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): June 30, 2025

ARCTURUS THERAPEUTICS HOLDINGS INC.

(Exact name of registrant as specified in its charter)

Delaware	**001-38942**	**32-0595345**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

10628 Science Center Drive, Suite 250
San Diego, California 92121
(Address of principal executive offices)

Registrant's telephone number, including area code: (858) 900-2660

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))

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, par value $0.001 per share	**ARCT**	**The Nasdaq Stock Market LLC**

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. ☐

Item 7.01. Regulation FD Disclosure.

On June 30, 2025, Arcturus Therapeutics Holdings Inc. (the "Company" or "Arcturus") issued a press release, announcing positive Phase 2 interim results in people with OTC deficiency treated with ARCT-810, an mRNA therapeutic candidate designed to replace the OTC enzyme and restore urea cycle activity preventing hyperammonemia crises (the "Release"). The Company also provided a corporate presentation regarding ARCT-810 via webcast, which is available on the Company's website (the "Presentation").

A copy of the Release is furnished herewith as Exhibit 99.1 and incorporated into this Item 7.01 by reference. A copy of the Presentation is furnished herewith as Exhibit 99.2 and incorporated into this Item 7.01 by reference.

The information in this Item 7.01 of this Current Report on Form 8-K, and Exhibit 99.1 and 99.2 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section or Sections 11 and 12(a)(2) of the Securities Act of 1933, as amended. The information contained in this Item 7.01, the Release attached as Exhibit 99.1, and in the Presentation attached as Exhibit 99.2 to this Current Report on Form 8-K, shall not be incorporated by reference into any filing with the Securities and Exchange Commission made by the Company, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	**Description of Exhibit**
99.1	Press Release dated June 30, 2025
99.2	Presentation dated June 30, 2025
104	Cover Page to this Current Report on Form 8-K in Inline XBRL

SIGNATURES

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.

Date: June 30, 2025

Arcturus Therapeutics Holdings Inc.

By: /s/ Joseph E. Payne
Name: Joseph E. Payne
Title: Chief Executive Officer

Arcturus Therapeutics Announces Positive Interim Phase 2 Multiple Dose Data for Ornithine Transcarbamylase (OTC) Deficiency Program

ARCT-810 significantly and consistently reduces biomarker glutamine to levels within normal range

^{15}N-ureagenesis data provide first evidence of an mRNA therapeutic improving urea cycle function

Ammonia remained stable and within normal range

Multiple administrations of ARCT-810 continue to be safe and well tolerated at all tested dose levels

Virtual KOL Presentation at 12:00 p.m. ET Today

SAN DIEGO--(BUSINESS WIRE)--Jun. 30, 2025-- Arcturus Therapeutics Holdings Inc. (the "Company", "Arcturus", Nasdaq: ARCT), a commercial messenger RNA medicines company focused on the development of infectious disease vaccines and opportunities within liver and respiratory rare diseases, today announces positive Phase 2 interim results in people with OTC deficiency treated with ARCT-810, an mRNA therapeutic candidate designed to replace the OTC enzyme and restore urea cycle activity preventing hyperammonemia crises.

"We are very pleased with these new ARCT-810 clinical results, where we have achieved strong biological effects in both Phase 2 studies, including significant and consistent reduction and normalization of abnormally elevated glutamine, an important biomarker to monitor urea cycle function," said Dr. Juergen Froehlich, Chief Medical Officer of Arcturus. "Furthermore, in our ongoing U.S. Phase 2 study, we are excited to report the first significant relative ureagenesis function (RUF) improvements using a new and optimized ^{15}N-ureagenesis assay. Along with the observation of stable ammonia levels in all patients during treatment, these data add a level of robustness to this new interim dataset. I am also very pleased to see that our LUNAR® delivery technology continues to be generally safe and well tolerated. The combined biomarker data is unprecedented for an mRNA rare disease therapeutic and, importantly, provides a potentially accelerated path forward to a multi-biomarker driven pivotal study."

"It is extremely rewarding to see the first mRNA therapeutic produce such solid clinical results in an area of important unmet medical need," said Dr. Marshall Summar, CEO of Uncommon Cures. "This is a very positive step for the OTC deficient community as there are currently limited options for symptomatic patients suffering from this devastating disease."

Multiple dosing data are available from two Phase 2 studies; a completed placebo-controlled study in Europe that randomized six participants to ARCT-810 doses and an open-label multiple ascending dose study with interim data from the initial three completed participants. The ongoing U.S. Phase 2 open-label study uses a modified and improved ^{15}N-ureagenesis assay (Allegri *et al.*, 2025). The assay measures relative ureagenesis function (RUF) against a normal range established from healthy controls (N = 29). The assay is not impacted by ammonia scavengers, has low intraindividual variability, and can distinguish between symptomatic and asymptomatic OTC deficient patients. Linear Mixed-Effects Model (LMM) was applied as an exploratory analysis to the Phase 2 glutamine and ureagenesis data. LMM is suitable for small-N analyses, i.e. rare disease trial datasets.

ARCT-810 treatment significantly reduces glutamine levels

In the combined analysis of both Phase 2 studies, significantly (p-value = 0.0055; LMM) decreased glutamine levels were observed following multiple ARCT-810 administrations to patients who remained on their standard of care therapy. These results provide statistical evidence that glutamine levels decrease over time in both Phase 2 studies, suggesting a robust effect across the patient cohorts. In the Phase 2 randomized European study, glutamine levels in patients who received multiple doses of ARCT-810 significantly (p-value = 0.016; LMM) decreased during the dosing period. In the Phase 2 open-label U.S. study, all three participants had a sustained and significant (p-value = 0.004; LMM) decrease in glutamine from baseline reaching normal levels after the first three doses.

Analysis	Number of Patients	Number of Observations	Fixed Effect Slope (µmol/L/day)	One-Tailed p-value (for slope < 0)
European Phase 2	5*	31	-1.82	0.016
U.S. Phase 2 (interim)	3	18	-4.38	0.004
Combined	**8**	**49**	**-2.50**	**0.0055**

*First of six enrolled participants randomized to ARCT-810 received an unoptimized infusion regimen and withdrew consent after the first dose due to a mild infusion related reaction and was therefore excluded from the analysis

These results provide strong evidence that glutamine levels decreased in both Phase 2 studies, with a steeper decline in the U.S. Phase 2 study, likely attributed to the two participants with more severe disease. After treatment completion, glutamine levels returned to baseline over a period of several weeks.

ARCT-810 treatment significantly increases ^{15}N-ureagenesis

In the first three participants in the ongoing Phase 2 open-label study, RUF statistically (p-value = 0.026, LMM) increased at all post treatment evaluations from a baseline of 29.0% (SD; 9.1%) to 43.7% (SD; 21.7%) at 28 days post-fifth dose. These results suggest a progressive increase of functional OTC enzyme in the liver with continued administrations. Two of the three participants achieved RUF > 50% indicating a clinically meaningful improvement in urea cycle flux. These encouraging ^{15}N-Ureagenesis data provide additional support and confidence in the favorable glutamine results.

Ammonia remained stable and within normal range

Further supporting the favorable glutamine and ureagenesis data, patients receiving ARCT-810, in both Phase 2 studies, maintained ammonia levels within the normal range following at least two doses and remained stable for approximately 28 days after completion of dosing. Two participants in the European Phase 2 randomized study (one receiving placebo, one receiving ARCT-810) reported a hyperammonemia event (ammonia ≥ 100 µmol/L). One participant had normal ammonia levels that remained stable during ARCT-810 treatment; four weeks after the last dose, this participant received an oral corticosteroid to treat an asymptomatic transaminase elevation (a laboratory SAE that did not meet Hy's law criteria). Subsequently, transaminase levels returned to normal range, and the temporary increase of ammonia was considered related to corticosteroid treatment.

ARCT-810 continues to be safe and well tolerated

ARCT-810 was generally safe and well tolerated in single dose Phase 1/1b and multi-dose Phase 2 studies, comprising 40 participants to date, including 20 OTC deficient participants. The early studies enabled the Company to improve the tolerability of the infusion regimen without using corticosteroid pre-treatment. To date, no serious IRRs have been observed using the improved 3-hour IV regimen (N = 8; up to 6 infusions) in the Phase 2 protocols.

Virtual KOL Event: Monday, June 30, 2025 @12:00 p.m. ET

- Domestic: 1-877-407-0784
- International: 1-201-689-8560
- Conference ID: Arcturus
- Webcast: https://viavid.webcasts.com/starthere.jsp?ei=1723089&tp_key=21003e1b34

About Ornithine Transcarbamylase Deficiency

Ornithine transcarbamylase (OTC) deficiency is the most common urea cycle disorder. Urea cycle disorders are a group of inherited metabolic disorders of the liver that make it difficult for affected patients to remove toxic waste products as proteins are digested. OTC deficiency caused by mutations in the X-linked OTC gene, leads to a non-functional or deficient OTC enzyme and usually affects males more severely. OTC is a critical liver enzyme which catalyzes a metabolic process that converts toxic ammonia to urea that is excreted by the kidney. This conversion does not occur properly in patients with OTC deficiency and, aside from the risk of high ammonia levels, leads to increased blood concentrations of glutamine with low to normal levels of citrulline and increases in urine orotic acid. High blood ammonia levels in OTC deficiency may cause health crises with seizures, progressive neurocognitive impairment, coma, and death. Severe cases of OTC deficiency usually present early in life, but patients with less severe symptoms may be diagnosed as adolescents and adults. There is currently no cure for OTC deficiency, apart from liver transplant. However, liver transplantation comes with significant risks of surgical and postsurgical complications such as organ rejection, and recipients must take immunosuppressant drugs for the rest of their lives. The current standard of care for OTC deficiency patients is a well-controlled, but challenging to maintain, low-protein diet, substitution of essential amino acids and treatment with nitrogen scavenging medications that keeps the ammonia from rising to acutely toxic levels but may not prevent chronic neurotoxic effects. These treatments do not address the underlying cause of disease. In Europe and the U.S., approximately 10,000 people have OTC deficiency.

About ARCT-810

ARCT-810 is an intravenously administered investigational mRNA therapeutic designed to express normal functional OTC enzyme in the liver of individuals with OTC deficiency. ARCT-810 has received Orphan Medicinal Product Designation and an approved pediatric investigation plan (PIP) from the European Medicines Agency (EMA), and Orphan Drug Designation, Fast Track Designation along with Rare Pediatric Disease Designation from the U.S. Food and Drug Administration (FDA) for the treatment of OTC deficiency. OTC is a key enzyme in the urea cycle which converts toxic ammonia into urea. Elevated ammonia can lead to metabolic crises with progressive and irreversible neurocognitive damage. A safe and effective mRNA therapeutic may restore normal functional OTC enzyme in the liver which could improve urea cycle activity, reduce abnormally elevated glutamine, maintain normal ammonia levels and potentially eliminate the risk of future metabolic crises. ARCT-810 is based on Arcturus' mRNA design construct and proprietary manufacturing process. ARCT-810 also utilizes Arcturus' extensive and propriety lipid library and employs the Company's LUNAR® delivery platform to deliver OTC mRNA to hepatocytes.

About Glutamine as a Biomarker

Glutamine is used as an important biomarker by clinicians to monitor urea cycle function in OTC deficient patients. Glutamine reflects the body's nitrogen buffering capacity. In urea cycle disorders, excess nitrogen is initially incorporated into glutamine, allowing glutamine to rise steadily as a compensatory mechanism before ammonia levels begin to spike. This role makes glutamine a more stable and predictive biomarker in patients who are not experiencing hyperammonemia. Glutamine assessments have significantly lower intra-subject variability than ammonia (15% vs. 56%), making it more reliable for monitoring metabolic control in stable conditions (Lichter-Konecki *et al*., 2016).

About Arcturus

Founded in 2013 and based in San Diego, California, Arcturus Therapeutics Holdings Inc. (Nasdaq: ARCT) is a commercial mRNA medicines and vaccines company with enabling technologies: (i) LUNAR® lipid-mediated delivery, (ii) STARR® mRNA technology (sa-mRNA) and (iii) mRNA drug substance along with drug product manufacturing expertise. Arcturus developed KOSTAIVE®, the first self-amplifying messenger RNA (sa-mRNA) COVID vaccine in the world to be approved. Arcturus has an ongoing global collaboration for innovative mRNA vaccines with CSL Seqirus, and a joint venture in Japan, ARCALIS, focused on the manufacture of mRNA vaccines and therapeutics. Arcturus' pipeline includes RNA therapeutic candidates to potentially treat OTC deficiency and cystic fibrosis (CF), along with its partnered mRNA vaccine programs for SARS-CoV-2 (COVID-19) and influenza. Arcturus' versatile RNA therapeutics platforms can be applied toward multiple types of nucleic acid medicines including messenger RNA, small interfering RNA, circular RNA, antisense RNA, self-amplifying RNA, DNA, and gene editing therapeutics. Arcturus' technologies are covered by its extensive patent portfolio (over 500 patents and patent applications in the U.S., Europe, Japan, China, and other countries). For more information, visit www.ArcturusRx.com. In addition, please connect with us on X (formally Twitter) and LinkedIn.

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, are forward-looking statements, including those regarding strategy, future operations, the likelihood of success of the Company's pipeline (including ARCT-810), the likelihood that clinical results will be predictive of future clinical results or of potential therapeutic benefit, likelihood of continuation of the OTC program, likelihood of further enrollment in the ongoing ARCT-810 Phase 2 study, the likelihood of a path toward and initiation of a multi-biomarker driven pivotal study, the likelihood that continued ARCT-810 administrations will result in a progressive increase of functional OTC enzyme, the likelihood of any regulatory agency recognizing any biomarker in determinations of regulatory approval including glutamine levels or 15N assay results, and the impact of general business and economic conditions. Arcturus may not actually achieve the plans, carry out the intentions or meet the expectations or projections disclosed in any forward-looking statements such as the foregoing and you should not place undue reliance on such forward-looking statements. These statements are only current predictions or expectations, and are subject to known and unknown risks, uncertainties, and other factors that may cause our or our industry's actual results, levels of activity, performance or achievements to be materially different from those anticipated by the forward-looking statements, including those discussed under the heading "Risk Factors" in Arcturus' most recent Annual Report on Form 10-K, and in subsequent filings with, or submissions to, the Securities and Exchange Commission (the "SEC"), which are available on the SEC's website at www.sec.gov. Except as otherwise required by law, Arcturus disclaims 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.

Arcturus Therapeutics
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KOL PRESENTATION

ARCT-810

June 30, 2025

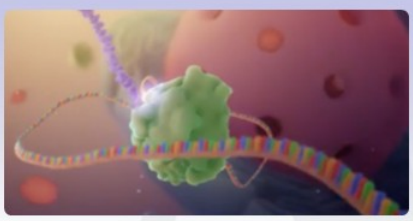
Forward Looking Statements

This presentation contains forward-looking statements. These statements relate to future events and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future performances or achievements expressed or implied by the forward-looking statements. Each of these statements is based only on current information, assumptions and expectations that are inherently subject to change and involve a number of risks and uncertainties. Forward-looking statements include, but are not limited to, statements about: our strategy, future operations, collaborations, the likelihood of success (including safety and efficacy) and promise of our pipeline (including ARCT-810), the planned initiation, design or completion of clinical trials, the ability to enroll subjects in clinical trials, the timing for receipt of data, the likelihood that clinical data will be predictive of future clinical results, or that interim data of the Phase 2 study will be predictive of the complete data sets from the Phase 2 study, the likelihood that the Company will continue the Phase 2 Study or the OTC program, the likelihood that a regulatory agency will agree with assessments of key biomarkers, the likelihood that clinical data will be sufficient for regulatory approval or completed in time to submit an application for regulatory approval within a particular timeframe, the anticipated timing for regulatory submissions, the timing of, and expectations for, any results of any preclinical or clinical studies or regulatory approvals, the potential administration regimen or dosage and any statements other than statements of historical fact.

In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "could," "would," "expects," "plans," "anticipates," "believes," "estimates," "projects," "predicts," "potential" and similar expressions (including the negative thereof) intended to identify forward looking statements. Arcturus may not actually achieve the plans, carry out the intentions or meet the expectations or projections disclosed in any forward-looking statements such as the foregoing, and you should not place undue reliance on such forward-looking statements. The forward-looking statements contained or implied in this presentation are subject to other risks and uncertainties, including those discussed under the heading "Risk Factors" in Arcturus' most recent Annual Report on Form 10-K with the SEC and in other filings that Arcturus makes with the SEC. 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.

Arcturus Therapeutics

Global mRNA Medicines Company



KOSTAIVE® Approved in **Japan & EU**

Nasdaq: ARCT

Headquarters: San Diego, CA

Founded: 2013

mRNA Medicine Candidates

ARCT-810 Ornithine Transcarbamylase Deficiency

ARCT-032 Cystic Fibrosis

Arcturus is a commercial mRNA medicines company with a pipeline of multiple therapeutic candidates in advanced clinical trial development

Ornithine Transcarbamylase (OTC) Deficiency

The most common urea cycle disorder

- 10,000 prevalence in U.S./Europe
- The urea cycle converts neurotoxic ammonia to water-soluble urea that can be excreted in urine
- Deficiency in OTC causes elevated blood ammonia, which can lead to neurological damage, coma, and death

Unmet Medical Need

- Present standard of care involves a strict diet (low protein, high fluid intake) plus ammonia scavengers
- Present standard of care does not effectively prevent life-threatening spikes of ammonia
- Severe OTC Deficiency patients are referred for liver transplant, currently the only cure

ARCT-810 Aims to Restore OTC Enzyme Function

- Establishing expression of OTC enzyme in liver has potential to restore urea cycle activity to detoxify ammonia, preventing neurological damage and potentially removing need for liver transplantation

ARCT-810: mRNA Rx to treat OTC Deficiency

ARCT-810 utilizes Arcturus' proprietary LUNAR® delivery technology and has potential to be the first and best-in-class mRNA therapeutic to treat OTC Deficiency

ARCT-810: Regulatory Achievements

Orphan Drug Designation (FDA)
- 26 June 2019

Orphan Medicinal Product Designation (EMA)
- 18 Jul 2022

Fast Track Designation (FDA)
- 30 May 2023

Rare Pediatric Disease Designation (FDA)
- 01 June 2023
- Potential for Priority Review Voucher (PRV)

Pediatric Investigational Plan (PIP) positive opinion in EU
- 30 Jun 2023

Regulatory designations highlight ARCT-810 potential to address unmet medical need and the opportunity for expedited regulatory approval

ARCT-810: European and U.S. Phase 2 Trials

Objectives

- Establish safety and tolerability in OTC deficient adolescents and adults
- Evaluate biomarker responses – glutamine, ureagenesis, ammonia

European Phase 2 Study – Completed (N = 8; 6 ARCT-810 / 2 placebo)

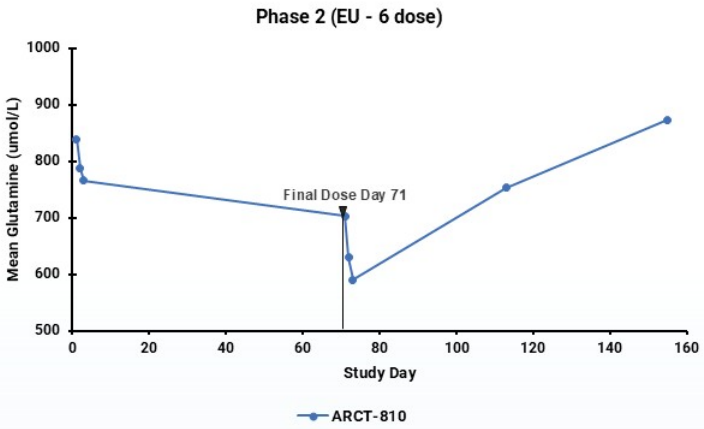
- Randomized, placebo-controlled
- 0.3 mg/kg ARCT-810; up to six biweekly IV infusions
- Entry criteria: Patients with stable disease

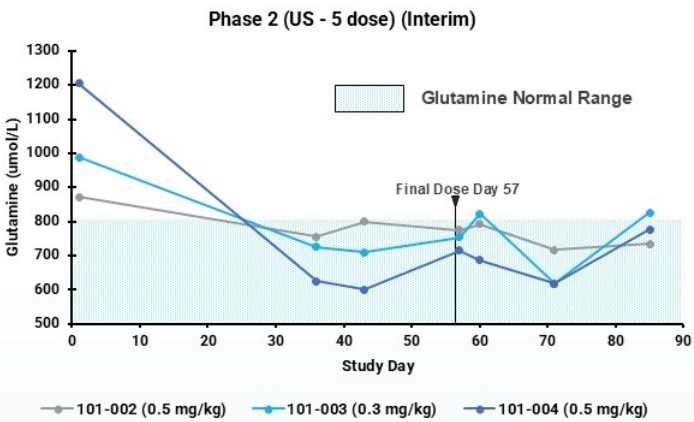
U.S. Phase 2 Study – Ongoing (N = 3 completed to date)

- Open-label, multiple ascending dose study
- 0.3 mg/kg and 0.5 mg/kg; five biweekly IV infusions of ARCT-810
- Entry criteria: Patients with more severe disease
- More frequent and optimized biomarker timepoints
- Includes ^{15}N-ureagenesis assay

Glutamine Normalization Following ARCT-810 Administration

Glutamine normal values range from ~400 to 800 umol/L





Interim data show significant reduction in glutamine levels following ARCT-810 administration
High glutamine levels are normalized during treatment course
Approximately one month after the final dose, glutamine levels elevate above normal

ARCT-810 Significantly Reduces Glutamine Levels

Combined Analysis of Both Phase 2 Studies

- Mean glutamine levels decreased significantly (N = 8, p-value = 0.0055)

Phase 2 Randomized European Study

- Mean glutamine levels decreased significantly (N = 5[a], p-value = 0.016)

Phase 2 Open-label U.S. Study

- Mean glutamine levels decreased significantly (N = 3, p-value = 0.004)
- All subjects achieved normal levels of glutamine after only three administrations

The Linear Mixed-Effects Model (LMM[b]) results provide statistical evidence that glutamine levels decrease over time in both Phase 2 studies

a: First of six enrolled participants randomized to ARCT-810 received an unoptimized infusion regimen and withdrew consent after the first dose due to a mild infusion related reaction and was therefore excluded from the analysis.
b: LMM is suitable for small-N designs. Wiley, *et al.* Aphasiology, 2018 Mar 21; 33(1):1–30.

^{15}N-Ureagenesis Assay: Background

New ^{15}N-Ureagenesis Assay published in 2025 (Allegri, *et al.*)

- Measures relative ureagenesis function (RUF)
- Less variable than the ^{13}C-Ureagenesis Assay
- Low intra-subject variability
- Not impacted by ammonia scavengers
- Asymptomatic patients have RUF > 50%

Arcturus utilized this new clinical assay in the Phase 2 open-label U.S. study
RUF > 50% is considered meaningful by KOLs

^{15}N-Ureagenesis assay can serve as a clinical biomarker to evaluate improvement in urea cycle function in people with OTC deficiency

ARCT-810 Significantly Increases ^{15}N-Ureagenesis

Interim Phase 2 Data U.S. Open Label Study (N = 3):

Mean RUF increased +14.7% from baseline to 28 days post-fifth dose
-- from 29.0% (SD 9.1%) to 43.7% (SD 21.7%)

Mean RUF increase is statistically significant
-- p-value = 0.026, LMM analysis

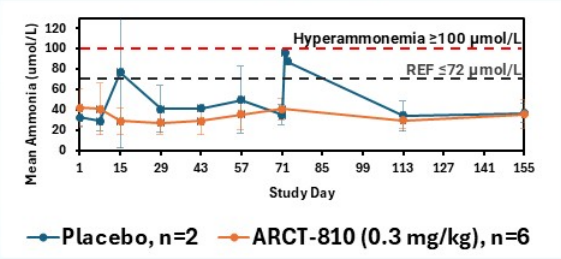
Two of three subjects achieved > 50% RUF

Data suggest ARCT-810 progressively increases functional OTC enzyme in the liver resulting in improved urea cycle function

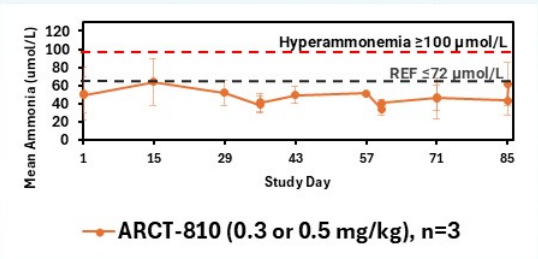
Encouraging ^{15}N-Ureagenesis data provide additional support and confidence in the favorable glutamine results

ARCT-810: Ammonia Stable and Within Normal Range

Phase 2 (Europe)



Interim Phase 2 (U.S.)



Ammonia levels stabilized within normal range following two administrations of ARCT-810 and remained stable for approximately 28 days after completion of dosing

Ammonia data add robustness to the favorable glutamine and ureagenesis data

ARCT-810: Safety and Tolerability

- ARCT-810 was generally safe and well-tolerated in single dose Phase 1/1b and multi-dose Phase 2 studies, comprising 40 participants to date, including 20 OTC deficient participants
- 9 OTCD subjects received multiple doses of ARCT-810 (up to 6 administrations)
- Phase 2 studies use an improved IV infusion regimen *without* corticosteroid pre-treatment
- No serious infusion-related reactions (IRRs) observed using improved regimen (N = 8, to date)
- One placebo and one ARCT-810 participant in the European Phase 2 randomized study reported a hyperammonemia event (ammonia ≥ 100 µmol/L).
- One participant received oral corticosteroid to treat asymptomatic transaminase elevation (a laboratory SAE not meeting Hy's law criteria) 4 weeks after last dose. Transaminase levels returned to normal. The temporary ammonia increase was considered a corticosteroid effect.

ARCT-810 Generally Safe and Well Tolerated in Phase 2 Studies at All Tested Dose Levels

Introduction of KOLs

Dr. Marshall Summar

Dr. Johannes Häberle

Glutamine Trends and Ureagenesis in Urea Cycle Patients with OTC Deficiency Treated with mRNA Therapy

Biochemical Findings from European Phase 2 Randomized Study (Study 03) and U.S. Phase 2 Open-Label Study (Study 04)

Prepared by Marshall Summar, MD

Marshall L. Summar, MD
Urea Cycle Disorder Experience

- Internationally recognized expert in **urea cycle disorders (UCDs)** with over four decades of clinical, research, and policy leadership
- Founding member and Executive Committee member of the **NIH UCD Consortium**; led national UCD diagnostic and treatment consensus efforts
- Served 20+ years on the **Scientific Advisory Board of the National UCD Foundation**; advisor to academic and industry UCD initiatives
- Author of **40+ UCD-related publications**, including GeneReviews, clinical guidelines, and multinational natural history studies
- Inventor on patents for **ammonia diagnostics and UCD-related technologies**; led translational studies on UCDs in critical care and neonatal disease
- Recipient of the **NORD Lifetime Achievement Award (2022)** for long-standing contributions to rare disease research and clinical infrastructure

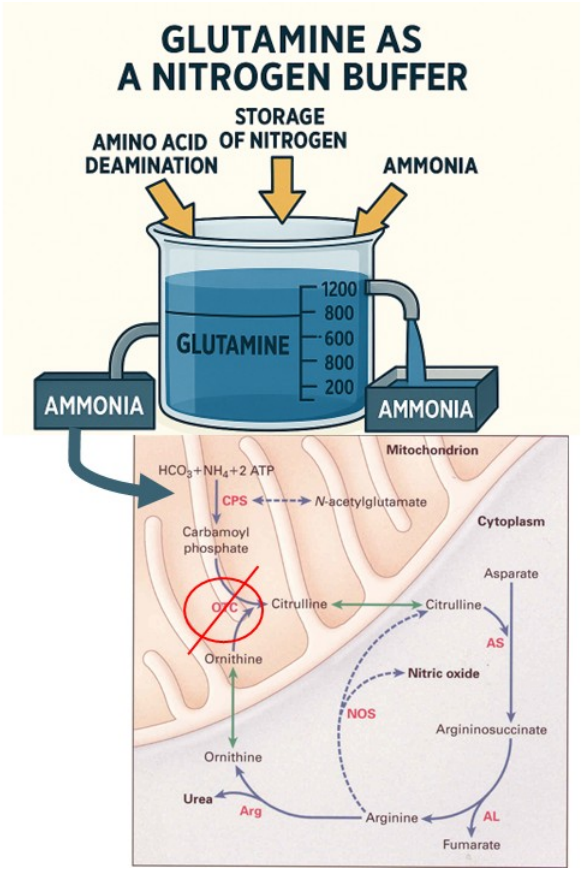
Urea Cycle & OTC Overview

- Urea Cycle is human pathway for clearing nitrogen as well as producing some essential biomolecules. Defects are referred to as Urea Cycle Disorders (UCDs)
- Ornithine Transcarbamylase Deficiency (OTCD) is the most common defect as it is located on the X chromosome.
- Restoration of activity restores critical nitrogen clearance (life threatening ammonia levels without treatment) and some of the synthetic function.

WHY FOCUS ON GLUTAMINE

In addition to the toxicity from the spillover into ammonia, glutamine has its own toxicity resulting in:

- Astrocytic Swelling and Edema
- Mitochondrial Dysfunction
- Microglial Apoptosis
- NO/cGMP Pathway Interference



Rationale for Using Glutamine and Ureagenesis for Efficacy in OTC mRNA Therapy

- Glutamine rises earlier than ammonia in OTC deficiency, reflecting nitrogen load before crisis onset
- Serves as a nitrogen buffer, offering a more stable indicator of urea cycle stress than ammonia. Used as routine clinical measure for efficacy of scavenger therapy.
- Lower variability: Glutamine shows 15% intra-subject variability vs. 56% for ammonia (Lichter-Konecki et al., 2016)
- Ureagenesis measured by 15N ammonia conversion to urea directly reflects cycle function, providing a clear readout of therapeutic efficacy
- Together, glutamine and ureagenesis offer more reliable, physiologically grounded markers than episodic ammonia levels

Goal of this study

- Hypothesis: infusion of a lipid nanoparticle containing OTC mRNA targeted at the liver will restore sufficient function to the urea cycle to affect the glutamine plasma levels and ureagenesis function that are relevant to patient health and cycle function.
- Our hypothesis tested plasma glutamine levels for presence of declining slope from baseline and N15 measured ureagenesis as a % of normal function for increasing slope from baseline

Methods

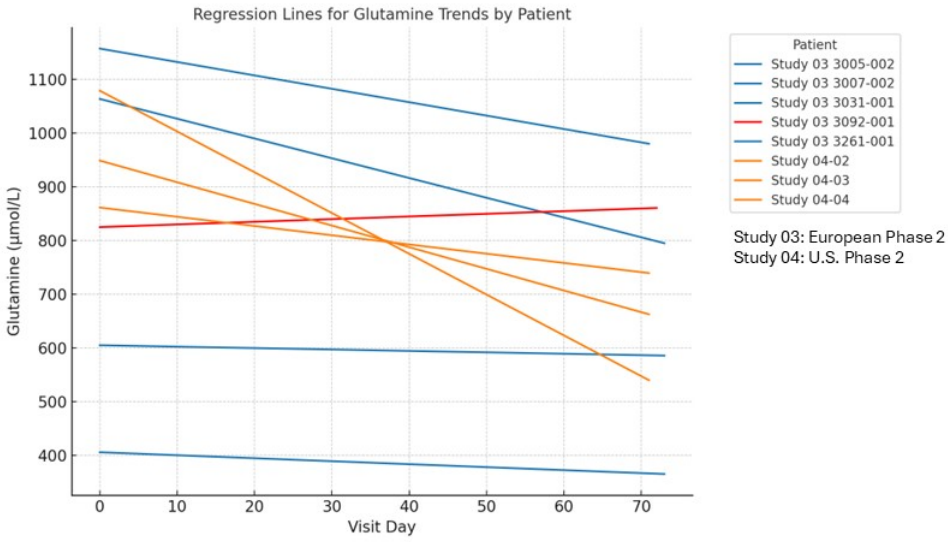
- Patients with molecular or enzymatic test proven OTC deficiency stable on some form of standard therapy.
- Patients on stable diet and therapy for the month preceding onset of study.
- 03 Study glutamine measured at Days: Base, d2, d3, d71, d72, d73. Values past 21 days last dose not used for analysis (94 days).
- 04 Study glutamine measure at Days: Base, d36, d43, d57, d60, and d71 (cutoff 71 days)
- 04 study ureagenesis at days Base, d36, d60, d71, and d85. Timepoints of 0, 30, 60, 90 and 120 minutes collected for each assay. Area under the curve of N15 Urea Calculated and determined as percent activity of normal controls.

Statistical Methods for Glutamine:
Glutamine Analysis (measured by standard laboratory amino acid analysis)

Chi-Square Test (Slope Direction): For each patient, we computed the trend of glutamine over time (linear slope from baseline). We then categorized each patient's slope as **negative (downward)** or **non-negative**. A chi-square goodness-of-fit test (assuming a 50/50 null distribution, df=1, one tail) assessed whether **downward trends occurred more often than chance**. This approach focuses on the **consistency of glutamine reduction** (direction of change), making it intuitive and robust even with a small sample or variable magnitudes of change.

Linear Mixed-Effects Model (LMM): We fit a LMM with **Visit Day as a fixed effect** (to capture the overall rate of glutamine change per day) and **Patient as a random intercept** (to account for individual baseline differences and repeated measures). This model leverages all longitudinal data to ask: "**On average, are glutamine levels decreasing over time?**" The LMM was chosen to handle within-patient correlations and heterogeneity in starting glutamine levels, providing a statistically powerful test for an overall downward trend across the cohort.

Slope Calculation: For each patient, we performed a simple linear regression of glutamine (µmol/L) vs. Visit Day to estimate the time trend (slope). A negative slope indicates a downward trend in glutamine over time.



Study 03: European Phase 2
Study 04: U.S. Phase 2

Chi Square Analysis: Was the slope of glutamine randomly negative or not

Analysis	Observed (Decreasing, Non-Decreasing)	Expected (Decreasing, Non-Decreasing)	Chi-Square Statistic	One-Tailed p-value
Study 3	(4, 1)	(2.5, 2.5)	1.8	0.090
Study 4	(3, 0)	(1.5, 1.5)	3.0	0.042
Combined	(7, 1)	(4, 4)	4.5	**0.017**

Conclusion: Downward trend was not random and significantly showed decrease in glutamine

Linear Mixed Model (LMM) Analysis

Model Specification: We fitted a linear mixed-effects model to glutamine vs. visit day, with Visit Day as a fixed effect and Patient as a random intercept. This accounts for repeated measures per patient. Multiple sensitivity tests did not change the outcome.

Analysis	Number of Patients	Number of Observations	Fixed Effect Slope (µmol/L per day)	One-Tailed p-value (for slope < 0)
Study 3	5	31	-1.82	**0.016**
Study 4	3	18	-4.38	**0.004**
Combined	8	49	-2.50	**0.0055**

Conclusion: The LMM results provide strong evidence that glutamine levels decrease over time in both studies, with a steeper decline in Study 4. The combined analysis reinforces this trend, suggesting a robust effect across the patient cohort, despite baseline differences and repeated measures. This stands up very well to sensitivity testing and the 2 studies provide a confirmation cohort.

Telegram bot

Urea Cycle Function Improvement Supported by Robust Reduction in Glutamine Levels and Increased ^{15}N-Ureagenesis

Both European Phase 2 randomized study (Study 03) and U.S. Phase 2 open-label study (Study 04) demonstrate a robust reduction in plasma glutamine levels during the treatment window with investigational mRNA therapy ARCT-810. Linear mixed model analyses confirm statistically significant downward trends pre-Day 80. Glutamine emerges as a reliable surrogate for urea cycle function in outpatient and clinical trial settings. Follow-up data suggest the drug's effect may wear off, emphasizing the value of glutamine tracking for dosing strategy.

The ^{15}N-ureagenesis data on the 3 patients in the U.S. Phase 2 open-label study (Study 04) supports this observation of increased urea cycle function after treatment with ARCT-810 (OTC mRNA).

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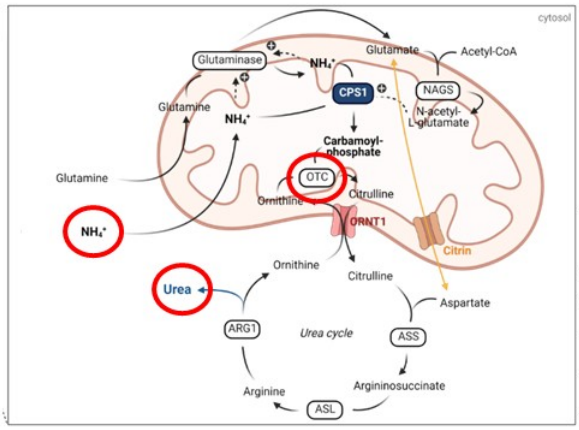
BIOSKETCH

2002	Board Certification in Pediatrics
2004	Certification in Neonatology
2008	Certification in Intensive Care
2008 – present	Consultant in Pediatric Metabolic Medicine, University Children's Hospital Zurich
2009 – present	Chair, European Working Group for Urea Cycle Disorders Guidelines
2012 – present	Adjunct Professor at University of Zurich
2016 – present	Head Metabolic Laboratory, University Children's Hospital Zurich
2016 – 2025	Council member Society for the Study of Inborn Errors of Metabolism (SSIEM)
2019 – 2025	Chair SSIEM Education And Training Advisory Committee (ETAC)
2025 – present	Director, Urea Cycle Disorders Translational Center Universität Zürich

The urea cycle: pathway for ammonia removal

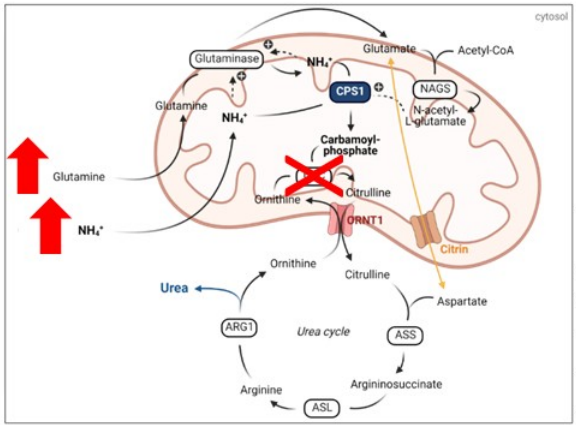


Produced with biorender.com

OTC: ornithine transcarbamylase

The usual diagnostic toolbox for OTC deficiency …

- Ammonia in blood
- Glutamine in blood



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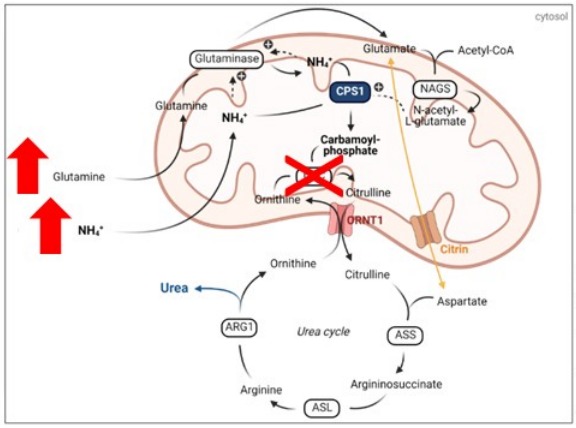


… benefits from functional studies measuring the total urea cycle flux

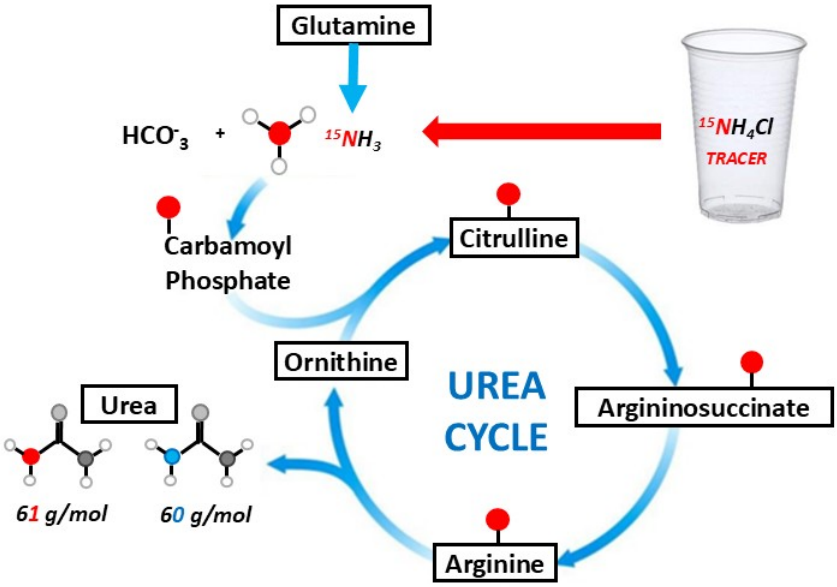
➡ **Ureagenesis assay**

OTC: ornithine transcarbamylase

Ureagenesis – factsheet published methods & tracers

	$[^{15}N]H_4Cl$ (Yudkoff M, *J Clin Invest*, 1996; Allegri G, *Metab Health Dis*, 2025)	$[1\text{-}^{13}C]$ or $[1,2\text{-}^{13}C]$ acetate (Tuchman M, *Pediatr Res*, 2008; Opladen *T, Mol Genet Med*, 2016)
Safety concerns	Patients prone to ↑ NH_3	Safe
Taste	Unpleasant (but little amount & volume)	Not mentioned
% of tracer into urea cycle	> 50% (because of hepatic first pass)	< 1%
Method	GC-MS; LC-MS/MS	GC-IRMS; monitor breath $^{13}CO_2$ [99%]
Analyte Analyzed	Urea & glutamine & other amino acids	Urea
Filter paper (DBS)	Possible	Not possible

The principle of ureagenesis quantification



Allegri G et al, *Clin Chim Acta*, 2017
Allegri G et al, *J Inher Metab Dis*, 2019
Allegri G et al, *Metab Health Dis*, 2025

npj | metabolic health and disease

Article

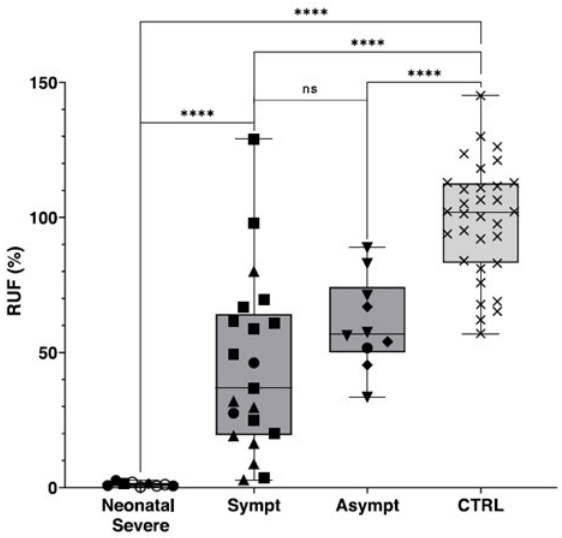
https://doi.org/10.1038/s44324-025-00051-8

Characterization and treatment monitoring of ureagenesis disorders using stable isotopes

Check for updates

Gabriella Allegri[1,12], Martin Poms[2,12], Nadia Zürcher[1], Véronique Rüfenacht[1], Nicole Rimann[1], Déborah Mathis[2,3], Beat Thöny[1,2], Matthias Gautschi[4], Ralf A. Husain[5], Daniela Karall[6], Karolina Orchel-Szastak[7], Francesco Porta[8], Dominique Roland[9], Barbara Siri[10], Carlo Dionisi-Vici[10], René Santer[11] & Johannes Häberle[1] ✉

RUF according to severity and presence or absence of symptoms



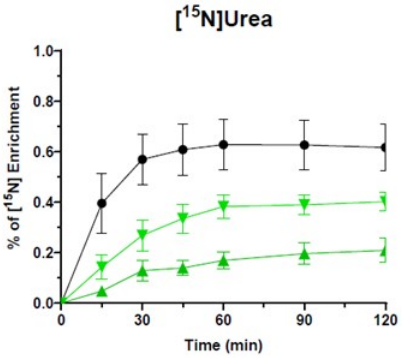
RUF: relative ureagenesis function
Sympt: symptomatic patients
Asympt: asymptomatic patients diagnosed through family screening
CTRL: controls

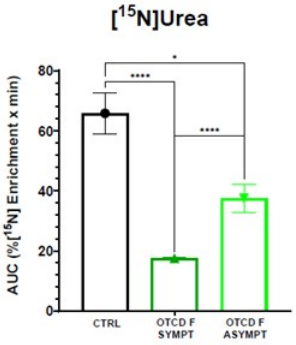
Allegri et al, *Metab Health Dis*, 2025

[^{15}N]urea enrichment for OTCD females ± symptoms and controls

	OTC_F_SYMPT	OTC_F_ASYMPT	CTRL
RUF (%):	31.36 ± 21.50***/*	63.14 ± 19.17*/*	98.73 ± 20.78

- CTRL: 39 investigations in 23 healthy subjects
- OTCD_F_SYMPT: 10 symptomatic females
- OTCD_F_ASYMPT: 8 asymptomatic females





Allegri et al, *Metab Health Dis*, 2025

[^{15}N]urea enrichment in 3 patients from ARCT-810 U.S. Phase 2 study

	Patient 002	Patient 003	Patient 004
	RUF	**RUF**	**RUF**
controls	78.0 – 122.0%	78.0 – 122.0%	78.0 – 122.0%
baseline	21.4%	26.7%	39.0%
day 36; 7 days post 3rd dose	11.0%	39.6%	50.2%
day 60; 3 days post 5th dose	28.6%	36.8%	40.0%
day 71; 14 days post 5th dose	8.7%	55.4%	57.7%
day 85; 28 days post 5th dose	19.7%	49.4%	61.9%

RUF: relative ureagenesis function

[^{15}N]urea enrichment in 3 patients from ARCT-810 U.S. Phase 2 study

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	RUF	**RUF**	**RUF**
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day 85; 28 days post 5th dose	19.7%	49.4%	61.9%

- Interim Phase 2 group: significant mean improvement of RUF (+14.7%, n=3, p=0.026, LMM)
- Two patients (003, 004) achieved RUF >50% indicating clinically meaningful improvement in urea cycle flux; patient 002: no change in RUF, but improved citrulline enrichment

RUF: relative ureagenesis function

Closing Comments

ARCT-810: Summary of Phase 2 Interim Data

- **Significant and consistent reduction in glutamine levels in both Phase 2 studies** – from abnormal to normal levels
- **Significant increase in ^{15}N-ureagenesis in the U.S. Phase 2 study** – additional evidence of urea cycle improvement
- **Ammonia – stable and within normal range**
- **ARCT-810 continues to be safe and well tolerated at all tested dose levels**

Arcturus to share these new clinical data with the OTCD community
Timing of Phase 2 completion / Phase 3 initiation to be provided on next quarterly call

Q & A

ARCTURUS therapeutics

KOL PRESENTATION

ARCT-810

June 30, 2025