Baseline Disease Characteristics of 47 Pediatric Classic Galactosemia Patients in the ACTION-Galactosemia Kids AT-007 Interventional Study Demonstrate the Multi-System Burden of Disease

Poster 0068

This research was funded by:

APPLIED THERAPEUTICS

R. Perfetti,[1] **A. Ahmad**[2], **H.C Phan**[3], **J. Thomas**[4], **F. Lawson**[1], **E. Bailey**[1], **L. Saltonstall**[1], **S. Shendelman**[1]

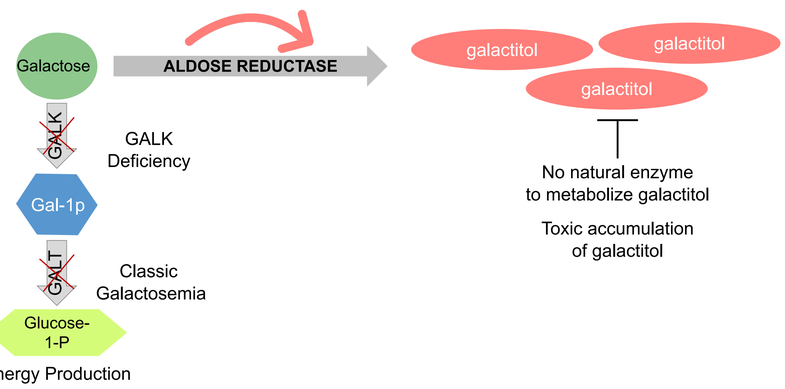
[1]Applied Therapeutics, New York, NY, USA; [2]Division of Pediatric Genetics, Metabolism and Genomic Medicine, University of Michigan, I, USA; [3]Rare Disease Research LLC, Atlanta, GA, USA; [4]University of Colorado School of Medicine and the Children's Hospital Colorado, CO, USA

Background

- Classic Galactosemia is an autosomal recessive progressive metabolic disease caused by a genetic inability to metabolize the sugar galactose[1]
- The enzyme Aldose Reductase (AR) converts galactose into galactitol, an aberrant toxic metabolite that accumulates in tissues and organs and causes long-term disease complications[2]
- Classic Galactosemia affects ~3,000 patients in the US & ~3,500 in the EU (200 new births per year).[3] Newborn screening is mandatory in the US and most EU countries[1,4]
- Classic Galactosemia results in acute life-threatening complications in newborns prior to initiation of the Galactosemia diet (including liver failure, jaundice, kidney failure, sepsis, cerebral edema, pseudotumor cerebri, and death).
- Chronic long-term complications including CNS complications (speech, cognition, behavior, and motor skills deficits), ovarian insufficiency, and cataracts persist despite dietary restriction [5]

CLASSIC GALACTOSEMIA: MECHANISM OF DISEASE

- Deficiency in GALT or GALK leads to an inability to metabolize galactose.
- Aldose Reductase converts excess galactose to toxic galactitol



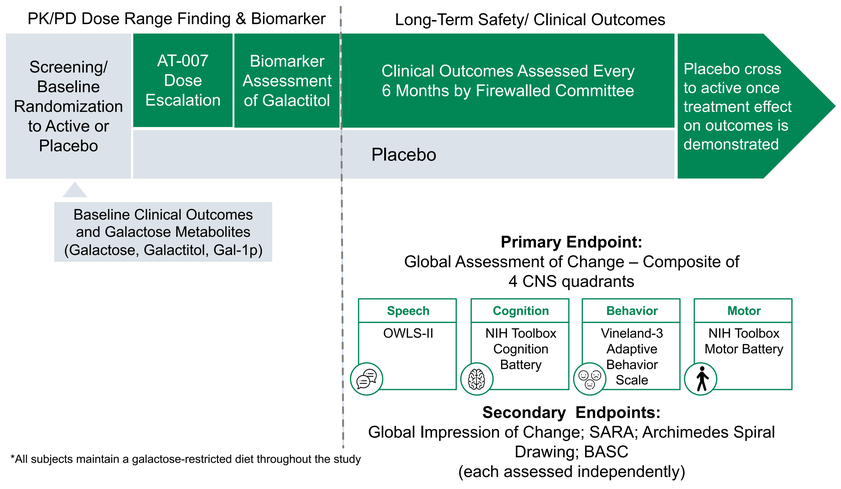
Objectives

This analysis in the ACTION-Galactosemia Kids study aimed to explore baseline disease characteristics of pediatric Classic Galactosemia patients.

Methods

- ACTION-Galactosemia Kids is a sequential, two-part, randomized double-blind, placebo-controlled study evaluating the clinical benefit, safety, pharmacokinetics and pharmacodynamics of AT-007 in pediatric patients with Classic Galactosemia

STUDY DESIGN



*All subjects maintain a galactose-restricted diet throughout the study

Results

- Forty-seven patients ranging in age from 2 to 16 years were enrolled at 3 US clinical sites across three predefined age groups (2–6 years old; 7–12 years old; 13–17 years old)

BASELINE DEMOGRAPHIC AND GENETIC CHARACTERISTICS

Demographic Characteristics	Patients (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	
Baseline Galactitol, Mean (ng/mL) (SD)	1794.3
Baseline GALT Enzyme Activity (nmol/h/mg) median (range)	0.0 (0.0-0.1)

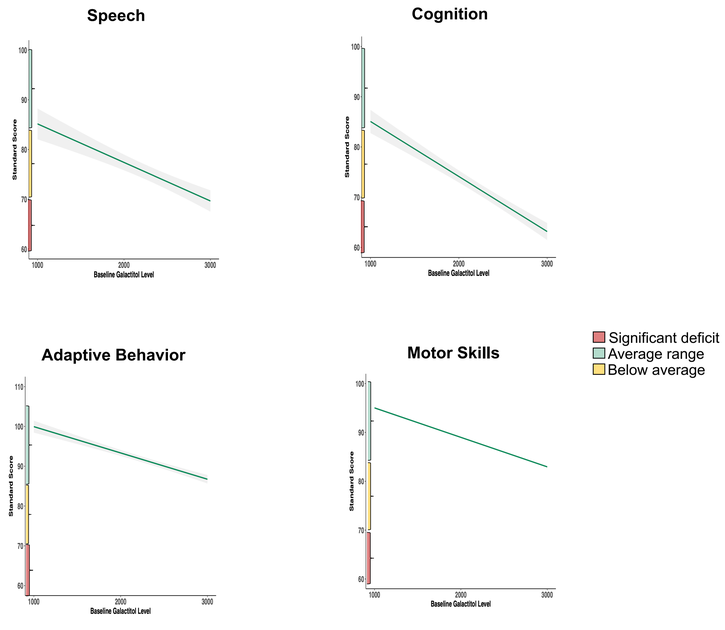
* One subject pending genetics with 0.0 GALT enzyme activity **p.Gln188Arg (Q188R) Compound Heterozygous ***p.Lys285Asn (K285N) Homozygous

Baseline Disease Characteristics	Ages 2–6 yrs (n=16)	Ages 7–12 yrs (n=18)	Ages 13–17 yrs (n=13)	Overall (n=47)
CNS				
Tremor, n (%)	3 (19)	4 (22)	3 (23)	10 (21)
Ataxia, n (%)	2 (13)	5 (28)	2 (15)	9 (19)
Seizures, n (%)	1 (6)	2 (11)	1 (8)	4 (9)
Dysarthria, n (%)	2 (13)	0 (0)	2 (15)	4 (9)
Dysphasia, n (%)	1 (6)	0 (0)	0 (0)	1 (2)
Apraxia, n (%)	5 (31)	9 (50)	5 (39)	19 (40)
ADD/ADHD, n (%)	0 (0)	3 (17)	5 (39)	8 (17)
Anxiety, n (%)	3 (19)	6 (33)	7 (54)	16 (34)
Depression, n (%)	0 (0)	0 (0)	2 (15)	2 (4)
Learning disorder, n (%)	5 (31)	12 (67)	8 (62)	25 (53)
Endocrine				
Delayed sexual maturation, n (%)	0 (0)	1 (6)	6 (46)	7 (15)
Primary ovarian insufficiency, n (%)	0 (0)	0 (0)	8 (100)	8 (17)
Vitamin deficiency, n (%)	3 (19)	6 (33)	6 (46)	15 (32)
Reduced bone density, n (%)	0 (0)	2 (11)	4 (31)	6 (13)
Bone fractures, n (%)	2 (13)	4 (22)	3 (23)	9 (19)

- The Action Galactosemia Kids patient population was reflective of pediatric Classic Galactosemia described in the published literature, including 100% of girls age 13–17 having primary ovarian insufficiency

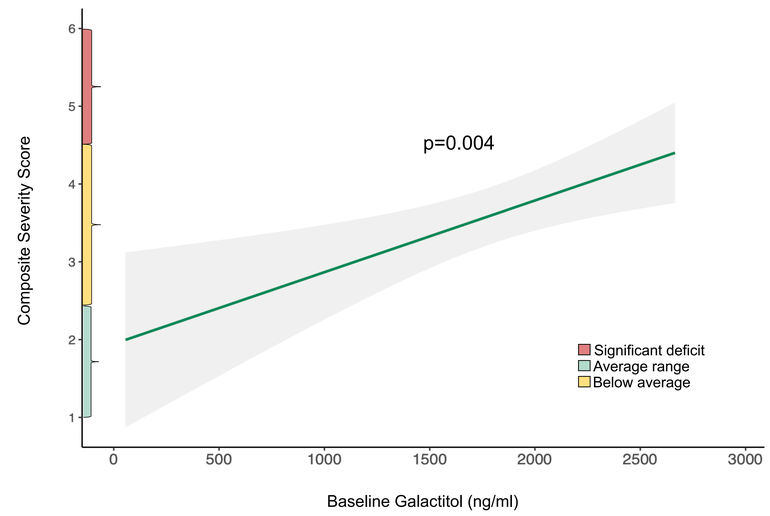
BASELINE PLASMA GALACTITOL LEVEL

- In children with Classic Galactosemia, plasma galactitol level correlates with severity of speech, cognitive, behavior and motor skills deficiencies[6]



Results (continued)

- Composite score comprised of 4 CNS quadrants: speech, cognition, behavior, and motor skills[6]



- Correlation of galactitol with disease severity was highly statistically significant (p=0.004)
- As expected, Gal-1p was elevated in all patients but did not correlate with disease severity (p=0.086)

EFFECT OF AT-007 ON PLASMA 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		

- AT-007 was administered as a once-daily oral suspension
- Treatment with AT-007 was safe and well tolerated
- There was no compensatory increase in galactose or Gal-1p

Summary and conclusions

- Classic Galactosemia is a progressive disease that results in long-term complications, including CNS complications, cataracts, and ovarian insufficiency
- The toxic metabolite galactitol is a major determinant of the long-term complications of disease and correlates with disease severity in pediatric patients with Classic Galactosemia
- Treatment with AT-007 was shown to safely and effectively reduce toxic galactitol in this patient population
- The ongoing Phase 3 ACTION-Kids study is assessing the impact of AT-007 on clinical outcomes in pediatric patients with Classic Galactosemia

References

1. Waisbren SE et al. Journal of inherited metabolic disease. 2012;35(2):279-286.
2. Demirbas D et al. Metabolism Clinical and Experimental. 2018;83:188-196.
3. Data on file: Decision Resources Group, Report Epidemiology of Galactosemia; 2020 June
4. Pyhtila BM et al. JIMD reports. 2015;15:79-93.
5. Rubio-Gozalbo ME et al. Orphanet Journal of Rare Diseases. 2019;14(1):1-11.
6. Perfetti R et al. Poster presented at: International Congress Inborn Errors of Metabolism Annual Meeting; 2021; Sydney, Australia.

Acknowledgements

Thank you to all the patients who participated in the trial, and their families, the trial investigators and staff, as well our colleagues at Applied Therapeutics who have enabled this research to take place.