UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): **April 21, 2020**

APPLIED THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**001-38898**	**81-3405262**
(State or Other Jurisdiction of Incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)

545 5th Avenue, Suite 1400 **New York, NY 10017** (Address of Principal Executive Offices)	**10017** (Zip Code)

Registrant's telephone number, including area code: **(212) 220-9226**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common stock	APLT	The Nasdaq Stock Market LLC

Item 7.01. Regulation FD Disclosure.

On April 21, 2020, Applied Therapeutics, Inc. (the "Company") issued a press release announcing that the Company will present data from the pivotal ACTION-Galactosemia study via webcast. This data was originally planned for the Society of Inherited Metabolic Diseases (which was cancelled due to Covid-19). The Company's presentation will be on Tuesday April 21, 2020 at 8:00am ET. A copy of this press release is attached as exhibit 99.1 hereto.

During the webcast, a corporate slide presentation will be presented. A copy of the Company's presentation slide deck, which will be referenced during the conference, including during the Company's webcast presentation, is furnished herewith as Exhibit 99.2.

The information provided under this Item (including Exhibits 99.1 and 99.2, attached hereto) shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, except as expressly set forth by specific reference in such a filing.

Item 8.01. Other Events.

On April 21, 2020, the Company provided the following updates regarding its clinical trials and business operations in light of the ongoing novel coronavirus (Covid-19) pandemic:

- The Company has taken steps in line with guidance from the U.S. Centers for Disease Control and Prevention (CDC) and the State of New York to protect the health and safety of its employees and the community. In particular, the Company has implemented a work-from-home policy for all employees and has restricted on-site activities to certain chemical, manufacturing and control (CMC) and clinical trial activities. The Company is continuing to assess the impact of the Covid-19 pandemic to best mitigate risk and continue the operations of its business.

- The Company is working closely with its clinical sites to monitor the potential impact of the evolving Covid-19 pandemic. The Company remains committed to its clinical programs and development plans. As of now, the Company has not experienced any significant delays to its ongoing or planned clinical trials. Notwithstanding the Company's current expected timing and milestones, the ability to continue to enroll patients, conduct patient follow-up and provide data readouts as planned may be impacted by the Covid-19 pandemic and is subject to rapid change as events proceed.

- A COVID-19 Investigational New Drug Application (IND) has been opened with the Food and Drug Administration (FDA) for AT-001, a novel potent Aldose Reductase inhibitor in global Phase 3 development for Diabetic Cardiomyopathy. Multiple AT-001 investigator-initiated trials are currently underway to address acute lung inflammation and cardiomyopathy in critical COVID-19 patients. Several New York City hospitals have initiated Emergency Investigational Drug applications for AT-001 use in critical COVID-19 patients. AT-001 is currently being accessed in these New York City hospitals via "Named Patient" Emergency INDs or Investigator-Initiated Trials, depending on the patient circumstance and hospital institution. Institutions that have initiated trials include Mount Sinai, NYU, and Columbia. Data is being gathered through these studies on the effect of AT-001 therapy in critical COVID-19 patients. Depending on the outcome of such studies, the Company may initiate a limited cost-effective company-sponsored study of AT-001 in critical COVID-19 patients.

- The Company continues to characterize AT-007's long-term safety in adult patients for the treatment of Galactosemia and to evaluate a potential pediatric trial. The Company has not experienced any meaningful delays in treatment or evaluations of patients in connection with this study. Many of the activities on the AT-007 program have been converted to home health visits.

- The Company is also continuing with its Phase 3 registrational trial for AT-001 in diabetic cardiomyopathy and has experienced some delays in patient enrollment for this trial, particularly in study sites associated with hospitals. The Company is taking actions to mitigate the impact of these delays on the timeline for the study, including adding additional study sites globally.

In addition, in light of recent developments relating to the Covid-19 pandemic, the Company is amending and restating the risk factor titled "Our business may be adversely affected by the recent coronavirus outbreak" previously disclosed in Part I., Item 1A. of its Annual Report on Form 10-K for the fiscal year ended December 31, 2019, filed with the Securities and Exchange Commission on March 13, 2020, as follows:

Our business may be adversely affected by the recent coronavirus outbreak.

In December 2019, a novel strain of coronavirus, referred to as 2019-ncov, Covid-19 coronavirus epidemic, or Covid-19, was reported to have surfaced in Wuhan, China. Covid-19 has since spread globally, including the United States where we have our executive offices and principal operations. Infections and deaths related to Covid-19 have disrupted the United States' healthcare and healthcare regulatory systems. Such disruptions could divert healthcare resources away from, or materially delay FDA approval with respect to, our clinical trials. It is unknown how long these disruptions could continue. In addition, other known and unknown factors caused by Covid-19 could materially delay our clinical trials, including our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to Covid-19. For example, with respect to our trials related to AT-001 for the treatment of Diabetic Cardiomyopathy, we have experienced delays in patient enrollment. Though we have undergone efforts to mitigate such delays, such efforts may not entirely avoid the effects of Covid-19 on our trials. Furthermore, we may experience additional delays in patient enrollment that we may not be able to mitigate. In addition, we have partnered with clinical research organizations, or CROs, to conduct clinical studies in jurisdictions, such as the EU, that have been affected by the spread of Covid-19. There is a possibility that such CROs may become unavailable or that the clinical trials they manage may be delayed due to Covid-19 or containment efforts associated with it. Such events may lead to termination of our relationship with affected CROs, affecting the development and study of our product candidates. Any elongation or de-prioritization of our clinical trials or delay in regulatory review resulting from such disruptions could materially affect the development and study of our product candidates, and increase the costs related to such development.

Government response to Covid-19 may also materially impact our business. Our executive offices and principal operations are located in New York and are currently subject to a statewide stay-at-home order. In addition, many of our potential partners and study participants worldwide are similarly impacted. In response, we have implemented a work-from-home policy for all employees and have restricted on-site activities to certain chemical, manufacturing and control (CMC) and clinical trial activities. However, many of our clinical trials sites and certain of our vendors, including our third-party contract manufactures, currently rely on exemptions from stay-at-home, shelter-in-place or similar orders for certain operations. Any of the applicable exemptions may be curtailed or revoked, which would further adversely impact our business.

In addition, we have in the past and may in the future source equipment and materials from China and other countries affected by Covid-19. If we were to engage with third party manufacturers in such countries in the future, there would be an increased risk of supply interruption, resulting in business/operational disruption. Covid-19's spread, which has caused a broad impact globally, such as restrictions on travel and quarantine policies put into place by businesses and governments, may materially affect us economically. While the potential long-term economic impact of the Covid-19 pandemic may be difficult to assess or predict, there has already been a significant disruption of the global financial markets and the world economy, including the United States economy. A prolonged recession or market correction resulting from the spread of Covid-19 could materially affect our business and the value of our common stock, and reduce our ability to access capital, which could in the future negatively affect our liquidity.

While it is too early to tell whether Covid-19 will have a material effect on our business over time, we continue to monitor the situation as it unfolds. The extent to which Covid-19 impacts our results will depend on many factors and future developments, including new information about Covid-19 and any new government regulations which may emerge to contain the virus, among others.

This Form 8-K contains "forward-looking statements" that involve substantial risks and uncertainties for purposes of the safe harbor provided by the Private Securities Litigation Reform Act of 1995. Any statements, other than statements of historical fact, included herein regarding strategy, future operations, prospects, plans and objectives of management, including words such as "may," "will," "expect," "anticipate," "plan," "intend," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are forward-looking statements. These include, without limitation, statements regarding (i) the design, scope and results of our clinical trials, (ii) the timing of the initiation and completion of our clinical trials, including that the Company may initiate a limited cost-effective company-sponsored study of AT-001 in critical COVID-19 patients, (iii) the likelihood that data from our clinical trials will support future development of our product candidates, (iv) the likelihood of obtaining regulatory approval of our product candidates and qualifying for any special designations, such as orphan drug designation, (v) our cash runway and the timing of our clinical development plan and (vi) the impact of the COVID-19 pandemic on the timing and progress of our ongoing clinical trials and our business in general. Forward-looking statements in this Form 8-K involve substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by the forward-looking statements, and we, therefore cannot assure you that our plans, intentions, expectations or strategies will be attained or achieved. Such risks and uncertainties include, without limitation, the uncertainties inherent in the initiation, execution and completion of clinical trials, in the timing of availability of trial data, in the results of the clinical trials, in the actions of regulatory agencies, in the commercialization and acceptance of new therapies as well as the impact of the COVID-19 pandemic on these plans and expectations. Factors that may cause actual results to differ from those expressed or implied in the forward-looking statements in this Form 8-K are discussed in our filings with the U.S. Securities and Exchange Commission, including the "Risk Factors" contained therein. Except as otherwise required by law, we disclaim any intention or obligation to update or revise any forward-looking statements, which speak only as of the date they were made, whether as a result of new information, future events or circumstances or otherwise.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits:

The following exhibits are attached with this current report on Form 8-K:

Exhibit No.	Description
99.1	Press Release, dated April 21, 2020.
99.2	Copy of Applied Therapeutics, Inc. slide presentation dated April 2020

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

APPLIED THERAPEUTICS, INC.

Dated: April 21, 2020

By: */s/ Shoshana Shendelman*
Name: Shoshana Shendelman, Ph.D.
Title: Chief Executive Officer

Applied Therapeutics Announces Full Data and Scientific Presentations from the Pivotal Phase 2 ACTION-Galactosemia Trial

AT-007 demonstrated rapid and sustained reduction in toxic galactitol levels with no accompanying increase in galactose

Positive trend on MRI outcomes, including indirect measures of edema, neuronal health and brain galactitol levels in AT-007-treated patients

40 mg/kg dose of AT-007 was well-tolerated with no drug-related adverse events reported in healthy volunteers; evaluation of 40 mg/kg dose in Galactosemia patients remains ongoing

NEW YORK, April 21, 2020 - Applied Therapeutics, Inc. (Nasdaq: APLT), a clinical-stage biopharmaceutical company developing a pipeline of novel drug candidates against validated molecular targets in indications of high unmet medical need, today announced new data and scientific presentations from the pivotal Phase 2 ACTION-Galactosemia trial. The full study data, originally planned to be presented at the Society for Inherited Metabolic Disorders conference this week, will be available on the company's website.

- Slides from the presentation ***"Development of AT-007 for the treatment of Galactosemia"***, presented by Riccardo Perfetti, MD, PhD, Chief Medical Officer of Applied Therapeutics, will be made available today, April 21, at 8:00 a.m. EDT on the Events page under the Investor Relations section of the Applied Therapeutics website at www.appliedtherapeutics.com. Key data from the presentation are summarized below.

- A **Galactosemia Educational Symposium** for healthcare providers hosted by Applied Therapeutics will be webcast with a live Q&A moderated by Eva Morava, MD, PhD, Professor of Clinical Genomics, Mayo Clinic, on April 27 at 1:00 p.m. EDT. The live event will be available on the Presentations & Publications section of the Applied Therapeutics website at www.appliedtherapeutics.com. A replay of the call will be available on the Applied Therapeutics website approximately two hours after the completion of the call and will be archived for 30 days.

The double-blind placebo-controlled ACTION-Galactosemia trial evaluated safety and pharmacokinetics of AT-007, a Central Nervous System (CNS) penetrant Aldose Reductase Inhibitor (ARI) in healthy volunteers, as well as safety, pharmacokinetics, and efficacy biomarkers in adult Galactosemia patients. The key biomarker outcome of the study was reduction in galactitol, an aberrant toxic metabolite of galactose, formed by Aldose Reductase in Galactosemia patients. Accumulation of galactitol causes long-term complications ranging from CNS dysfunction to cataracts.

"We are pleased to share the full results of ACTION-Galactosemia," said Riccardo Perfetti, MD, PhD, Chief Medical Officer of Applied Therapeutics. "Patients with this devastating disease experience life-long accumulation of galactitol in the CNS and in other tissues, and our data demonstrates rapid and sustained reduction in this toxic metabolite."

“We remain steadfast in our commitment to bring this treatment to patients as quickly as possible, and understand the urgency to potentially prevent worsening of disease in adults and onset of disease-related complications in children,” said Shoshana Shendelman, PhD, Founder and CEO of Applied Therapeutics. “We look forward to initiating a pediatric study in Q2 and remain on track to submit an NDA later this year.”

Galactitol Reduction

As previously announced, once-daily 20mg/kg AT-007 reduced galactitol levels by approximately 50% in Galactosemia patients. Reduction in galactitol levels was rapid (within 6 days of consecutive AT-007 treatment) and sustained throughout the treatment period of 27 days. Reduction in galactitol from baseline was statistically significant at the 20mg/kg vs placebo ($p<0.01$). The lower dose tested, 5mg/kg, demonstrated a similar trend in reducing galactitol levels approximately 20% from baseline (p=NS from placebo).

Other Galactose Metabolites

Reduction in galactitol was not accompanied by any increase in galactose. This data confirms that reduction of the toxic metabolite galactitol through Aldose Reductase inhibition does not result in derangement of other metabolites in the galactose pathway as previously demonstrated in animal models of Galactosemia.

MRI/MRS Data

Patients treated with AT-007 (once-daily over 27 days) demonstrated a positive trend in MRI outcomes, specifically on measures of edema and overall neuronal health. AT-007 treated patients demonstrated improvement in ventricular volume, a measure of edema, which has been shown to occur in the brain of Galactosemia patients due to osmotic dysregulation caused by galactitol. Patients treated with AT-007 also demonstrated improvements in N-acetyl-aspartate, a marker of neuronal health. Galactitol was visible on MRI in the brain of all patients at baseline, and a positive trend toward decreased brain galactitol levels in AT-007 treated patients was observed by quantitative MR Spectroscopy (MRS).

40mg/kg Data

As no drug-related adverse events were seen at the once-daily 20mg/kg dose, a once-daily 40mg/kg dose was subsequently studied in healthy volunteers and is ongoing in Galactosemia patients. The 40mg/kg dose was safe and well tolerated. Evaluation of once-daily 40mg/kg AT-007 in Galactosemia patients remains ongoing and this data will be shared when available.

Safety

No drug-related adverse events were reported at any dose of AT-007 in ACTION-Galactosemia. This robust safety data includes all 80 healthy volunteers and 8 adult Galactosemia patients who received active drug during the core study.

Future Development

A 90-day safety extension study for ACTION-Galactosemia is ongoing. The extension study is open to patients from the core study and to new adult Galactosemia patients. A pediatric study with a safety and biomarker design similar to ACTION-Galactosemia is planned to commence in Q2 of this year. Both the extension study and the pediatric study are designed to incorporate primarily home health visits in order to limit travel and risk of exposure to COVID-19. More information on the pediatric study will be shared in coming weeks.

About Applied Therapeutics

Applied Therapeutics is a clinical-stage biopharmaceutical company developing a pipeline of novel drug candidates against validated molecular targets in indications of high unmet medical need. The Company's lead drug candidate, AT-007, is a novel central nervous system penetrant aldose reductase inhibitor (ARI) for the treatment of Galactosemia, a rare pediatric metabolic disease. The Company initiated a Phase 1/2 clinical trial in June 2019 and read out positive top-line biomarker data in adult Galactosemia patients in January of 2020. The Company is also developing AT-001, a novel potent ARI that is being developed for the treatment of Diabetic Cardiomyopathy, or DbCM, a fatal fibrosis of the heart. The Company initiated a Phase 3 registrational study in DbCM in September 2019. The preclinical pipeline also includes AT-003, an ARI designed to cross through the back of the eye when dosed orally, for the treatment of diabetic retinopathy, expected to advance into a Phase 1 study in 2020, as well as novel dual PI3k inhibitors in preclinical development for orphan oncology indications.

Forward-Looking Statements

This press release contains "forward-looking statements" that involve substantial risks and uncertainties for purposes of the safe harbor provided by the Private Securities Litigation Reform Act of 1995. Any statements, other than statements of historical fact, included in this press release regarding strategy, future operations, prospects, plans and objectives of management, including words such as "may," "will," "expect," "anticipate," "plan," "intend," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are forward-looking statements. These include, without limitation, statements regarding (i) our plan to move quickly towards regulatory filing following our pivotal Phase 2 ACTION-Galactosemia study, while preparing for Galactosemia commercial launch and growing our organization, (ii) the design, scope and results of our clinical trials, (iii) the timing of the initiation and completion of our clinical trials, (iv) the likelihood that data from our clinical trials will support future development of our product candidates, and (v) the likelihood of obtaining regulatory approval of our product candidates and qualifying for any special designations, such as orphan drug designation. Forward-looking statements in this release involve substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by the forward-looking statements, and we, therefore cannot assure you that our plans, intentions, expectations or strategies will be attained or achieved. Such risks and uncertainties include, without limitation, (i) our plans to develop and commercialize our product candidates, (ii) the initiation, timing, progress and results of our current and future preclinical studies and clinical trials and our research and development programs, (iii) our ability to take advantage of expedited regulatory pathways for any of our product candidates, (iv) our estimates regarding expenses, future revenue, capital requirements and needs for additional financing, (v) our ability to successfully acquire or license additional product candidates on reasonable terms, (vi) our ability to maintain and establish collaborations or obtain additional funding, (vii) our ability to obtain regulatory approval of our current and future product candidates, (viii) our expectations regarding the potential market size and the rate and degree of market acceptance of such product candidates, (ix) our ability to fund our working capital requirements and expectations regarding the sufficiency of our capital resources, (x) the implementation of our business model and strategic plans for our business and product candidates, (xi) our intellectual property position and the duration of our patent rights, (xii) developments or disputes concerning our intellectual property or other proprietary rights, (xiii) our expectations regarding government and third-party payor coverage and reimbursement, (xiv) our ability to compete in the markets we serve, (xv) the impact of government laws and regulations and liabilities thereunder, (xvi) developments relating to our competitors and our industry, (xvii) the impact of the COVID-19 pandemic on the timing and progress of our ongoing clinical trials and our business in general and (xviii) other factors that may impact our financial results. In light of the significant uncertainties in these forward-looking statements, you should not rely upon forward-looking statements as predictions of future events. Although we believe that we have a reasonable basis for each forward-looking statement contained in this press release, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur at all. Factors that may cause actual results to differ from those expressed or implied in the forward-looking statements in this press release are discussed in our filings with the U.S. Securities and Exchange Commission, including the "Risk Factors" contained therein. Except as otherwise required by law, we disclaim any intention or obligation to update or revise any forward-looking statements, which speak only as of the date they were made, whether as a result of new information, future events or circumstances or otherwise.

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917.297.5956
media@appliedtherapeutics.com

Exhibit 99.2

ACTION-GALACTOSEMIA: April 2020 Trial Results

Development of AT-007 for the Treatment of Galactosemia

Riccardo Perfetti, MD, PhD
Chief Medical Officer

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Summary: ACTION-Galactosemia Study Results

Safety/ PK/ PD

- AT-007 was safe and well-tolerated
- PK/PD data supports once-daily oral dosing
- AT-007 is CNS penetrant – important in Galactosemia, which includes significant CNS clinical presentation

Efficacy in Galactosemia Patients

- AT-007 induced rapid and sustained reduction in plasma galactitol, an aberrant, toxic metabolite formed in Galactosemia patients
- 20mg/kg dosing resulted ~50% reduction in plasma galactitol ($p<0.01$ vs. placebo)
- Positive AT-007 MRI/MRS impact

Overview of Galactosemia

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AT-007 for Treatment of Galactosemia

Pathogenesis of Disease

- Rare genetic metabolic disease caused by inability to break down galactose
- Galactose is a natural sugar formed by metabolism of lactose, but is also produced endogenously by the body
- **In patients with Galactosemia, Aldose Reductase converts galactose to galactitol, an aberrant toxic metabolite**

Standard of Care

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

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Galactosemia Clinical Presentation

Acute Newborn

- Hepatic and renal failure
- Brain swelling (edema; encephalopathy)
- Potentially life threatening if not identified and managed immediately

Chronic/ Long-Term

- CNS complications
  - Low IQ/ intellectual impairment
  - Motor skills
  - Speech/ language
  - Learning, behavioral, social impairments
  - Psychiatric problems (anxiety, depression)
- Primary ovarian insufficiency
- Cataracts

Galactosemia Effects ~2,800 Patients in the US; Potential for Abbreviated Regulatory Approval & Low Burden of Development

- **~2,800 living** US patients ; **~80 new births per year**
- Majority of patients are under the age of 40, as newborn screening was adopted in the 1980s and 1990s
- Regulatory pathway:
  - Galactosemia is a "slowly progressive, low prevalence rare disease" disease
  - Under new FDA guidance, surrogate metabolic biomarkers may be acceptable for demonstration of therapeutic activity
  - Potential low burden of clinical development

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

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Rm. 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

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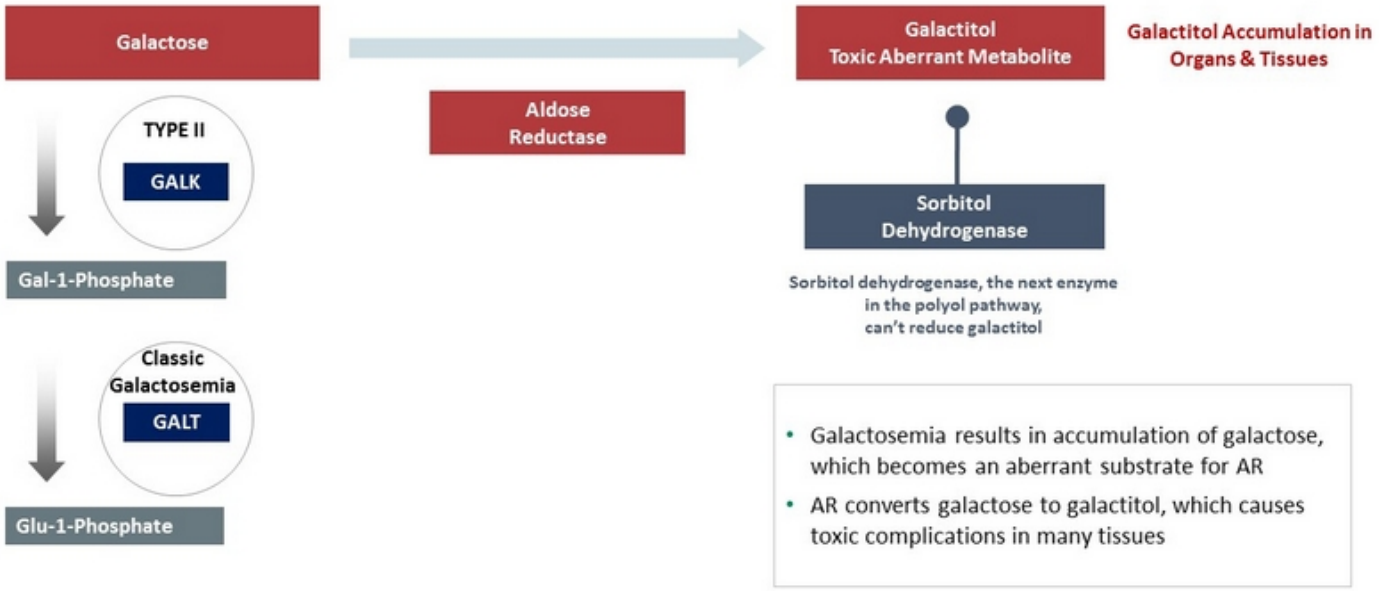
Aldose Reductase Activity Causes Toxic Accumulation of Galactitol in Galactosemia



- 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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AT-007, a CNS-Penetrant Novel Aldose Reductase Inhibitor, Prevents Galactitol Formation and Accumulation

- 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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Galactosemia Preclinical Data

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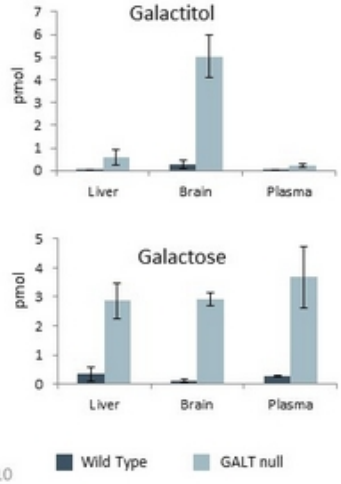
GALT Deficient Rat Model Closely Mirrors Human Disease

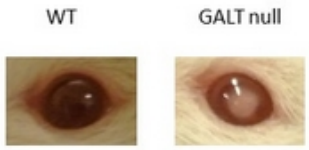
Biochemical Effects

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



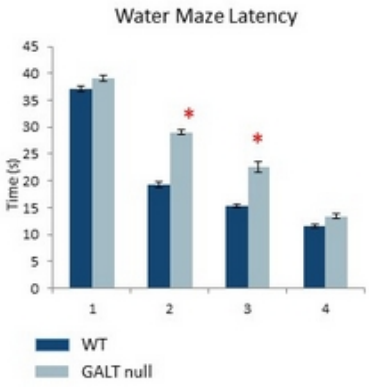
Tissue Deposition of Galactitol

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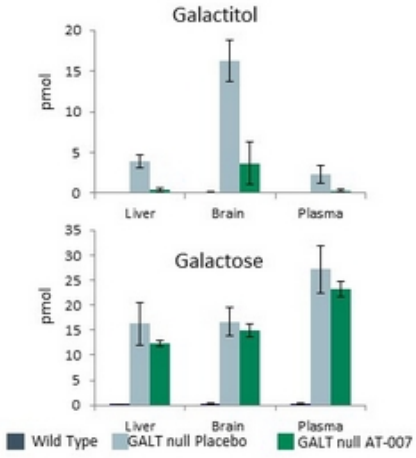
AT-007 Treatment Corrects All 3 Aspects of Disease in the Galactosemia Rat Model

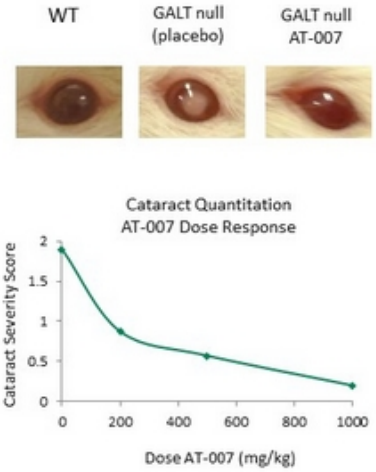
Biochemical Effects

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



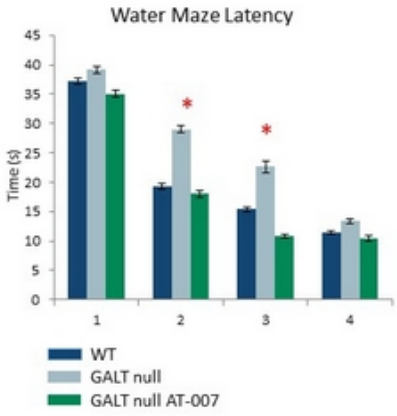
Tissue Deposition of Galactitol

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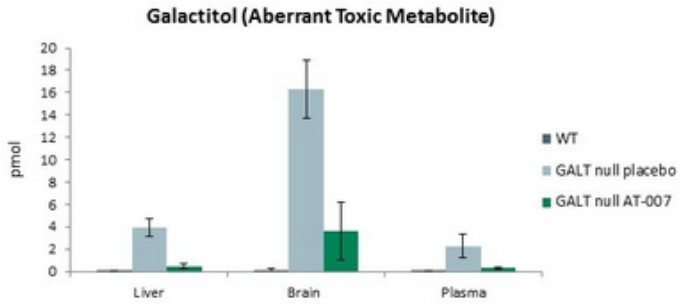
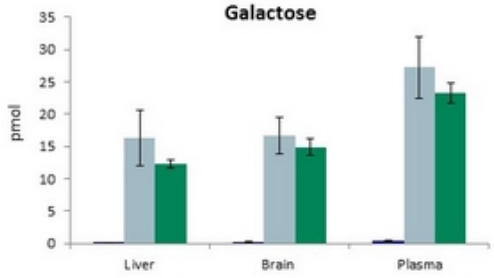
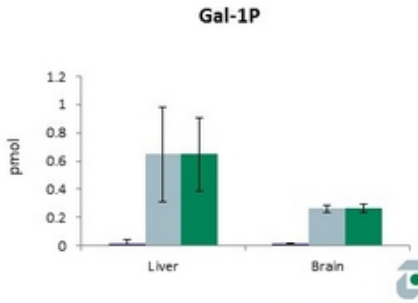
A Closer Look: AT-007 Significantly Reduces Galactitol Levels in all Target Tissues Without Increasing Galactose or Gal-1P



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





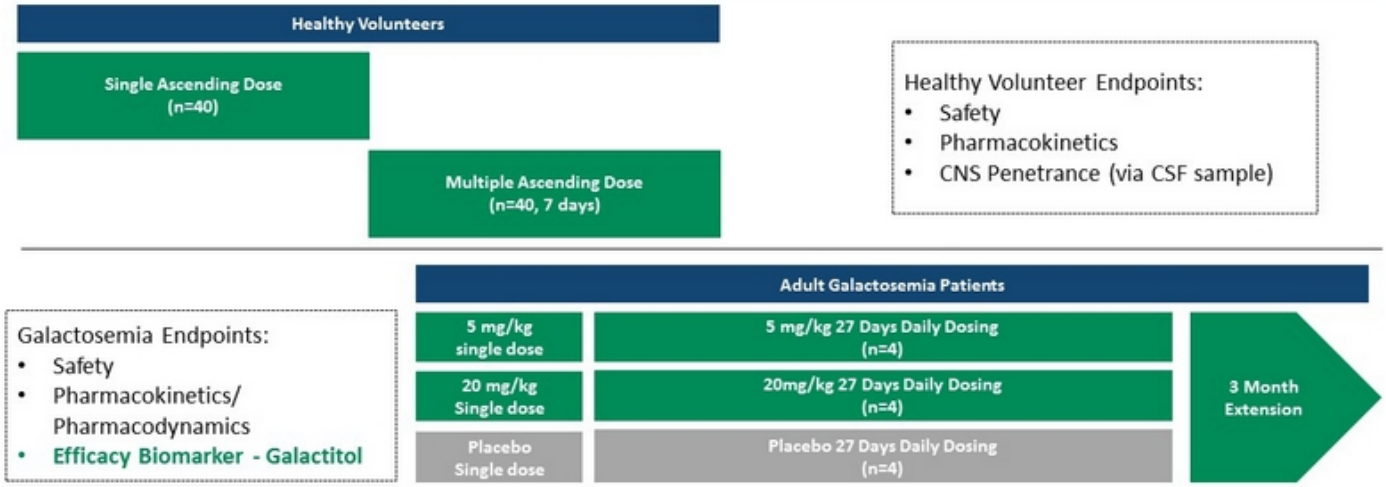
APPLIED THERAPEUTICS

Clinical Program: ACTION-Galactosemia Trial
April 2020 Data

APPLIED THERAPEUTICS

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

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

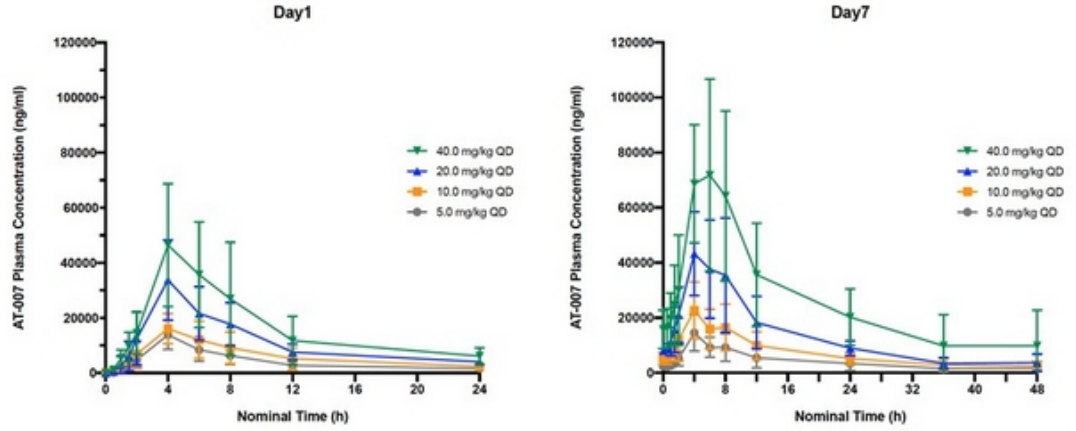


Based on initial topline data from Jan 2020, the study was expanded to include a 40mg/kg dose in healthy volunteers and then Galactosemia patients

APPLIED THERAPEUTICS

Healthy Volunteer Data
AT-007 Was Safe and Well Tolerated; PK Supports Once-Daily Dosing

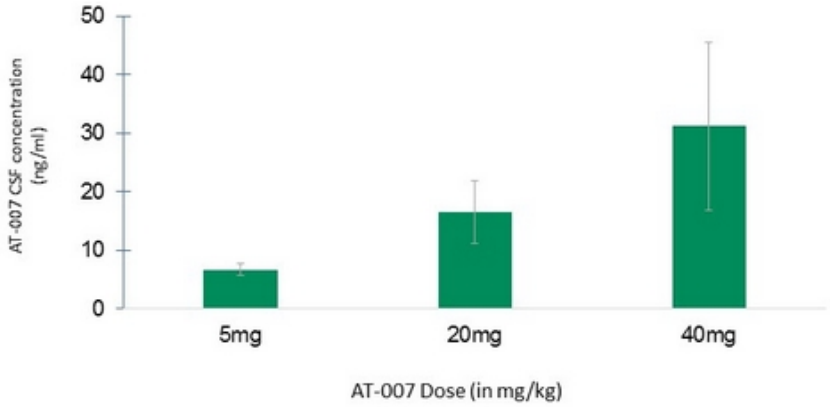
- AT-007 was safe and well tolerated at all doses, including 40mg/kg
- No treatment-related discontinuations
- Dose-dependent increase in exposure
- PK results supportive of once daily oral dosing



APPLIED THERAPEUTICS

AT-007 is Brain Penetrant
Important in Galactosemia Given CNS Complications

Dose-Dependent Increase in CSF Concentration in Healthy Volunteers (via lumbar puncture)



APPLIED THERAPEUTICS

ACTION-Galactosemia Trial Data

Adult Galactosemia Patient Baseline Demographics

APPLIED THERAPEUTICS

Baseline Demographic and Diagnostic Characteristics (n=11*)
Broad Age Range, Multiple Genetic Mutations Represented

Subject	Age	Gender	Ethnicity	BMI	Gene mutation	Urine galactitol (mM/urine creatine mol/L) Baseline	Plasma galactitol (ng/ml) Baseline	GALT enzyme activity (Mmol/h/mg)
2003-101	33	M	Caucasian	24.3	Q188R/Q188R	208	2630	0
2003-102	51	M	Caucasian	21.7	Q188R/Q188R	123	2390	0
2003-104	19	M	Caucasian	21.6	Q188R/Q188R	137	2150	0
2003-105	22	F	Caucasian	22.7	Q188R/Q188R	255	2860	0
2004-001*	37	M	Caucasian	21.3	Q188R/Q188R	152	2700	0
2004-004	40	M	Caucasian	32.7	N314D/ c119-116 deletion	102	2500	0
2004-005	24	F	Caucasian	23.1	Q188R/Q188R	142	2210	0
2002-002	19	F	Caucasian	23.9	K285N/c119-116 deletion	139	2500	0
2004-007	19	F	Caucasian	21.4	Q188R/Q188R	133	2450	0
2004-008	22	M	Caucasian	17.4	Q188R/Q188R	130	1930	0
2004-009	28	M	Caucasian	20.5	Q188R/Q188R	99	2630	0
Summary	**28.55 ± 10.5**	**4F and 7M**	**Caucasian**	**22.78 ± 3.8**	**9 Q118R homozygous and 2 compound heterozygous**	**147.27 ± 45.8**	**2450 ± 268.7**	**0**

*One placebo patient in cohort 1 crossed over to active for total of n=12

APPLIED THERAPEUTICS

Galactosemia Patient Baseline Clinical & Descriptive Characteristics (n=11*)

Clinical Characteristics

CNS Disorders	Psychiatric Disorders
Seizures (n=5)	Anxiety (n=4)
Dementia (n=1)	Depression (n=3)
Encephalopathy (n=1)	ADHD (n=3)
Tremor	

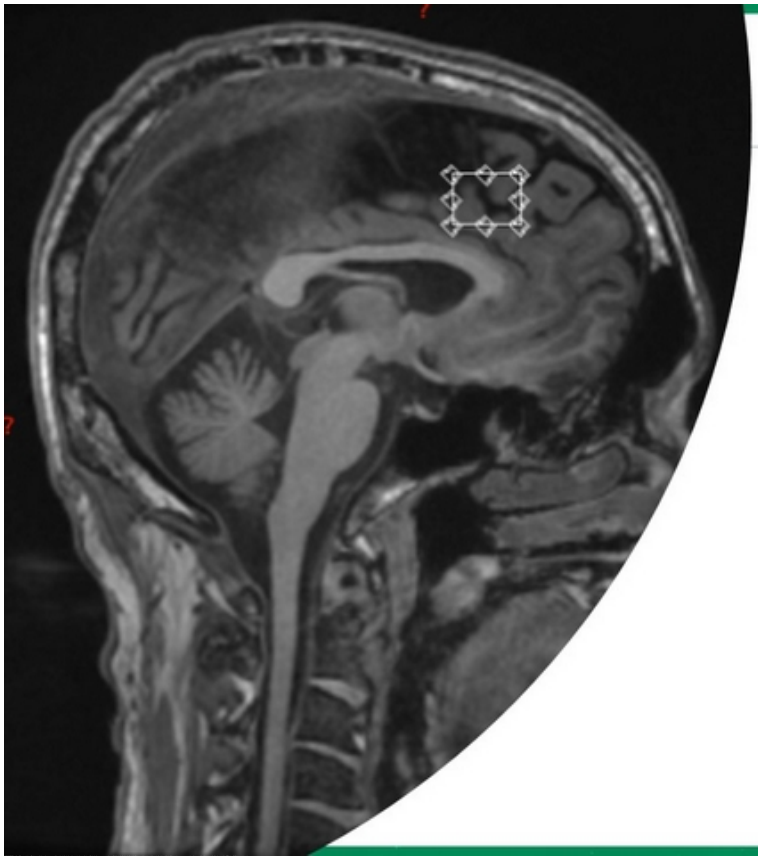
Endocrine Disorders	
Primary ovarian insufficiency (All Females)	Short stature (n=1)
Gynecomastia (n=1)	Osteopenia (n=2)
Erectile dysfunction (n=1)	Vitamin D deficiency (n=6)
Hypothyroidism (n=1)	

Descriptive Characteristics

Patient Quality of Life
Living with family members or proximity of caregiver (all, n=11)
Able to travel only with caregiver (n=9)
Unemployed and/or not in school (n=5)
Employed (primarily manual employment, unskilled labor n=6)
Secondary education (n=2)

*One placebo patient in cohort 1 crossed over to active for total of n=12

APPLIED THERAPEUTICS



MRI/MRS Baseline Characteristics

- Brain morphology changes caused by galactitol-induced osmotic dysregulation
- Galactitol was present and quantifiable in the brain of all adult Galactosemia patients (absent in healthy adults)
- N-acetyl-aspartate, a marker of neuronal health, was markedly decreased (-75%) in all Galactosemia patients

APPLIED THERAPEUTICS

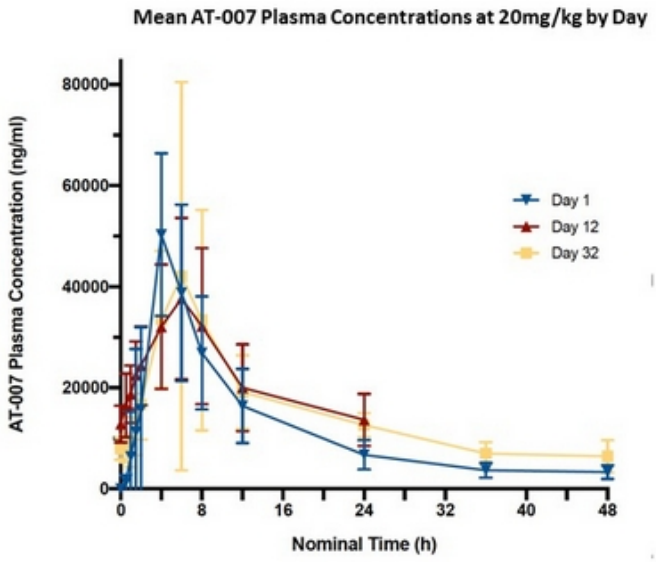
ACTION-Galactosemia Trial Data

AT-007 Pharmacokinetics and Safety Data in Galactosemia Patients

APPLIED THERAPEUTICS

Pharmacokinetic Results Support Once Daily Dosing in Galactosemia Patients

- Plasma PK parameters of AT-007 support once daily oral dosing
- PK profile in Galactosemia patients was similar to healthy volunteers, suggesting similar drug metabolism and clearance
- PK profile suggests no first pass clearance or other PK effects (de-sensitization or induction)



APPLIED THERAPEUTICS

Detailed Safety Findings

AT-007 Safe and Well-Tolerated: No Drug-Related Adverse Events

SYSTEM ORGAN CLASS PREFERRED TERM	NUMBER (%) OF PATIENTS, NUMBER OF EVENTS				
	Placebo N=4	AT-007 (5 mg/kg) N=4	AT-007 (20 mg/kg) N=4	Overall N=12*	Significance
Any Adverse Event	1 (25.0), 3	3 (75.0), 6	2 (50.0), 2	6 (50.0), 11	Not Significant
Cardiac Disorders	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1	Not Significant
Tachycardia	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1	Not Significant
Ear and Labyrinth Disorder	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1	Not Significant
Ear discomfort	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1	Not Significant
Gastrointestinal Disorders	1 (25.0), 1	1 (25.0), 1	0 (0.0), 0	2 (16.7), 2	Not Significant
Dyspepsia	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1	Not Significant
Abdominal Discomfort	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1	Not Significant
General Disorder and Administration site conditions	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1	Not Significant
Feeling hot	1 (25.0), 1	0 (0.0), 0	0 (0.0), 0	1 (8.3), 1	Not Significant
Infections	0 (0.0), 0	2 (50.0) 2	0 (0.0), 0	2 (16.7) 2	Not Significant
Upper respiratory tract infection	0 (0.0), 0	2 (50%) 2	0 (0.0), 0	2 (17%) 2	Not Significant
Injury/ Procedural Complications	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1	Not Significant
Contusion	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1	Not Significant
Musculoskeletal and Connective Tissue Disorders	0 (0.0), 0	0 (0.0), 0	1 (25.0), 1	1 (8.3), 1	Not Significant
Mobility decreased	0 (0.0), 0	0 (0.0), 0	1 (25.0), 1	1 (8.3), 1	Not Significant
Psychiatric Disorder	0 (0.0), 0	0 (0.0), 0	1 (25.0), 1	1 (8.3), 1	Not Significant
Anxiety	0 (0.0), 0	0 (0.0), 0	1 (25.0), 1	1 (8.3), 1	Not Significant
Skin and Subcutaneous Tissue Disorders	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1	Not Significant
Pruritus	0 (0.0), 0	1 (25.0), 1	0 (0.0), 0	1 (8.3), 1	Not Significant

Detailed Laboratory Findings
No Drug-Related Changes in Hepatic or Renal Function

PARAMETER/VISIT	Placebo N=4	AT-007 5 mg/kg N=4	AT-007 20 mg/kg N=4	Significance
ALT (U/L) – Mean (SD)				
Baseline	21.50 (7.00)	17.75 (9.0)	18.25 (9.07)	Not Significant
Post-Dosing (Day 32)	23.00 (10.15)	14.5 (8.39)	22.00 (6.38)	Not Significant
AST (U/L) – Mean (SD)				
Baseline	22.00 (2.58)	19.25 (6.70)	21.75 (9.43)	Not Significant
Post-Dosing (Day 32)	21.33 (4.04)	17.25 (7.14)	23.33 (5.51)	Not Significant
Bilirubin (mg/dL) – Mean (SD)				
Baseline	0.44 (0.18)	0.51 (0.14)	0..38 (0.19)	Not Significant
Post-Dosing (Day 32)	0.38 (0.21)	0.44 (0.12)	0.5 (0.28)	Not Significant
GFR (mL/min/1.73/m^2) – Mean (SD)				
Baseline	116.50 (27.40)	98.75 (12.04)	109.75 (22.65)	Not Significant
Post – Dosing (Day 32)	108.67 (17.79)	88.50 (3.87)	115.25 (28.30)	Not Significant

APPLIED THERAPEUTICS

Safety and PK Summary in Galactosemia Patients

Pharmacokinetics

- PK supports once-daily dosing
- Linear increase in AT-007 dose-dependent plasma concentration
- Similar exposure levels in Galactosemia patients and healthy volunteers

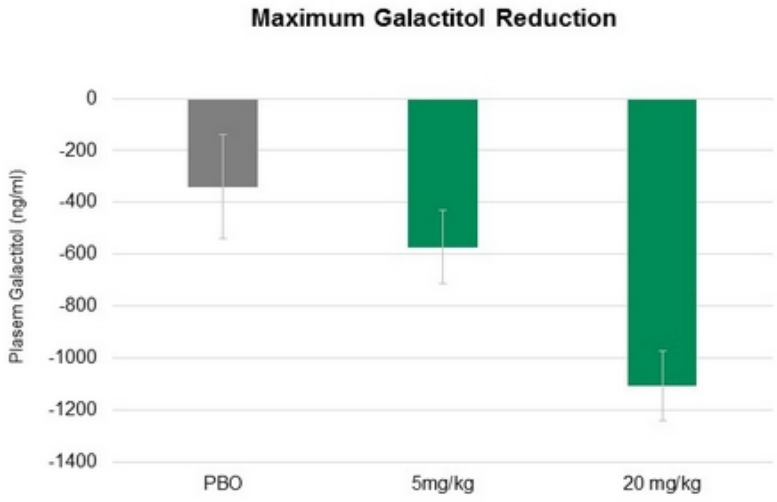
Safety

- AT-007 was safe and well-tolerated
- No treatment-related discontinuations
- No treatment-related Adverse Events
- No treatment-related lab abnormalities

ACTION-Galactosemia Trial Data
AT-007 Efficacy Results in Galactosemia Patients

APPLIED THERAPEUTICS

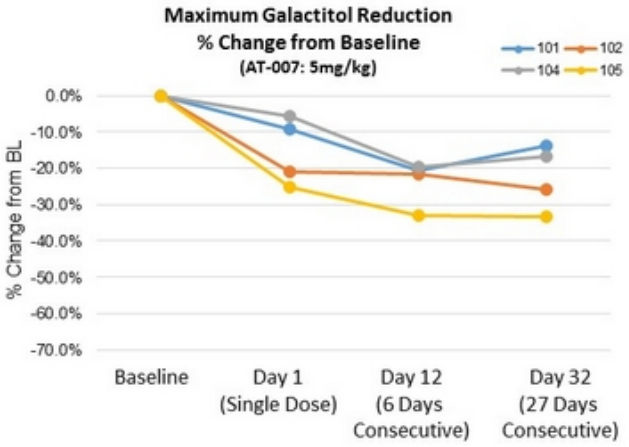
AT-007 Treatment Significantly Reduced Plasma Galactitol Levels in Adult Galactosemia Patients in a Dose-Dependent Fashion



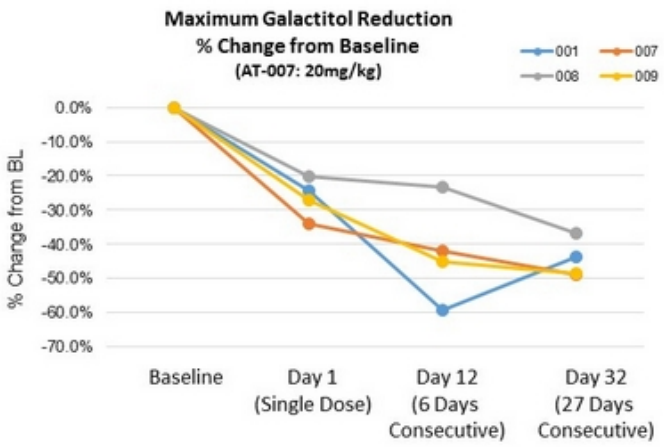
APPLIED THERAPEUTICS

AT-007 Decreased Galactitol Levels in All Treated Patients
Galactitol Reduction Was Rapid and Sustained

Reduction in Galactitol at 5mg/kg ~20%



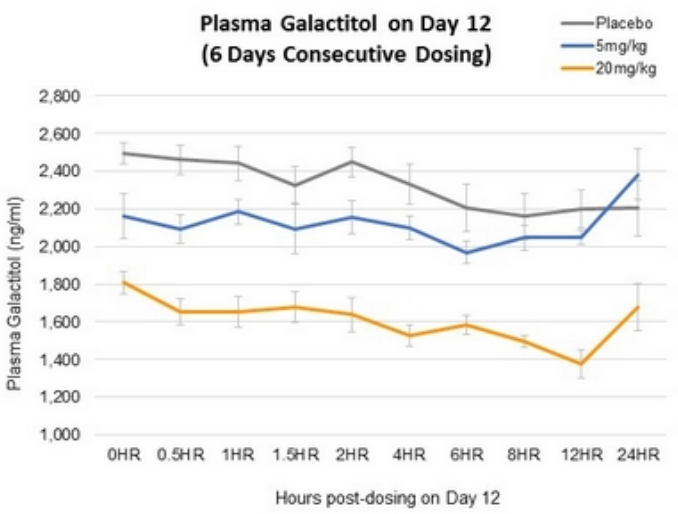
Reduction in Galactitol at 20mg/kg ~50%

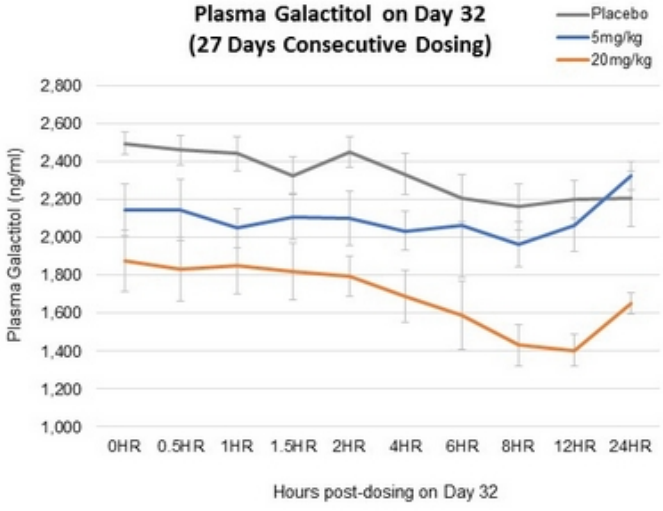


APPLIED THERAPEUTICS

AT-007 Reduction in Galactitol Was Maintained Throughout the 24-Hour Treatment Period, Supporting Once Daily Dosing

Reductions of ~20% at 5mg/kg and ~50% at 20mg/kg were stable throughout the 24-hour dosing period

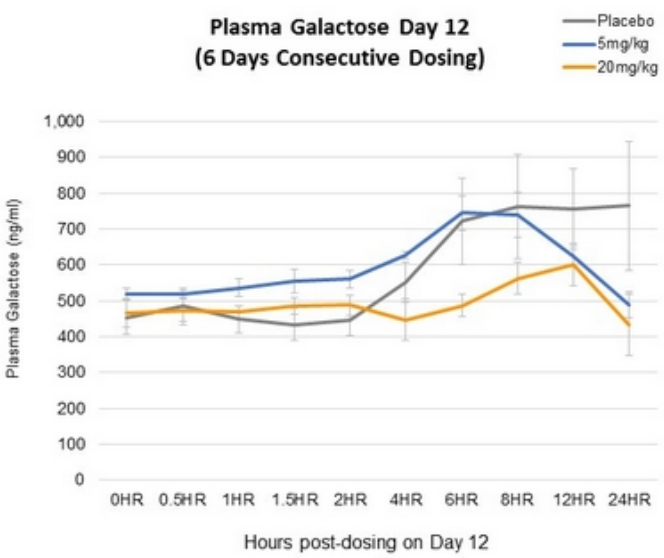


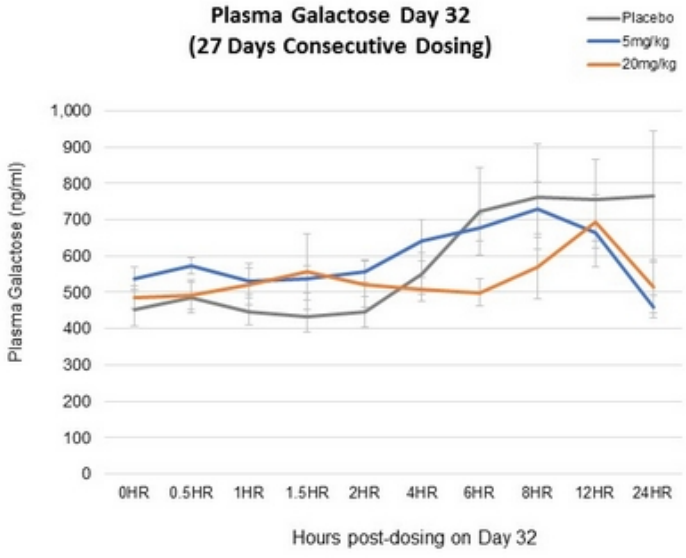


APPLIED THERAPEUTICS

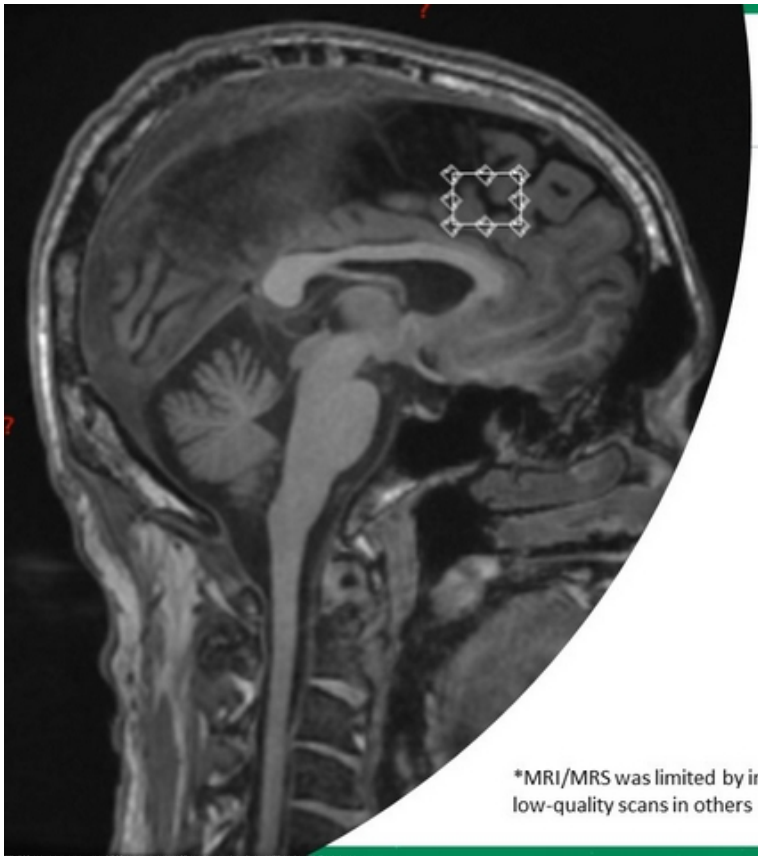
Treatment with AT-007 Does Not Increase Galactose Levels

Supports Pre-Clinical Data Demonstrating AT-007 Does Not Cause Derangement of Galactose or Other Galactose Pathway Metabolites





APPLIED THERAPEUTICS



MRI/MRS Results

MRI

- AT-007 treated patients demonstrated a trend towards decreased ventricular volume, a measure of edema (brain swelling)

MRS

- AT-007 treated patients (4 out 6)* demonstrated decreased galactitol levels in the brain
- AT-007 treated patients (4 out of 6) demonstrated an improvement in N-acetyl-aspartate (NAA, a marker of neuronal health)

*MRI/MRS was limited by inability of some patients to withstand MRI (anxiety) and low-quality scans in others (due to tremor/ movement)

APPLIED THERAPEUTICS

A Closer Look at Seizures

Seizures

- 5 patients had a history of seizures (generalized onset)
- All 5 patients were maintained on antiepileptic medications
- 4 patients had < 1 seizure per year
- 1 patient had > 1 seizure per month
- Due to the low frequency of seizures in the majority of patients, no significant changes in seizure frequency during the ACTION-Galactosemia core study (1 month treatment) could be assessed

ACTION-Galactosemia Trial Data

AT-007 for Treatment of Galactosemia: Future Development Plans

APPLIED THERAPEUTICS

AT-007 Extension Study: Designed to Confirm Long-Term Safety

- 90 Day Safety Extension
- Open to those who participated in 28-day core study and new patients
- Placebo-controlled; 3:1 randomization (active to placebo)
- Active dose flexible to allow 20mg/kg and potentially 40mg/kg
- Safety monitoring & biomarker assessments (as conducted in core study)
- Revised to primarily at-home visits (limited to no travel required) to address burden of travel to sites/ impact on families and COVID-19 concerns
- Study remains on track despite COVID-19
- Will be included in NDA filing

Adult European Study Cohort to Recruit GALK-Deficient Patients and Support EU Approval

- Primarily designed to recruit GALK deficient patients
  - More prevalent in Europe, but still extremely rare
  - Display similar CNS complications to Classic Galactosemia (GALT-deficient) patients
- Secondary objective to include European patients to support EU approval
- UK site (University College London)
  - One cohort of patients (~6) planned at UK site, but large pool of patients exists (~70 at single site)

- Czech Republic alternative site for GALK deficient patients (given incidence in Romani/ Irish Traveler population)

Proposed AT-007 Pediatric Study (Under Discussion with FDA)

Proposed Study Design

- 2-Part Multiple Dose Study
- Several age groups investigated
  - ≥ 2 – 6
  - ≥ 7 – 12
  - ≥ 13 <18
  - Children 2 months – 2 yrs may be added following initial safety data (newborns/ infants)

Study Objectives

- Safety
- Dose determination (via PK/PD)
- Efficacy biomarker effects (plasma galactitol)
- Exploratory: MRI/MRS effects
  - Galactitol quantitation
  - Brain morphometry & cerebral edema
  - NAA concentration (neuronal health biomarker)

ACTION-Galactosemia Trial Data
Summary & Conclusions

APPLIED THERAPEUTICS

Summary: ACTION-Galactosemia Study Results

Safety/ PK/ PD

- AT-007 was safe and well-tolerated
- PK/PD data supports once-daily oral dosing
- AT-007 is CNS penetrant – important in Galactosemia, which includes significant CNS clinical presentation

Efficacy in Galactosemia Patients

- AT-007 induced rapid and sustained reduction in plasma galactitol, an aberrant, toxic metabolite formed in Galactosemia patients
- 20mg/kg dosing resulted ~50% reduction in plasma galactitol ($p<0.01$ vs. placebo)
- Positive AT-007 MRI/MRS impact

Thank you

APPLIED THERAPEUTICS