APPLIED THERAPEUTICS

Applied Therapeutics ACTION-Galactosemia MRS Update

Dec 9, 2020

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Background & Objectives of ACTION-Galactosemia MRS Study

Background:

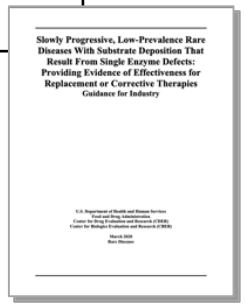
- Prior to ACTION-Galactosemia, galactitol in the brain had only been quantitated in Galactosemia patients who had consumed exogenous lactose/galactose
- No studies had previously been performed on endogenous galactitol quantitation in patients on a strict diet
- MRS quantitation of galactitol was an exploratory endpoint in ACTION-Galactosemia and was performed for scientific exploration, not for regulatory purposes

Objectives:

- Determine whether galactitol in the brain can be quantitated in Galactosemia patients on a restricted diet
  - Identify technical limitations and assess potential for future clinical use
- Determine whether galactitol reduction in the brain can be demonstrated via AT-007 treatment
- Determine whether plasma galactitol reduction correlates with brain galactitol reduction in patients treated with AT-007

Galactosemia Approval Requirements

Required for approval?	Plasma Galactitol Reduction	Brain Galactitol Reduction	Clinical Outcomes
Animal Model	✓	✓	✓
Adult Clinical Study	✓	Not required for approval	Not required for approval
Pediatric Clinical Study	✓	Not required for approval	✓ Post-approval requirement in US under Accelerated Approval


Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Result From Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies Guidance for Industry

Under 2020 FDA guidance on low prevalence, slowly progressive rare disease

Study Resulted in Usable Data in ~50% of Patients

Due to Disease-Related Limitations and Data Quality

18

Total Participants in ACTION-Galactosemia

11

Scans Including Both Baseline & End of Treatment Completed

8

MRI/MRS Data of Sufficient Quality

Breakdown by Cohort:

0 placebo
4 (5mg/kg)
2 (20mg/kg)
2 (40mg/kg)

Brain vs. Plasma Galactitol Reduction

Patient	Dose	Plasma Galactitol % Change from Baseline*	Brain Galactitol % Change from Baseline*
101	5mg/kg	-7.3%	+20.87%
102	5mg/kg	-22.4%	-4.95%
104	5mg/kg	-15.4%	-12.06%
105	5mg/kg	-31.7%	-27.83%
009	20mg/kg	-46.6%	+3.75%
014	20mg/kg	-47.4%	-61.94%
018	40mg/kg	-54.1%	-68.67%
019	40mg/kg	-46.3%	-69.80%

Mean % Reductions By Dose †

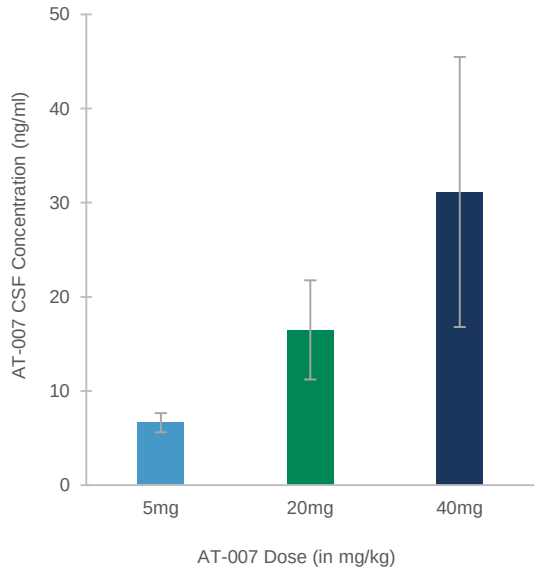
Dose	Plasma	Brain
5mg/kg	-19.20%	-5.99%
20mg/kg	-47.00%	-29.10%
40mg/kg	-50.20%	-69.24%

*% Change from baseline calculated at study Day 32, which corresponds to the 28th day of drug or placebo treatment
† Due to the low number of patients per cohort, mean should be considered only within the limited scope of the available data. Mean reductions in plasma calculated only for those patients for whom brain galactitol was analyzed, not for the full cohort.

AT-007 Dose Dependent Increase in CNS Drug Levels (CSF) and Reduction in Brain Galactitol

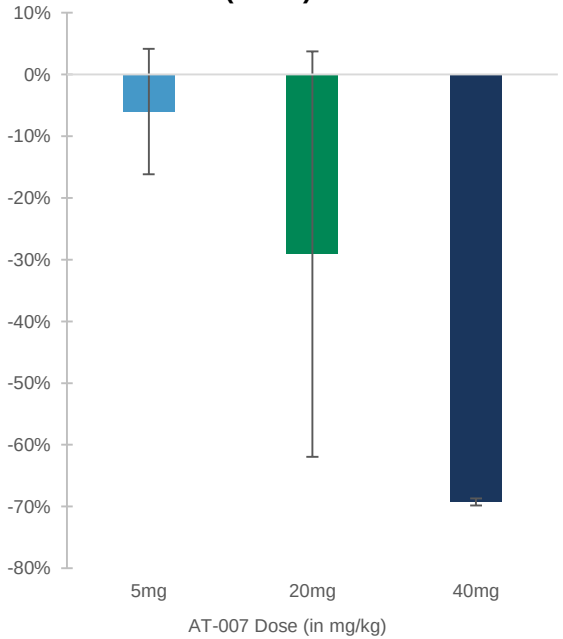
AT-007

Brain Penetrance in Healthy Volunteers

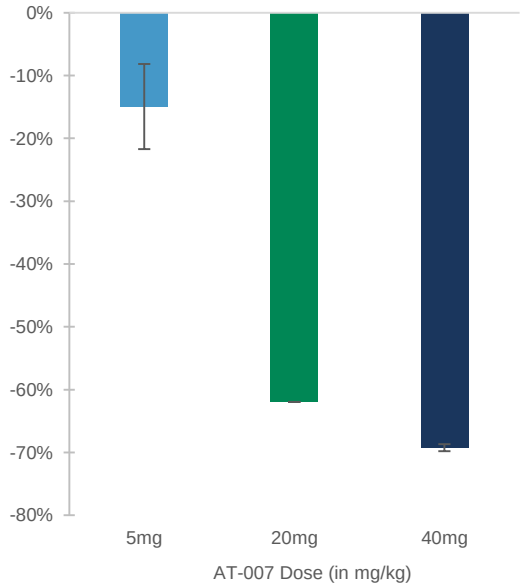


Brain Galactitol % Change from Baseline

(mean)



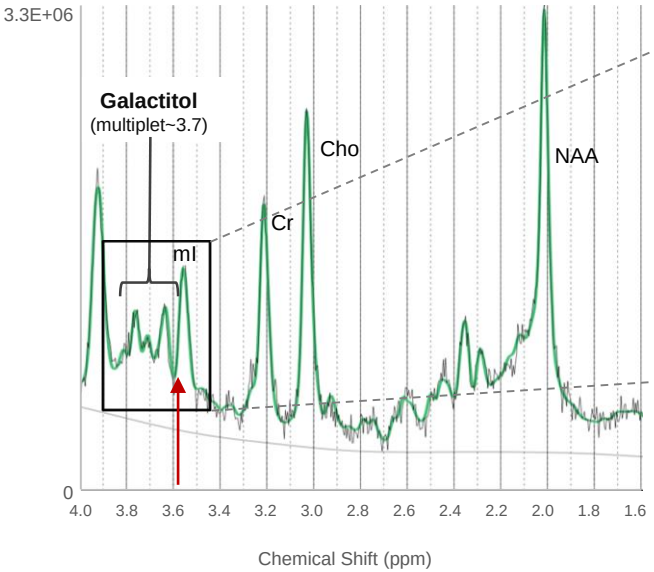
Brain Galactitol % Change from Baseline (mean; excludes patients 101 and 009)



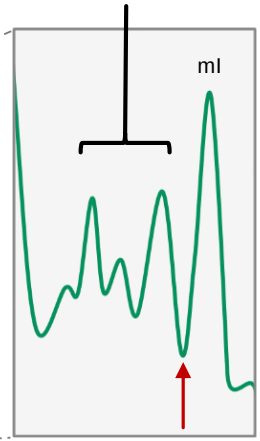
Oral presentation, Galactosemia Foundation Conference, July 2020; MRS data on file

A Closer Look at Myoinositol/Galactitol Peak Separation

Representative baseline MRS of adult Galactosemia patient from ACTION-Galactosemia study
(on galactose-free diet; 3T MRI)



Galactitol



Representative scan **with** clear peak separation between galactitol & myoinositol

Galactitol

Representative scan **without** clear peak separation between galactitol & myoinositol
(Patient 101)

Arrow *represents separation point between galactitol triplet and adjacent myoinositol (mI) peak*

Conclusions

- Galactitol quantitation in the brain is feasible in patients with Galactosemia on a restricted diet, but several technical limitations exist
- In the small number of patients studied here, AT-007 treatment at higher doses (20mg/kg and 40mg/kg) reduced brain galactitol levels
  - One exception at 20mg/kg may be the result of peak overlap between galactitol and myoinositol; another patient at the low dose 5mg/kg also demonstrated a similar issue
- This was an exploratory study conducted for scientific information purposes and not as an endpoint for regulatory approval; all data should be taken within the context of the small number of patients and associated limitations