AT-007, a Novel CNS Penetrant Aldose Reductase Inhibitor Prevents the Metabolic and Tissue Specific Abnormalities of Galactosemia in a GALT Deficient Rat Model of Disease

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Riccardo Perfetti, MD, PhD
Chief Medical Officer, Applied Therapeutics

Disclosures

Employee of Applied Therapeutics

Shareholder of Applied Therapeutics, Sanofi

AT-007 for Galactosemia

Burden of Disease

- Rare genetic metabolic disease caused by inability to break down galactose
  - Metabolite of lactose
  - Produced de novo by cells
- Even with strict dietary restriction of external lactose, endogenous galactose is produced within the body, leading to toxic build-up of galactitol
- Long-term consequences of disease include: Frequent pre-senile cataracts, significant motor, speech, cognitive, and psychiatric impairments, seizers, and ovarian insufficiency

Standard of Care

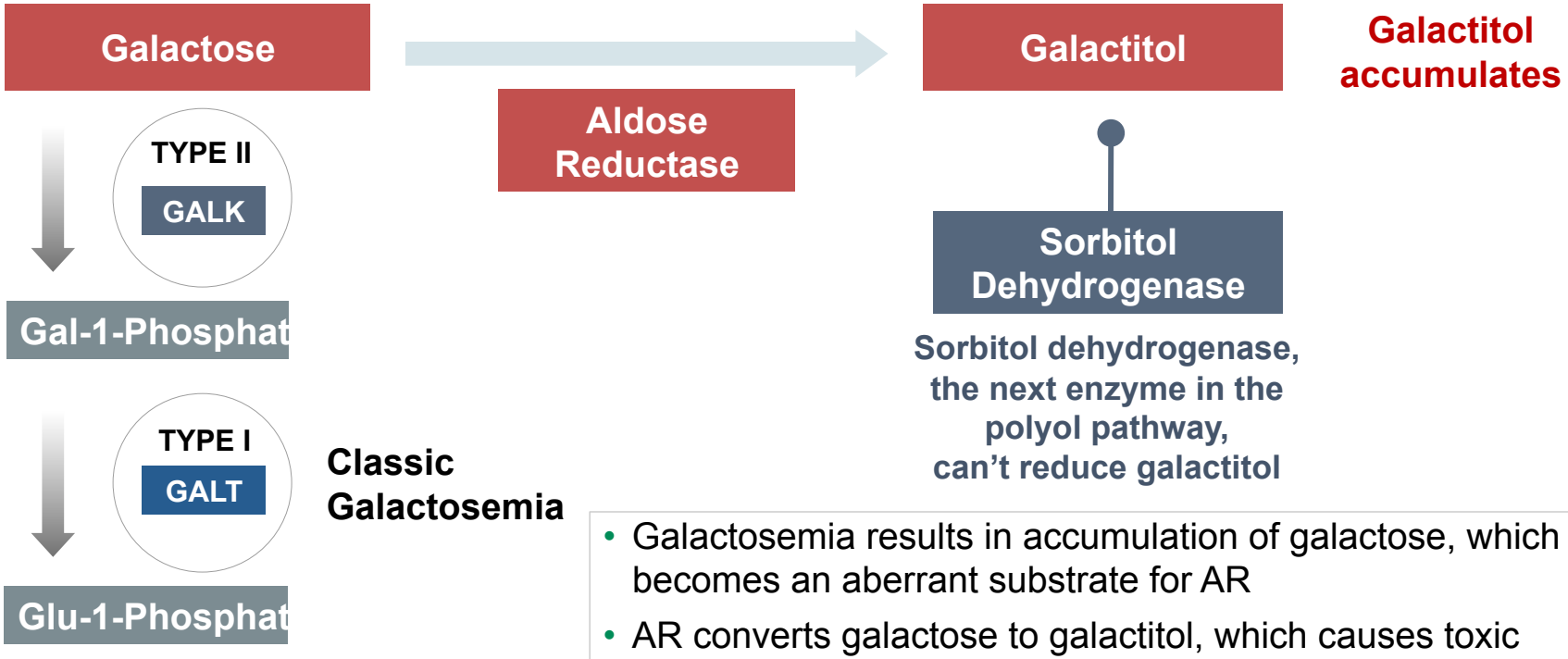
- Mandatory newborn screening in the US/EU; potentially fatal if undetected in first weeks of life and infant is exposed to lactose in breast milk or formula
- No approved therapies
- Standard of care is strict dietary restriction of lactose and galactose, which prevents fatalities, but **does not prevent long term consequences of disease**
- Greatly impacts children's development potential and quality of life (causes severe and permanent cognitive, intellectual and speech deficiencies)
- In adults, frequent cataracts due to galactitol build up in the eye; many develop persistent tremors

US Galactosemia Epidemiology

- Incidence **1:50,000-1:90,000**
- **~2,800** US patients
- Majority of patients are under the age of 40
- Is a “low prevalence” disease as defined by the FDA

Regulatory Guidelines: Because Galactosemia is a “slowly progressing” rare metabolic disease, under new FDA guidance, surrogate metabolic biomarkers may be acceptable for demonstration of therapeutic activity = low burden of clinical development

Aldose Reductase Activity Causes Toxic Accumulation of Galactitol in Galactosemia



- Galactosemia results in accumulation of galactose, which becomes an aberrant substrate for AR
- AR converts galactose to galactitol, which causes toxic complications in many tissues

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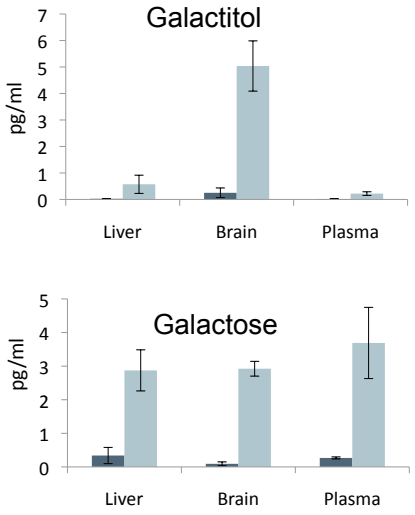
GALT Deficient Rat Model Closely Mirrors Human Disease

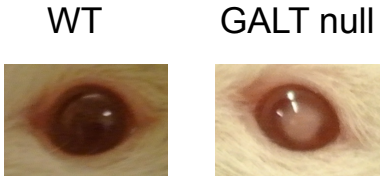
Biochemical Effects

GALT null rats have exponentially higher levels of galactose and galactitol, as well as Gal1p



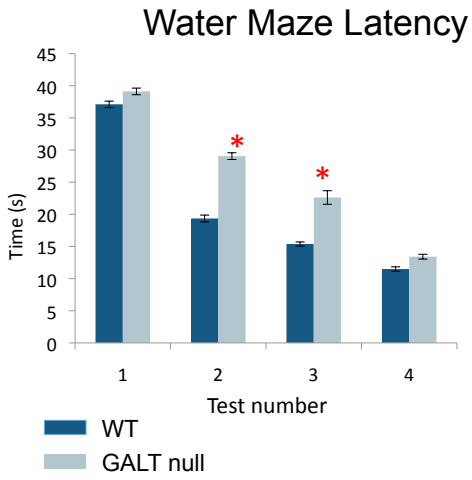
Tissue Deposition of Galactitol

All GALT null rats display cataracts (caused by galactitol deposition in the eye) vs. none of the WT rats



CNS Outcomes

GALT null rats display deficiencies in learning, cognition, and motor skills as measured by rotarod and water maze



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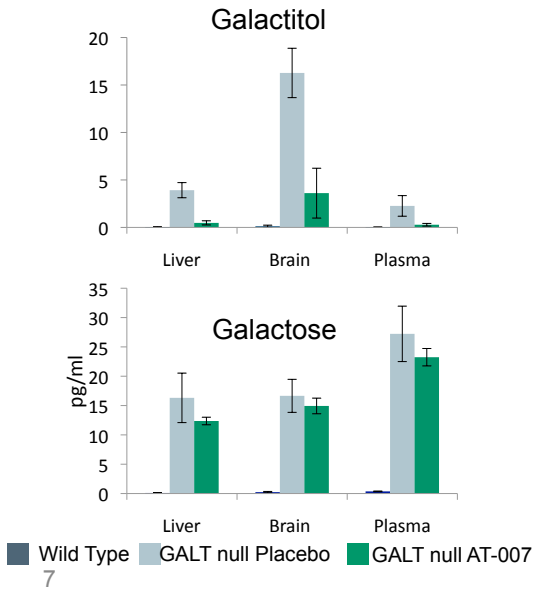
AT-007 Treatment Corrects All 3 Aspects of Disease in the Galactosemia Rat Model

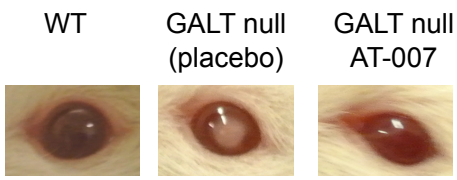
Biochemical Effects

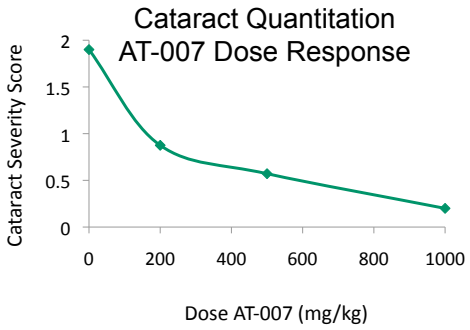
AT-007 treatment significantly reduced galactitol levels in all tissues without increasing galactose or Gal1p



Tissue Deposition of Galactitol

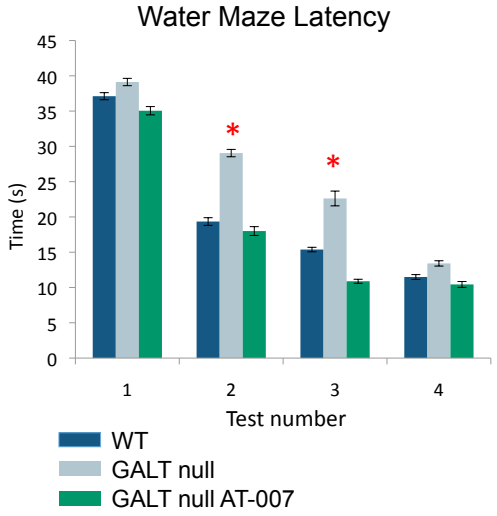
AT-007 treatment prevented galactitol accumulation in tissues, resulting in absence of cataracts





CNS Outcomes

AT-007 treatment normalized CNS outcomes on both water maze and rotarod



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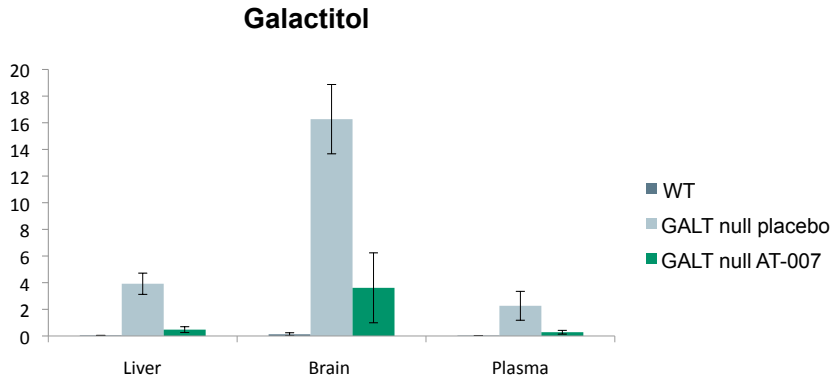
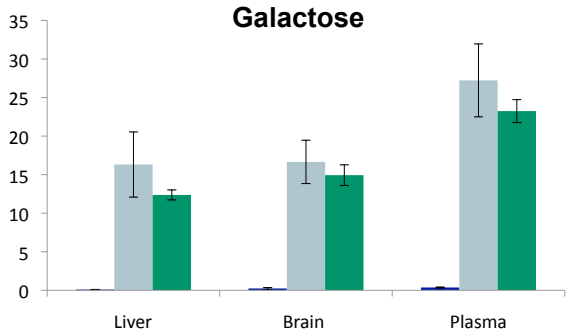
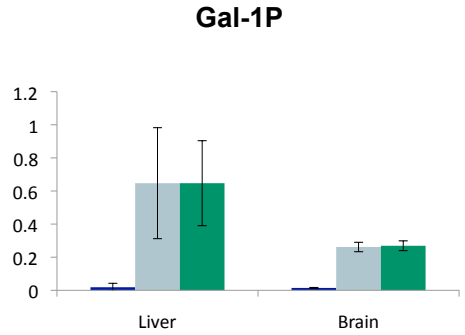
A Closer Look: AT-007 Significantly Reduces Galactitol Levels in all Target Tissues Without Increasing Galactose or Gal-1P







- AT-007 treatment from neonatal Day 1 to Day 10 significantly reduced galactitol in liver, brain and plasma
- Treatment did not increase galactose or Gal1P levels; similar results seen at Day 22 and age 5 months

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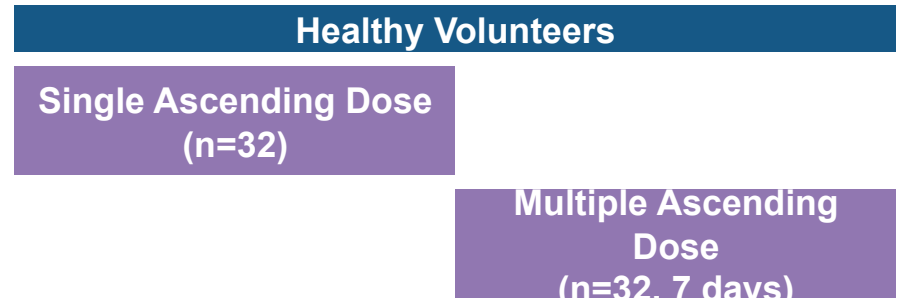
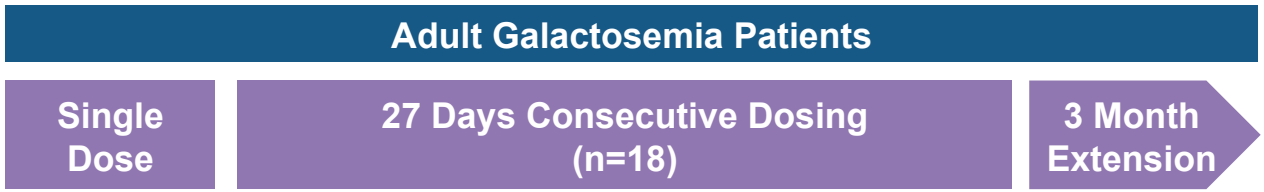
Galactosemia Phase 1/2 Registrational Study (ACTION-Galactosemia)

Multi-Center Placebo-Controlled Study in Healthy Volunteers & Adult Galactosemia Patients



Healthy Volunteer Endpoints:

- Safety
- Pharmacokinetics
- Pharmacodynamics



Galactosemia Endpoints:

- Safety
- Pharmacokinetics/ Pharmacodynamics
- **Efficacy Biomarker - Galactitol**

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Study Endpoints

Primary

- Overall safety and adverse events (AEs)
- Safety will be assessed by the following:
  - AEs
  - Clinical safety laboratory tests (hematology, chemistry, urinalysis)
  - Physical examinations
  - Vital signs
  - Electrocardiograms (ECGs)

Secondary

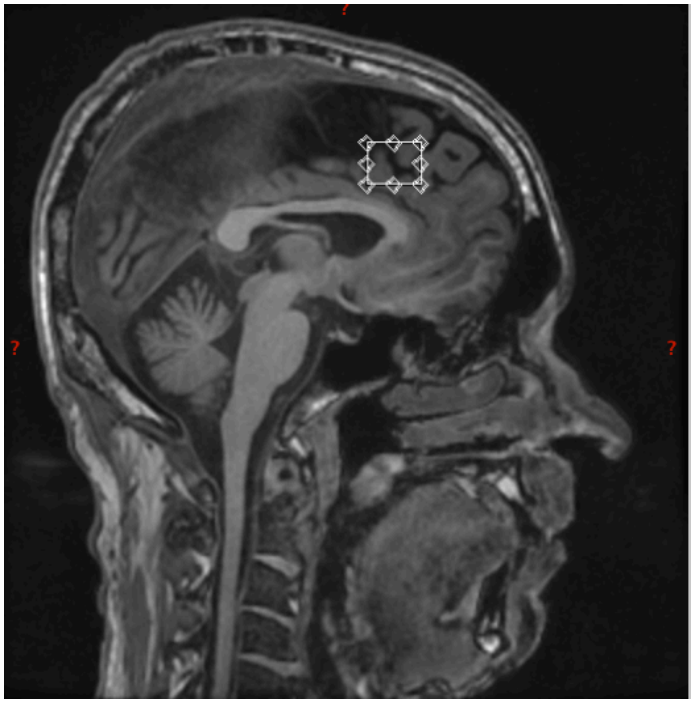
- PK parameters in healthy subjects and subjects with CG
- Galactitol in the blood of subjects with CG
- Galactose and galactose metabolites in the blood of subjects with CG
- Urine galactitol for subjects with CG

Exploratory

- Major metabolites of AT-007 (if any) in the urine of healthy subjects and subjects with CG
- AT-007 level in the CSF of healthy subjects (Part C only)
- MRI/MRS scans of the brain in a subset of subjects with CG

Baseline Characteristics of Patients with Classic Galactosemia Enrolled to Date

- Elevated urine galactitol, all patients
- Brain accumulation of galactitol, all patients
- EKG conduction abnormalities, most patients
- Anxiety and depression, most patients
- Relevant cognitive deficits, most patients
- History of seizures, many patients



Summary and Conclusions

- AT-007 treatment of GALT null rats corrects
  - Biochemical characteristics of Classic Galactosemia
  - Phenotypical characteristics of Classic Galactosemia
  - Behavioral characteristics of Classic Galactosemia
- A clinical study in healthy volunteers and in patients with Classic Galactosemia is currently undergoing
  - AT007 is well tolerated with no drug-related adverse events to date
  - Baseline characteristics of patients with Classic Galactosemia further confirm the severity of the disease in this population

Thank you

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