Galactitol – but not Gal-1p – Level is a Predictor of Disease Severity in Children with Classic Galactosemia on Galactose Restricted Diet

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APPLIED THERAPEUTICS

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Background

- Classic Galactosemia (CG) is a rare inborn metabolic disease caused by an autosomal recessive mutation that severely depletes galactose-1-phosphate uridyltransferase (GALT), leading to the accumulation of galactose and its metabolites: galactitol and galactose-1-phosphate (Gal-1p).[1,2]
- Newborn screening is mandatory in the US and most EU countries.[1,3]
- Despite early dietary intervention, children continue to develop significant impairments in speech, cognition, behavior, and motor function, which progressively worsen with age; other impairments include cataracts and primary ovarian insufficiency.[4]
- The ongoing ACTION-Galactosemia Kids study (NCT04902781) is evaluating the efficacy of AT-007, an oral CNS penetrant Aldose Reductase Inhibitor (ARI), on both biomarker and functional outcomes in children with CG.

Objective

This analysis of the ACTION-Galactosemia kids study evaluated the relationship between galactitol and Gal-1p levels and severity of clinical phenotype in children with CG adhering to a galactose-restricted diet from the perinatal period of life.

Methods

- The study population included 47 children aged 2–16 years.
- Diagnosis was confirmed by genetic testing and evaluation of GALT enzyme activity (< 1%).
- Fasting plasma galactitol and whole blood Gal-1p were measured by liquid chromatography-mass spectrometry.
- Verbal communication, cognition, motor skills and behavior were assessed by the following methods:
  - Language skills were evaluated using the Oral and Written Language Scale (OWLS-II).
  - Cognition was evaluated using the National Institute of Health (NIH) Toolbox Cognition Battery.
  - Motor skills (dexterity) were evaluated using the NIH Toolbox Motor Battery.
  - Adaptive behavior was evaluated using the Vineland-3 Adaptive Behavior Scales.
- For each of the assessed tests/domains, a categorical severity score from 1-6 was derived for each patient (higher scores correlate with significant deficit). The composite severity score was then calculated for each patient, by deriving the average of all the categorical severity scores (average of all non-missing severity score values).

Results

SUMMARY OF BASELINE CHARACTERISTICS

Baseline characteristic	Total (N=47)
Age, median (range) years	**9.1 (2–16)**
Gender, n (%)	
Female	**24 (51)**
Male	**23 (49)**
Race, n (%)	
White	**46 (98)**
Hispanic	**1 (2)**
Genetics*, n (%)	
Q188R Compound Heterozygous	**22 (47)**
Q188R Homozygous	**15 (32)**
K285N Homozygous	**1 (2)**
Other Compound Heterozygous	**8 (17)**
Biochemistry, mean**	
Galactitol, ng/mL (n=46)	**1794.3**
Gal-1p, ng/mL (n=37)	**15318.0**

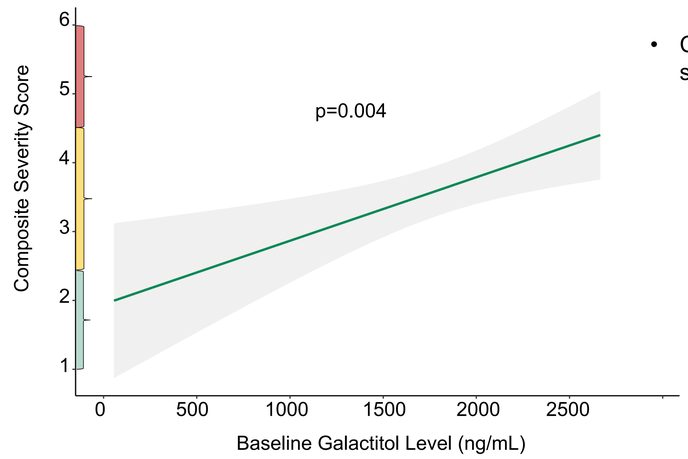
* One subject pending genetics with 0.0 GALT enzyme activity
**Note: Gal-1p measurements are obtained from whole blood, 37 subjects had whole blood samples; Galactitol is measured by plasma, 46 subjects had baseline plasma samples

CORRELATION OF BASELINE PLASMA GALACTITOL LEVEL WITH CNS FUNCTION

Assessment	Galactitol			Gal-1p		
	n	Adjusted R-squared	p-value	n	Adjusted R-squared	p-value
OWLS-II (Expressive Language)	44	0.117	0.013	35	0.045	0.116
NIH-Cognitive Composite (Cognitive Function)	44	0.131	0.009	35	0.035	0.143
Vineland-3 (Adaptive Behavior)	46	0.114	0.013	37	-0.007	0.393
NIH 9-Hole Pegboard (Manual Dexterity)	44	0.051	0.075	35	-0.002	0.338
Composite Severity Score	46	0.152	0.004	37	0.056	0.086

Results continued

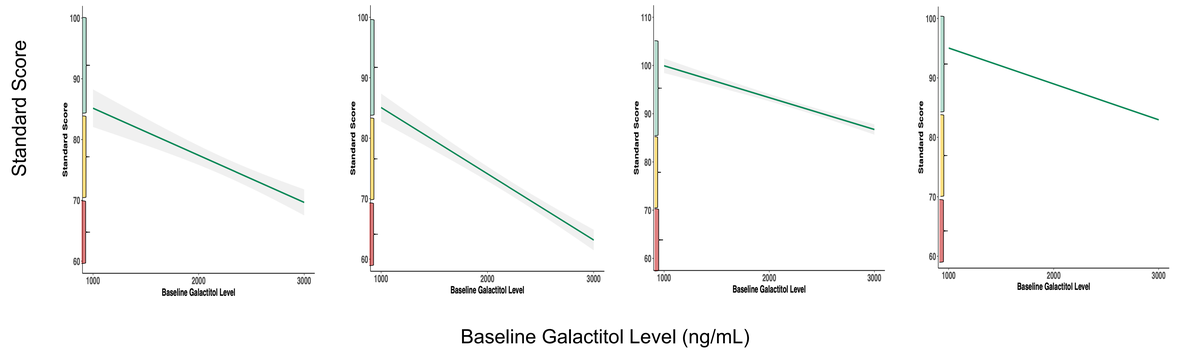
CORRELATION OF BASELINE PLASMA GALACTITOL WITH DISEASE SEVERITY



- Composite score comprised of 4 CNS quadrants: speech, cognition, behavior, motor skills
  - Correlation of galactitol with total disease severity was highly statistically significant (n=46; Adjusted R-squared=0.152; p=0.004)

Significant deficit
Below average
Average range

Quadrants of CNS function



EFFECT OF AT-007 ON GALACTITOL LEVELS

Weight group	AT-007 dose	Galactitol reduction from baseline (%)	Overall galactitol reduction from baseline (%)	p-value
>40 kg	15 mg/kg	38.29		
20–40 kg	20 mg/kg	41.43	40.19	<0.001
<20kg	30 mg/kg	39.83		

- Exposure to AT-007 in pediatric patients with Galactosemia reduced plasma galactitol levels, did not result in any compensatory increase in galactose or Gal-1p.

Summary and conclusions

- Despite maintenance of a life-long galactose restricted diet, this evaluation of the CNS phenotype in a cohort of 47 children with Galactosemia demonstrated deficits in speech, cognition, adaptive behavior. and motor skills.
- Galactitol is the only biomarker demonstrating correlation with disease severity in pediatric patients with CG.
- Linear models demonstrated that higher galactitol levels, but not higher Gal-1p levels, were associated with greater disease severity overall and on each of the four quadrants of CNS function.
- In pediatric patients with Galactosemia, AT-007 reduced the accumulation of galactitol, the toxic metabolite of galactose.

References

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