APPLIED THERAPEUTICS

ACTION-Galactosemia Kids (AT-007-1002) Clinical Trial Update

April 24, 2023

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Overview

- We believe that govorestat (AT-007) impacts clinically meaningful aspects of the Galactosemia disease phenotype alongside a favorable safety profile, and we plan to seek approval in both US and EU based on current data.
- Govorestat has previously demonstrated a significant reduction in galactitol level (a toxic metabolite formed in Galactosemia patients), which has now translated into consistent improvement on clinical and functional endpoints, including behavior, daily living skills, cognition, fine motor skills, adaptive skills and tremor over 18 months of treatment compared to placebo.
- The primary endpoint and pre-specified sensitivity analysis including cognition showed clinically meaningful trends toward improvement with p-values of 0.1030 and 0.0698, respectively.
- All components of the primary endpoints are positively impacted with govorestat treatment, except for speech; post-hoc analysis of primary endpoint without speech showed statistical significance (p= 0.0205 at 18 months).
- Key secondary endpoints of adaptive behavior skills and tremor achieved robust and clinically meaningful improvement with p-values of 0.0265 and 0.0428, respectively, over 18 months of treatment compared to placebo.
- Govorestat was safe and well-tolerated with no serious adverse events (SAEs) in the trial and no imbalance in adverse events (AEs) or lab values between the active and placebo groups in the pediatric study.

Next Steps and Market Opportunity

- If approved, govorestat will be the first and only treatment for Galactosemia, a devastating rare neurological disease that progressively worsens over time; dietary restriction prevents death, but does not prevent progression of long-term complications of Galactosemia due to endogenous synthesis of galactose by the body.
- Galactosemia affects approximately 3,000 patients in the US and 4,000 in Europe, with a growth year over year of approximately 200 patients (due to new births); the patient population is well-identified and diagnosed in the US and Europe due to mandatory newborn screening.
- Govorestat treatment for Galactosemia represents a substantial revenue opportunity.
- The European Medicines Agency (EMA) has already provided feedback supportive of potential approval in Europe for govorestat for Galactosemia based on existing data; an MAA submission is planned for Q3 2023
- The Company will request a pre-NDA meeting as soon as possible to discuss an FDA submission based on the current data; if acceptable to the FDA, will target NDA submission in Q3 2023
- The Company also plans in the near-term to request a pre-NDA meeting with the Neurology Division regarding SORD approval based on existing sorbitol reduction data. We believe SORD 12 month clinical outcomes data and DbCM Phase 3 data also provide meaningful catalysts towards the end of the year.

AT-007 ACTION-Galactosemia Kids Pediatric Registrational Clinical Study (47 Children Age 2-17)

PK/PD Dose Range Finding & Biomarker Data | **Long-Term Clinical Outcomes**

Screening/ Baseline 2:1 Randomization to Active or Placebo

AT-007 Dose Escalation

Biomarker Assessment of Galactitol

Clinical Outcomes Assessed Every 6 Months by Firewalled Committee

Placebo

Placebo cross to active once treatment effect on outcomes is demonstrated

Baseline Clinical Outcomes

Weight-based dosing: 15mg/kg>40kg; 20mg/kg 20-40kg; 30mg/kg<20kg

Primary Endpoint:
Global Assessment of Change (Global Statistical Test)
Composite Sum of Change in CNS function

- **Speech**: OWLS 2 Oral Expression Listening Comprehension
- **Behavior**: BASC-Behavioral Symptoms BASC-Daily Living Skills

Primary Sensitivity Analysis

- **Cognition**: NIH Toolbox Cognition Battery
- **Motor**: NIH Toolbox 9-Hole Pegboard Test

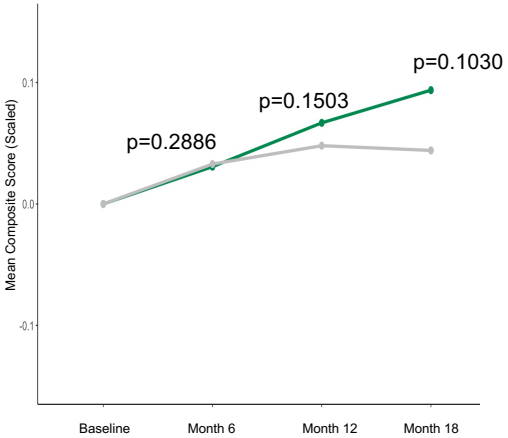
Key Secondary Endpoints

- **Adaptive Skills**: BASC-Adaptive Skills Index
- **Tremor**: Archimedes Spiral Drawing Test

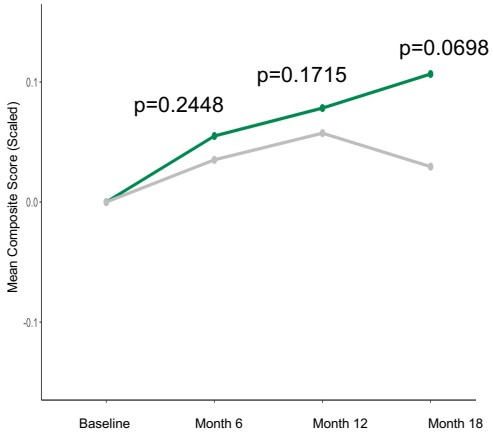
Changes in primary endpoint (movement of cognition and motor skills to sensitivity analyses) was based on recent FDA advice letters

Compelling Improvement in Primary Endpoint over 18 Months Across Multiple Clinical Domains

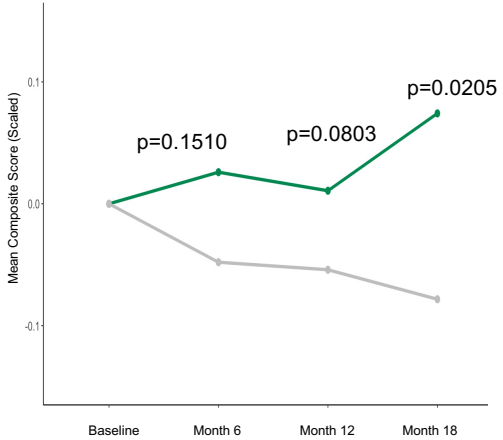
Primary Endpoint: Global Statistical Test (Composite Sum of Change): Activities of Daily Living, Behavior, and Speech



Primary Sensitivity Analysis: Primary Endpoint + Cognition



Post-hoc analysis of primary endpoint without speech (Activities of Daily Living + Behavior)

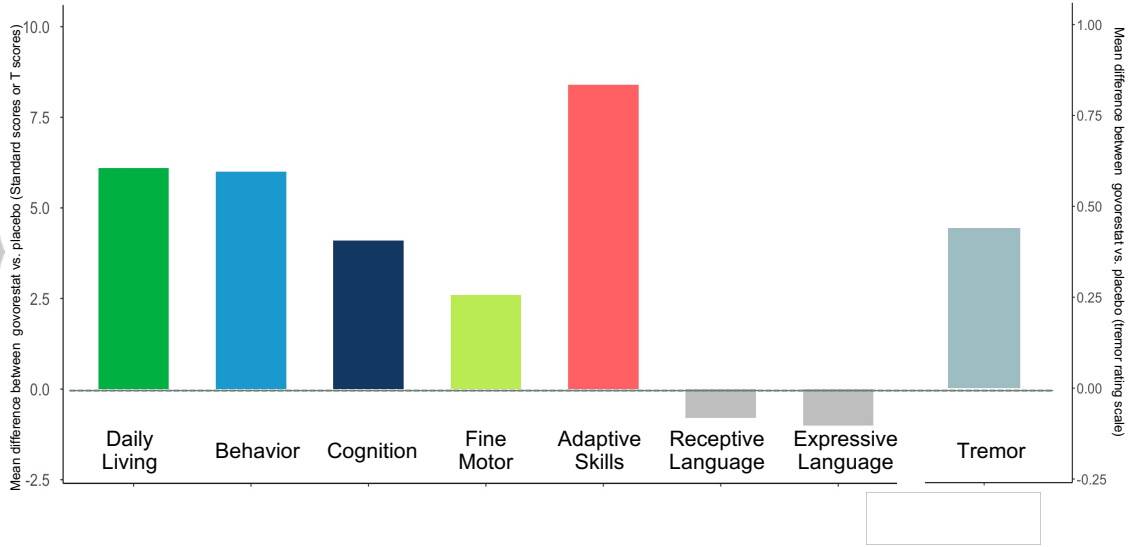


Activities of Daily Living (BASC-ADL); Behavior (BASC-Behavioral Index); Speech includes Expressive Language (OWLS-OE) & Receptive Language (OWLS-LC)
Sensitivity analysis including 9-Hole PegBoard Test p = 0.0937 at 18 months)

Improvement in Galactitol Biomarker Translates into Consistent Clinical Benefit Across Activities of Daily Living, Behavior, Cognition, Adaptive Skills and Tremor

Weight Group	AT-007 Dose (QD)	% 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)**

- Significant improvement in galactitol biomarker vs. placebo
- Sustained over time through 18 months of treatment
- No compensatory increase in galactose or Gal-1p



Speech endpoints were not impacted by govorestat treatment, which is suspected to be due to lack of progression in the placebo group and concomitant speech therapy received by almost all children in the trial. Of note, patients with severe speech deficits showed a favorable trend towards improvement with AT-007 vs. placebo. Tremor is measured on a different scale vs. other tests, and is referenced by the right hand y axis

Consistent Improvement on Activities of Daily Living with Govorestat vs. Placebo

Biomarker

Activities of Daily Living

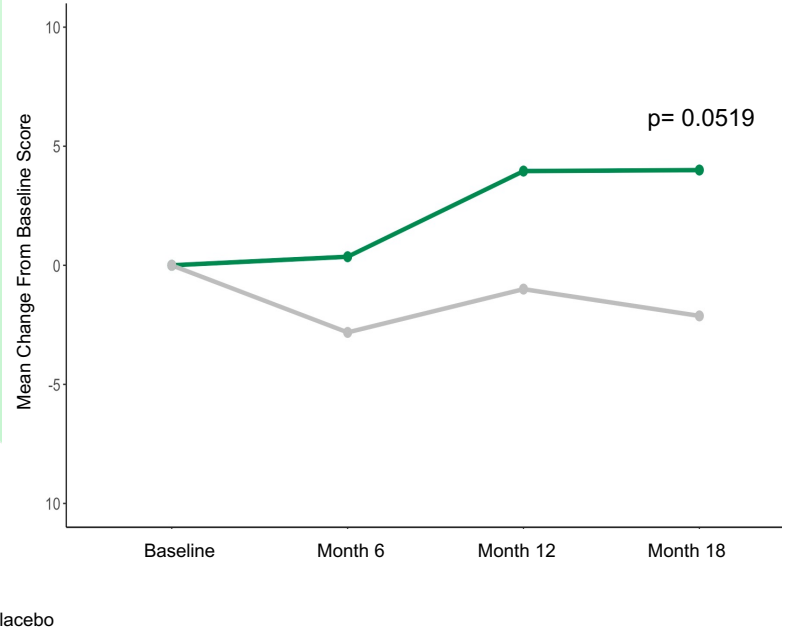
Behavior

Cognition

Adaptive Skills

Tremor

Improvement in Activities of Daily Living (ADL) as Measured by Behavioral Assessment Scales for Children (BASC)



Consistent Improvement in Behavioral with Govorestat vs. Placebo

Biomarker

Activities of Daily Living

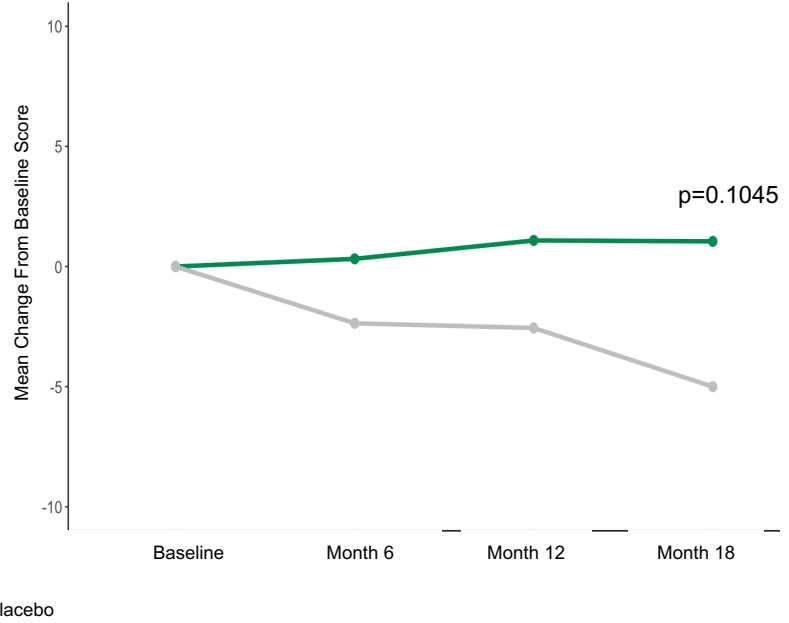
Behavior

Cognition

Adaptive Skills

Tremor

Improvement in Behavioral Symptoms Index as Measured by BASC



Consistent Improvement in Cognition with Govorestat vs. Placebo

Biomarker

Activities of Daily Living

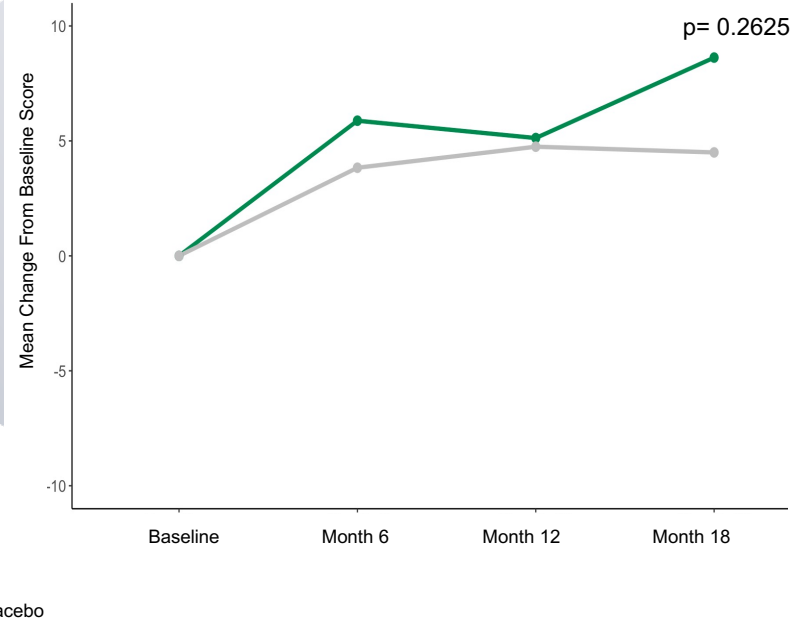
Behavior

Cognition

Adaptive Skills

Tremor

Improvement in Cognition as Measured by NIH Toolbox Cognition Battery



Consistent Improvement in Adaptive Skills with Govorestat vs. Placebo

Biomarker

Activities of Daily Living

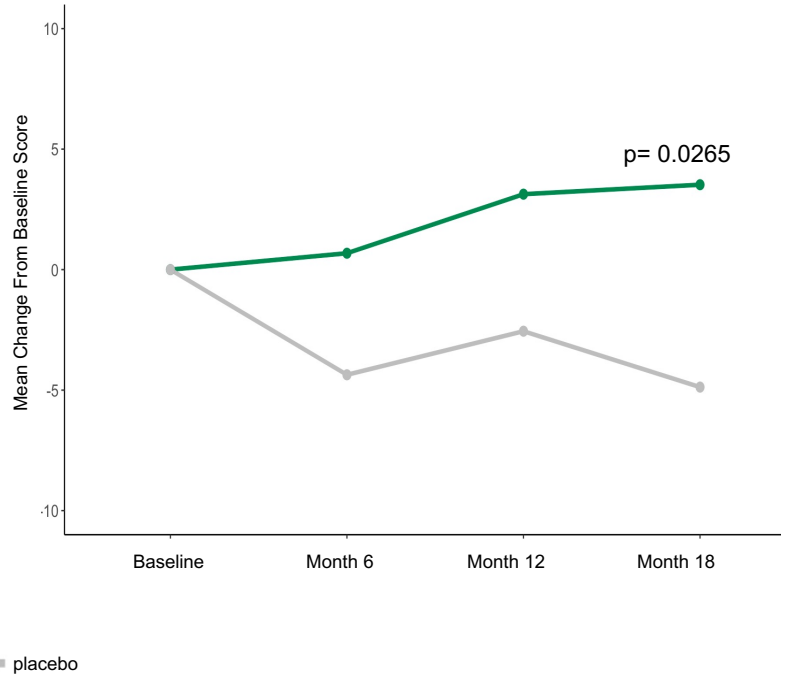
Behavior

Cognition

Adaptive Skills

Tremor

Improvement in Adaptive Skills as Measured by BASC



Consistent Improvement in Tremor with Govorestat vs. Placebo

Biomarker

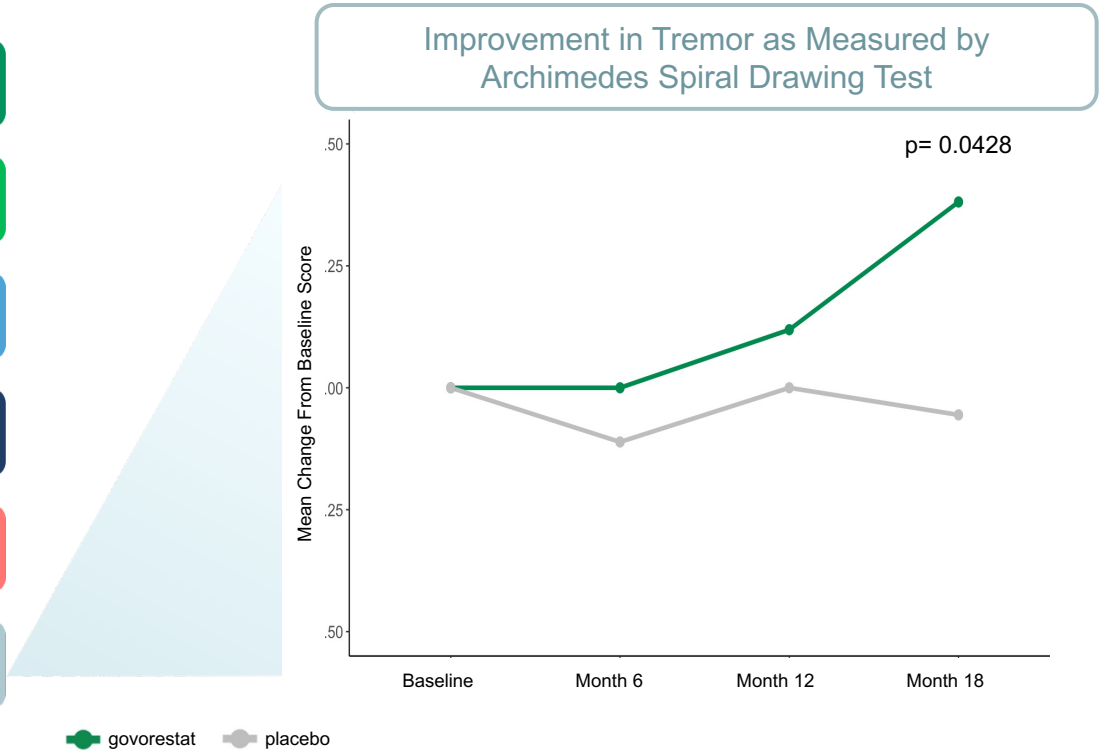
Activities of Daily Living

Behavior

Cognition

Adaptive Skills

Tremor



Note: Spiral drawing is scored on a much smaller scale of 0-4; as compared to other tests (BASC is scaled on a T score of 0-50 and NIH Cognition is scaled on a standard score of 0-100)

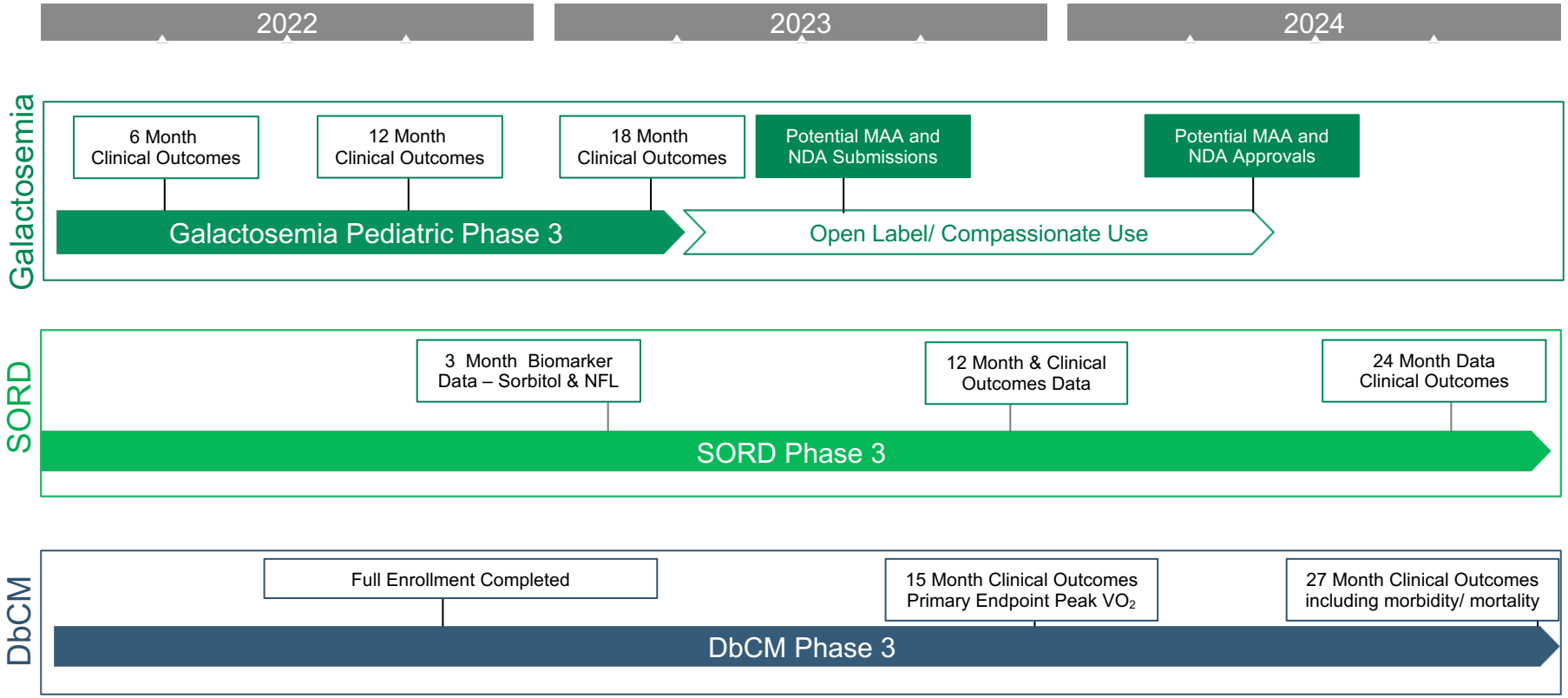
Safety Summary

- AT-007 was safe and well-tolerated with no serious adverse events
- All AEs were mild to moderate
- AEs & lab values between AT-007 and placebo groups were balanced

	Placebo (N=16) Number (%) of Subjects	**Govorestat (N=31)** Number (%) of Subjects
Subjects Reporting at Least One TEAE	16 (100%)	30 (96.8%)
Gastrointestinal disorders	11 (68.8%)	23 (74.2%)
Hepatic enzyme increased	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%)
Renal & Urinary Disorders	1 (6.3%)	3 (9.7%)
Infections and infestations	10 (62.5%)	18 (58.1%)

Refers to patients having reported at least 1 term in AE category; AE, adverse event

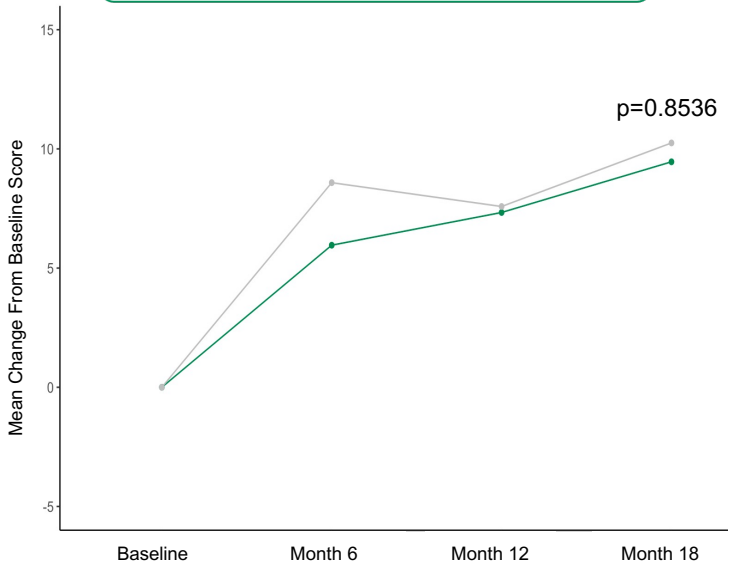
Key Projected Milestones by Program



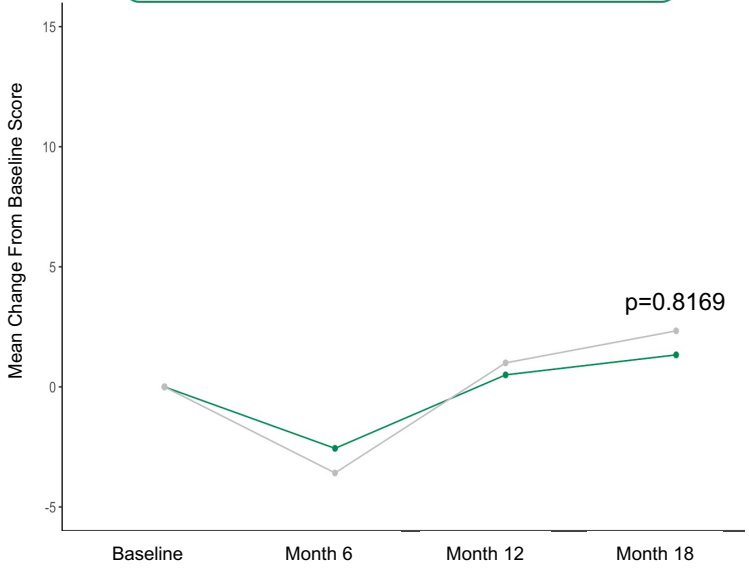
Appendix

Speech Endpoints Were Not Impacted by Govorestat Treatment, Likely Due to Speech Therapy Across Both Active and Placebo Groups

Expressive Language (OWLS-OE)



Receptive Language (OWLS-LC)



govorestat placebo

Note: for 9-Hole Pegboard test, a baseline imbalance existed between the govorestat and placebo group with more patients on speech therapy in the placebo arm at baseline; additionally children who were not on speech therapy at baseline started speech therapy over the course of the trial in both active and placebo groups