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ASGCT 2026, Boston, MA

Decreased rate of hyperammonemic crises in infants with neonatal-onset OTC deficiency post ECUR-506 administration: preliminary update from the OTC-HOPE study.

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Disclosures

- Gabriel M. Cohn, is an Employee of IECURE, INC.

Ornithine Transcarbamylase Deficiency (OTCD): Neonatal & Post-Neonatal-Onset OTCD

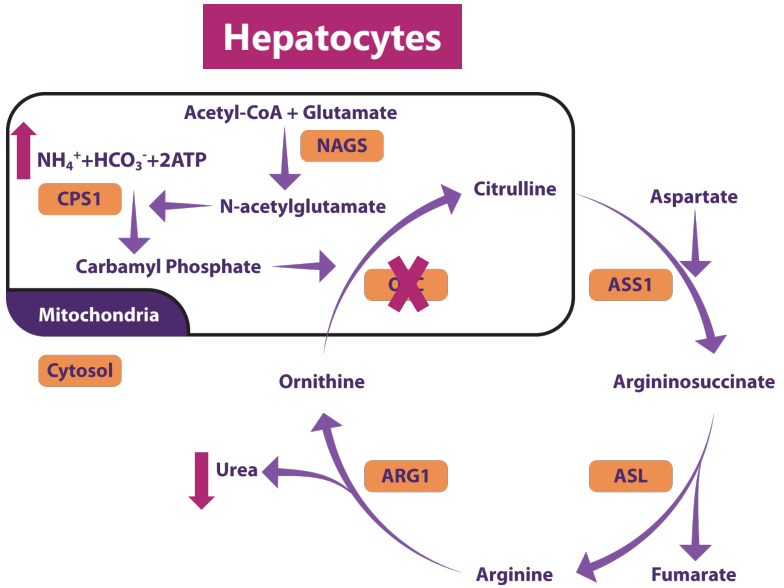
- Neonatal-Onset OTCD Presents in the First Month of Life
- Presentation in the First Week of Life is the Most Severe Form of OTCD

Ornithine Transcarbamylase Deficiency (OTCD)

- XL condition: OTC gene (400+ unique pathogenic variants)
- Deficiency in the liver enzyme, ornithine transcarbamylase, responsible for the detoxification of ammonia

Outcomes

- High ammonia levels can lead to lethargy, seizures, coma, death and neurodevelopmental delays among survivors
- Hyperammonemic crisis (HACs): NH3 >100 umol/L & neurological status change



OTCD Incidence

1:56,500[1]

Mortality Rates

- Neonatal-onset OTCD is the most severe form of OTCD
- Onset in the first week of life is the most severe form of neonatal-onset OTCD

Up to
74%[2]

[1] *Ah Mew N, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. 2003 Apr 29 [Updated 2017 Jun 22]. In: Adam MP,*
[2] *Brassier et al. Orphanet Journal of Rare Diseases. 2015*

Management Of Neonatal-Onset OTCD

Goals of Treatment[3-7]

- Improve survival
- Promote growth & development
- Manage & prevent hyperammonemic Crisis (HACs):
    - HACs: Associated with mortality, neurocognitive & developmental deficits

Acute Management[3, 8]

- Promotion of anabolism
- Protein restriction diet
- Ammonia lowering drugs (nitrogen scavengers)
- Often extracorporeal detoxification

Honeymoon Period[4]

- Infants are metabolically stable for some months due to rapid growth and high protein tolerance
- As growth slows, patients begin experiencing breakthrough hyperammonemia & HACs on standard of care (SOC) management

Long-Term Management[3, 4]

- Low protein diet
- Oral nitrogen-scavenging drugs
- Essential amino acid supplementation

Liver Transplant (LTx)[3,4,7,8]

- Performed to prevent further HACs & neurodevelopmental deterioration

[3]*Donovan K et al. Ornithine Transcarbamylase Deficiency. StatPearls [Internet]. 2026*
[4]*Lichter-Konecki U 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.*
[5]*Maestri NE et al.. Long-Term Treatment of Girls with Ornithine Transcarbamylase Deficiency. NEJM 335, (12), 1996: 855-860*
[6]*Kent JD and Holt RJ. Hyperammonemic crises in patients with urea cycle disorders on chronic nitrogen scavenger therapy with either sodium phenylbutyrate or glycerol phenylbutyrate. Neuropsychiatry . 2017;7(2):131–136.*
[7] *EIMD: European Registry and network for intoxication type Metabolic Disease: Urea cycle disorders: Quick reference guide*
[8]*Garcia Vega M e al. Urea cycle disorders and indications for liver transplantation. Front. Pediatr. 11:1103757. doi: 10.3389/fped.2023.1103757*

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ECUR-506 Is Being Developed For The Treatment Of OTCD

- Safe Harbor, Variant-Agnostic, Gene Insertion Approach
- Dual AAV Vectors: ARCUS Nuclease & OTC Donor Gene; Safe Harbor: PCSK9 Locus

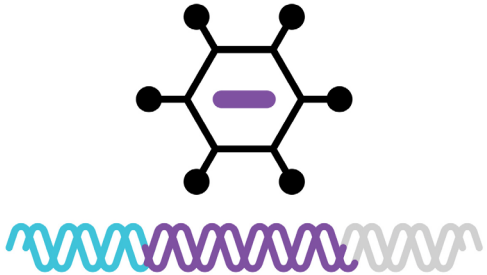
Nuclease Gene Cassette

+

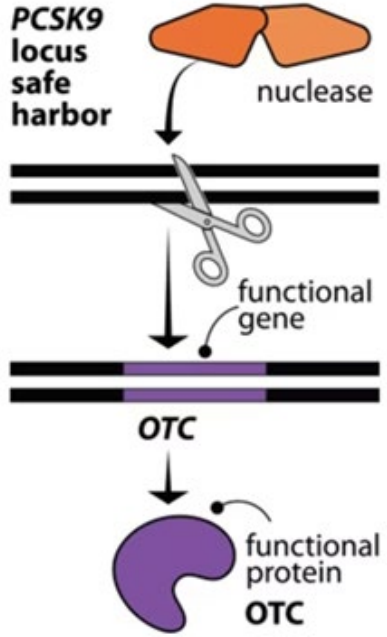
Donor Gene Cassette

Each Vector Consists of an AAVrh79 Capsid

Nuclease ECUR-506A



Therapeutic Gene ECUR-506D



ECUR-506
3:1 Donor to Arcus Ratio

The **ARCUS®** encoding vector targets the exon 7 of PCSK9 and can be combined with **any donor vector** containing disease relevant therapeutic genes for insertion into the same locus

iECURE has licensed the ARCUS® nuclease from Precision BioSciences for four gene insertion programs including OTC, CTLN1 and PKU.

OTC-HOPE Clinical Trial Design (NCT06255782)*

- Patients 0 to 9 Months with Severe, Neonatal-Onset OTC Deficiency
- Dose Escalation/Dose Finding Phase is Ongoing

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*As of 20APR2026

Trial Design	• **PH 1/2/3**, **global,** multi-center trial, **open label,** FIH, **adaptive, dose finding** and **dose confirmation study** - Low Dose: $1.3x10^{13}$ GC/kg - Intermediate Dose: $2.4x10^{13}$ GC/kg - High Dose: $4.0x10^{13}$ GC/kg
Intervention	• **One time, single IV infusion of ECUR-506**
Study Duration	• **Pre-dose: (3 weeks - 9 months):** Enrollment, Screening, Stabilization • **Post-dose follow up: 6-months** - 14.5-year long-term follow up study (NCT06805695)
Primary Endpoints	• Assessment of **safety and tolerability** of **ECUR-506** • **Efficacy**: - **Complete clinical response (CCR) by end of study** ○ 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
Select Secondary & Clinical Endpoints**	• **Efficacy**: - **Incidence and number/p-y of HAC resulting in hospitalization (SAEs)**. ○ **HAC** is defined as **plasma NH_3 >100 µmol/L** with associated **neurological status changes**

***For a more complete listing of secondary and exploratory endpoints visit: https://clinicaltrials.gov/study/NCT06255782?cond=Ornithine%20Transcarbamylase%20Deficiency&term=iECURE&rank=2*

OTC-HOPE Clinical Trial Dose Finding Phase*

- Dose Cohort Assessments are Ongoing
- Preliminary Clinical Outcomes Analysis

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*As of 20APR2026

Descriptive Outcomes & Descriptive Statistics

- Data cut date: 20APR2026
- Data source: Electronic data capture & safety reports
- Data QC'd & discrepancies resolved

Preliminary Safety Observations To Date

- Generally, well tolerated, no thrombotic microangiopathy (TMA)
- Asymptomatic, non-dose dependent, transient Grade 2-3 transaminitis, resolved with reactive immunosuppression (in 5 of 7 pts)
- One death: Hypoxemic respiratory failure unrelated to ECUR-506

Preliminary Efficacy Observations Evaluated To Date

- Incidence & annualized rate of HACs of all dosed participants (n=7):
  - Pre-ECUR-506 (Enrollment to the day of dosing)
  - Post-ECUR-506 (Dosing to end of study or to data cut date)
- Primary efficacy endpoint evaluation (CCR):
  - To be performed once dosing in all three dose cohorts has been completed & all participants have completed their 6-month post-treatment evaluations

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HACs – Preliminary Observations*

- 71% (5 of 7) of Participants Have Experienced NO HACs Post ECUR-506
- 60% Risk Reduction in # of Participants Who Experience a HAC Post ECUR-506

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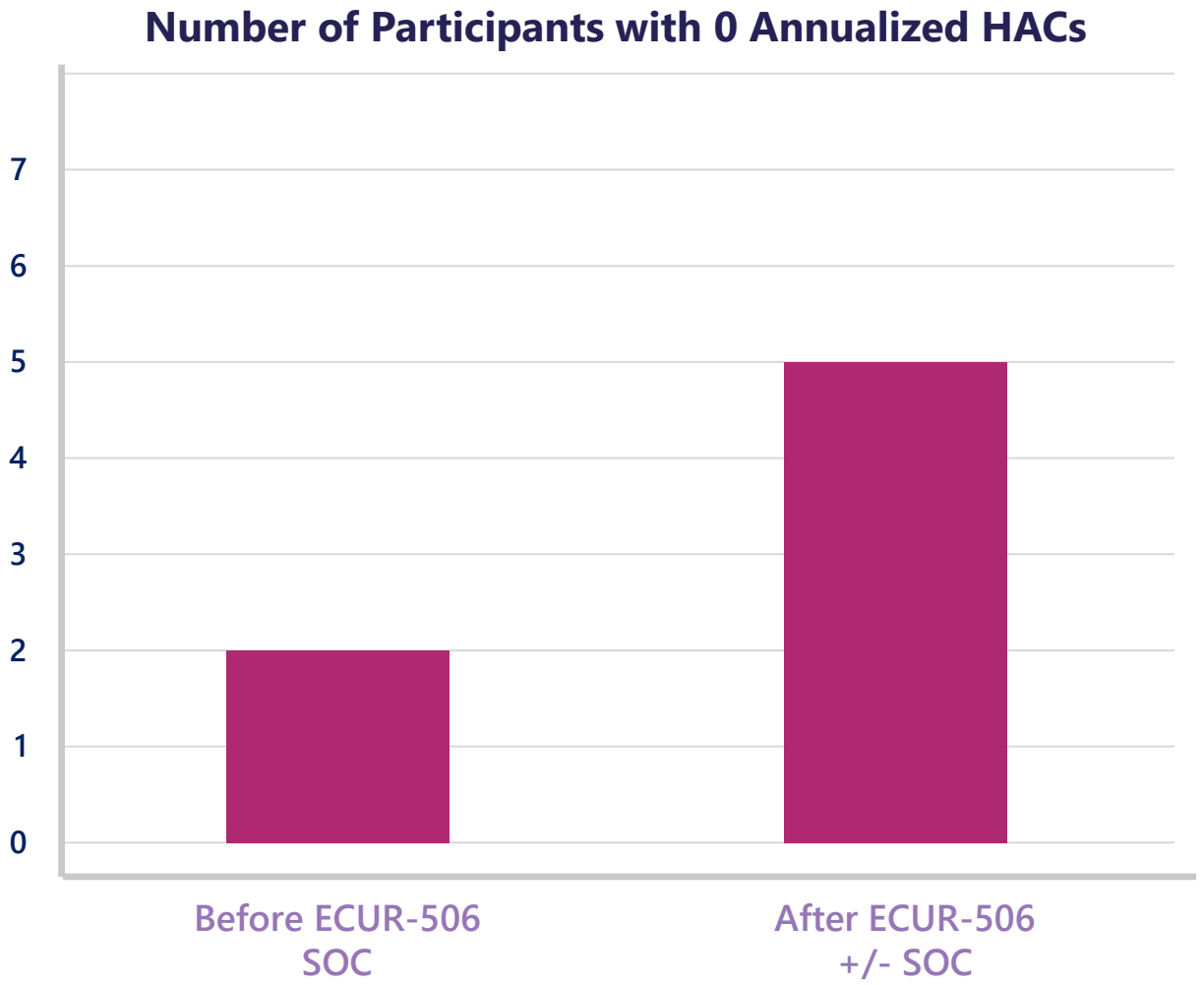

71%
HAC-Free
Post ECUR-506

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Preliminary Observations*

- 52% Risk Reduction in Annualized HAC Rate Following ECUR-506

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Dose	Participant	Pre-ECUR-506 (Enrollment to Dosing Day) (SOC)		ECUR-506	Post-ECUR-506 (+/- SOC)	
		# HACs (Days Observed)	Annualized Rate	Age at RX (Days)	# HACs (Days Observed)	Annualized Rate
Low	1	1 (87)	4.20	194	0 (165)	0
Low	2	0 (87)	0	140	0 (166)	0
Low	3	2 (86)	8.49	244	2 (169)	4.32
Intermediate	4	1 (126)	2.90	142	2 (164)	4.45
Intermediate	5	0 (120)	0	266	0 (138)	0
Intermediate	6	1 (65)	5.62	191	0 (103)	0
High	7	1 (130)	2.81	275	0 (76)	0
	Totals	**6 (701)**	**3.12**		**4 (981)**	**1.49**

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Summary & Conclusions
Preliminary Clinical Observations*

OTC HOPE
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*As of 20APR2026

Treatment Goal for Neonatal-Onset OTCD

- Manage & prevent HACs which are associated with mortality, neurocognitive deficits, and the need for LTx
- Honeymoon period: Initial metabolic control; as infant growth slows → breakthrough hyperammonemia on SOC → LTx

OTC-HOPE Trial

- Severe, neonatal OTCD
- Dose escalation is ongoing
- Safety & efficacy assessments are ongoing

Preliminary Post-ECUR-506 Safety Observations

- Generally, well tolerated
- Transient, non-dose related, Grade 2-3 transaminitis managed with reactive immunosuppression
- One death unrelated to ECUR-506

Preliminary Post-ECUR-506 Efficacy Observations

- Post-ECUR-506 HACs (+/-SOC):
  - 71% (5 of 7) participants have experienced NO HACs following ECUR-506 administration
  - 52% risk reduction in annualized HAC rate following ECUR-506 administration

The observed safety profile and reduction in HACs support the continued, ongoing evaluation of ECUR-506

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Acknowledgements

GENE THERAPY PROGRAM

Perelman School of Medicine
University of Pennsylvania

The technology and science behind iECURE's genome editing approach was developed from early research done at the University of Pennsylvania's Gene Therapy Program (GTP) led by **Dr. James M. Wilson**.

PRECISION BIOSCIENCES

iECURE has licensed the ARCUS® nuclease for ECUR-506 from Precision BioSciences.

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Patients & Their Families