AT-007: Development of an Oral Treatment for Patients with Galactosemia
Galactosemia Foundation Conference
July 17-19, 2020
Shoshana Shendelman, PhD, CEO and Founder
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AT-007 is an investigational drug being studied in patients with Classic Galactosemia. It has not been approved by the FDA.
Our mission is to create transformative, life-changing treatments for patients who desperately need them.
## Agenda

### This presentation

- Overview of Galactosemia
- Mechanism of Disease
- AT-007 Preclinical (animal) Data
- AT-007 Clinical (human) Data
- Brief Overview of AT-007 Pediatric Study

### Other Presentations at the Galactosemia Foundation 2020 Conference

- ACTION-Galactosemia: Clinical Experience with Adult Galactosemia Patients and Path Forward; 4:15pm – 5:00pm (Eastern)
- ACTION-Galactosemia Kids: Pediatric Study of AT-007 in Children with Galactosemia; 5:30pm – 6:15pm (Eastern)

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Overview of Galactosemia & Stages of Disease

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Galactosemia Overview

**Rare metabolic disease** affecting ~2,800 patients in the US; ~80 new births per year

**Caused by enzyme deficiency** and inability to metabolize the simple sugar galactose

Galactose is formed by metabolism of external lactose, but **Galactose is also produced naturally by the body** (endogenously)

**No approved therapies;** mandatory newborn screening and initiation of dairy free diet; Dietary restriction prevents fatalities, but **does not prevent long term consequences of disease**

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Galactosemia Clinical Presentation

**Acute Newborn**
Life threatening if not identified and managed immediately:
- Hepatic and Renal Failure
- Brain Swelling (Edema/ Encephalopathy/ Pseudotumor Cerebri)
- Sepsis

**Chronic/Long-Term**
- **CNS Complications**
  - Low IQ / intellectual deficits
  - Motor skills / coordination
  - Seizures
  - Tremors
  - Speech/ language
  - Learning, behavioral, social impairments
  - Psychiatric problems (anxiety, depression)
- Primary Ovarian Insufficiency
- Cataracts
Galactosemia: Disease at Different Stages of Life

**Newborns**

Newborns are screened for Galactosemia, but sometimes symptoms can develop before the results are available; acute complications may be serious, requiring intensive care or even causing death.

**Infants & Toddlers**

Toddlers may develop early signs of developmental delays including growth and coordination, as well as speech problems.

**Primary School Children**

Developmental delays, learning, motor skill, behavioral and emotional problems may become more noticeable during this stage as children go to school.

**Teens**

Teens with Galactosemia can struggle as a result of behavioral, cognitive, or developmental issues, including puberty delays (& fertility issues in females).

**Adults**

Because of long-term health issues, including seizures, tremors or cataracts, it may be difficult for adults with Galactosemia to become independent.

Everyone with Galactosemia will experience disease differently, but this slide includes some common health issues that can occur at different stages of life.

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Dietary Restriction and Endogenous Galactose Production

Diet Can Reduce Exposure to Galactose From Lactose-Containing Foods

• Acute complications in the newborn period may be caused by external galactose (breast milk or dairy formula)
• Dietary restriction of lactose is important to prevent acute disease and death in infancy

However, the Body Produces Galactose On Its Own, Even With Diet

• Every cell in the human body makes galactose on its own ("endogenous")
• Long-term complications of Galactosemia are caused by endogenous production of galactose, not by lack of dietary control
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The Role of Aldose Reductase in Galactosemia

Galactose → Gal-1p → GALT Enzyme Deficiency

GALK

Energy Production

Gal-1p

Cell & Tissue Damage

Galactitol

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Galactosemia: Enzyme Deficiency in GALT or GALK Leads to Inability to Metabolize Galactose

Galactose Metabolism

Galactose → GALK → Gal-1p → GALT → Glucose-1-P

Energy Production

Classical Galactosemia

Galactose → GALK → Gal-1p → GALT → Glucose-1-P

GALT Enzyme Deficiency

Galactokinase Deficiency

Galactose → GALK → Gal-1p → GALT → Glucose-1-P

GALK Enzyme Deficiency

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The Role of Aldose Reductase in Galactosemia

- When galactose levels are abnormally high in blood and tissues, the enzyme Aldose Reductase can convert galactose to galactitol.
- This does not happen in healthy people, and galactitol is a toxic, abnormal metabolite.
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Galactitol is Toxic to Cells and May Cause Complications in Galactosemia

- **Ovarian Cells**: Ovarian Insufficiency
- **Neurons**: Tremor, Neuropathy
- **Brain**: Speech, Motor, Developmental Delay, Cognition, Memory, Seizures
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AT-007 is an investigational drug that blocks Aldose Reductase activity and stops conversion of galactose to galactitol.

- AT-007 was specifically designed to penetrate the Central Nervous System – to cross into the brain and reach neurons.
- In clinical trials, AT-007 is dosed orally once daily as a capsule or as a liquid suspension for children.

AT-007 is designed to block the enzyme Aldose Reductase, thereby preventing the conversion of galactose to galactitol, which can cause cell and tissue damage.
If Blocking AR Doesn’t Increase Galactose or Gal-1p..... Where Does the Extra Substrate Go?

Galactose can also be converted to a non-toxic intermediary called galactonate, which can then be metabolized by the body.

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What Evidence is There That Galactitol is Toxic?
3 Lines of Evidence Support Galactitol as the Toxic Metabolite Responsible for Galactosemia Complications

1. **Human genetic and clinical data**¹,²,³
   - GALK deficient patients demonstrate similar developmental abnormalities to GALT deficient patients
   - GALK deficient patients don’t produce Gal-1p; they only have elevated galactose and galactitol (because GALK is the enzyme that converts galactose to Gal-1p)
   - Galactitol accumulation in the brain causes cerebral edema and seizures in both GALT (Classic Galactosemia) and GALK patients

2. **Aldose Reductase expression is necessary to produce a disease phenotype in animal models**⁴,⁵
   - Mice deficient for GALT show no disease phenotype (they are normal)
   - Mice express extremely low levels of AR and therefore do not produce high levels of galactitol as humans do
   - Rats produce near-human levels of AR, and do produce galactitol when GALT is knocked out
   - The Rat GALT knock-out model shows a phenotype of disease similar to that in humans (cataracts plus developmental deficiencies)

3. **When galactitol is reduced via AR inhibition, the disease phenotype is prevented**⁶,⁷
   - In the GALT null rat, AT-007 treatment reduced galactitol levels (but not galactose or Gal-1p) and prevented cataracts and CNS abnormalities
   - Galactose-induced ovarian insufficiency in rats is prevented by ARI treatment

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Human Genetic and Clinical Data

GALK Patients Do Not Produce Gal-1P, But Have Similar Clinical Presentation and Long-Term Complications to Those With Classic Galactosemia

- GALK-deficient patients do not produce Gal-1P (as the GALK enzyme is necessary to convert Galactose into Gal-1P)
- Clinical symptoms observed in GALK-deficient children include mental retardation, microcephaly, failure to thrive, seizures, deafness, hepatomegaly
- Suggests galactitol (not Gal-1p) is responsible for chronic complications, such as learning, cognition and growth deficiencies

<table>
<thead>
<tr>
<th>Clinical Features in GALK Deficiency (Berlin Group shown)</th>
</tr>
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<tbody>
<tr>
<td>Number of patients: 18</td>
</tr>
<tr>
<td>Cataract: 9/18</td>
</tr>
<tr>
<td>Hypoglycemia: 6/18</td>
</tr>
<tr>
<td>Microcephaly: 6/18</td>
</tr>
<tr>
<td>Mental retardation: 5/16</td>
</tr>
<tr>
<td>Failure to thrive: 4/18</td>
</tr>
<tr>
<td>Hepatosplenomegaly: 1/18</td>
</tr>
<tr>
<td>Seizures: 1/18</td>
</tr>
<tr>
<td>Bilateral deafness: 1/18</td>
</tr>
<tr>
<td>Pseudotumor cerebri: 0/18</td>
</tr>
<tr>
<td>Hypercholesterolemia: 4/13</td>
</tr>
</tbody>
</table>

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**Human Genetic and Clinical Data**

**GALK Patients Develop Acute CNS Complications, Such as Seizures, Pseudotumor Cerebri and Edema in the Brain, Just Like GALT (Classic) Patients**

- GALK-deficient and GALT-deficient patients both develop similar CNS (brain) complications
  - Edema (swelling of the brain)
  - Pseudotumor Cerebri (pressure around the brain)
  - Seizures
- Galactitol can be measured in the brain at high concentration by MRI/MRS or autopsy of brain tissue

- “The same mechanism of intracellular solute accumulation which causes cataract formation in both transferase [GALT] and kinase [GALK] deficiencies appears also to affect the brain resulting in pseudotumor cerebri, seizures, and possible mental retardation in each of the enzyme defects.”¹
- “In a newborn infant with galactose-1-phosphate uridyltransferase [GALT] deficiency and encephalopathy, brain magnetic resonance imaging revealed cytotoxic edema in white matter. Using in vivo proton magnetic resonance spectroscopy, we detected approximately 8 mmol galactitol per kilogram of brain tissue, an amount potentially relevant to the pathogenesis of brain edema.”²
- “Increased activity of the alternate galactose pathway enzyme, aldose reductase, catalyzes the conversion of galactose to galactitol. It has been speculated that brain edema, as well as cataract formation, is secondary to galactitol accumulation. Indeed, galactitol had been reported to be markedly increased in the brain, the highest of the examined tissues obtained at autopsy from an infant with brain edema.”²


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Animal Data

Aldose Reductase Expression is Necessary to Produce a Disease Phenotype in Animal Models; Mouse GALT Knock-Out (No Elevated Galactitol) is Normal

- Mice express very low levels of Aldose Reductase (unlike humans)
- When a GALT knock-out mouse was created, the mice had high galactose and Gal-1p levels, but not high galactitol levels (only a “trace”)
- These mice were normal and healthy

“...mice that have no detectable GALT activity accumulate large amounts of galactose as well as galactose-1-phosphate but still appear healthy”

“This study suggests that alternative routes of galactose metabolism are important in the pathogenesis of galactosemia......Galactitol, on the other hand, may assume a more important role in future studies of pathophysiology”

Animal Data

Aldose Reductase Expression is Necessary to Produce a Disease Phenotype in Animal Models; Rat GALT Model Has Elevated Galactitol & Human Disease Characteristics

- Rats express human levels of Aldose Reductase
- GALT rat model has elevated galactose, Gal-1p and galactitol – just like humans with Classic Galactosemia
- Rat model displays human-like disease complications, including cognitive, learning, motor and growth deficiencies

“Here we introduce a new GALT-null rat model of CG and demonstrate that these rats display cataracts, cognitive, motor, and growth phenotypes reminiscent of patients outcomes.”

“With regard to mechanism, the results presented here provide a foundation for questioning the relative roles of different galactose metabolites as likely contributors to pathophysiology in CG…Our results raise serious concern about using RBC Gal-1P as a biomarker for disease, and suggest that plasma galactose or galactitol, and by extension perhaps urinary galactitol, may provide a more meaningful proxy”


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Animal Data

Reduction of Galactitol Prevents Complications of Disease in Animal Models

- Reducing galactitol levels in rats improves CNS outcomes and prevents ovarian insufficiency\(^1,2\)
- GALT null rats treated with AT-007 demonstrate reduced galactitol and improved CNS outcomes\(^1\)
  - Water maze and rotarod
- Normal rats treated with high galactose to induce high galactitol levels have ovarian insufficiency
- Reduction in galactitol with an “old” AR inhibitor prevents ovarian insufficiency\(^2\)


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Galactosemia History Timeline

1980’s
Newborn screening initiated

2003
First GALT knockout mouse model – no elevated galactitol, no disease phenotype

2004
Discovery of endogenous galactose production; dietary restriction does not prevent problems

2011
First GALK deficient patient study published: supports galactitol as causative of CNS complications

2018
First GALT knockout rat model developed: biochemical + CNS abnormalities

2019
AT-007 treatment/ reduction in galactitol prevents biochemical + CNS abnormalities in GALT rat model
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### Stages of Preclinical and Clinical Development

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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</table>
| Animal Studies                | • Demonstrate effectiveness of the investigational drug on the disease in animals  
                                | • Determine safety and safe/efficacious dosing window for human treatment    |
| Adult Healthy Volunteers      | • Initial human safety in “healthy” people without disease complications  
                                | • Are not on any other treatment medications                                 |
| Adult Galactosemia Patients   | • To determine safety and effectiveness in adults with Galactosemia         
                                | • Have disease complications and are on typical treatments for symptoms of disease |
| Pediatric Galactosemia Patients| • To determine safety and effectiveness in children with Galactosemia       
                                | • Determine long-term potential to impact clinical outcomes                  |
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AT-007 treatment significantly reduced galactitol levels in all tissues without increasing galactose or Gal1p.

Biochemical Effects

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

Tissue Deposition of Galactitol

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

CNS Outcomes

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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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
- AT-007 treatment did not increase galactose or Gal-1P levels; similar results seen at Day 22 and age 5 months
Reduction in Plasma (Blood) Galactitol Correlates With Reduction in the Brain

- Levels of galactitol in plasma and brain correlated in individual animals
- Reduction in galactitol induced by AT-007 treatment correlated in plasma and brain
### Extensive Preclinical Toxicology / Safety Studies Completed to Date

#### Chronic Toxicology
- 1-Month Treatment (in rats)
- 1-Month Treatment (in canines)
- 3-Month Treatment (in rats)
- 3-Month Treatment (in canines)
- 6-Month Treatment (in rats)
- 9-Month Treatment (in canines)

#### Specialized Studies
- Juvenile Toxicology (newborn to adult rats)
- Developmental/ Reproductive Toxicology (in rats & rabbits)
- Enzyme Inhibition / Drug Metabolism Studies
- Drug Transporter Studies (to predict potential drug-drug interactions)
Summary: AT-007 Preclinical (Animal) Studies

<table>
<thead>
<tr>
<th>Safety &amp; PK/PD</th>
<th>Biochemical Manifestations</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT-007 was safe and well tolerated in animals, with a broad dosing/exposure window to humans</td>
<td>In an animal model of Galactosemia, AT-007 prevented biochemical manifestations of disease; prevented production of toxic galactitol in blood and tissues, without adversely impacting galactose or Gal-1p</td>
<td>Prevented clinical manifestations of disease in animals including CNS abnormalities (learning, cognition, motor)</td>
</tr>
</tbody>
</table>
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Galactosemia Phase 1/2 Registral Study (ACTION-Galactosemia)
Multi-Center Placebo-Controlled Study in Healthy Volunteers & Adult Galactosemia Patients

Healthy Volunteer Endpoints:
- Safety
- Pharmacokinetics
- CNS Penetration (via CSF sample)

Healthy Volunteers

- Single Ascending Dose (n=40)
- Multiple Ascending Dose (n=40, 7 days)

Adult Galactosemia Patients**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Study Duration</th>
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</thead>
<tbody>
<tr>
<td>5 mg/kg, single dose</td>
<td>5 mg/kg, 27 Days Daily Dosing (n=4)</td>
</tr>
<tr>
<td>20 mg/kg, single dose</td>
<td>20 mg/kg, 27 Days Daily Dosing (n=4)</td>
</tr>
<tr>
<td>40 mg/kg, single dose</td>
<td>40 mg/kg, 27 Days Daily Dosing (n=4)</td>
</tr>
<tr>
<td>Placebo, single dose</td>
<td>Placebo, 27 Days Daily Dosing (n=6)</td>
</tr>
</tbody>
</table>

3 Month Extension

Galactosemia Endpoints:
- Safety
- Pharmacokinetics/Pharmacodynamics
- Efficacy Biomarker - Galactitol

*Based on initial topline data from Jan 2020, the study was expanded to include a 40mg/kg dose in healthy volunteers and then Galactosemia patients. This cohort also included 2 additional placebo patients.

**Due to the small size of the population and burden of study participation (travel, missed work for caregivers etc), the protocol proactively allowed for patients to participate in more than 1 cohort. If participating in a second cohort, the patient had to remain blinded, washout for >1 month, and a new baseline was taken. (Crossover design is in line with FDA guidance)

Patients were on lactose-restricted diet prior to enrollment and throughout study

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Summary: Healthy Volunteer Data

AT-007 Was Safe and Well Tolerated; PK Supportive of Once-Daily Dosing

Safety
~80 healthy volunteers treated; AT-007 was safe and well tolerated at all doses

Brain Penetrance
Drug crosses into brain when dosed orally (CNS penetrant)

Pharmacokinetics
Dose-dependent increase in exposure; supportive of once daily oral dosing

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**Galactosemia Phase 1/2 Registralional Study (ACTION-Galactosemia)**

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

<table>
<thead>
<tr>
<th>Healthy Volunteers</th>
<th>Adult Galactosemia Patients**</th>
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<tbody>
<tr>
<td>Single Ascending Dose (n=40)</td>
<td>5 mg/kg single dose</td>
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<tr>
<td>Multiple Ascending Dose (n=40, 7 days)</td>
<td>5 mg/kg 27 Days Daily Dosing (n=4)</td>
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<tr>
<th>Healthy Volunteer Endpoints:</th>
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<tbody>
<tr>
<td>• Safety</td>
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<td>• Pharmacokinetics/Pharmacodynamics</td>
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<tr>
<td>• Efficacy Biomarker - Galactitol</td>
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<table>
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<tr>
<th>Adult Galactosemia Patients**</th>
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<tbody>
<tr>
<td>20 mg/kg Single dose</td>
</tr>
<tr>
<td>40 mg/kg* Single dose</td>
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</table>

| Placebo Single dose | Placebo 27 Days Daily Dosing (n=6) |

*Based on initial topline data from Jan 2020, the study was expanded to include a 40mg/kg dose in healthy volunteers and then Galactosemia patients. This cohort also included 2 additional placebo patients.

**Due to the small size of the population and burden of study participation (travel, missed work for caregivers etc), the protocol proactively allowed for patients to participate in more than 1 cohort. If participating in a second cohort, the patient had to remain blinded, washout for >1 month, and a new baseline was taken. (Crossover design is in line with FDA guidance; Patients were on lactose-restricted diet prior to enrollment and throughout study)

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## AT-007 Safety in Adult Galactosemia Patients

<table>
<thead>
<tr>
<th>Laboratory &amp; clinical assessments demonstrated safety and tolerability</th>
<th>Pharmacokinetics (drug levels over time) supports once-daily dosing</th>
</tr>
</thead>
</table>

AT-007 was safe and well tolerated at all doses tested.

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Biomarker Results

AT-007 Significantly Decreased Galactitol Levels in Plasma at 20 and 40mg/kg

Maximum Galactitol Reduction vs. Baseline

P<0.01 for 20mg/kg vs. placebo and 40mg/kg vs. placebo; Placebo group updated to include 2 additional patients who participated in 40mg/kg cohort; Maximal reduction on Day 32

All biomarker assays were developed, validated, and performed by Icon Labs Whitesboro, NY (independent 3rd party lab)

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AT-007 Decreased Galactitol Levels in All Treated Patients
Decrease was Dose-Dependent, Rapid and Sustained; Statistically Significant at 20 & 40mg/kg

Individual Maximum Reduction in Galactitol Percent Change From Baseline

Further Characterization of AT-007 in adult Galactosemia patients in ongoing long-term safety study

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AT-007 Galactitol Reduction is Rapid and Sustained
Reduction Begins on 1st Day of Treatment and is Sustained Over 1 Month of Treatment

Galactitol Reduction is Sustained Over the 24hr Dosing Period at Steady State (Day 12 and Day 32), Supporting Once Daily Oral Dosing

Data for each cohort is shown as mean +SEM; Baseline mean galactitol was not statistically different between cohorts

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Galactitol Can be Measured in the Brain

- Galactitol can be quantitatively assessed in the brain by MR Spectroscopy.
- Galactitol is not present in the brain of healthy volunteers and is only present in Galactosemia patients.
- In “old” studies with low power magnets, the abnormal galactitol peak was only visible in patients who were not on a compliant diet.
- Higher power 3T MRI/MRS now allows detection and quantitation of galactitol in the brain of patients on a galactose-free diet, representing galactitol in the brain formed by endogenous galactose production.

**Effects of AT-007 on brain galactitol will be presented at upcoming conference**

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AT-007 was safe & well-tolerated in the ACTION-Galactosemia adult study

- Includes 80 healthy volunteers and 14 Classic Galactosemia patients

AT-007 was shown to be CNS penetrant

- Important in Galactosemia, which includes significant CNS clinical presentation
- Supports once-daily oral dosing

Galactitol is a toxic metabolite formed in Galactosemia patients

- Not formed in healthy people
- Detectable in blood and tissues, including the brain

AT-007 induced rapid and sustained reduction in plasma galactitol

- 20 and 40mg/kg dosing resulted in significant reduction in plasma galactitol (p<0.01 vs. placebo)
- No significant change in galactose or Gal-1p

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ACTION-Galactosemia Kids Pediatric Registrational Clinical Study Underway

**PK/PD Dose Range Finding**
- Single Dose
- 7 days Consecutive Dosing

**3 Month Treatment**
- Biomarker-Based Outcome

**Long-Term Safety/Outcomes**
- "Open-Label” Long-Term Treatment (no placebo) Includes Clinical Outcomes of Feel/Function Over >5 Yrs

- Dose range finding PK/PD study to determine optimal dose in children, followed by 3-month biomarker-based assessment of galactitol reduction for NDA submission
  - Initial study (pre-NDA) will enroll children ages 2-17
  - Additional cohort will enroll infants age 2 mo-2 yrs (timing TBD)

- A long-term clinical outcomes study (not required for approval) will follow post-NDA submission to assess impact on how patients feel and function and provide long-term data to support long-term market access, adherence and persistence on therapy

Planned NDA submission

For more details please see pediatric study presentation, today at 5:30pm – 6:15pm

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Thank you to all of the families who participated in the ACTION-Galactosemia study and help make this development program possible.

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Thank you to the Galactosemia community for welcoming us!