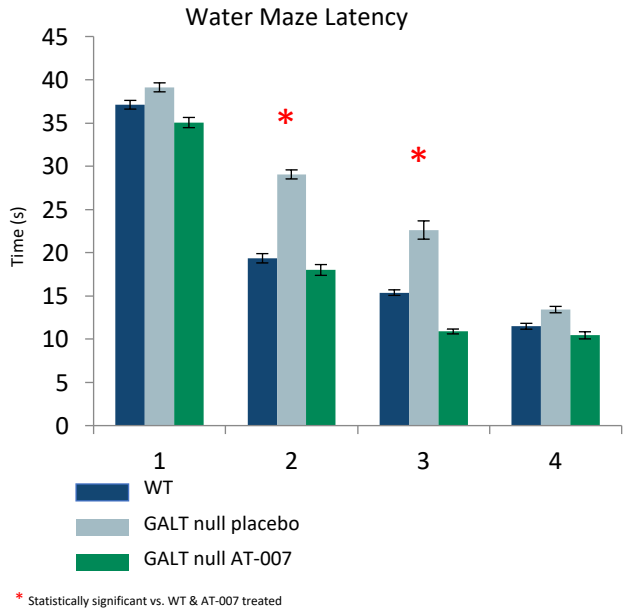
Tissue Deposition of Galactitol

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



CNS Outcomes

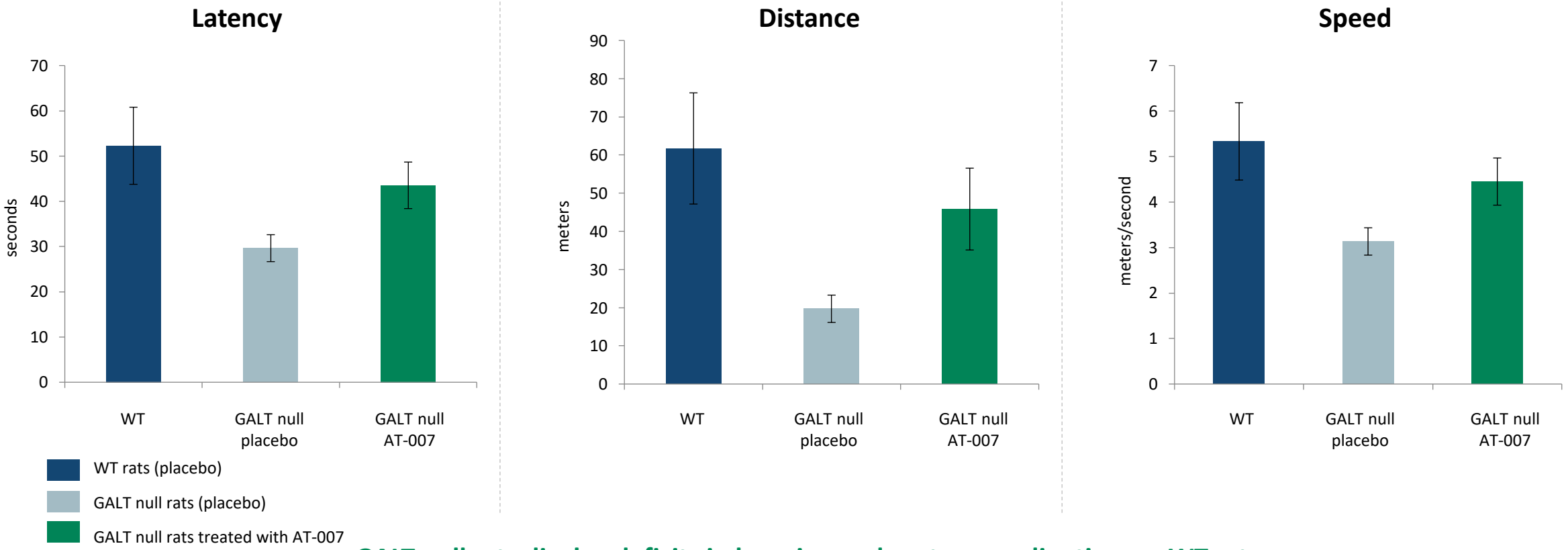
AT-007 treatment normalized CNS outcomes on both water maze and rotarod



* 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

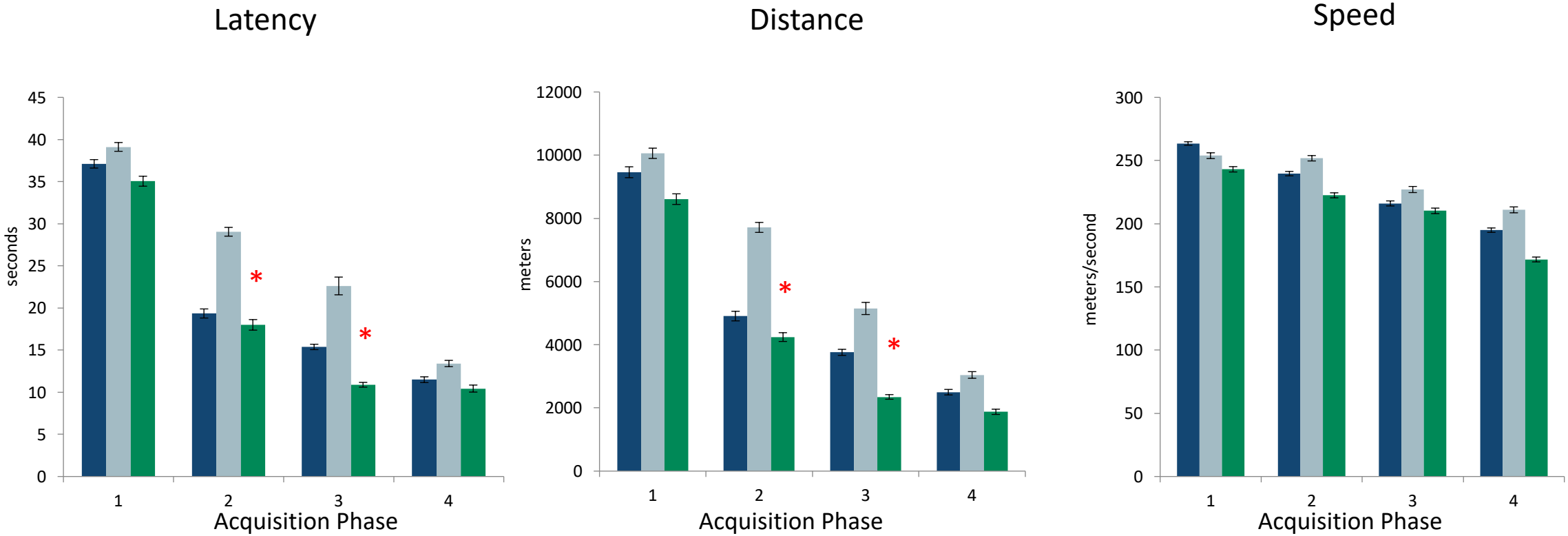
Neurological Phenotype: AT-007 Treatment Prevents CNS Deficits in Galactosemia Rat Model (Rotarod)



GALT null rats display deficits in learning and motor coordination vs. WT rats

Treatment with AT-007 prevented these deficiencies and normalized cognitive and motor function

Neurological Phenotype: AT-007 Treatment Prevents Learning Deficits in Galactosemia Rat Model (Water Maze)



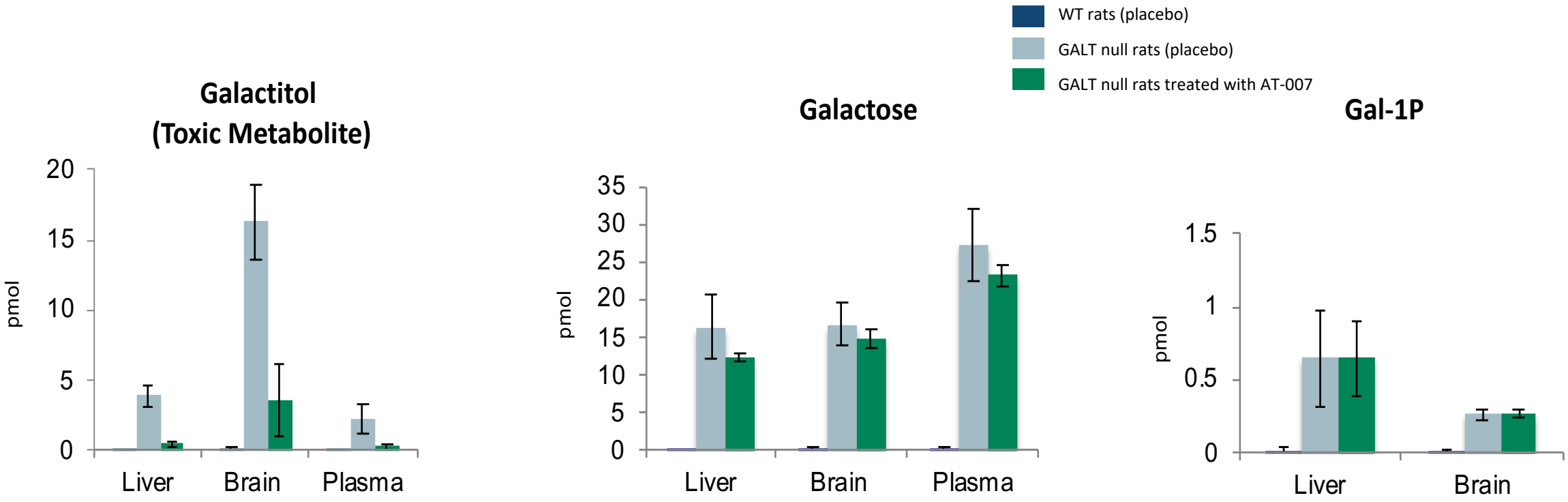
WT rats (placebo)

GALT null rats (placebo)

GALT null rats treated with AT-007

Water maze was performed via submerged platform to eliminate any potential impact of cataracts/mild vision impairment on performance

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

Conclusion

- Phenotypical manifestation of Galactosemia in GALT-null rats closely reproduces the clinical and biochemical characteristics of Galactosemia in humans
- In an animal model of Galactosemia, AT-007 prevented biochemical manifestations of disease and prevented production of toxic galactitol in blood and tissues, without adversely impacting galactose or Gal-1p
- Post-natal treatment of GALT-null rats with AT-007 prevents the development of the Galactosemia phenotype including cataracts and motor CNS manifestations of disease
- These findings suggest that post-natal treatment with AT-007 is effective and may represent an effective disease modifying therapy in patients with Galactosemia