APPLIED THERAPEUTICS

Development of Govorestat (AT-007), the First Potential Treatment for Patients with Classic Galactosemia

Chair: Dr. Barbara Burton, Chicago, IL

4 September 2024

AT-007 (GOVORESTAT) is an investigational drug; it has not been approved for any use by FDA or any other regulatory body

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Riccardo Perfetti, M.D., Ph.D. has served as Chief Medical Officer of Applied Therapeutics since August 2018. Before joining us, Dr. Perfetti served as a Senior Medical Officer, Vice President and Head of Global Medical Affairs, Diabetes and Cardiovascular Business Unit at Sanofi S.A., a publicly traded pharmaceutical company, from October 2007 to August 2018. Prior to joining Sanofi, Dr. Perfetti served in various roles at Amgen Inc., a publicly traded biopharmaceutical company, including as a Director and Global Development Leader in diabetes, obesity, metabolism and endocrinology from December 2004 to August 2007. Dr. Perfetti was previously an associate professor of medicine at University of California in Los Angeles and a professor of medicine at the National Institutes of Health (NIH). Dr. Perfetti practiced as an endocrinologist at Cedars-Sinai Medical Center and also served as Director of the Diabetes Research Laboratory and Director of the Outpatient Diabetes Program. Dr. Perfetti received his M.D. and Ph.D. in Endocrinology from University La Sapienza in Rome, Italy and received post-graduate training in endocrinology and molecular biology at NIH.

Evan Bailey, MD
Vice President Clinical Development, Applied Therapeutics

Evan Bailey, M.D. is the medical lead for Galactosemia at Applied Therapeutics. Prior to joining Applied, Evan served as the Global Medical Lead for the Cystic Fibrosis pipeline at Vertex Pharmaceuticals. He served as the North American Medical Lead for TRIKAFTA® launch. Prior to Vertex, Evan was the Director of the Cystic Fibrosis Center at the University of Massachusetts Medical Center where he led the clinical and research efforts of the multi-disciplinary team.

Evan is a Board-Certified pediatrician and completed his training at Boston Children's Hospital after earning his M.D. at the Stritch School of Medicine of Loyola University Chicago.

Agenda

Introduction	**Barbara Burton, MD** Professor of Pediatrics (Genetics, Genomics, and Metabolism) Northwestern University Feinberg School of Medicine
Galactosemia Mechanism of Disease Pathogenesis	**Riccardo Perfetti, MD, PhD** Chief Medical Officer Applied Therapeutics
Designing the First Pediatric Clinical Outcomes Study in Classic Galactosemia	**Evan Bailey, MD** Vice President Clinical Development Applied Therapeutics
Data in Adults with Classic Galactosemia	**Evan Bailey, MD** Vice President Applied Therapeutics
Classic Galactosemia: A Progressive Disease	**Barbara Burton, MD** Professor of Pediatrics (Genetics, Genomics, and Metabolism) Northwestern University Feinberg School of Medicine
Q&A	

Evan Bailey, MD and Riccardo Perfetti, MD, PhD are employees of Applied Therapeutics

Introduction

Overview of Classic Galactosemia[1,2]

- Classic Galactosemia is a rare, autosomal recessive metabolic disease caused by severe deficiency in the GALT enzyme resulting in the inability to metabolize the sugar galactose
- Galactose is present in foods, and is also synthesized endogenously by the body
- Classic Galactosemia has a prevalence of ~3,300 patients in the US and ~4,000 in Europe
- Greatly impairs patients
  - Behavior
  - Cognition
  - Adaptive skills
  - Motor skills
  - Ability to perform activities of daily living

Classic Galactosemia, GALT, Galactose-1 Uridyltransferase;; US, United States of America.

1. Rubio-Gozalbo, M E et al. *Orphanet journal of rare diseases*. 2019;14,1 86. doi:10.1186/s13023-019-1047-z. 2. Pyhtila, B M et al. JIMD reports. 2015; 15:79-93. doi:10.1007/8904_2014_302..

Newborn Screening Exists for Galactosemia in the US and Many EU Countries[1-3]

Newborn screening for Galactosemia universal in US since 2005

Prior to screening most infants with Classic Galactosemia died shortly after birth

Current population with Classic Galactosemia primarily children and young adults < 30 years

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EU, European Union; US, United States

1. Berry GT GeneReviews®. 2021. Classic Galactosemia and clinical variant Galactosemia. 2. Demirbas D, et al. *Metabolism*. 2018;83:188–96; 3. Pyhtila, B M et al. JIMD reports. 2015; 15:79-93.

Classic Galactosemia Standard of Care

Universal newborn screening is conducted in the US and most EU countries

Patients identified via newborn screening are immediately placed on a galactose-restricted diet (soy or elemental formula) and must adhere to a galactose-restricted diet for life

To date there are no drugs approved to treat Classic Galactosemia

Pyhtiila. *JIMD reports* vol. 15 (2015): 79-93. doi:10.1007/8904_2014_302.

Galactosemia Need for Pharmacological Treatment

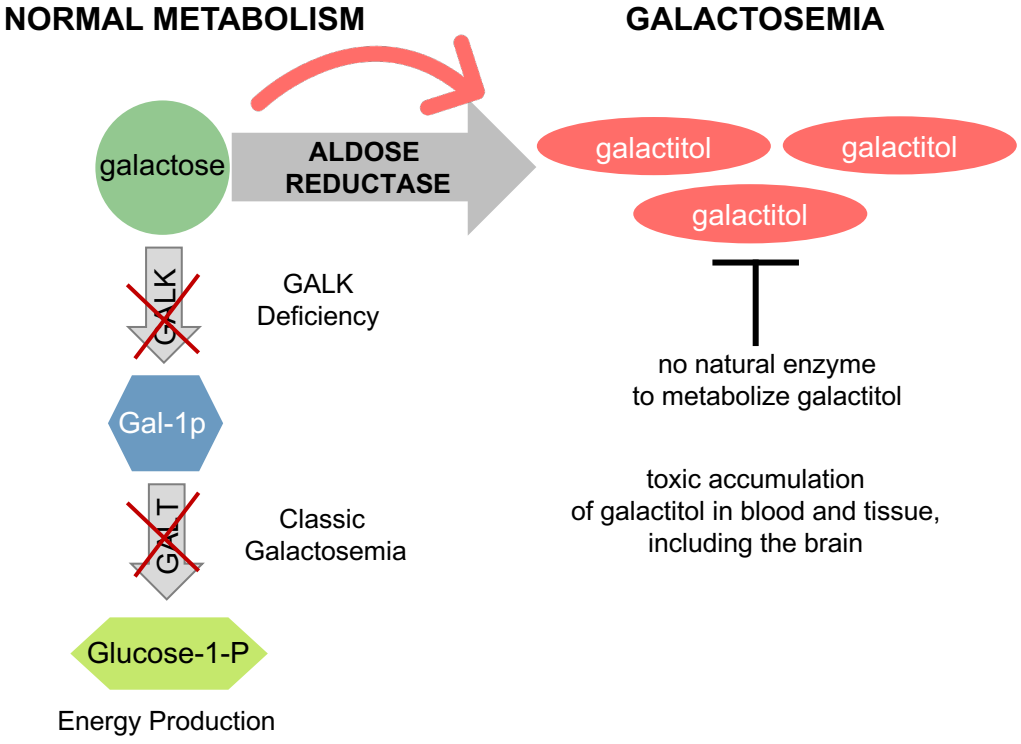
- Endogenous production of galactose will continue for the entire life of affected patients, even if the exogenous intake of galactose is restricted
- While newborn screening and dietary restriction prevent most fatalities caused by acute external galactose intake, they do not prevent long-term complications from developing
- Long-term neurological complications greatly impact patients' quality of life:
  - Ability to live independently
  - Ability to hold gainful employment
  - Ability to form social and emotional relationships with others

Randall JA, et al. *Orphanet J Rare Dis. 2022; 17:138.*

Classic Galactosemia Mechanism of Disease

Galactosemia is Caused by Deficiencies in the GALT or GALK Enzymes, Resulting in Inability to Metabolize the Sugar Galactose

Galactose Becomes a Substrate for the Enzyme Aldose Reductase



AR, Aldose Reductase; GALK, Galactokinase deficiency; GALT,galactose-1-phosphate uridylyltransferase; Glucose-1-P, Glucose 1-Phosphate

Berry GT. Classic Galactosemia and Clinical Variant Galactosemia. 2000 Feb 4 [Updated 2021 Mar 11]. GeneReviews® [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1518.

Types of Galactosemia and High Unmet Need for Pharmacological Treatment

Classic Galactosemia	• <1% GALT enzyme activity • Galactose and metabolites accumulate even while on a restricted diet • Develop long-term complications
Biochemical Variant	• 1-10% GALT enzyme activity; residual enzyme activity can metabolize endogenously produced galactose • Do not manifest long-term complications if diet is maintained
Duarte Galactosemia	• 10-30% GALT enzyme activity • Do not require dietary restriction • No complications – not a “disease”
GALK Deficiency	• Point mutation eliminating GALK enzyme activity • Galactose and galactitol accumulate even when on a restricted diet • Develop long-term complications similar to Classic Galactosemia

- For patients with **Classic Galactosemia** and **GALK Deficiency**, dietary restriction is not sufficient to prevent disease progression
- Long-term complications develop despite dietary restriction
  - CNS Complications:
    - Cognition/Learning/IQ/Memory
    - Behavior/Psychiatric
    - Motor Skills (fine and gross)
    - Tremor
    - Seizures
    - Speech Deficiencies
  - Other Complications:
    - Ovarian Insufficiency
    - Cataracts
- Unmet need for a treatment

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CNS, Central Nervous System; IQ, Intelligence Quotient; GALK, Galactokinase; GALT, Galactose-1 Uridyltransferase.

Berry GT. Classic Galactosemia and Clinical Variant Galactosemia. 2000 Feb 4 [Updated 2021 Mar 11]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1518/(accessed June 27,2024).

Classic Galactosemia Results in Acute Life-Threatening Complications in the Newborn Phase Followed by Chronic Long-Term Complications[1-3]

Acute Newborn Complications

- Liver failure
- Jaundice
- Kidney Failure
- Sepsis
- Cerebral edema, Pseudotumor cerebri
- Death

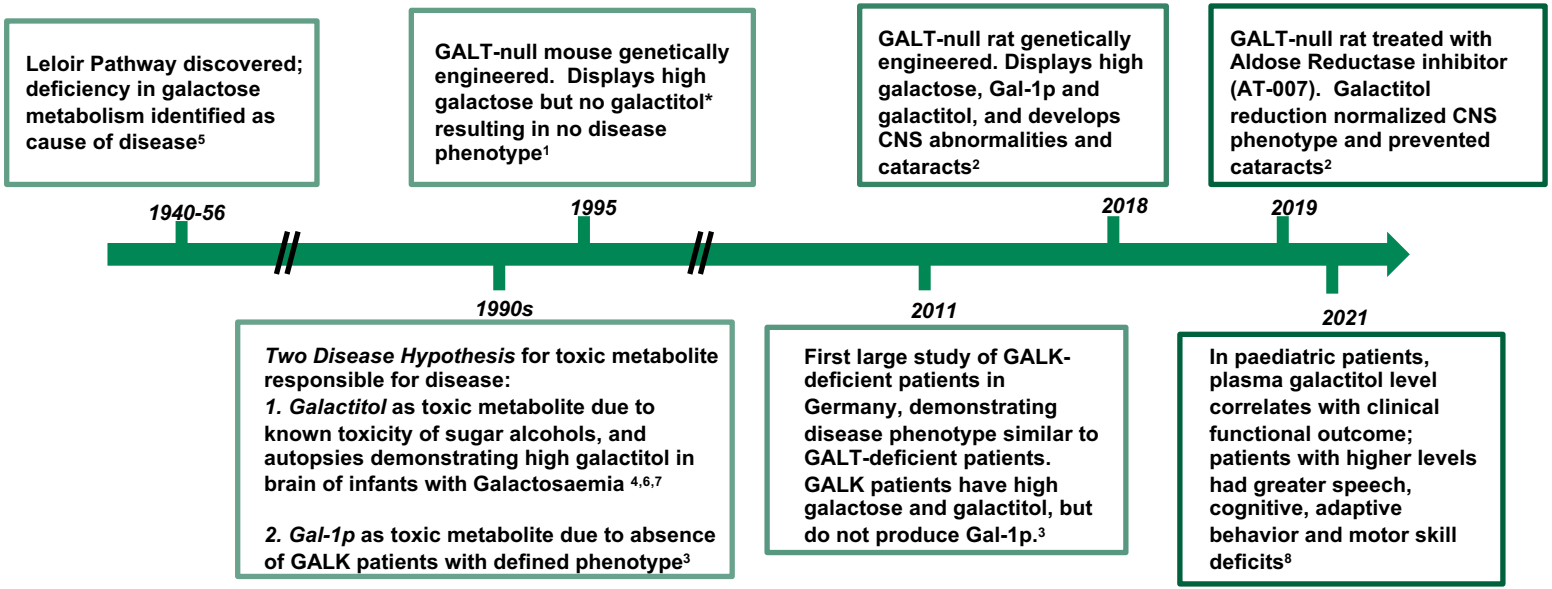
Chronic Long-Term Complications

- CNS Complications:
  - Cognition/Learning/IQ/ Memory
  - Behavior/Psychiatric
  - Motor Skills (Tremor, Ataxia)
  - Seizures
  - Speech Deficiencies
- Ovarian Insufficiency
- Cataracts

CNS, Central Nervous System; IQ, Intelligence Quotient.

1. Coelho AI, et al. *J Inherit Metab Dis.* 2017;40(3):325–42; 2. Demirbas D, et al. *Metabolism.* 2018;83:188–96; 3. Berry GT GeneReviews®. 2021. Classic Galactosemia and clinical variant Galactosemia.

Decades of Evolving Evidence Demonstrates Galactitol is the Toxic Metabolite in Galactosemia Responsible for Long-Term Complications



CNS, Central Nervous System;Gal1-p, galactose-1phosphate; GALK,galactokinase; GALT=,galactose-1-phosphate uridylyltransferase
*Mice do not express aldose reductase

1.Leslie ND. Insights into the pathogenesis of galactosemia. Annu Rev Nutr. 2003;23(1):59-80. 2. Rasmussen SA, Daenzer JMI, MacWilliams JA, et al. A galactose-1-phosphateuridylyltransferase-null rat model of classic galactosemia mimics relevant patient outcomes and reveals tissue-specific and longitudinal differences in galactose metabolism. J Inherit Metab Dis. 2020;43(3):518-528. 3. Hennermann JB, Schadewaldt P, Vetter B, Shin YS, Mönch E, Klein J. Features and outcome of galactokinase deficiency in children diagnosed by newborn screening. J Inherit Metab Dis. 2011;34(2):399-407. 4. Berry, G.T. (2008), *Galactosemia and Amenorrhea in the Adolescent.* Annals of the New York Academy of Sciences, 1135: 112-117. 5. Didem Demirbas, Xiaoping Huang, Vikram Daesety, et al. The ability of an LC-MS/MS-based erythrocyte GALT enzyme assay to predict the phenotype in subjects with GALT deficiency, Molecular Genetics and Metabolism, 2019;126(4):368-376. 6.M.C.G. Otaduy, C.C. Leite, M.T.C. Lacerda et al. Proton MR Spectroscopy and Imaging of a Galactosemic Patient before and after Dietary treatment. AJNR Am J Neuroradiol 2006;27:204-207. 7. Diego Martinelli, Bruno Baernardi, Anotnio Napolitano, et al. Teaching NeuroImages: Galactitol peak and fatal cerebral edema in classic galactosemia. American Academy of Neurology. 2016;96:e32-e33. 8. Pediatric Study AT-007-1002.

AT-007 (GOVORESTAT) is an investigational drug; it has not been approved for any use by FDA or any other regulatory body

Evidence Supporting Galactitol as the Metabolite Responsible for Long-Term Complications

Animal Data

- Galactitol is required for development of the CNS phenotype in animals
  - GALT-null mice (which do not express Aldose Reductase) produce high levels of galactose and gal-1p but **no galactitol, and do not demonstrate a disease phenotype.** [1]
  - In contrast GALT-null rats (which express human-like levels of Aldose Reductase) produce high levels of galactose, Gal-1p **and high galactitol, and develop a human-like CNS phenotype**, demonstrating cognitive and learning abnormalities.[2]
- In the GALT-null rat model, reduction in galactitol via govorestat treatment (which had no effect on galactose or Gal-1p) prevented the CNS phenotype of disease.

Human Data

- Humans with GALK deficiency develop high galactose and high galactitol levels but do not have any measurable Gal-1p levels demonstrate a similar CNS phenotype to Classic Galactosemia, supporting the role of the shared metabolite, galactitol, as causative of CNS symptoms in both Classic Galactosemia (GALT Deficiency) and GALK Deficiency[3]
- In a cross-sectional analysis of patients with Classic Galactosemia galactitol level correlated with severity of disease at baseline[4]

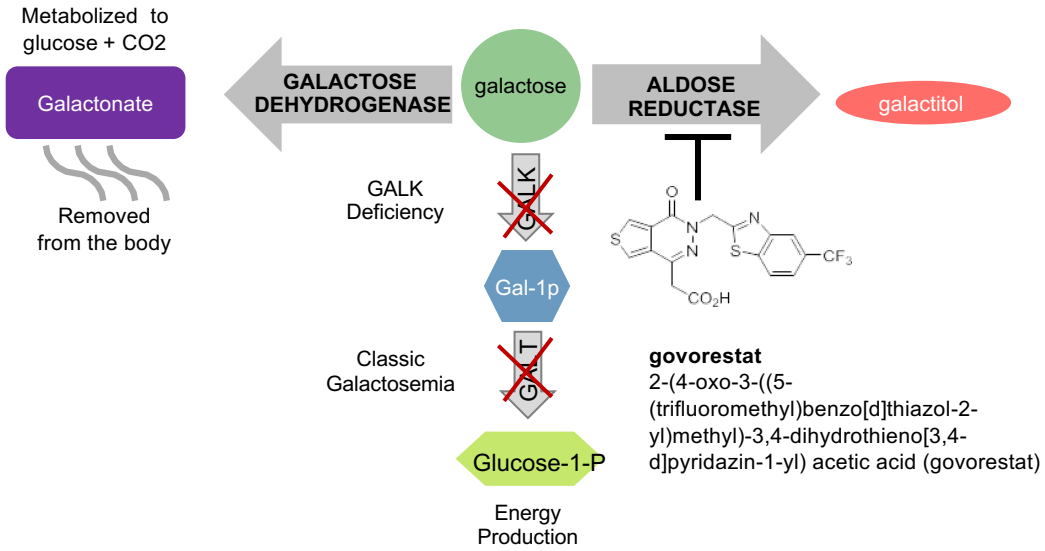
CNS, Central Nervous System, GALK, Galactokinase; Gal-1p, Galactose-1-phosphate; GALT, Galactose-1 Uridyltransferase.

1.Leslie ND. *Annu Rev Nutr.* 2003;23(1):59-80. 2. Rasmussen SA, et al. *J Inherit Metab Dis.* 2020;43(3):518-528. 3. Hennermann JB, et al. *J Inherit Metab Dis.* 2011;34(2):399-407. 4. Abstract eP011: Progressive Worsening of Central Nervous System Phenotype in Children with Classic Galactosemia: a Cross-Sectional Analysis; ACMG 2021 conference; Perfetti R et al.

Development of Govorestat, an Aldose Reductase Inhibitor to Block Galactitol Production

Govorestat (AT-007) is a Selective, CNS Penetrant Aldose Reductase Inhibitor

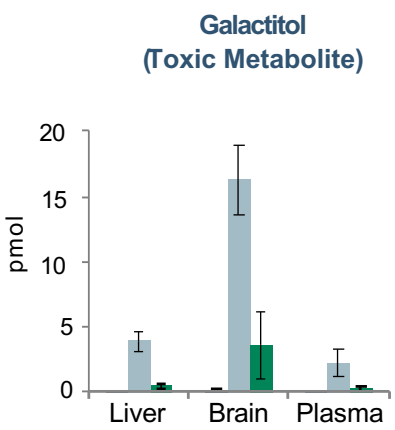
Blocks Production of the Toxic Metabolite Galactitol

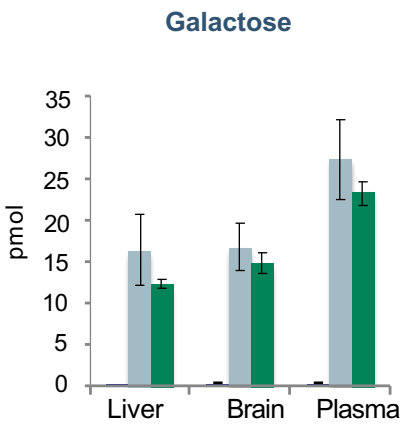


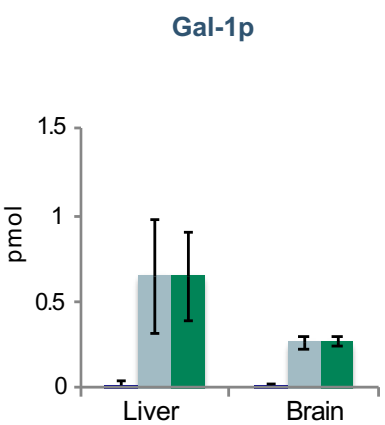
- Govorestat has been studied as a 200mg/mL oral suspension (for once-daily dosing)
- Dosed by weight to achieve uniform exposure in both pediatric and adults patients

1. Phytila et al. *JIMD Rep*. 2015; 15: 79–93; 2. Burgard et al. *R J Inherit Metab Dis*.2012 Jul;35(4):613-25; 3. Swaiman et al. *Pediatric Neurology*. 2018.

Govorestat Significantly Reduces Galactitol Levels in all Target Tissues without Compensatory Increase in Galactose or Gal-1p







- Significant lowering of toxic galactitol with govorestat treatment in the GALT-null rat
- No compensatory increase in Gal-1p

Wild type rats
GALT-null rats
Govorestat-treated GALT-null rats

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.

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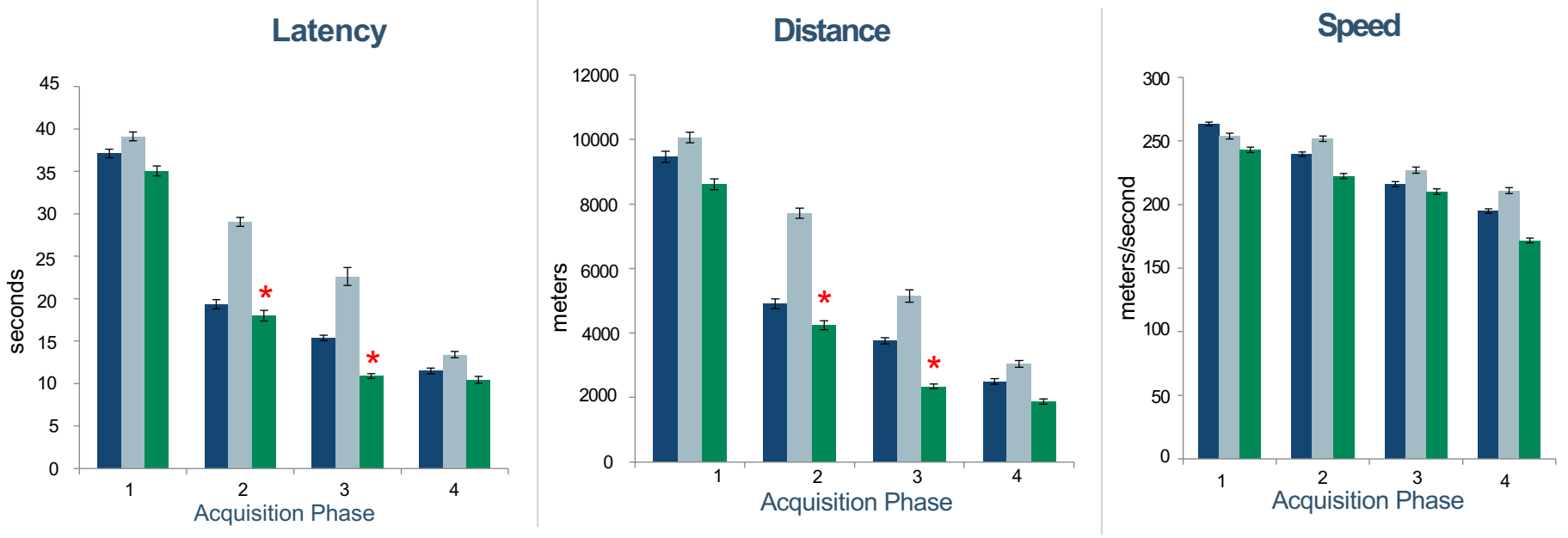
CNS, Cetnral Nervous System; Gal-1p, galactose1-phosphate; GALT, Galactose-1 Uridyltransferase; pmol, picomole.

Shendelman S. Post-Natal Galactitol Reduction is Associated with Normalization of CNS Phenotype in Animal Model of Galactosemia. ASHG 2020 poster.

Govorestat Treatment Prevents Learning & Memory Deficits in Classic Galactosemia Rat Model (Water Maze)



Wild type rats
GALT-null rats
Govorestat-treated GALT-null rats

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

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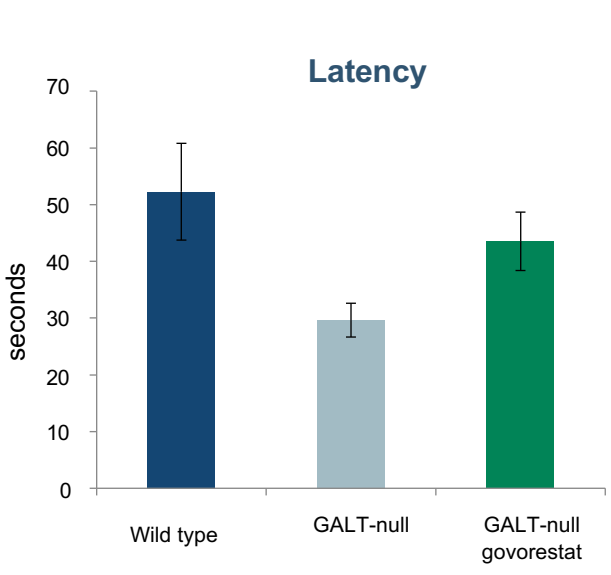
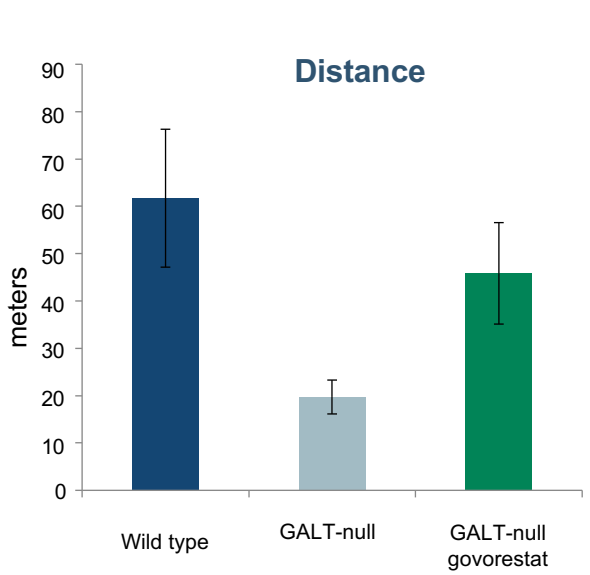
*Indicates statistical significance compared to placebo

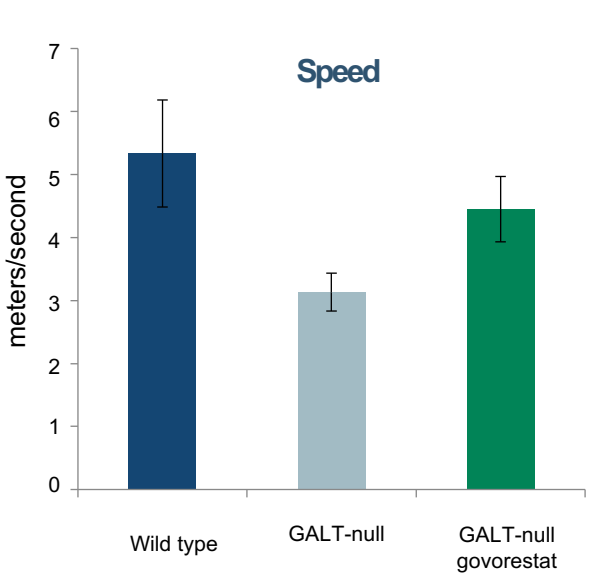
Rats were on a lactose-restricted diet similar to humans; rat breast milk contains very low lactose levels; supplemented with soy formula; rat chow has low galactose levels similar to allowed foods such as legumes.

Shendelman S. Post-Natal Galactitol Reduction is Associated with Normalization of CNS Phenotype in Animal Model of Galactosemia. ASHG 2020 poster.

Govorestat Treatment Prevents CNS Deficits in Galactosemia Rat Model (Rotarod)







- GALT-null rats display deficits in learning and motor coordination vs WT rats
- Treatment with govorestat prevented these deficiencies and normalized cognitive and motor function

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CNS, Central Nervous System; GALT, Galactose-1 Uridyltransferase; WT, Wild Type.
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.
Shendelman S. Post-Natal Galactitol Reduction is Associated with Normalization of CNS Phenotype in Animal Model of Galactosemia. ASHG 2020 poster.

Summary

- Classic Galactosemia is a devastating rare disease with no treatments approved
- Dietary restriction of galactose is important for survival, but does not stop long-term neurological complications due to endogenous synthesis of galactose by the body
- Symptoms progressively worsen over time with age, even when patients are strictly adherent to the galactose-restricted diet
- Long-term complications are caused by aberrant conversion of galactose to the toxic metabolite, galactitol
- Govorestat is a CNS-penetrant aldose reductase inhibitor that blocks conversion of galactose to toxic galactitol
- In a rat model of Classic Galactosemia, reduction of galactitol with govorestat treatment prevented the neurological phenotype as assessed by water maze and rotarod

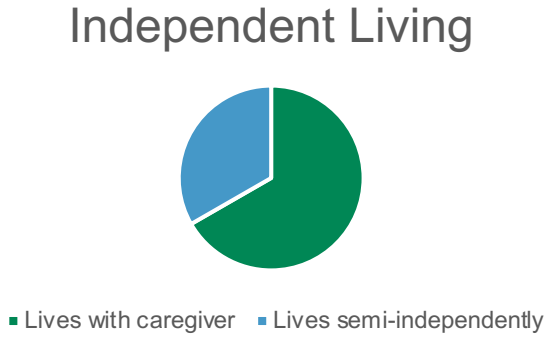
Designing the First Clinical Outcomes Study in Classic Galactosemia

Prior Clinical Outcomes Data Available in Classic Galactosemia Patients

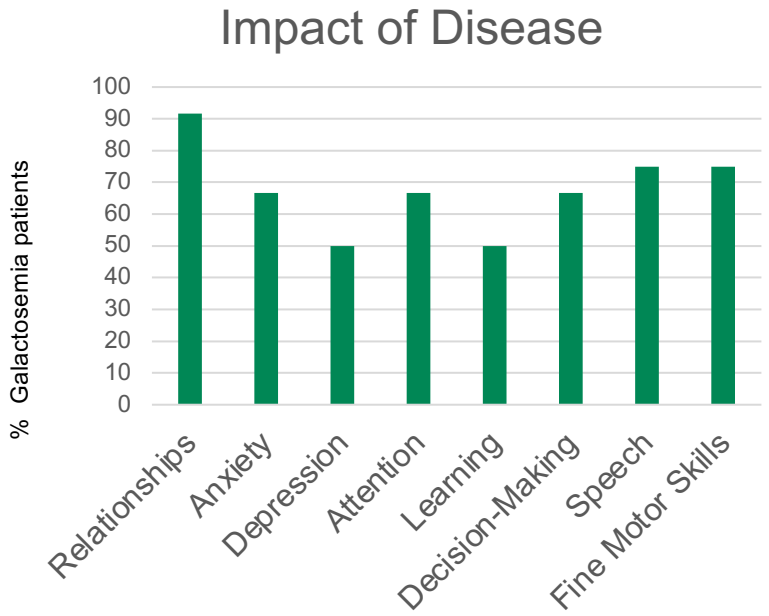
- Burden of illness studies (caregivers of adults and children) based on qualitative interviews → also provided quantitative data on occurrence and severity of symptoms
- GalNet registry-based cross-sectional survey referred to as the “Natural History of Galactosemia” study
- Cross-sectional data on children 3-16 examining impact of age and galactitol level on clinical outcomes (via standardized assessments)

Prior to the AT-007-1002 ACTION-Galactosemia Kids study there were no longitudinal studies or longitudinal natural history data in Classic Galactosemia patients

Burden of Illness Studies: Galactosemia Significantly Impacts Daily Living and Ability to Live Independently[1,2]



67% Live with a caregiver or care-group
33% Live semi-independently



Randall JA, et al. *Orph J Rare Dis* 2022; 17:138.2.Bailey E et al. 2021; ICIEM Poster1.

GalNet Registry “Natural History” Findings

Design

- Registry based reporting of symptoms - no functional tests performed
- Incidence and severity of symptoms across age groups were merged together (509 patients)
- Included 18% biochemical variant patients (>1% GALT activity) as compared to 82% true Classic Galactosemia patients (<1% GALT activity)

Findings

- 85% of patients in the GalNet registry had “brain impairments” (most likely inclusive of all the Classic Galactosemia patients)
- 52% had “global developmental delay”
- 52% had “neurological complications”
- 31% of patients had tremor; appearing more often as age progressed
  - 24% first symptoms in the pre-school years
  - 35% in the first decade of life but after preschool
  - 41% in the second decade of life

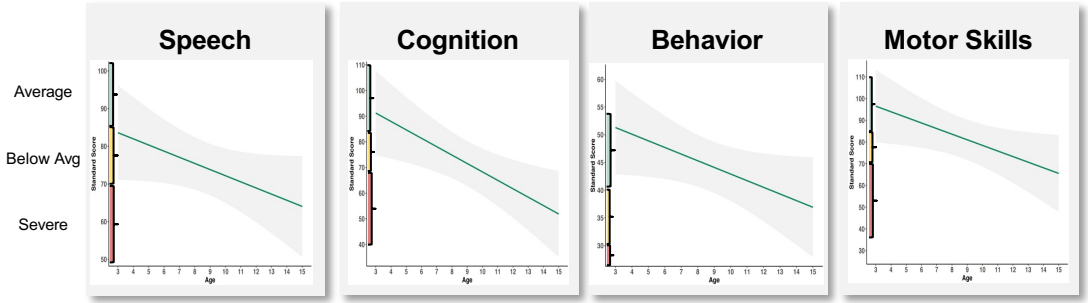
GALT, galactose-1-phosphate uridylyltranserase

Rubio-Gozalbo, M.E., et al. *Orphanet J Rare Dis.* 2019;14:86..

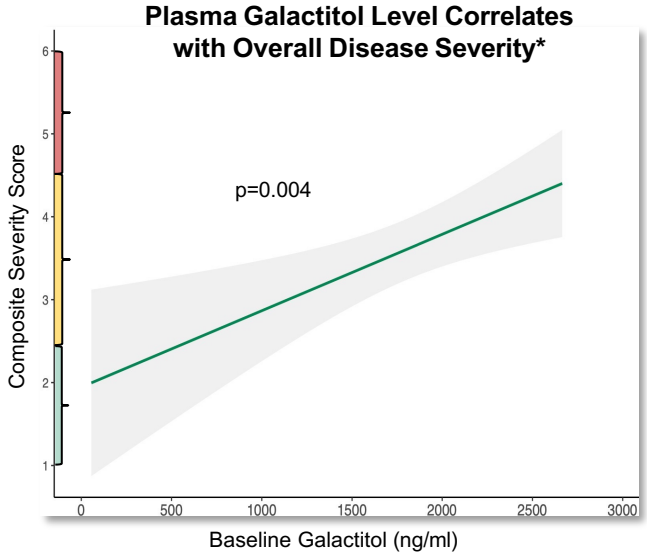
Classic Galactosemia is a Progressive Disease that Worsens with Age; Disease Severity Correlates with Plasma Galactitol Level

Cross-Sectional Standardized Test Data from Children Ages 3-16

Natural history of disease demonstrates progressive worsening with age



Baseline galactitol level correlates with severity of clinical functional outcomes



*Overall severity based on composite score comprised of 4 CNS quadrants

No correlation observed between Gal-1p and disease severity

Gal-1P, galactose1-phosphate; ng, nanogram; ml, milliliter.

Abstract eP011: Progressive Worsening of Central Nervous System Phenotype in Children with Classic Galactosemia: a Cross-Sectional Analysis; ACMG 2021 conference; Perfetti R et al. Galactitol Level is a Predictor of Disease Severity in Children with Classic Galactosemia on Galactose Restricted Diet. Poster presented at: International Congress Inborn Errors of Metabolism Annual Meeting; November 21-23, 2021; Sydney, Australia.

Designing a Clinical Outcomes Study in the Absence of Longitudinal Natural History Data

Challenge	Approach
What domains to measure?	• Consult expert physicians who see Classic Galactosemia patients often in clinical practice • Conduct burden of illness studies patient/caregiver interviews • EL-PFDD meeting (NORD/ Galactosemia Foundation)

• What tests to measure changes in those domains?
  • Relevant to the disease phenotype
  • Sensitive to change
  • Age-appropriate
  • Measurable longitudinally
	• Consult expert assessors (neuropsychologists, neurologists, speech therapists, occupational therapists) regarding tests used in Galactosemia patients and/or similar diseases
	• Conduct cross-sectional evaluations across age range using proposed tests to support ability to measure decline over time
	• No tests will have been validated in this patient population longitudinally

How to determine clinical meaningfulness of changes in clinical outcome measures?	Utilize anchoring and exit interviews to assess overall well-being of patients based on caregiver assessment of change and value of change

The Classic Galactosemia Phenotype

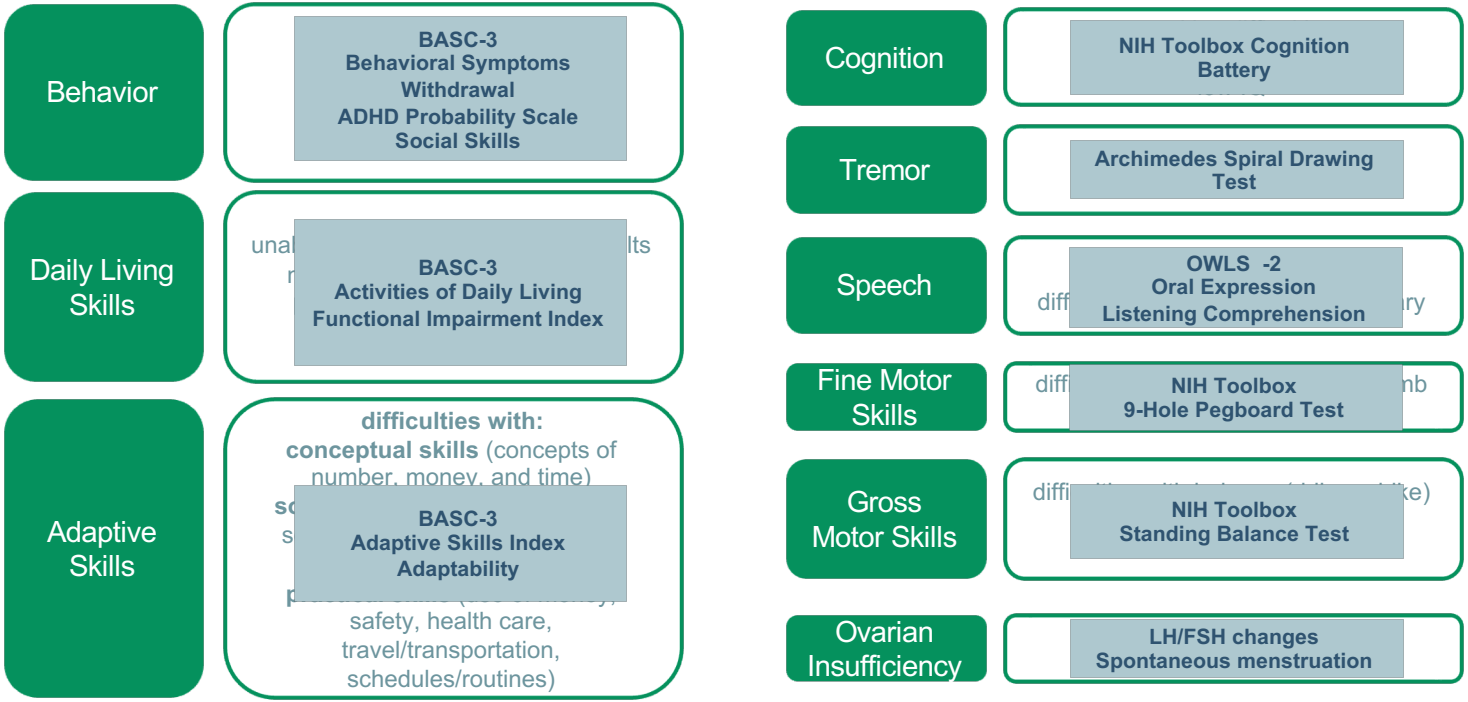
Behavior	withdrawal/ social isolation deficiencies in social skills ADD/ADHD depression
Daily Living Skills	unable to live independently as adults need assistance with self-care, preparing meals, healthy food choices, chores
Adaptive Skills	**difficulties with:** **conceptual skills** (concepts of number, money, and time) **social skills** (interpersonal skills, social problem solving, avoiding being victimized) **practical skills** (use of money, safety, health care, travel/transportation, schedules/routines)

Cognition	cognitive difficulties slow processing; “brain fog” low IQ
Tremor	often positional
Speech	speech apraxia difficulty with expression, vocabulary
Fine Motor Skills	difficulties most often with upper limb fine motor skills
Gross Motor Skills	difficulties with balance (riding a bike) trip and falls ataxia
Ovarian Insufficiency	in females

ADD, Attention Deficit Disorder;ADHD, Attention Deficit Hyperactivity Disorder; IQ, intelligence quotient.

Welling L, et al. *J Inherit Metab Dis*. 2017;40:171-176.

Outcomes Tests to Measure Changes in the Disease Phenotype

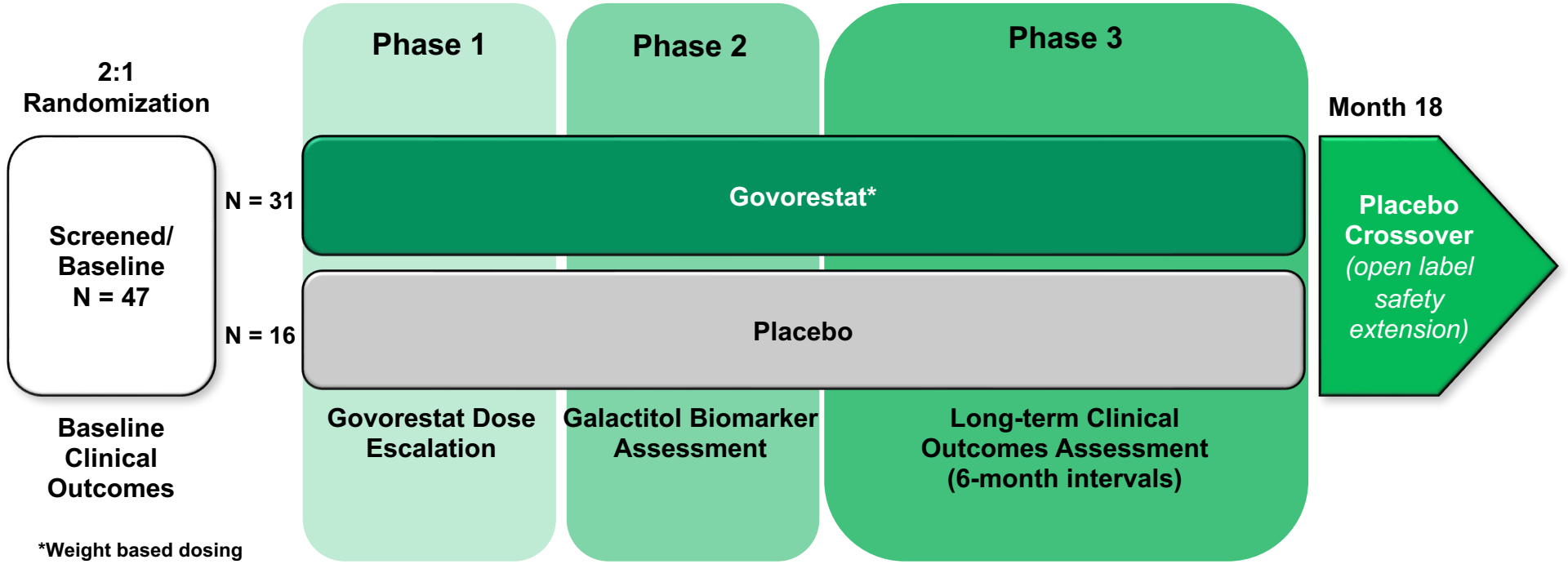


BASC-3, Behavioral Assessment Scales for Children-3; FSH, follicle stimulating hormone; LH, luteinizing hormone; NIH, National Institute of Health; OWLS, Oral and Written Language Skills Assessment.

Welling L, et al. *J Inherit Metab Dis*. 2017;40:171-176.

AT-007-1002 ACTION Galactosemia Kids Pediatric Longitudinal Study

ACTION-Galactosemia Kids Pediatric Registrational Clinical Study Design (47 Children Ages 2-17)



*Weight based dosing

Primary Endpoint

Primary Composite Endpoints

- Composite of change in:
  - OWLS-2 Oral Expression (OE)
  - OWLS-2 Listening Comprehension (LC)

  } Speech and language

  - BASC-3 Behavior Symptoms Index (BSI)
  - BASC-3 Activities of Daily Living (ADL)

  } Behavior and daily living skills

Prespecified Sensitivity Analyses

- NIH Toolbox Cognition Battery (NIH-CB) – addition of cognition to primary endpoint
- 9-Hole Pegboard Test (9HPT) – addition of fine motor skills to primary endpoint

Secondary Endpoints

Secondary Endpoints

- Changes in plasma galactitol levels
- Changes in individual components of primary composite endpoint
- Changes in cognition
- Changes in gross and fine motor skills and tremor
- Specific behavioral symptoms (withdrawal, social skills, ADHD); adaptive skills

Key Enrollment Criteria

- Prior diagnosis of Classic Galactosemia
- <1% GALT enzyme activity
- No major health complications outside of Classic Galactosemia
- Adherent to the galactose-restricted diet

Baseline Demographics and Disease Characteristics Comparable Between Govorestat and Placebo Groups

	Govorestat N = 31	Placebo N = 16
Age* (years), mean	**8.9**	**9.7**
Sex, male (%)	**48%**	**50%**
Race, White (%)	**97%**	**100%**
BMI, mean (SD)	**16.4** (1.9)	**17.4** (4.1)
GALT enzyme activity, mean (SD) (mmol/h/mg)	**0.01** (0.03)	**0.02** (0.04)
Plasma galactitol mean (SD) (ng/mL)	**1,807** (459)	**2,202** (214)

APPLIED THERAPEUTICS

ng, nanogram; mL,milliliter; mmol/h/mg, miliimole/hour/milligram; SD, standard deviation.
Part B (Safety Population); *Age at time of study entry
Data on File

Patient Disposition

	Placebo	Govorestat (all doses 15, 20, 30mg/kg)
Dose Escalation		
**Dose Escalation	6	10
Long-Term Clinical Outcomes	16	31
Primary Reason for Discontinuation in Part B of Study		
Total Discontinuations	2	5
Adverse Event	1	2
Pregnancy	0	0
Protocol Deviation	0	0
Investigators Decision	0	0
Withdrawal by Subject or Parent	1	3
Other	0	0

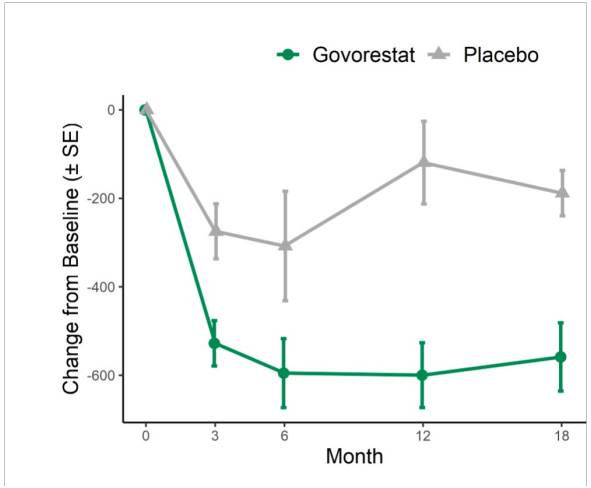
**All patients completed dose escalation and enrolled in the long-term clinical outcomes portion of the study

Biomarker Effects

Govorestat Treatment Reduced Plasma Galactitol Levels by 40% (p<0.001 vs. placebo)

Galactitol reduction began on the first day of treatment, and was sustained over 18 months

Weight Group	Govorestat Dose (QD)	% Galactitol Reduction From Baseline
>40kg	15mg/kg	38.29%
20-40kg	20mg/kg	41.43%
<20kg	30mg/kg	39.83%
All groups	**15-30mg/kg**	**40.19% (p<0.001)**

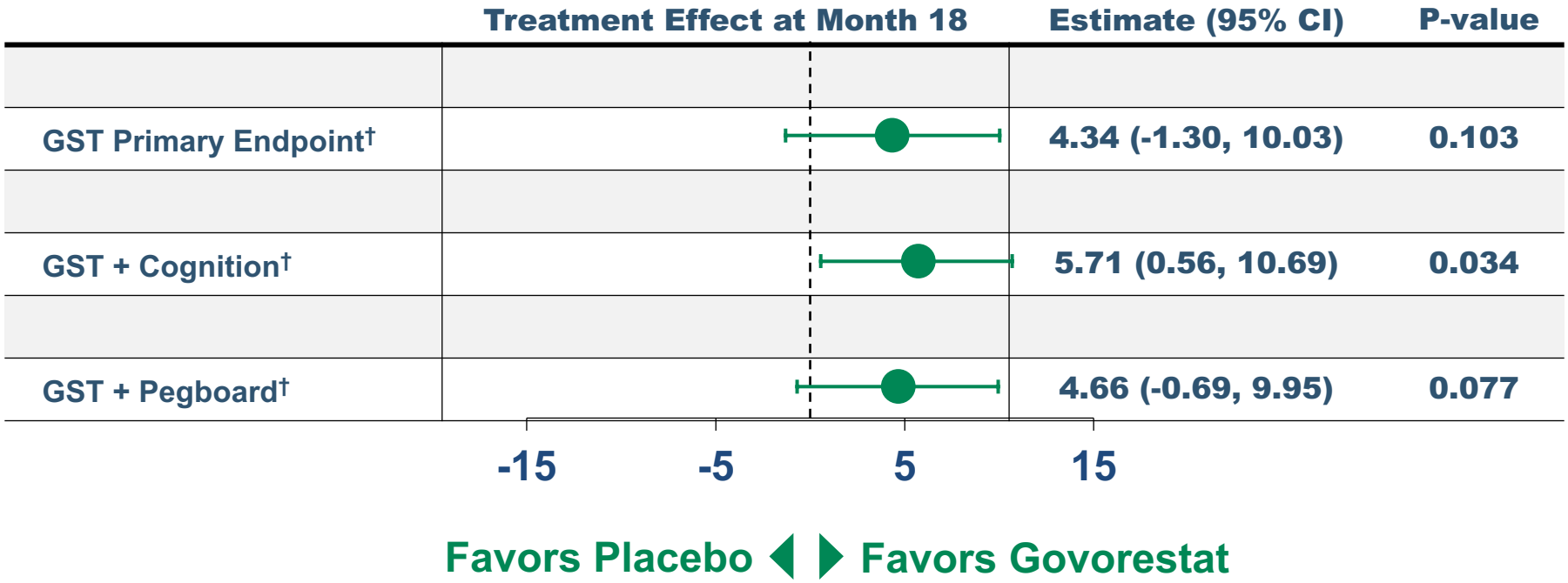


No compensatory increase in galactose or Gal-1p

Perfetti et al. 2022 Annual Meeting SIMD Presentation: 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.

Clinical Outcome Results

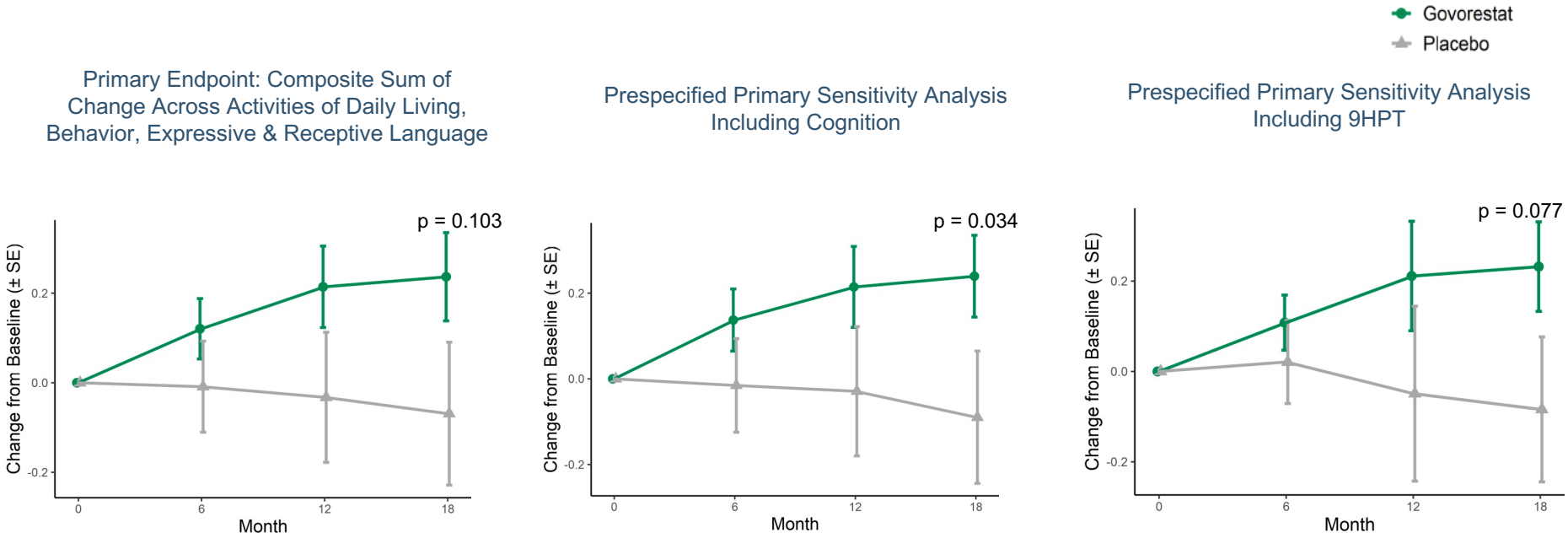
Primary Endpoint and Primary Endpoint Sensitivity Results Favor Govorestat; Sensitivity Analysis Including Cognition Statistically Significant



APPLIED THERAPEUTICS

† GSTs were multiplied by 5 to match scales; CI, Confidence Interval GST, Global Statistical Test

Govorestat Treatment Benefit Increases Over Time
Primary Endpoint and Sensitivity Analyses at 6, 12 and 18 Months



9HPT, 9 Hole Pegboard Test; SE, standard error.

Data on File

Treatment Effect on Primary Endpoint Individual Components and Secondary Clinical Outcomes at 18 Months

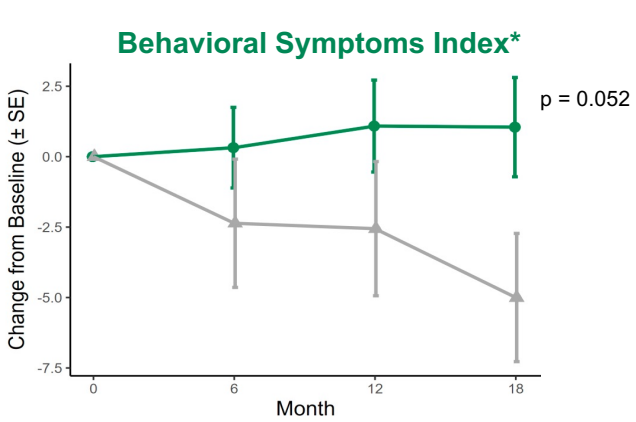
	Treatment Effect at Month 18	Estimate (95% CI)	p-value
BSI*		**6.05** (-0.06, 12.15)	**0.052**
Activities of Daily Living		**6.12** (-1.53, 13.78)	0.105
Oral Expression		**-0.79** (-9.53, 7.95)	0.854
Listening Comprehension		**-1.0** (-9.87, 7.87)	0.817
NIH Cognitive Battery		**7.99** (0.73, 15.26)	**0.032**
9-hole Pegboard		**3.58** (-2.63, 9.79)	0.247
Withdrawal*		**15.11** (5.15, 25.08)	**0.006**
Adaptability		**10.32** (2.88, 17.76)	**0.011**
Functional Impairment Index*		**9.83** (2.84, 16.81)	**0.009**
Adaptive Skills Index		**8.40** (1.20, 15.60)	**0.027**
Social Skills		**7.98** (1.00, 14.96)	**0.029**
ADHD Probability Index*		**7.03** (0.28, 13.79)	**0.042**
Archimedes Spiral*†		**4.36** (0.16, 8.57)	**0.043**
Standing Balance		**-0.9** (-8.63, 6.84)	0.811

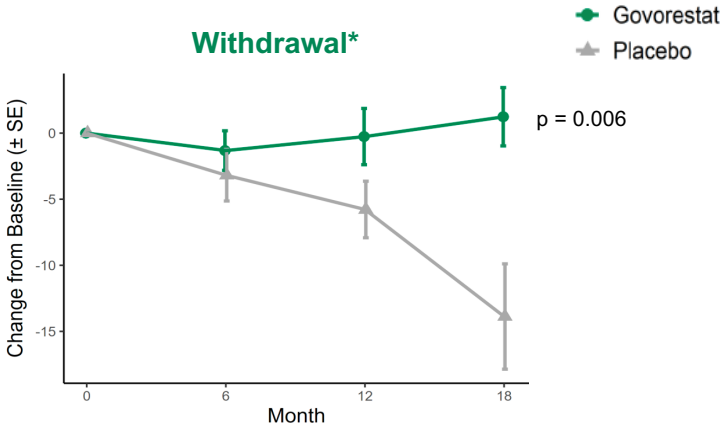
APPLIED THERAPEUTICS

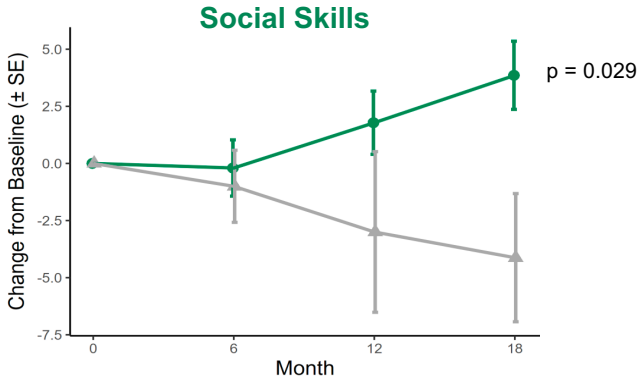
* Variables were reversed so that higher scores represented improvement

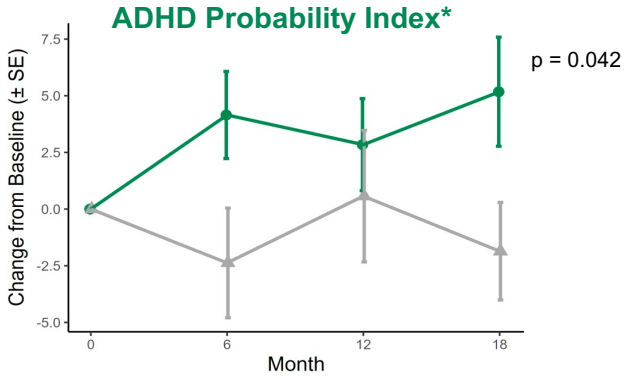
Data on File

Secondary Endpoint: Govorestat Treatment Improved or Stabilized Behavior









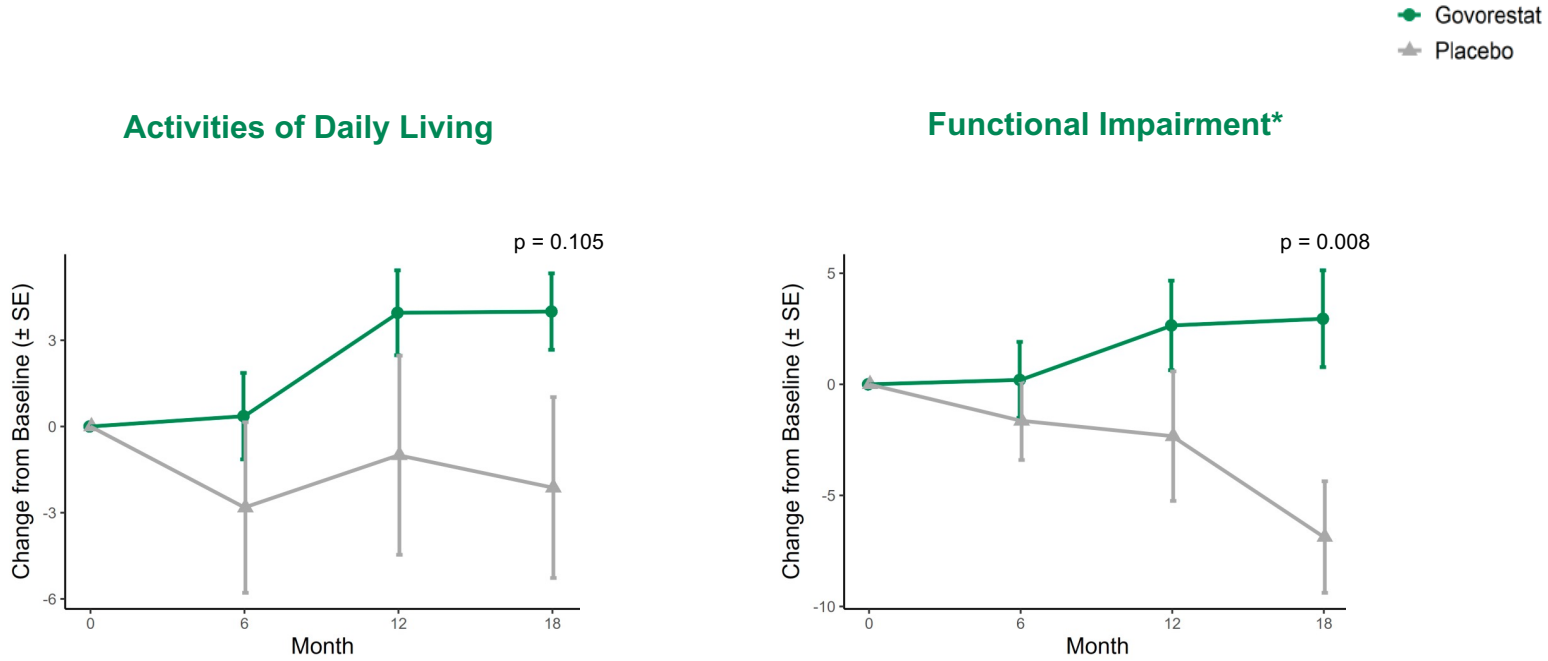
*Variables were reversed (multiplied by -1) so that higher scores represented improvement

BASC-3 (Behavioral Assessment Scales for Children 3);

BASC is a 0-50 point scale, where 10 points=a SD of change from age-normed healthy controls40-50 = age-normed healthy controls; 30-40= moderately impacted vs. healthy controls; <30= severely impacted vs. healthy controls

Data on File

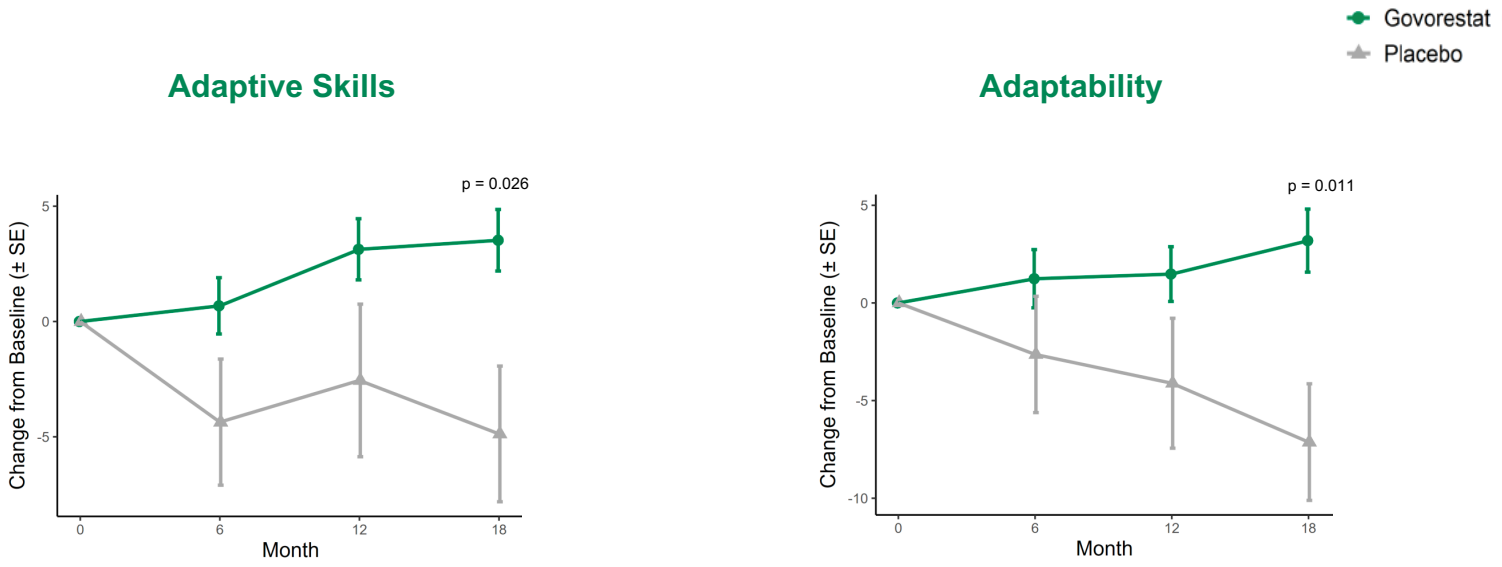
Secondary Endpoint: Govorestat Treatment Improved or Stabilized Daily Living Skills



BASC-3 (Behavioral Assessment Scales for Children 3)
BASC is a 0-50 point scale, where 10 points=a SD of change from age-normed healthy controls
40-50 = age-normed healthy controls; 30-40= moderately impacted vs. healthy controls; <30= severely impacted vs. healthy controls

*Variables were reversed (multiplied by -1) so that higher scores represented improvement
Data on File

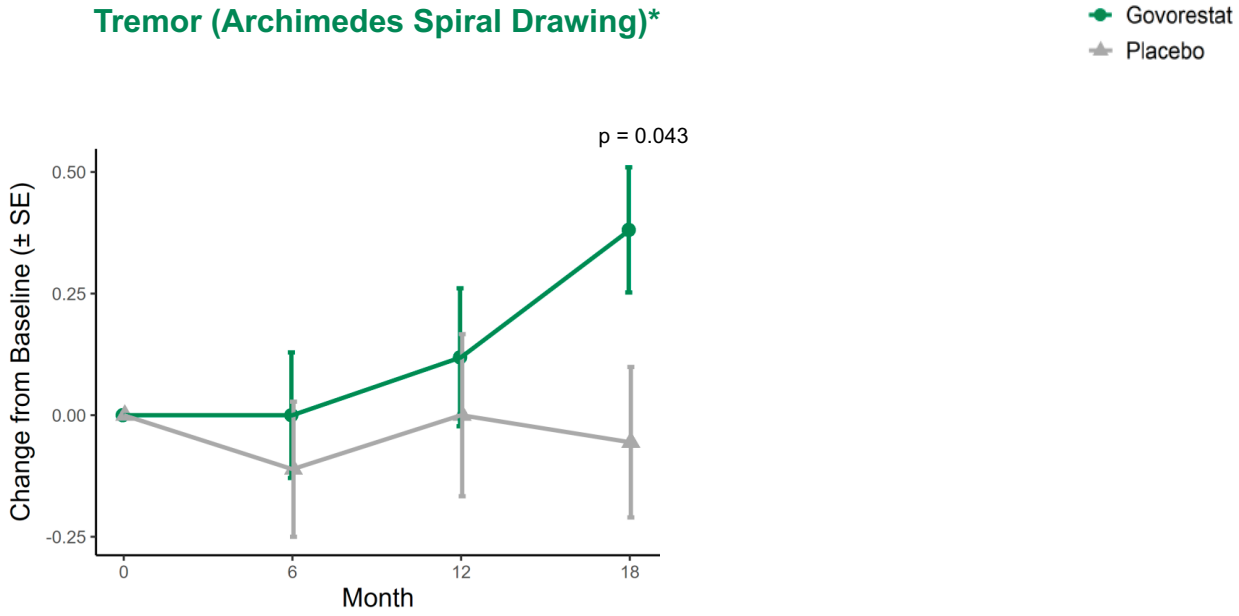
Secondary Endpoint: Govorestat Treatment Improved or Stabilized Adaptive Skills and Adaptability



BASC-3 (Behavioral Assessment Scales for Children 3)
BASC is a 0-50 point scale, where 10 points=a SD of change from age-normed healthy controls
40-50 = age-normed healthy controls; 30-40= moderately impacted vs. healthy controls; <30= severely impacted vs. healthy controls

Secondary Endpoint: Govorestat Treatment Improved or Stabilized Tremor

Tremor (Archimedes Spiral Drawing)*

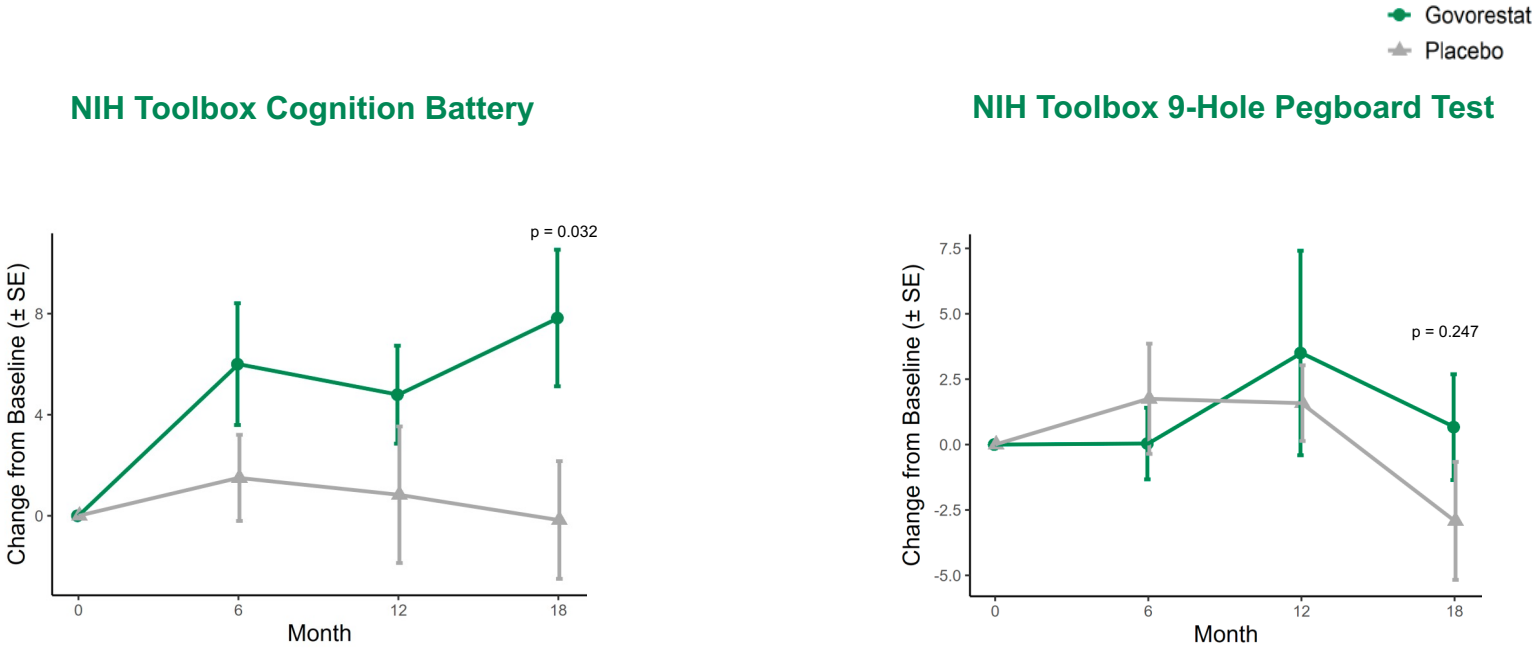


Archimedes Spiral Drawing Test (Scale 0-4); 0=no tremor and 4=most severe tremor possible

*Variables were reversed (multiplied by -1) so that higher scores represented improvement

Data on File

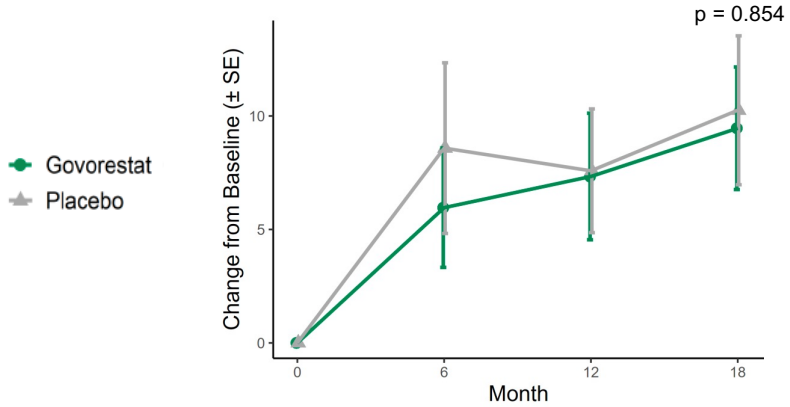
Secondary Endpoint: Govorestat Treatment Improved or Stabilized Cognition



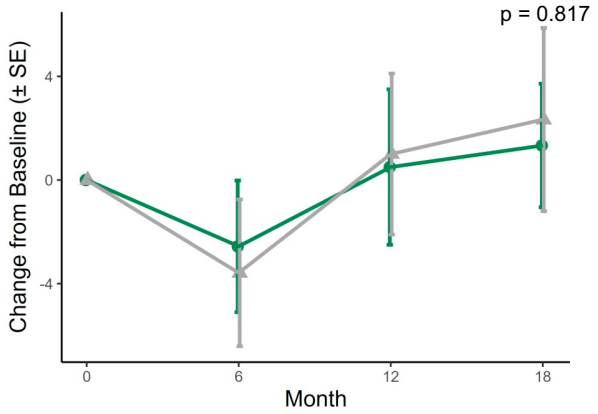
NIH Toolbox, National institutes of Health Toolbox
Cognition Battery is on a 0-100 point scale, where 15 points=a SD of change from age-normed healthy controls
85-100= age-normed healthy controls; 70-85= moderately impacted vs. healthy controls; <70= severely impacted vs. healthy controls

Secondary Endpoint: Speech Endpoints*

OWLS Oral Expression



OWLS Listening Comprehension

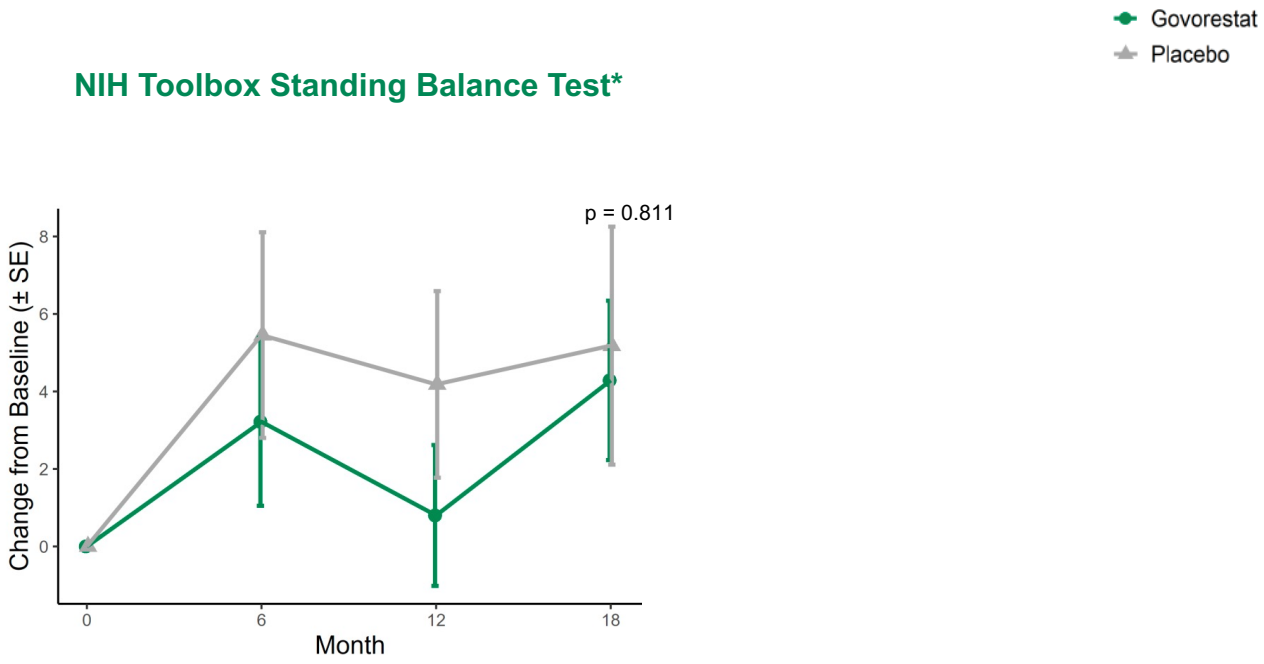


*Endpoint did not demonstrate a treatment effect: this was hypothesized to be due to confounding use of speech therapy which was not controlled over the course of the study. All groups (including placebo) improved over 18 months.

OWLS, Oral & Written Language Skills test
OWLS is on a 0-100 point scale, where 15 points=a SD of change from age-normed healthy controls
85-100= age-normed healthy controls; 70-85= moderately impacted vs. healthy controls; <70= severely impacted vs. healthy controls

Secondary Endpoint: Gross Motor Skills

NIH Toolbox Standing Balance Test*



*Endpoint did not demonstrate a treatment effect

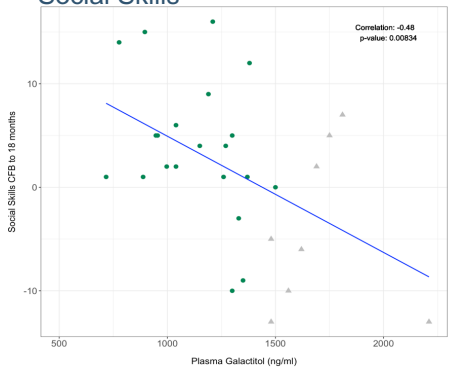
NIH Toolbox, National institutes of Health Toolbox

Data on File

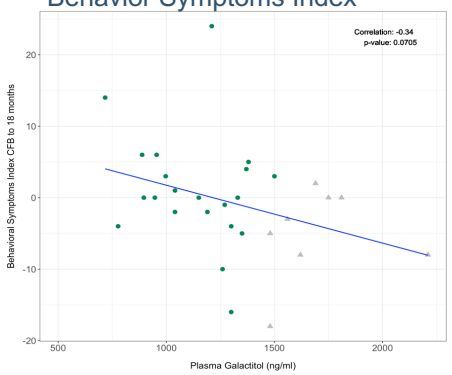
Galactitol Reduction Correlated with Clinical Outcomes Benefit

Galactitol level at 3 months statistically correlated with change in clinical outcomes at 18 months

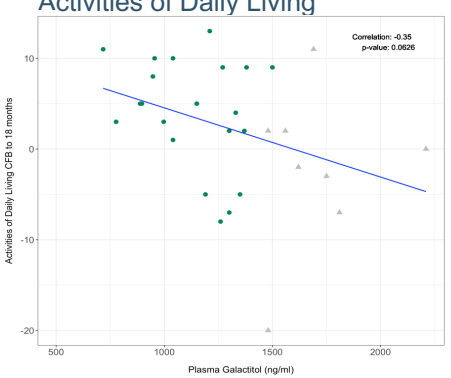
Social Skills



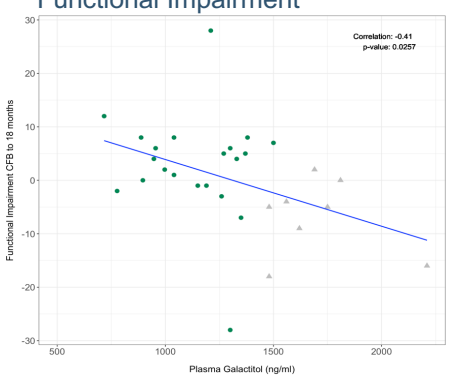
Behavior Symptoms Index



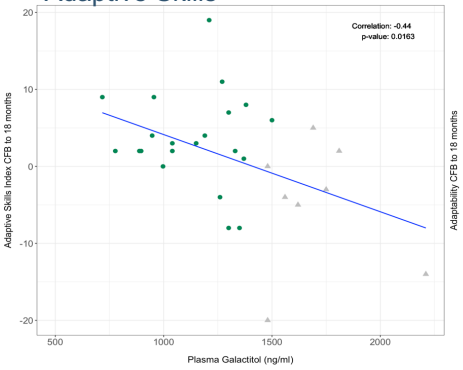
Activities of Daily Living



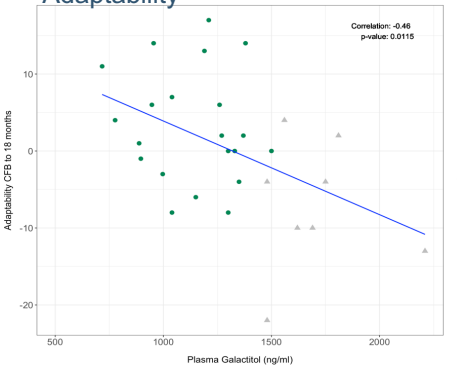
Functional Impairment



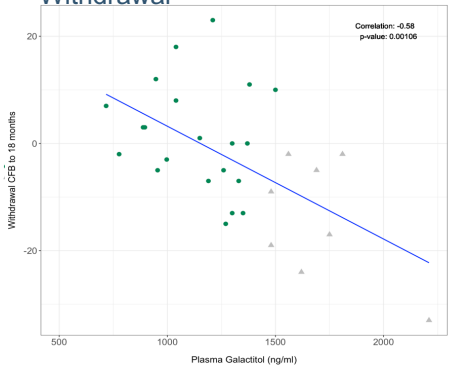
Adaptive Skills



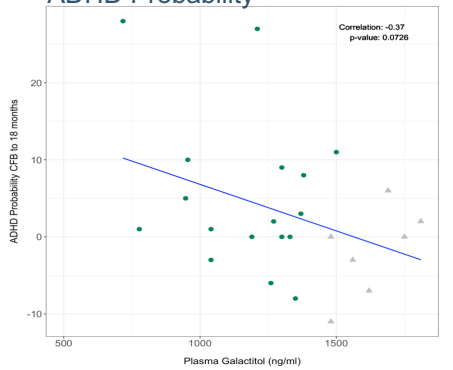
Adaptability



Withdrawal

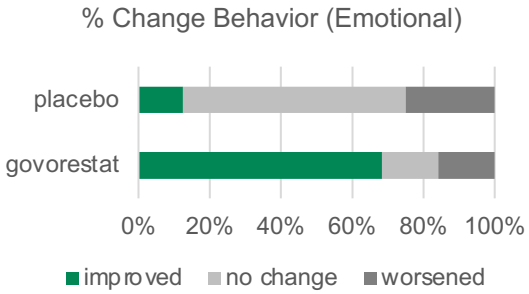


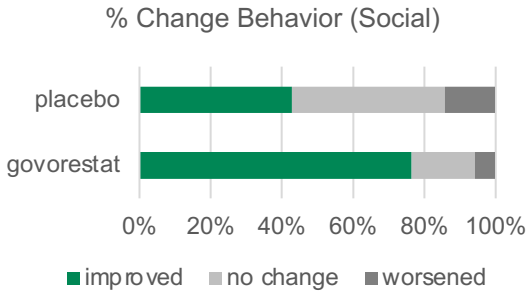
ADHD Probability

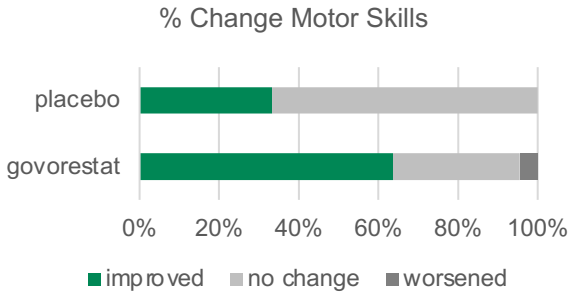


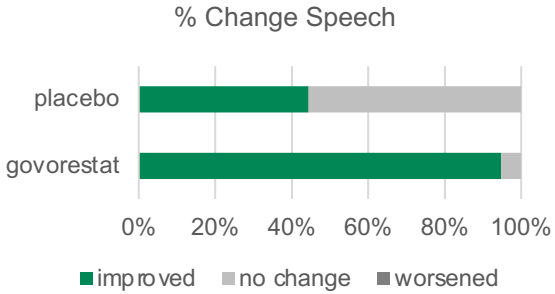
CFB= Change From Baseline; correlation plots include data for all subjects who completed the same BASC test at baseline and 18 months (e.g. preschool, child, adolescent)

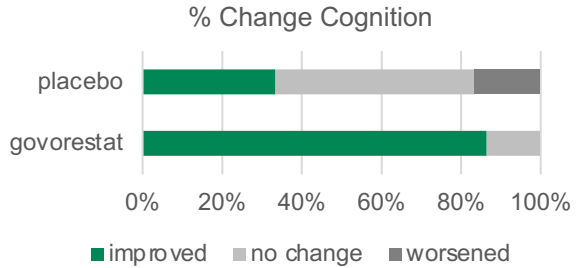
Caregiver Exit Interviews Support the Clinical Meaningfulness of Govorestat Treatment











Caregivers noted an improvement or stabilization of disease on all categories of symptoms in the govorestat treated group vs. placebo.*

*Exit interviews were performed prior to study unblinding to prevent bias

Safety Summary

- Govorestat was safe and well-tolerated with no serious adverse events
- All adverse events were mild to moderate
- Adverse events & lab values were generally balanced between govorestat and placebo groups
  - Slightly higher incidence elevated ALT/AST in govorestat-treated patients; all were reversible – no bilirubin increase (no Hy's Law cases)

AE, n (%)	Placebo (n=16)	Govorestat (n=31)
Gastrointestinal disorders	11 (68.8)	23 (74.2)
Vomiting	5 (31.3)	15 (48.4)
Diarrhea	2 (12.5)	8 (25.8)
Hepatic enzyme increased (ALT/AST)	2 (12.5)	8 (25.8)
Urine albumin/creatinine ratio increased*	7 (43.8)	5 (16.1)
Urine protein/creatinine ratio increased*	3 (18.8)	2 (6.5)
Infections and infestations	10 (62.5)	18 (58.1)
Viral upper respiratory tract infection	3 (18.8)	14 (45.2)

*Govorestat interferes with the colorimetric assay to measure serum creatinine. Any elevation in serum creatinine during the study was due to this and confirmed to be normal on repeat using the enzymatic assay to measure serum creatinine. As such, there were no elevations in serum creatinine nor cases of Acute Kidney Injury in the study.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase; TEAE, treatment emergent adverse event; Refers to patients having reported at least 1 term in AE category. Data on File

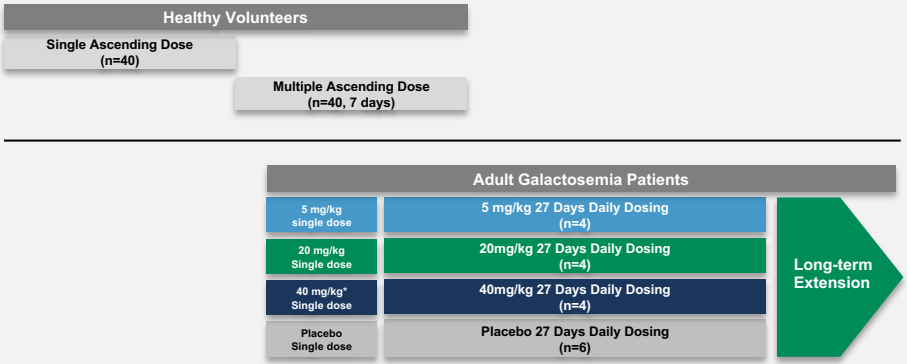
Summary of Pediatric Clinical Data

- Govorestat treatment impacted meaningful elements of the disease phenotype (behavior, daily living skills, adaptive skills, tremor, cognition, fine motor skills).
  - Impact on clinical outcomes was often a full standard deviation of change on a T scale or standard scale
- Govorestat induced substantial reductions in serum galactitol levels, which were statistically significant compared to placebo, and correlated with change in clinical outcomes
- The clinical benefit of govorestat was meaningful to caregivers as assessed by exit interviews (performed prior to unblinding the study)
- Govorestat was safe and well tolerated, with adverse events balanced between active and placebo treated groups and no SAE's reported

Govorestat Treatment in Adults with Classic Galactosemia

Govorestat Significantly Reduced Galactitol Levels in the Galactosemia Adult Phase 1/2 Study

Adult Phase 1/2 Study Design



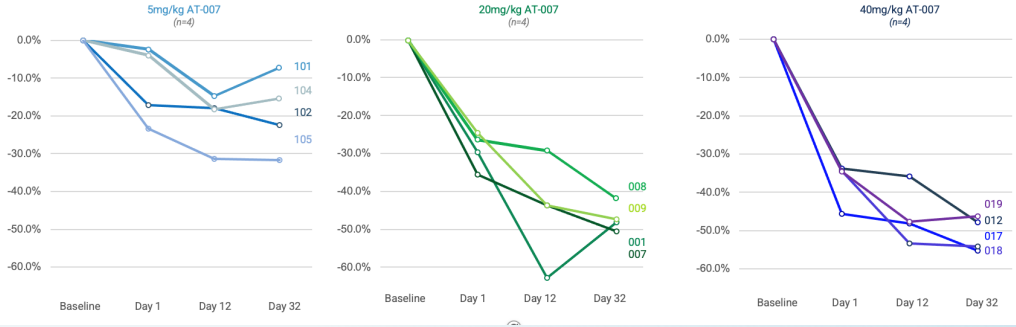
Safety

- Favorable safety and tolerability in core study and 3-month extension

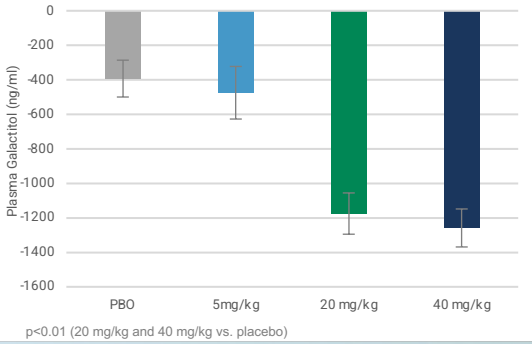
Pharmacokinetics/ Pharmacodynamics

- 20mg/kg dose selected as optimal dose
- PK supports once-daily dosing
- Rapid, sustained and significant reduction in plasma galactitol
- Galactitol reduction in the brain demonstrated by MR Spectroscopy
- No compensatory increase in galactose or Gal-1p

Galactitol Reduction vs. Baseline (Individual Patient Values)



Maximum Galactitol Reduction vs. Baseline



p<0.01 (20 mg/kg and 40 mg/kg vs. placebo)

Perfetti R et al. *J Clin Pharmacol*. 2024. doi: 10.1002/jcph.2495.

AT-007 (GOVORESTAT) is an investigational drug; it has not been approved for any use by FDA or any other regulatory body

Summary of Adult Data and Next Steps

- Govorestat treatment induced a rapid and sustained reduction in plasma galactitol level in adults with classic galactosemia
- Reduction in the brain (as assessed by quantitative MR Spectroscopy) was similar as compared to plasma
- In children, a similar level of galactitol reduction resulted in clinical outcomes benefit, and galactitol level correlated with change in clinical outcomes
- There is a reasonable expectation of clinical benefit in adults based on biomarker data and comparison to pediatric data; however, a future clinical outcomes study in adults will be conducted to assess clinical benefit in adults with Classic Galactosemia

Is Classic Galactosemia a Progressive Disease?

What Did We Know About Disease Progression Prior to the ACTION-Galactosemia Kids Trial?

- Infants and young children with Classic Galactosemia often appear “normal” or unaffected after implementation of the galactose-restricted diet
- Symptoms often appear around school age and worsen over time
- New symptoms continue to appear in adulthood-specifically tremor and seizures
- General Alignment that the gap between children with Classic Galactosemia and their peers widens over time
- Children fall further and further away from their normative peers and never catch up

What Did We Learn About Disease Progression from the ACTION-Galactosemia Kids Trial?

- Scores on age-standardized tests for behavior, cognition, daily living skills and adaptive skills worsen over 18 months in the placebo group
- On many tests, this worsening was substantial
- The performance tests used in the trial evaluated skills in **Raw Scores** (correct or incorrect answers on performance tests, behavior exhibited or not exhibited on parent-reported outcomes, etc)
- Then, raw scores are converted to **Standard Scores** (age-standardized to expectations of correct answers or behaviors for children of that age)
- By evaluating raw scores as compared to standard score changes over time, we can assess whether children lost skills they had previously (negative raw score change), or
- If they gained skills over time (positive raw score change) but not at the rate expected for age-normed peers (negative standard score change)

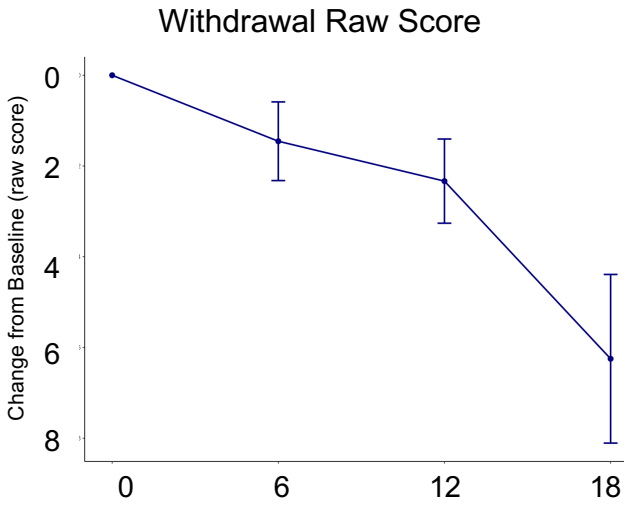
Definition of a Progressive Disease

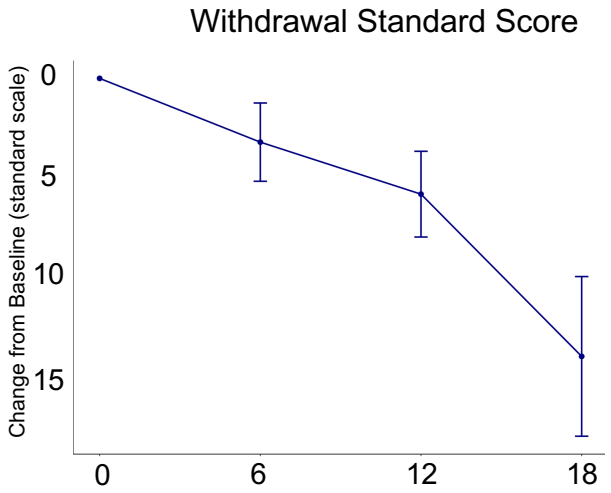
“A progressive disease is a disease that increases in severity or extent”

“In medical terms, progressive can also mean advancing, worsening, or going forward”

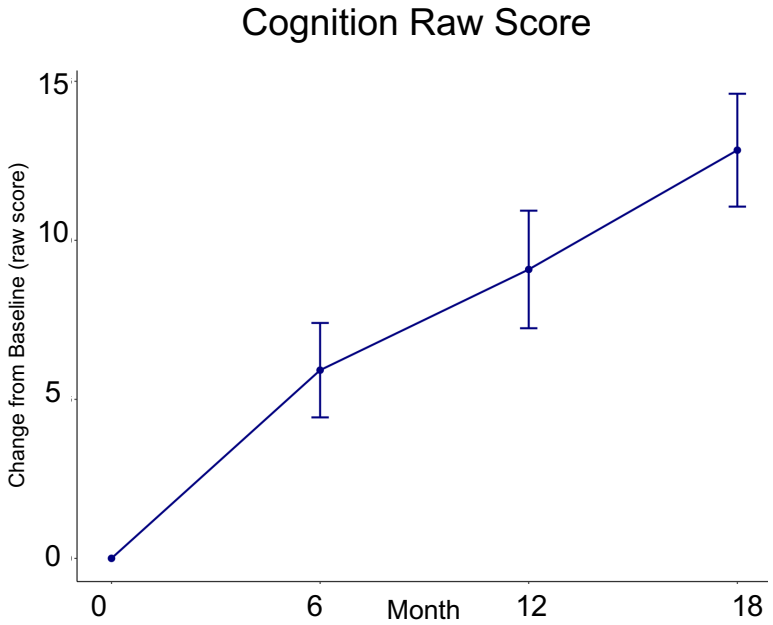
(Merriam-Webster Dictionary)

In the Placebo Group, Children Lost Social Skills That They Previously Had Over 18 Months, in Addition to Falling Behind Their Peers





Children Gained Cognitive Skills, But Not at the Rate of Their Peers, With a Widening Gap Over Time



Summary

- Classic Galactosemia is a Progressive Disease that worsens over time
- Discussion of Raw Scores vs. Standard Scores is semantic – the gap between these patients widens over time no matter what metrics or words we use
- An urgency to treat exists to prevent disease worsening over time

APPLIED THERAPEUTICS

Q&A