KOL PRESENTATION

ARCT-810

June 30, 2025

Forward Looking Statements

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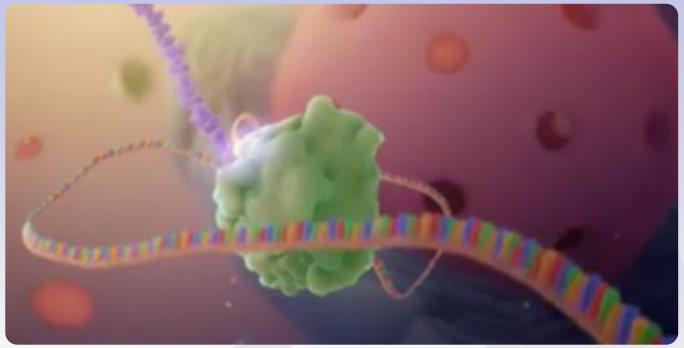
Arcturus Therapeutics

Global mRNA Medicines Company



KOSTAIVE® Approved in **Japan & EU**

Nasdaq: ARCT

Headquarters: San Diego, CA

Founded: 2013

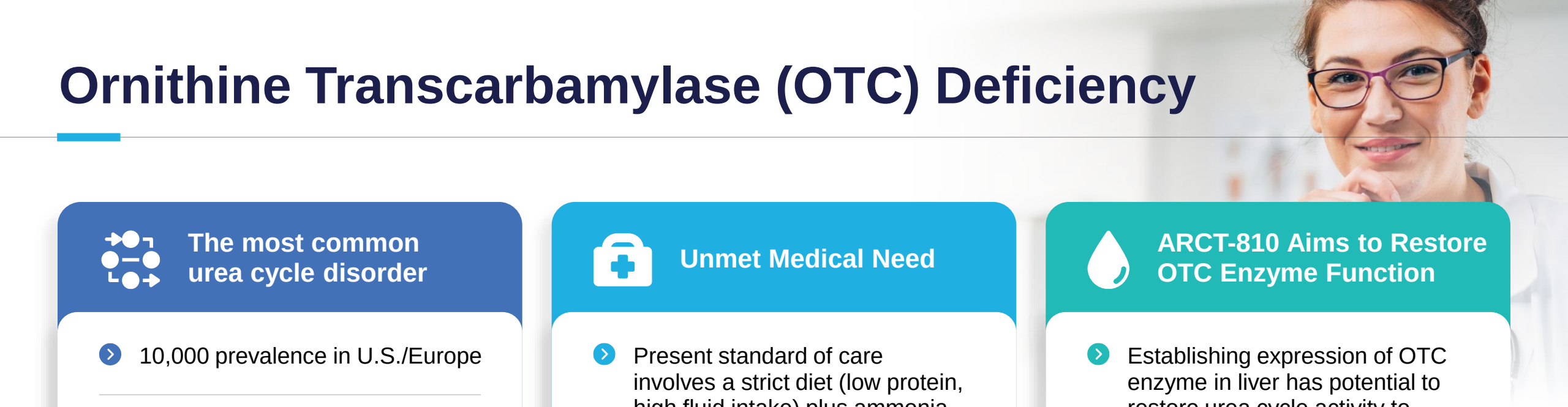
mRNA Medicine Candidates

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)

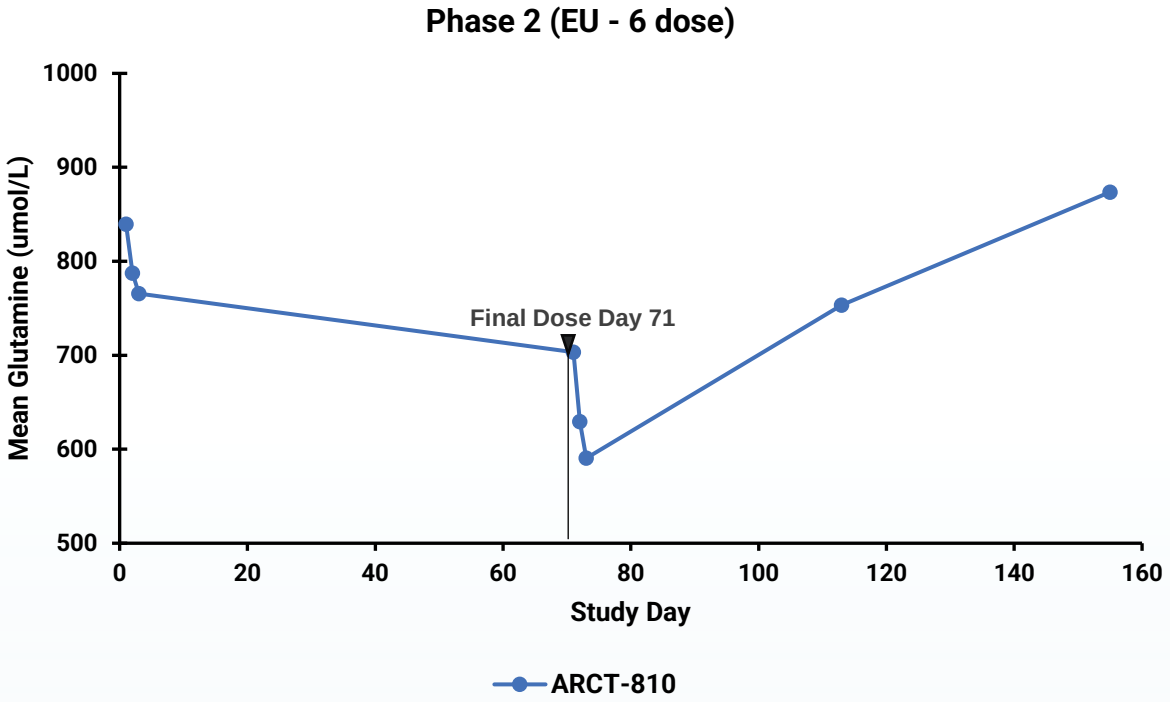
- Randomized, placebo-controlled
- 0.3 mg/kg ARCT-810; up to six biweekly IV infusions
- Entry criteria: Patients with stable disease

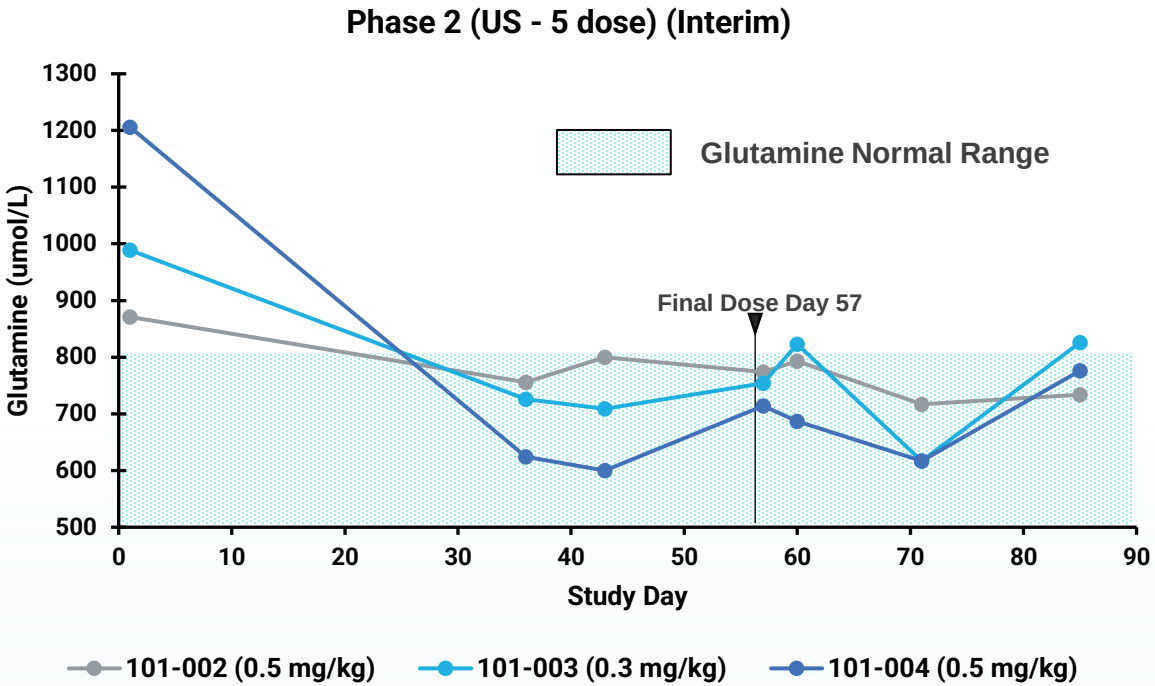
U.S. Phase 2 Study – Ongoing (N = 3 completed to date)

- 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

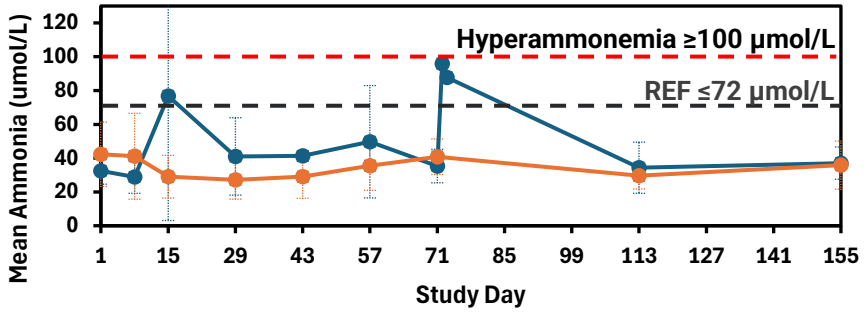
Two of three subjects achieved > 50% RUF

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

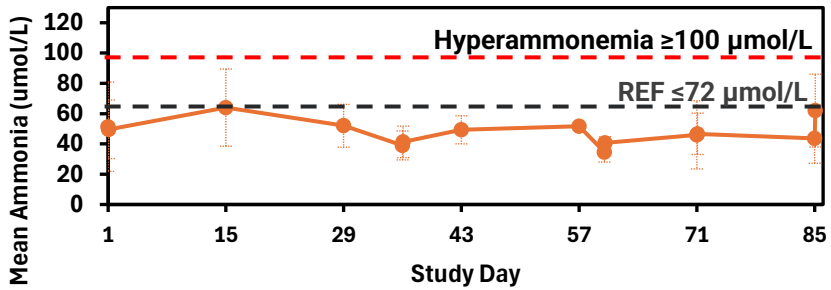
Encouraging ^{15}N-Ureagenesis data provide additional support and confidence in the favorable glutamine results

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

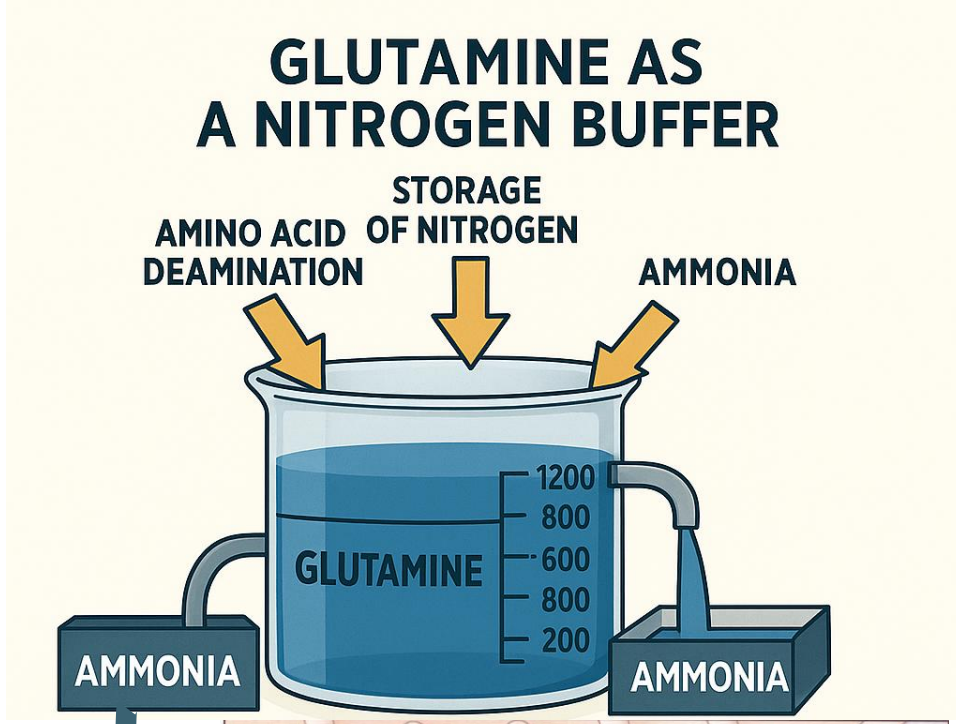
Urea Cycle & OTC Overview

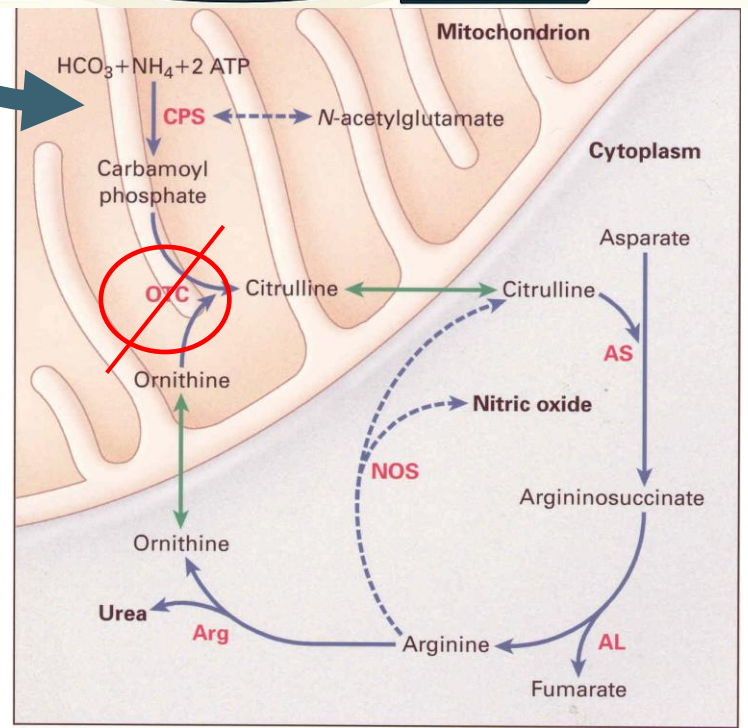
- Urea Cycle is human pathway for clearing nitrogen as well as producing some essential biomolecules. Defects are referred to as Urea Cycle Disorders (UCDs)
- Ornithine Transcarbamylase Deficiency (OTCD) is the most common defect as it is located on the X chromosome.
- Restoration of activity restores 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

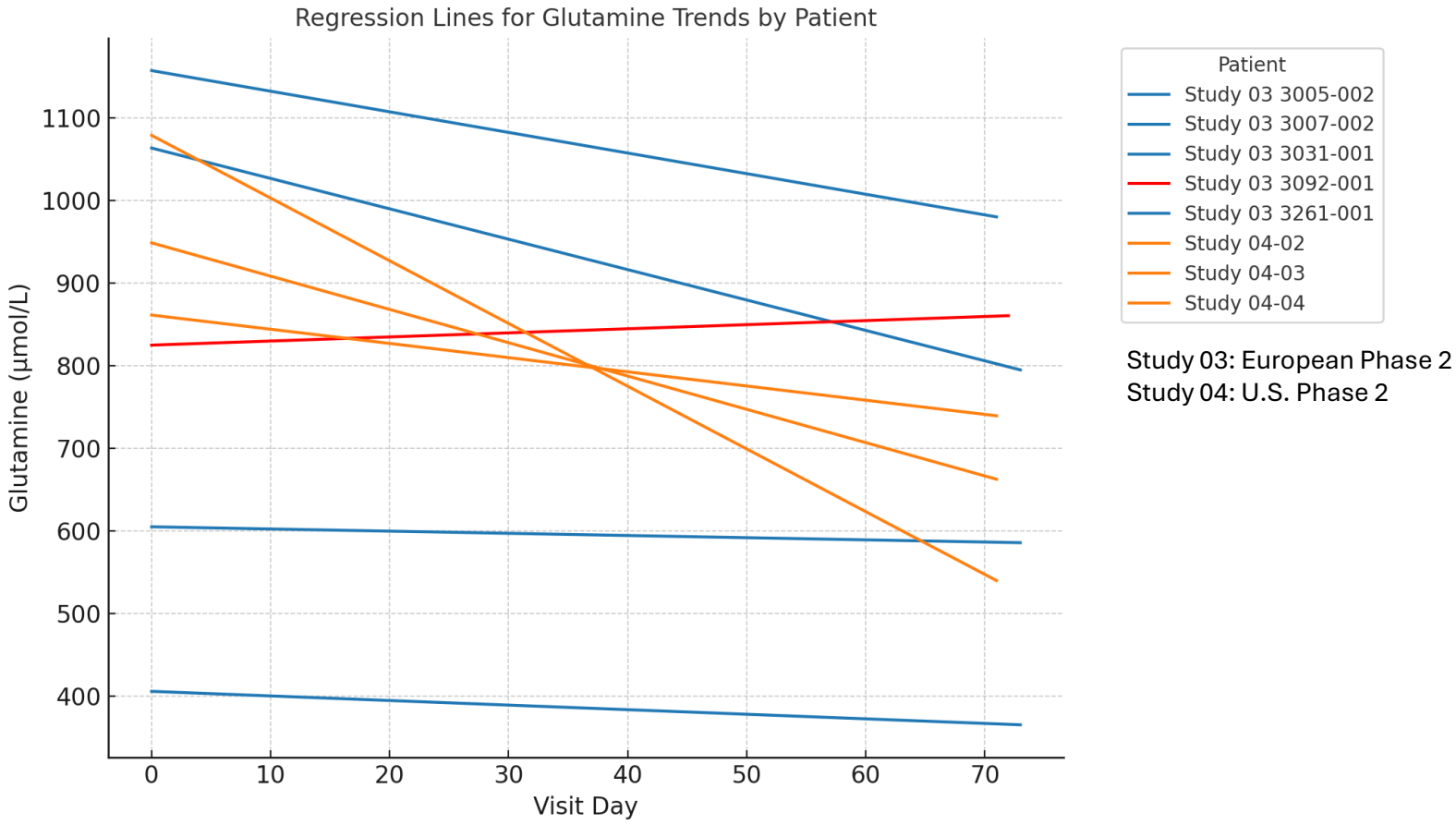
- Patients with molecular or enzymatic test proven OTC deficiency stable on some form of standard therapy.
- Patients on stable diet and therapy for the month preceding onset of study.
- 03 Study glutamine measured at Days: Base, d2, d3, d71, d72, d73. Values past 21 days last dose not used for analysis (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.

^{15}N-Ureagenesis Data

Participant/Dose	Day Base	Day 36	Day 60	Day 71	Day 85
101-002 (0.5 mg/kg)	21.4	11.0	28.6	8.7	19.7
101-003 (0.3 mg/kg)	26.7	39.6	36.8	55.4	49.4
101-004 (0.5 mg/kg)	39.0	50.2	40.0	57.7	61.9
Mean (SD)	**29.0 (9.1)**	**33.6 (20.3)**	**35.1 (5.9)**	**40.6 (27.6)**	**43.7 (21.7)**

- **The positive coefficient of 0.167 means that % ureagenesis increased on average by 0.167 percentage points per day.**
- **The p-value = 0.026 indicates this increase is statistically significant at the 5% level.**
- **The limitation is the small sample size.**

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).

Johannes Häberle

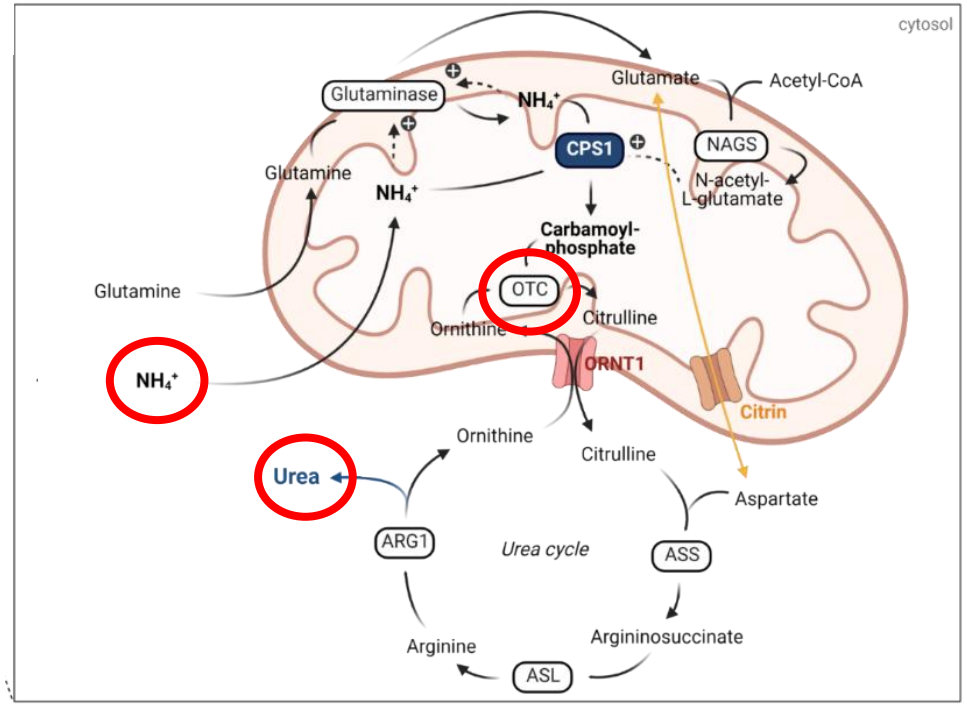
Division of Metabolism and Children's Research Center

University Children's Hospital Zurich, Switzerland

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



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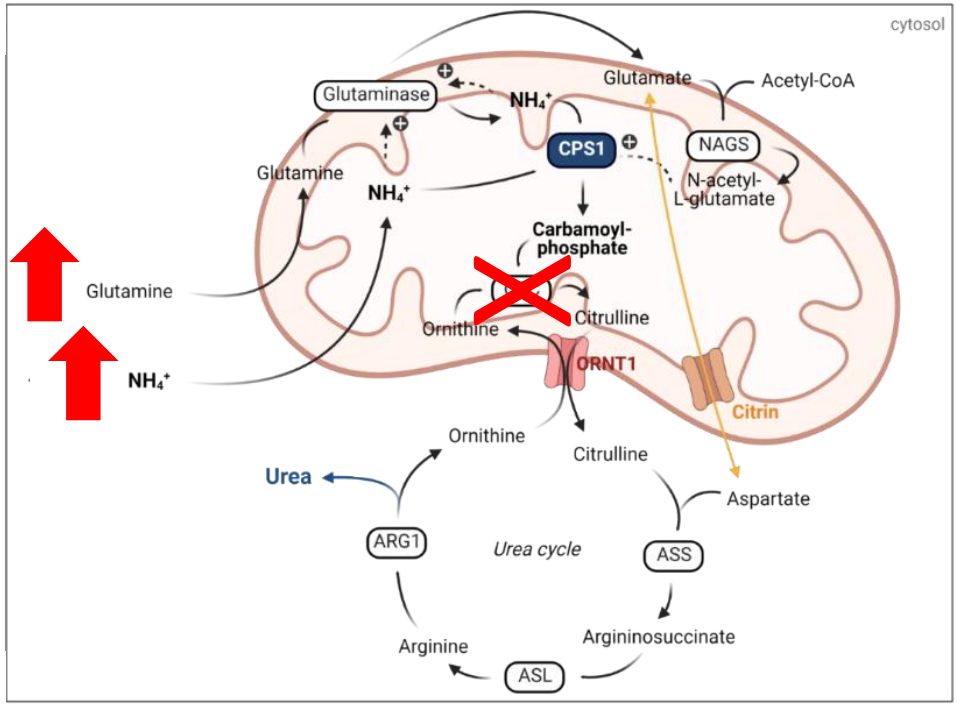
OTC: ornithine transcarbamylase

The usual diagnostic toolbox for OTC deficiency …

- Ammonia in blood
- Glutamine in blood



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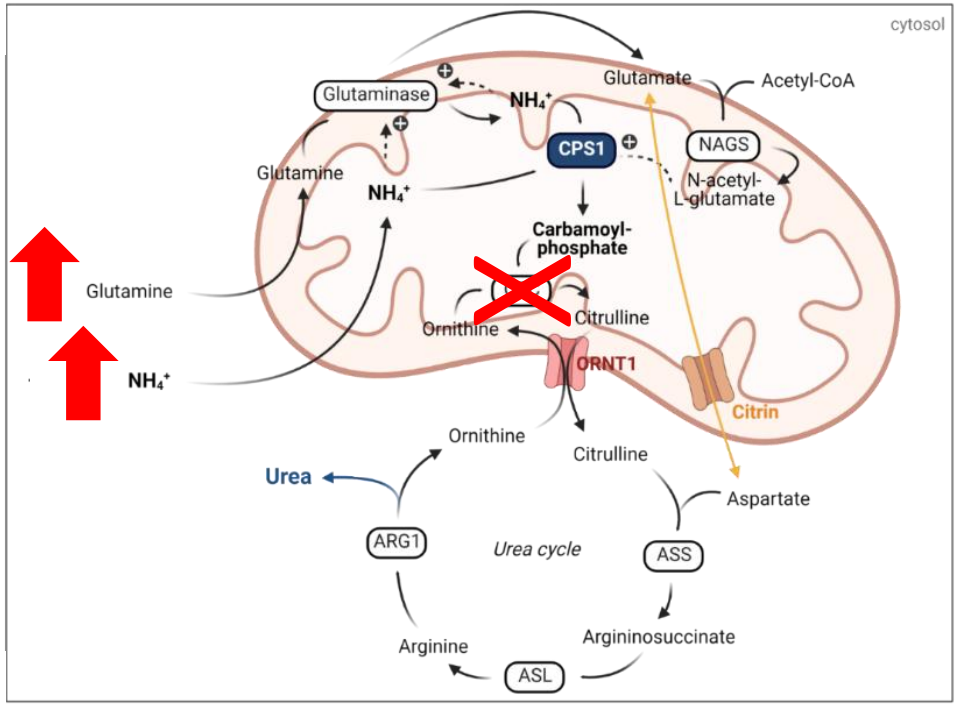

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… benefits from functional studies measuring the total urea cycle flux

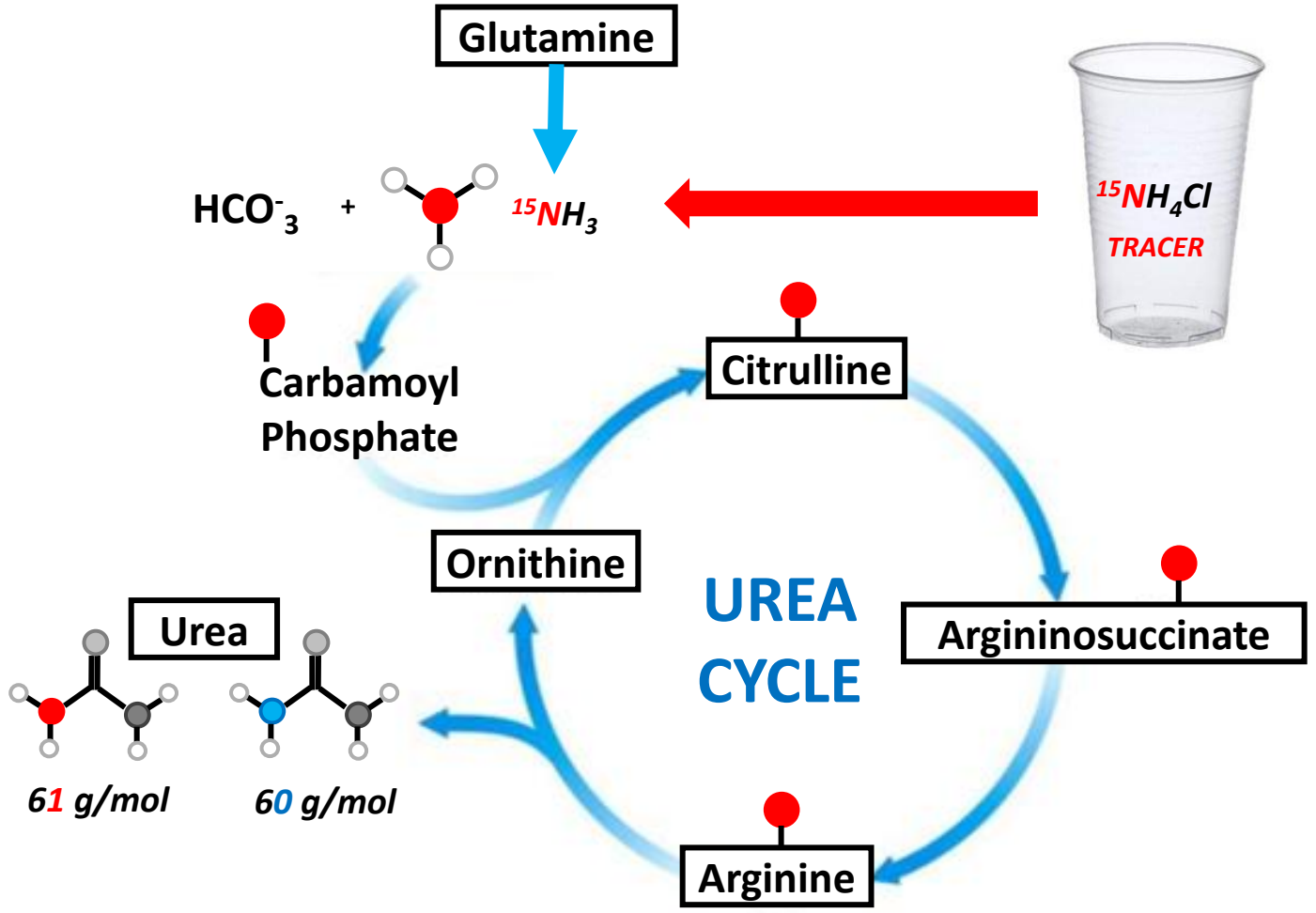
➡ **Ureagenesis assay**

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

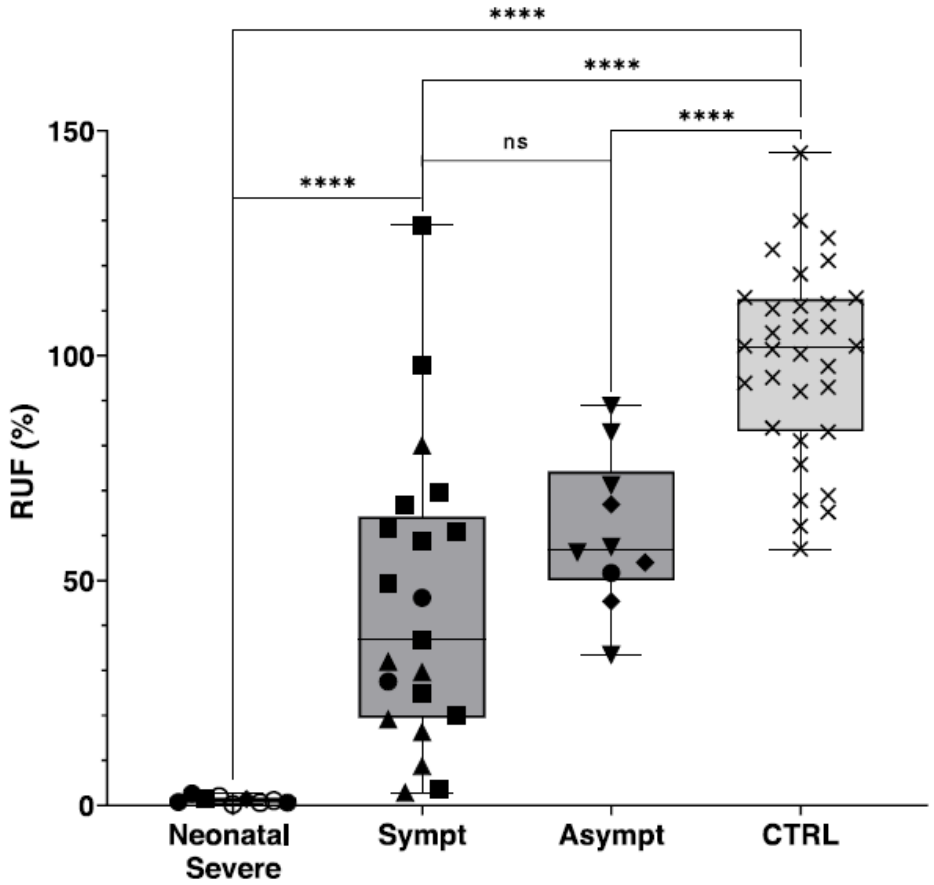
Article

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

Characterization and treatment monitoring of ureagenesis disorders using stable isotopes

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



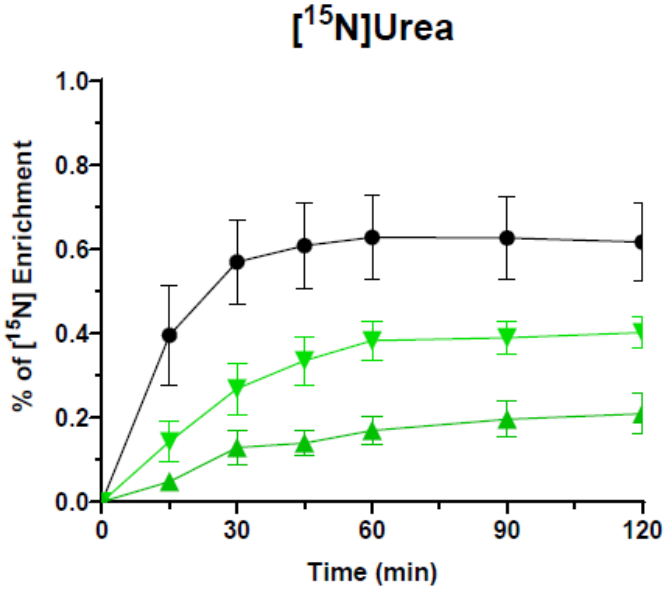
RUF: relative ureagenesis function
Sympt: symptomatic patients
Asympt: asymptomatic patients diagnosed through family screening
CTRL: controls

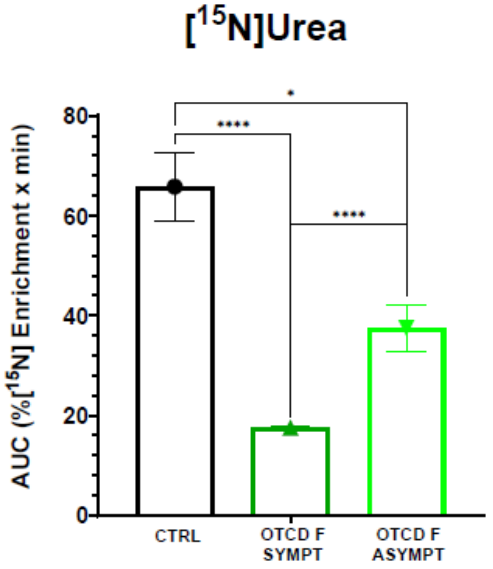
Allegri et al, *Metab Health Dis*, 2025

[^{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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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%

- 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

KOL PRESENTATION

ARCT-810

June 30, 2025