Decreased rate of hyperammonemic crises in infants with neonatal-onset OTC deficiency (OTCD) post ECUR-506 administration.

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Disclosures

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Neonatal-onset OTCD: Unmet Need

- Approximately 30% of individuals with OTCD present during the neonatal period[1]
  - hemizygous males typically exhibit the most severe phenotype
  - mortality rates up to 74%[1]
- Liver transplantation provides durable metabolic correction but is complicated
  - donor availability
  - immunosuppression risks (malignancy, renal dysfunction, infections)[2,3]
  - 5-year graft failure rate of ~15%[4]

Neonatal Crisis

Hyperammonemic encephalopathy, 48–72h of life

Apparent Stability

Early metabolic stability during rapid growth

Recurrent HAEs/HACs

Despite standard of care

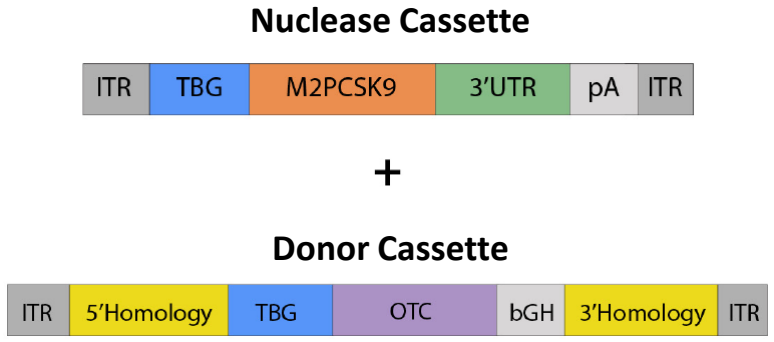
Cumulative Neurologic Injury

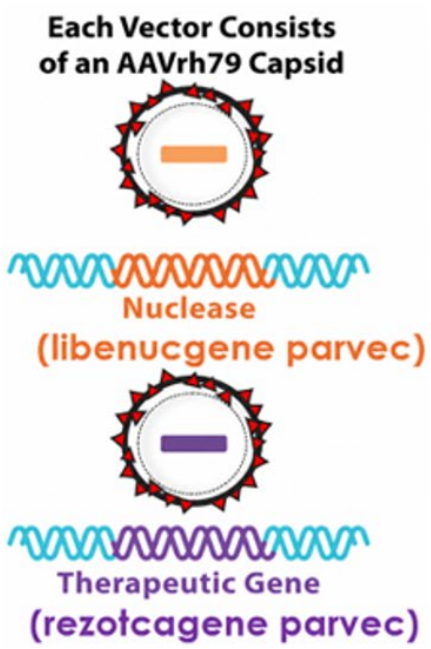
Irreversible damage over time

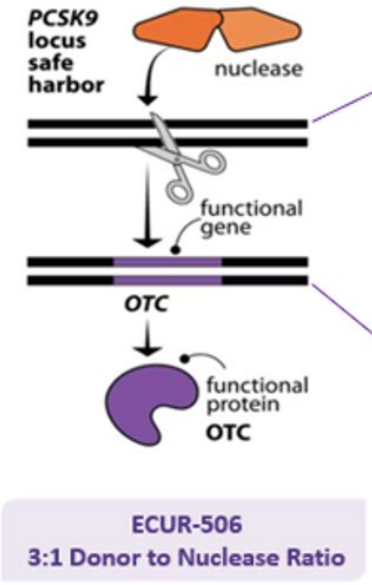
1.Brassier A, Gobin S, Arnoux JB, et al. Long-term outcomes in ornithine transcarbamylase deficiency: a series of 90 patients. Orphanet J Rare Dis. 2015;10:58. 2. Blondet NM, Healey PJ, Hsu E. Immunosuppression in the pediatric transplant recipient. Semin Pediatr Surg. 2017;26:193-198. 3. Yanik EL, Smith JM, Shiels MS, et al. Cancer risk after pediatric solid organ transplantation. Pediatrics. 2017;139:e20163893. 4. Ziogas IA, Wu WK, Matsuoka LK, et al. Liver transplantation in children with urea cycle disorders: the importance of minimizing waiting time. Liver Transpl. 2021;27:1799-1810.

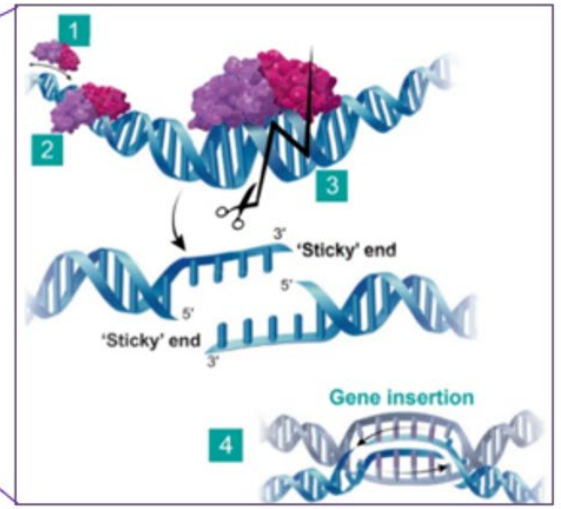
Targeted Gene Insertion Approach

- **Gene addition** approaches have the potential to restore OTC activity
  - HOWEVER episomal transgene dilution during rapid hepatocyte proliferation in infancy may limit long-term durability.
- **Base and prime editing** are potentially more durable approaches
  - HOWEVER >600 *OTC* pathogenic/likely-pathogenic variants limit the usefulness of this approach









OTC-HOPE

Six-month Phase 1/2/3 study with 14.5-year Long-Term Follow-Up

BUILDING HOPE ONE GENE AT A TIME®

Eligibility criteria:

- 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
- 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

Why this is different

Inverted Development Paradigm

OTC-HOPE begins with the youngest and most severely affected populations.

Rigorous Durability Test

Rapid hepatocyte proliferation and liver growth occur during the first years of life.

Disease-Specific Insights

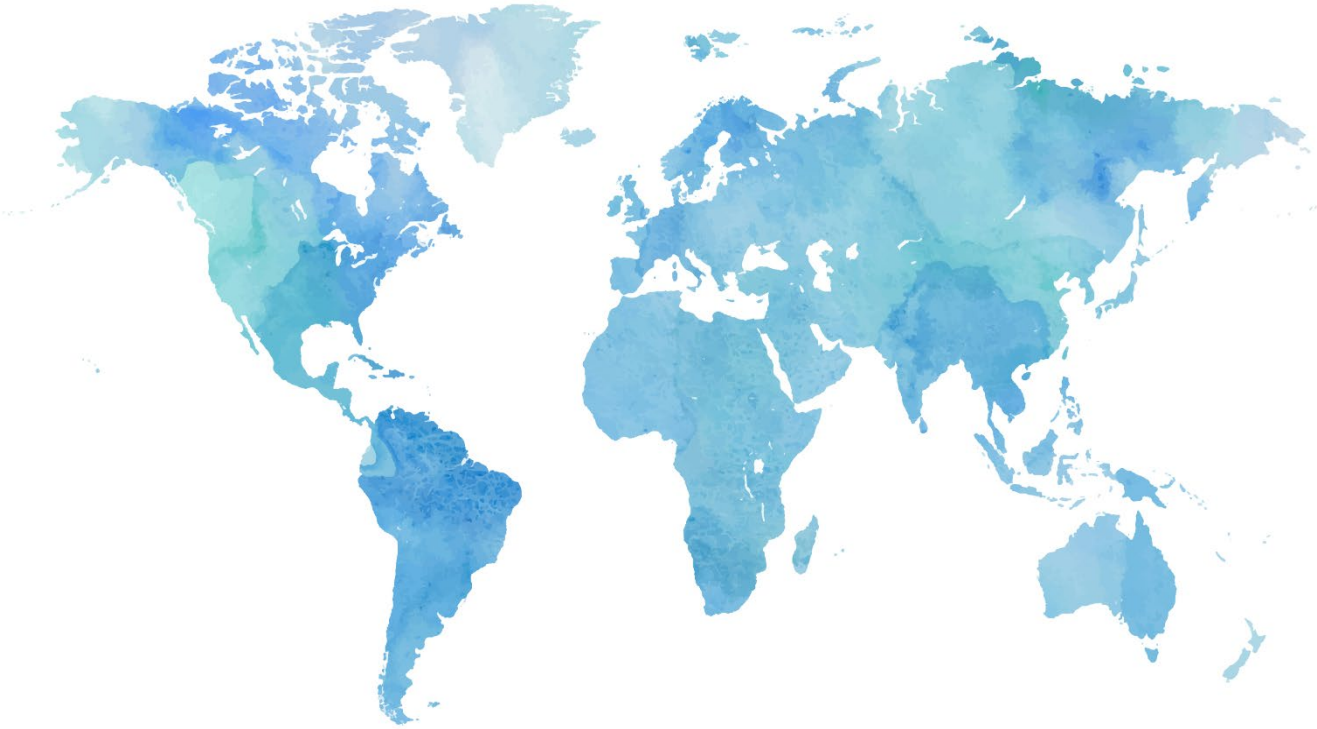
May better identify disease-specific factors, including baseline disease severity and immune maturation, that influence safety and therapeutic response which may not be apparent in older or less severely affected populations.

Global Clinical Program

IND/CTA Clearances

- United States
- United Kingdom
- Spain
- Australia

- Harmonized global protocol;
- International referral network with patient trans
  programs for families outside approved geograp



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)

Safety

Preliminary Safety Observations (n=9)

Data as of 28JUL2026

Generally well tolerated across all three dose cohorts ($1.3x10^{13}$, $2.4x10^{13}$ and $4.0x10^{13}$ GC/kg), n=3 in each group

- No unexpected safety events
- Asymptomatic, non-dose-dependent, transient Grade 2–3 transaminitis resolved with reactive immunosuppression (7 of 8 patients)*
- No thrombotic microangiopathy
- No infusion reactions
- One death: hypoxemic respiratory failure, determined **unrelated** to ECUR-506

*One patient did receive prophylactic corticosteroids post-ECUR-506, per protocol

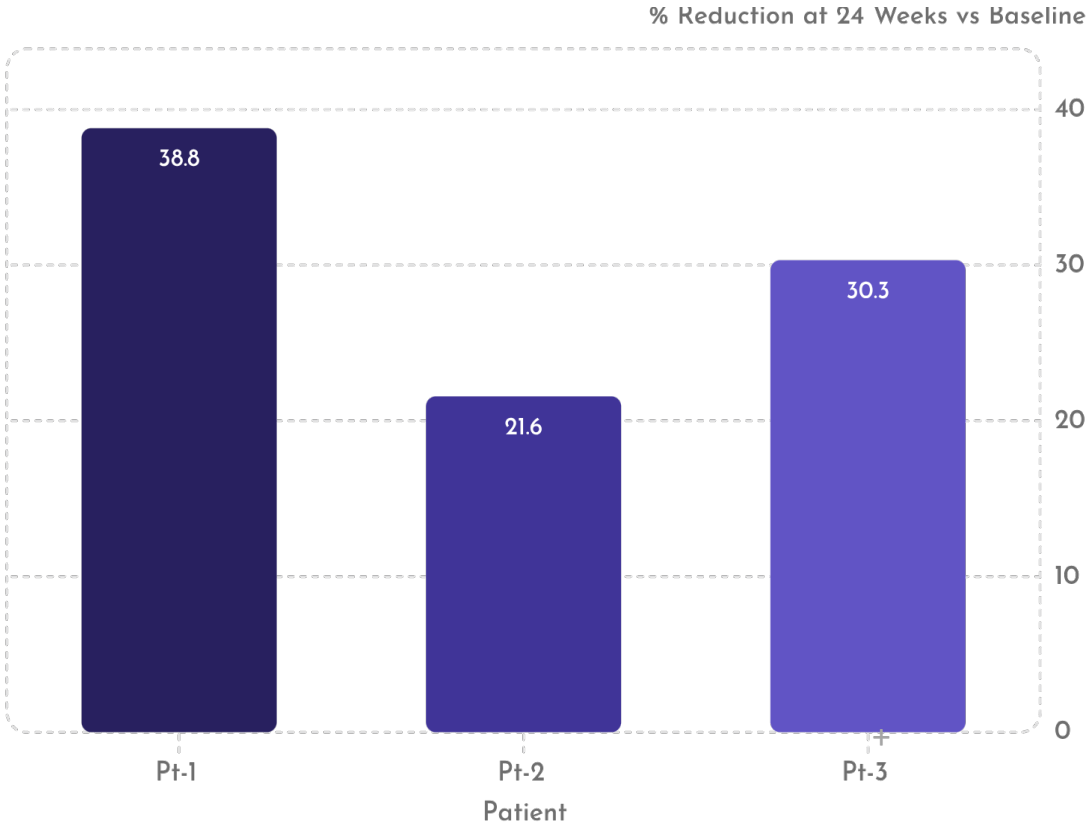
Editing Efficiency

Liver biopsy was performed at 24 weeks in low dose cohort (1 patient's family withdrew consent to biopsy). Liver biopsy results from intermediate and high dose cohorts are pending.

	Pt-1	Pt-2
In-Situ Hybridization (%)	12.6	14.5
Immunofluorescence (%)	1.5	1.9
Indel (%)*	1.5	0.7

*The assay only detects small insertion/deletion events and does not reflect events in which insertion of transgene cassettes have occurred

Serum PCSK9 % Reduction Post ECUR-506



+ results are from Week 20 visit

Clinical Response

Low-dose cohort; Data as of 28JUL2026

Participant (Pt)	Age at Presentation (day)	Peak NH_3 at presentation (µmol/L)	*OTC* variant	Age at enrollment (month)	Age at dosing (month)	Weight at dosing (kg)	Pre-Rx Breakthrough HAEs (days observed)	Post-Rx Breakthrough HAEs (days observed)	Pre-Rx Breakthrough HACs (days) observed)	Post-Rx Breakthrough HACs (days) observed)
Pt-1	7	840	c.77G.C p.(Arg26Pro)	3.5	6.5	8.4	1 (87)	0 (165)	1 (87)	0 (165)
Pt-2	5	2106	c.403G>C p.(Ala135Pro)	1.7	4.7	7.3	1 (87)	0 (166)	1 (87)	0 (166)
Pt-3	3	1600	c.533C>T p.(Thr178Met)	5.3	8.1	11.5	4 (86)	5 (169)	2 (86)	2 (169)

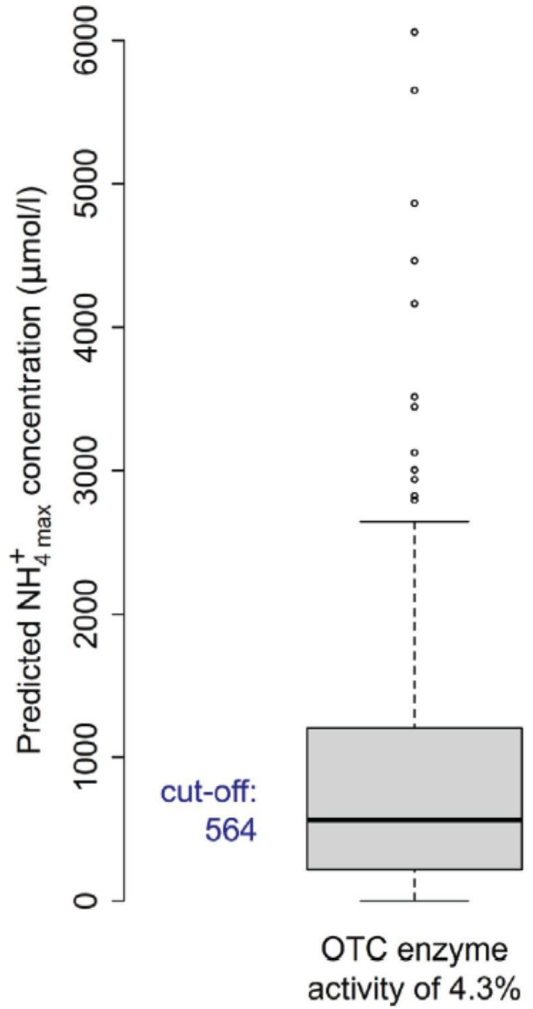
Annualized HAE and HAC rates, pre- and post-ECUR-506, were reduced by 57% (p = 0.02) and 74% (p = 0.01), respectively.

Baseline Disease Severity May Influence Treatment Response

- **Posset et al. – Natural history establishes a severity–enzyme activity relationship.**
  - Residual OTC activity ≤4.3% of normal was associated with higher initial ammonia and mortality

- **Cohort 1: Same low dose, heterogeneous clinical response**
  - Participant 1, peak ammonia 840 µmol/L
    - Complete clinical response (d/c scavenger therapy and protein restriction)
  - Other participants, peak ammonia ≥ 1600 µmol/L
    - Less pronounced responses. Consistent with a more severe underlying enzymatic deficiency.

The greater the underlying OTC deficiency, the greater the amount of restored enzyme activity that may be required to achieve metabolic stability.



Source: Posset R et al.; Urea Cycle Disorders Consortium (UCDC); European registry and network for Intoxication type Metabolic Diseases (E-IMD) Consortia Study Group. Severity-adjusted evaluation of liver transplantation on health outcomes in urea cycle disorders. Genet Med. 2024 Apr;26(4):101039.

Summary

- OTC-HOPE represents the **first clinical use** of *PCSK9* as a safe harbor target, the first clinical use of the AAVrh79 capsid, and the first clinical application of a dual-AAV, variant agnostic, targeted gene therapy approach in infants.
- Low-dose ECUR-506 demonstrated an expected and **manageable safety profile** along with **targeted hepatic editing** and evidence of **improved metabolic control**.
- **Baseline disease severity** may influence treatment response.
- Safety and efficacy data to date **support continued evaluation of higher ECUR-506 dose** levels.

Acknowledgements

Patients and families

OTC-HOPE principal investigators

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