Eighteen-Month Clinical Update from the First Patient Dosed in OTC-HOPE

An In Vivo Liver-Directed AAV Gene Insertion Trial for Neonatal-Onset Ornithine Transcarbamylase Deficiency

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Disclosures

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iECURE, Inc – Primary Investigator

Neonatal-Onset OTC Deficiency

Ornithine transcarbamylase deficiency (OTCD) is neurometabolic disorder arising from a genetic defect in a liver urea cycle enzyme responsible for ammonia detoxification. Neonatal-onset OTCD is a severe, early form that appears in the first days of life.

Incidence

1 : 56,500 live births[1]

Neonatal Mortality

Mortality rates as high as **74%** when onset occurs within the first month of life[2]

Clinical Presentation

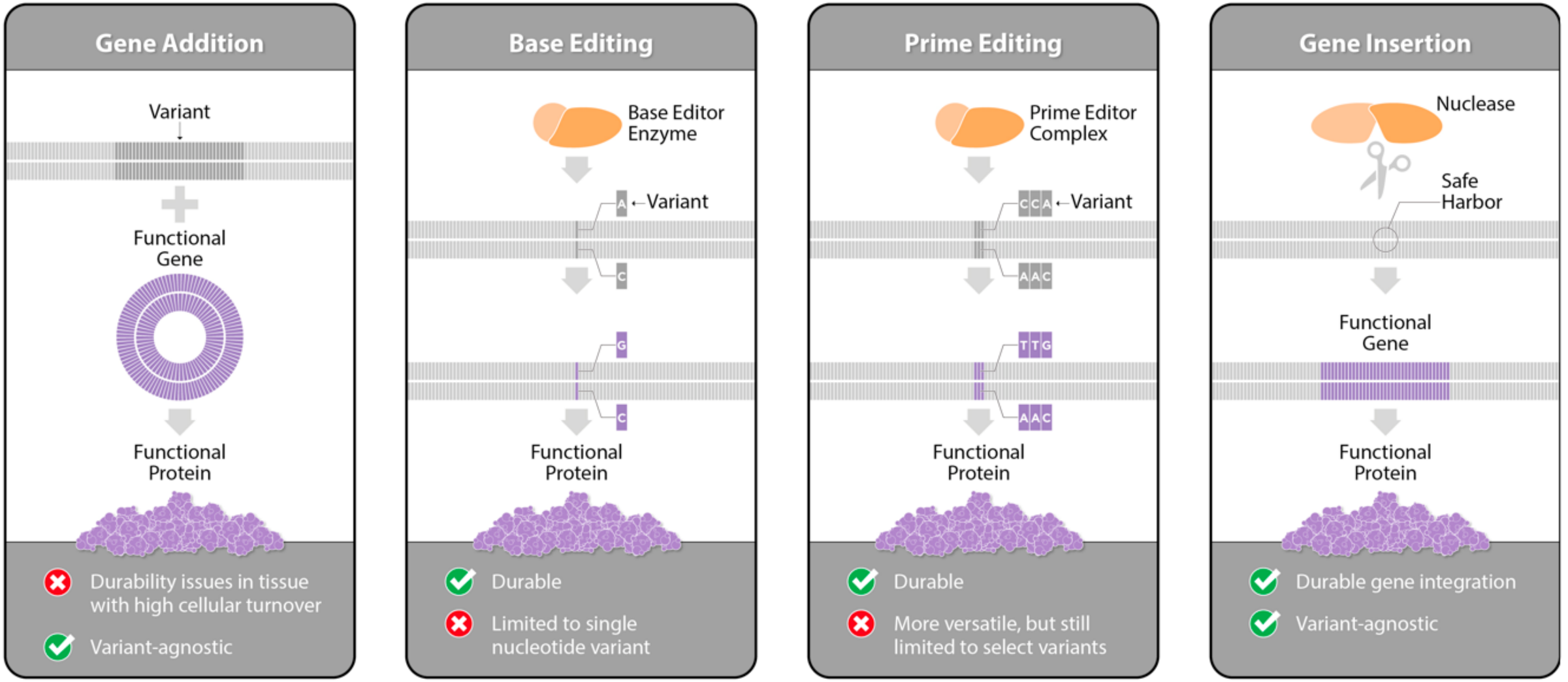
Hyperammonemic crises (HACs) causing lethargy, vomiting, tachypnea, seizures, coma and neuropsychological sequelae

Standard of Care

Protein restriction, nitrogen scavenger therapy; **orthotopic liver transplantation** is the only curative option

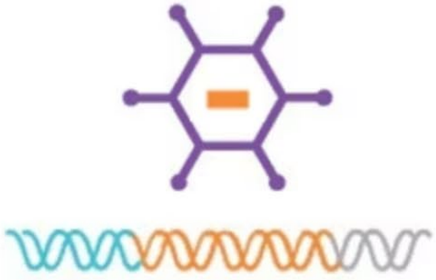
1 Summar ML et al, European R, Network for Intoxication Type Metabolic Diseases. The incidence of urea cycle disorders. Mol Genet Metab. 2013;110:179-80. 2 Brassier et al. Orphanet Journal of Rare Diseases. 2015

Gene Therapy Approaches



Dual AAV / ARCUS Nuclease / Donor Gene

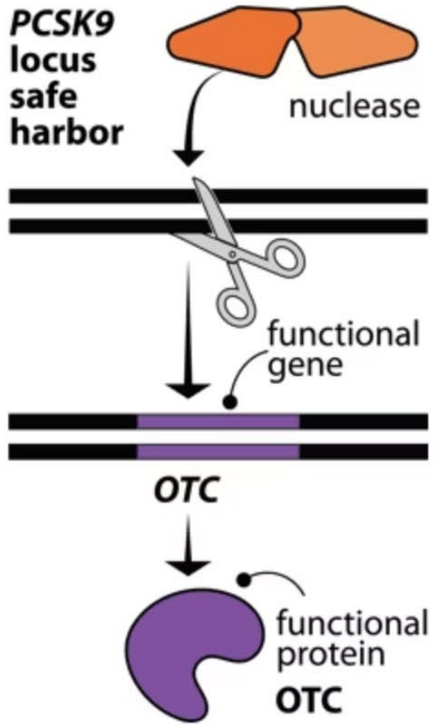
Each Vector Consists of an AAVrh79 Capsid



Nuclease vector to be utilized across all indications

Future programs will only vary donor gene cassette

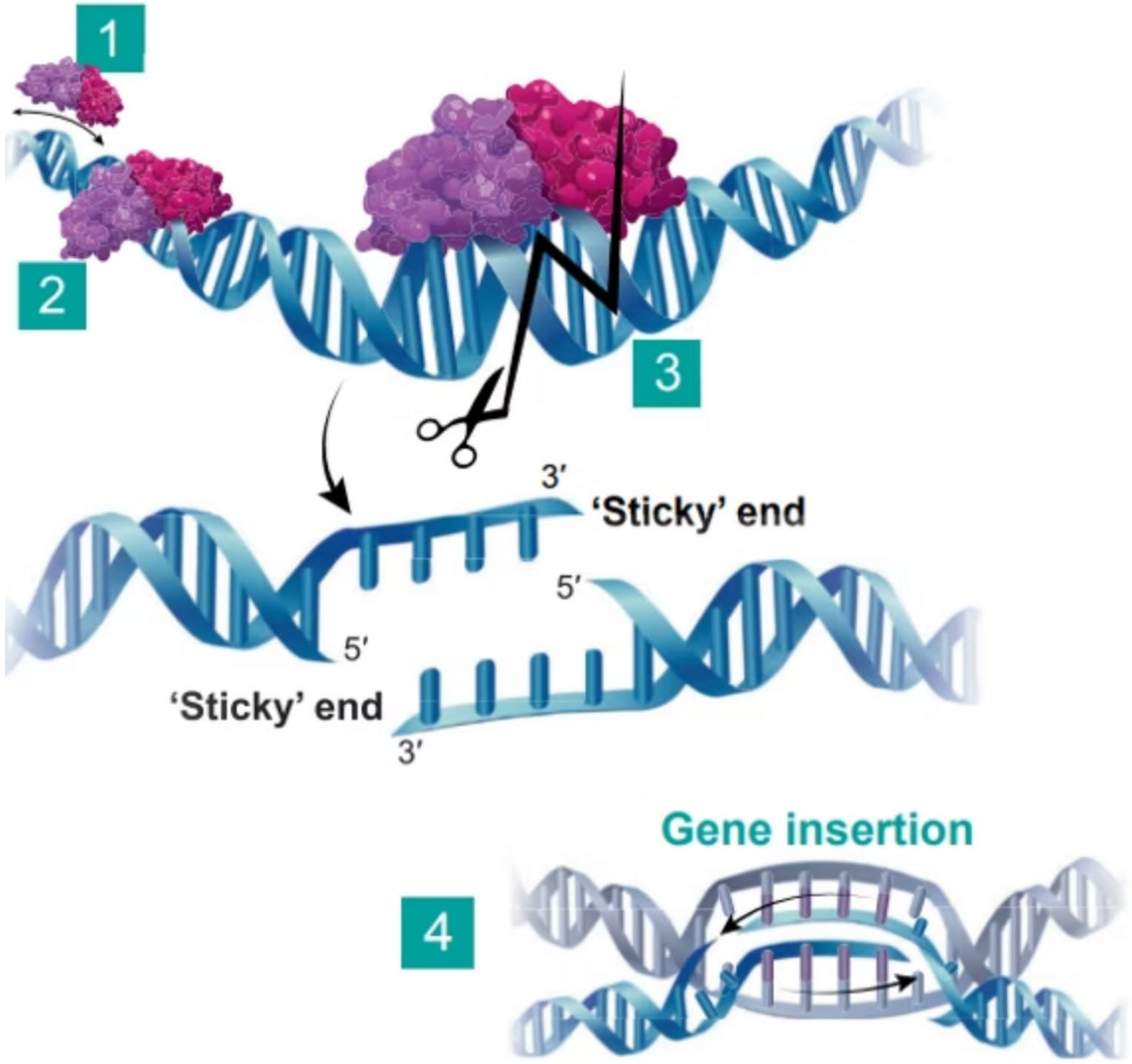
Platform approach expected to provide significant efficiencies in future clinical development programs



ECUR-506
3:1 Donor to Arcus Ratio

hOTC = ornithine transcarbamylase

ARCUS: A Well-Differentiated Genome Editing Platform



01

The ARCUS nuclease scans DNA for the target site

02

The ARCUS nuclease binds to the target site

03

The target DNA sequence is cut, creating a 'sticky' 4-base 3' overhang

04

The cut target site is repaired via homology-directed repair (HDR) or non-homologous end joining (NHEJ)

Compared with some other gene-editing technologies, an ARCUS nuclease is relatively small (~1.1 kilobases and ~360 amino acids), making it possible to deliver via adeno-associated virus (AAV), which has a packaging capacity of ~4.4 kb.

OTC-HOPE

A first-in-human clinical trial evaluating **ECUR-506** in newborn males with neonatal-onset OTC deficiency — the most severe and life-threatening form of the disease

OTC-HOPE: Clinical Trial Design

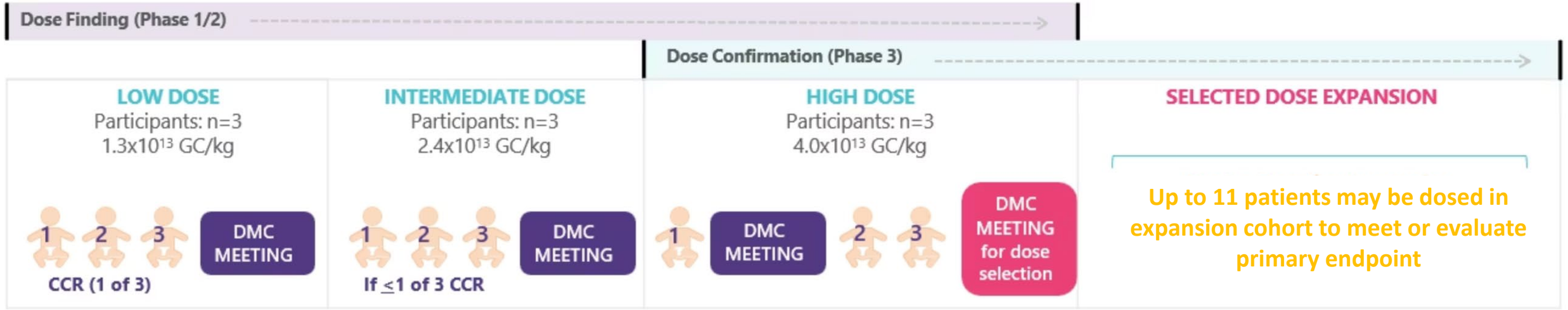
Trial Design*	• PH 1/2/3, global multi-center trial, open label, FIH, adaptive, dose finding and dose confirmation study • First participant dose: 1.3×10^{13} GC/kg • Dose escalation up to 4.0×10^{13} GC/kg
Vector	• IV delivery of dual AAV with ARCUS Nuclease and donor OTC gene
Study Duration	• 6-month post dose follow up • 14.5-year long-term follow up study
Primary Endpoint**	• Assessment of safety and tolerability of ECUR-506 • Efficacy: ◦ Complete clinical response (CCR) by EOS, defined as the discontinuation of scavenger medication for a minimum duration of 28 days without reductions in prescribed daily protein intake during this time period, compared to systematic literature review (SLR)
Key Secondary Endpoint**	• Efficacy: ◦ Rate of hyperammonemic events (HAE)/person-year where HAE is defined as fasting plasma ammonia levels > 100 µmol/L, Day 1 post dose through Week 24, compared to peer-reviewed published literature

*Initial dosing cohorts require an 8-week safety stagger between participants

**For a more complete listing of secondary and exploratory endpoints visit: https://clinicaltrials.gov/study/NCT05251782?cond=Ornithine%20transcarbamylase%20deficiency&term=iECURE&rank=2

Dose Confirmation Scenario

All remaining participants to be dosed in 2026. Adaptive design with DMC oversight at each cohort transition.



Inclusion Criteria

Patient Demographics

- Male sex
- Gestational age ≥ 37 weeks
- Age at screening is 24 hours to 7 months
- Weight ≥ 3.5 kg and ≤ 13.5 kg at screening
- Has received all age-appropriate vaccinations

Disease Confirmation & Treatment

- Genetically confirmed OTCD
- Current or past hyperammonemic crisis (including ammonia levels >560 µmol/L, lethargy, poor feeding, coma, or seizure) within first week of life

OR

- Genetic confirmation of an OTC variant (pathogenic or likely pathogenic) associated with severe neonatal OTCD or the same OTC variant as a family member who had severe neonatal OTCD within first week of life

AND

- Currently receiving treatment with both dietary protein restriction and scavenger therapy
- Current or historical biochemical profile consistent with OTCD
- Participant's parent(s)/LAR must be able to comprehend and be willing to provide a signed IRB/IEC-approved ICF

Exclusion Criteria

Neurological / Hepatic

Neonatal diagnosis of severe to profound Hypoxic Ischemic Encephalopathy due to birth injury; Requiring urgent liver transplant due to liver failure as assessed by the PI.

Genetic / Structural

Contiguous gene deletion involving the OTC gene; Known or suspected major organ injury/dysfunction/anomalies.

Prior / Concurrent Therapy

Treatment with any other gene therapy or gene editing therapy; Co-enrollment in any other clinical study with an investigational product.

Investigator Discretion

Any condition that, in the opinion of the Investigator, would compromise participant safety or study data.

Infectious / Teratogenic Exposure

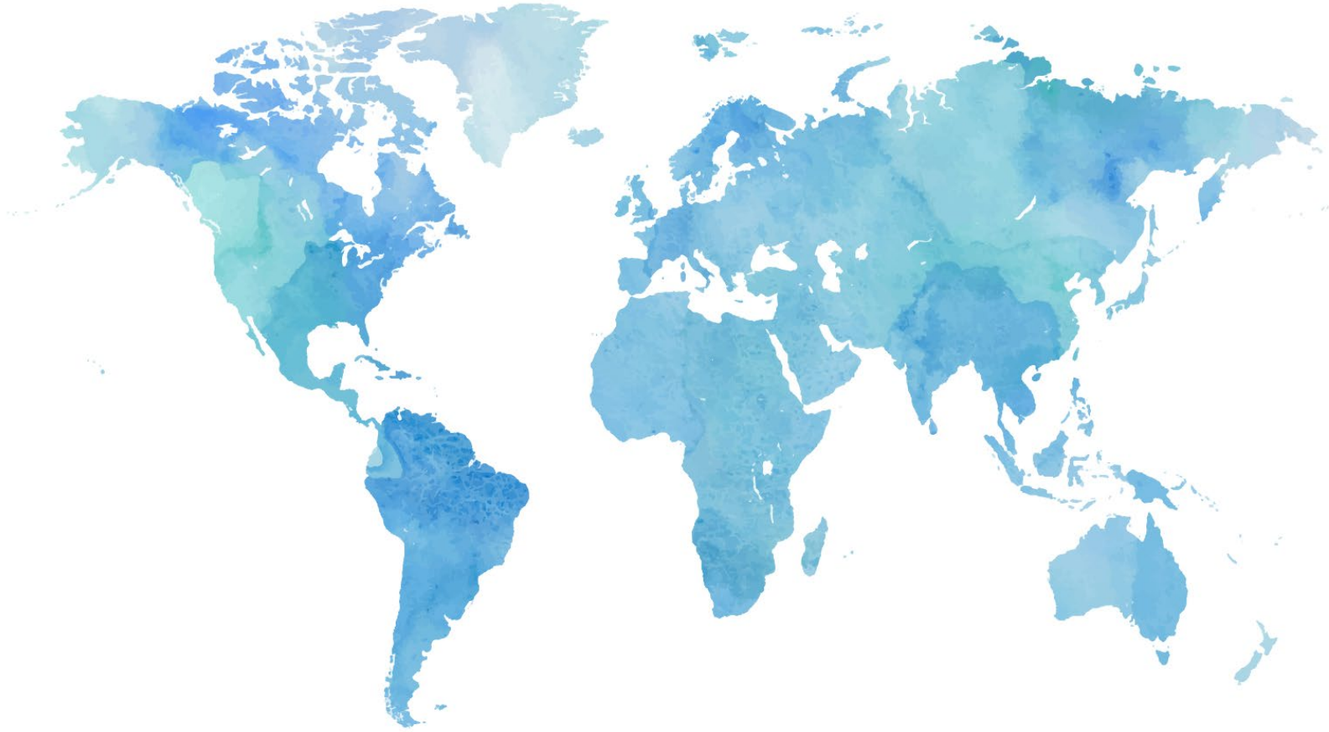
Documented vertical transmission of HepA/HepB/HepC; Documented in-utero teratogen, substance, and/or alcohol exposure.

Global Clinical Program

IND/CTA Clearances

- United States
- United Kingdom
- Spain
- Australia

Harmonized global protocol; international referral network with patient transport programs for families outside approved geographies.



Regulatory Designations

- **FDA:** Orphan Drug; Rare Pediatric Disease; Chemistry, Manufacturing, and Controls Development and Readiness Pilot (CDRP); Fast Track and Regenerative Medicine Advanced Therapy (RMAT) designations
- **European Commission:** Orphan Designation, Pediatric Investigational Plan (PIP) agreement
- **MHRA:** Innovative Licensing and Access Pathway (ILAP)

First Infant Dosed: Clinical Data

Eighteen months of follow-up from the first participant dosed with ECUR-506 in the OTC-HOPE trial

Patient 1: Clinical Timeline

6 Days Old

NH_3 823 µmol/L

Managed with hemodialysis and started on scavenger therapy/protein restriction

OTC variant c.77G>C (Arg26Pro) confirmed

4 Months

Enrolled in OTC-HOPE

5.5 Months

2nd HAC

6.5 Months

ECUR-506 1.3×10^{13} GC/kg

12.5 Months

Entered LTFU

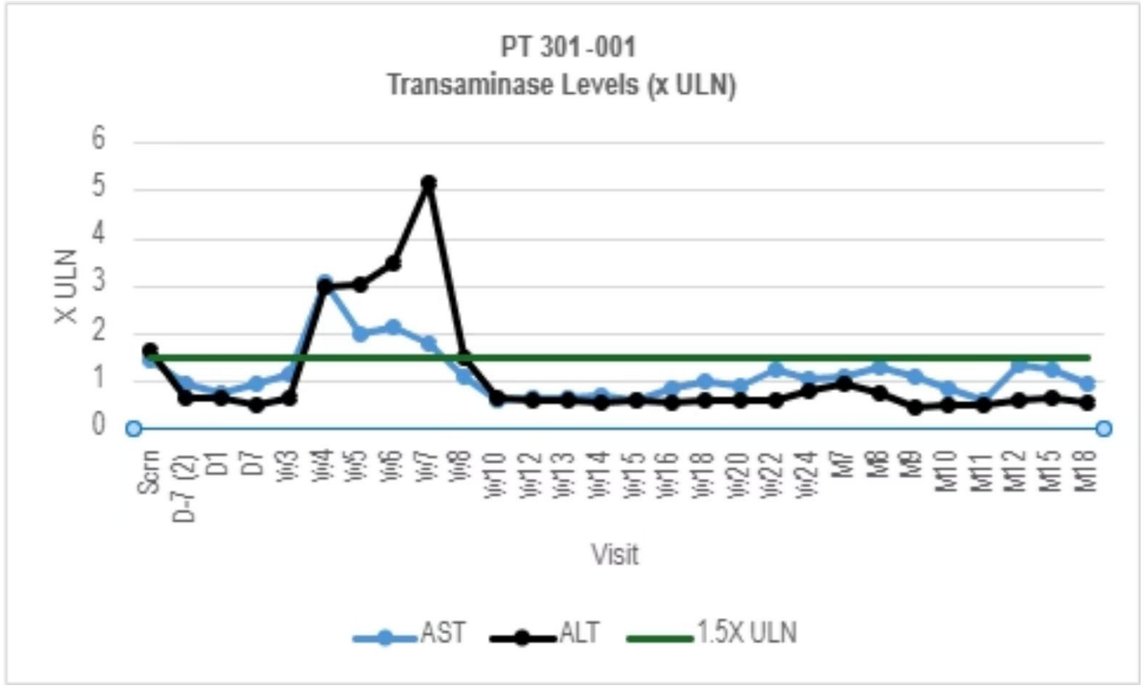
24.5 Months

Age at data cut

The patient presented with severe neonatal-onset OTCD requiring urgent metabolic stabilization. A second hyperammonemic crisis at 5.5 months preceded dosing at 6.5 months of age. The patient successfully transitioned to long-term follow-up at 12.5 months.

Grade 3 Transaminitis Episode: Management Timeline

Data as of 11FEB2026



Week 4 – ALT 3× ULN

Admitted; IV methylprednisolone initiated at **5 mg/kg**

Week 6 – Steroid Dose Escalation

IV methylprednisolone increased to **10 mg/kg** and liver biopsy

Week 7 – Transition

Converted to oral prednisone (10 mg/kg); tacrolimus initiated at 0.5 mg/kg/day

Weeks 8-14 – Steroid Wean

Corticosteroid taper completed successfully

Weeks 12-23 – Tacrolimus Wean

Tacrolimus taper completed; immunosuppression discontinued

Liver Biopsy Histopathology Results

For-cause liver biopsy taken at 6 weeks post ECUR-506 dosing to help determine underlying cause of inflammation and guide immunosuppressant choice.

Mild portal and minor interface inflammation

Widespread glycogen accumulation within hepatocytes

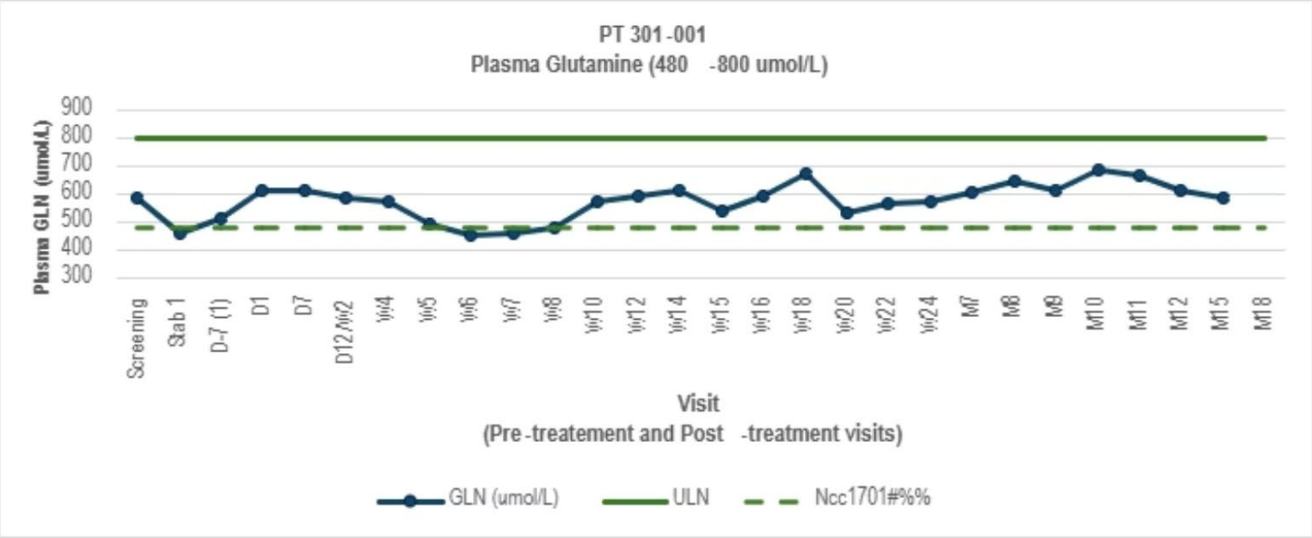
Focal mild fibrosis

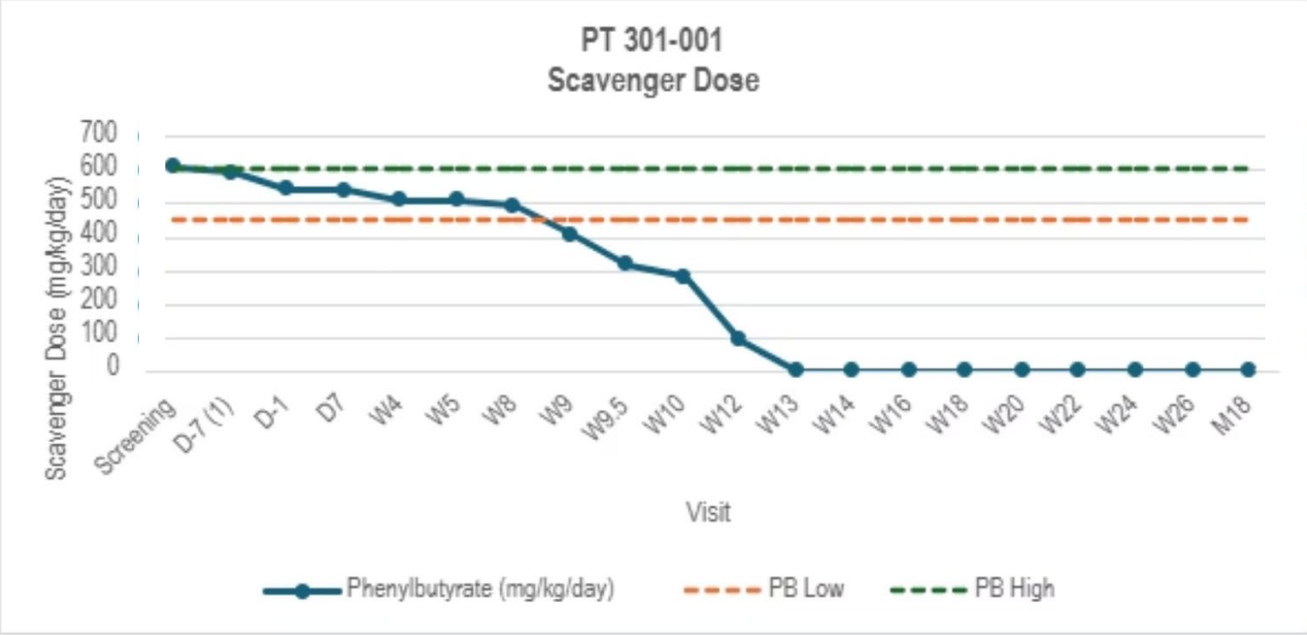
Mild portal lymphocytic inflammation with mild interface reaction with occasional associated acidophil bodies / single necrotic hepatocytes identified.

Infiltrating population of lymphocytes were predominantly T-cells (CD3+), with only very scanty scattered B-cells (CD20+) consistent with a typical inflammatory profile.

OTC-HOPE: Clinical Endpoints — Patient 1

Data as of 11FEB2026





Plasma Glutamine Decline

Glutamine declined below the lower limit of normal between **weeks 6–8** post-dosing, even during high-dose corticosteroid administration.

Scavenger Discontinuation

Prompted complete weaning of nitrogen scavenger therapy from weeks 8–13 post-ECUR-506 — meeting the protocol-defined CCR criterion.

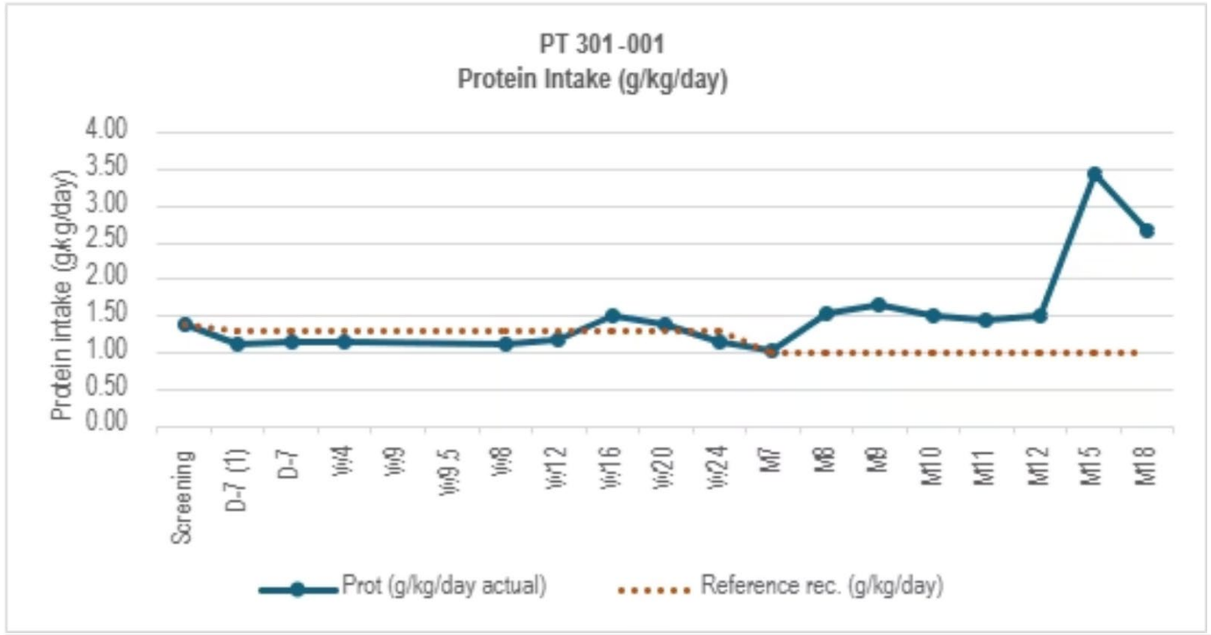
Sustained Response

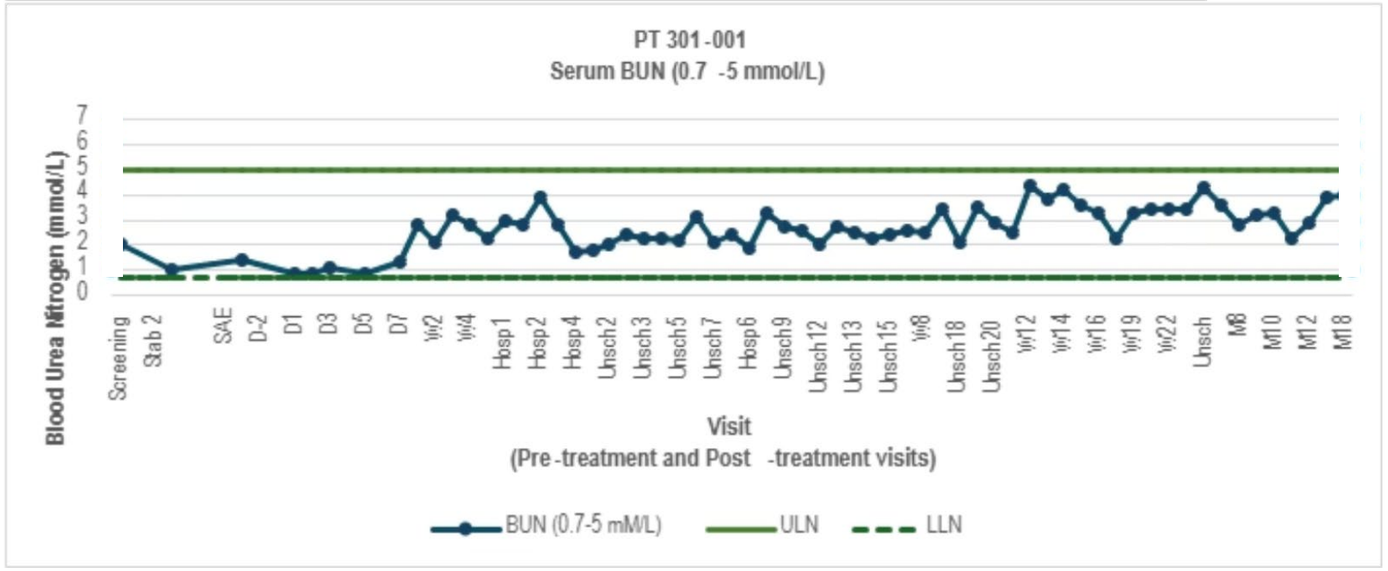
Normal plasma glutamine maintained at **12 months post-discontinuation** of standard of care. No biochemical relapse observed.

- CCR defined as discontinuation of scavenger medication for ≥28 days without reduction in prescribed daily protein intake.

Protein Intake Liberalization

Data as of 11FEB2026





Diet Liberalized

Liberalized after scavenger wean post ECUR-506 dosing.

Full Intake

Age-appropriate intake achieved without hyperammonemia.

Sustained 18 Months

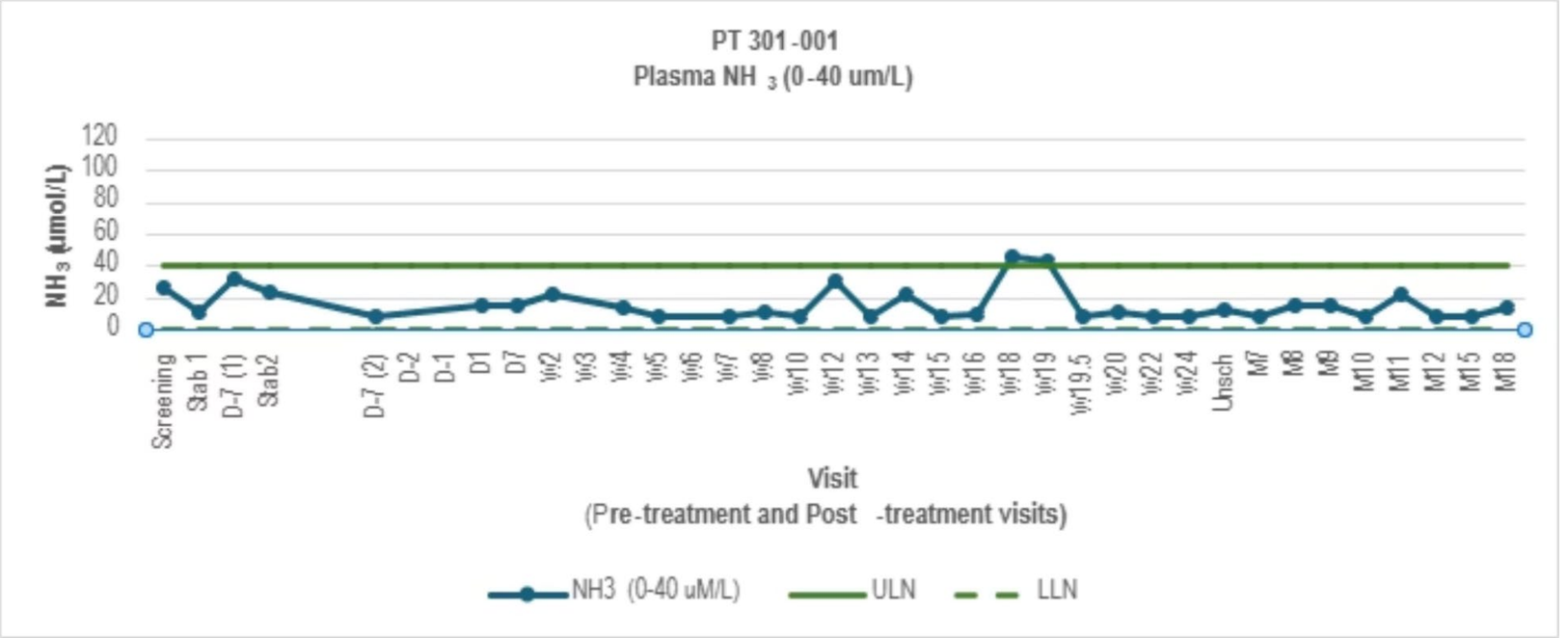
Liberalization maintained through 18 months post-dose.

BUN Increased

Consistent with restored ureagenesis.

Plasma Ammonia: LTFU Data

Data as of 11FEB2026



Ammonia Control

Plasma ammonia levels remain within the **normal reference range** throughout long-term follow-up.

No HAE Events

Zero hyperammonemic crises recorded since ECUR-506 administration, despite viral illness. A contrast to the natural history of neonatal-onset OTCD[1].

Transplant De-listed

Patient has been **removed from the liver transplant waiting list**.

1.Lichter-Konecki et al. Ornithine Transcarbamylase Deficiency. 2013 Aug 29 [Updated 2022 May 26]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2026. Available from: https://www.ncbi.nlm.nih.gov/books/NBK154378/

Dose-Finding Cohorts: Summary

Low– 1.3×10^{13} GC/kg

- n=3 dosed
- Generally well tolerated
- Transient transaminitis (Grade 3) resolved with reactive immunosuppression
- **Patient 1: CCR achieved**
- Biomarker response in Patients 2 & 3*

Intermediate– 2.4×10^{13} GC/kg

- n=3 dosed
- Generally well tolerated
- Biomarker response observed across cohort*
- Potential scavenger medication reductions pending efficacy evaluations

High– 4.0×10^{13} GC/kg

- n=1 dosed
- Generally well tolerated
- Biomarker response observed*
- Potential scavenger medication reductions pending efficacy evaluations

Pre and post ECUR-506 HAC data across all dose cohorts to be presented at ASGCT 2026.

* *Biomarker response defined as reductions in plasma glutamine and plasma ammonia levels and elevation in BUN level

Summary

→ Disease Severity

Neonatal-onset OTCD is the most severe form of urea cycle disorders, with mortality rates up to 74% and no durable non-surgical treatment.

→ ECUR-506 Platform

A dual-AAV, ARCUS nuclease–mediated gene insertion therapy offering variant-agnostic, potentially durable correction via PCSK9 safe-harbor integration.

→ OTC-HOPE Trial

Phase 1/2/3, open-label, global trial currently enrolling. Seven participants dosed across three dose cohorts; all remaining participants to be dosed in 2026.

→ Patient 1 Outcomes

- Grade 3 transaminitis at week 4 resolved with immunosuppression by week 8.
- **Complete clinical response** beginning at 13 weeks.
- Ammonia control, zero HAE events, and transplant de-listing maintained through 18 months, post-ECUR-506 treatment, without the need for scavenger medications or protein restriction.