SUSTAINED CLINICAL RESPONSE IN FIRST PATIENT DOSED WITH ECUR-506 ONE YEAR POST DISCONTINUATION OF STANDARD OF CARE

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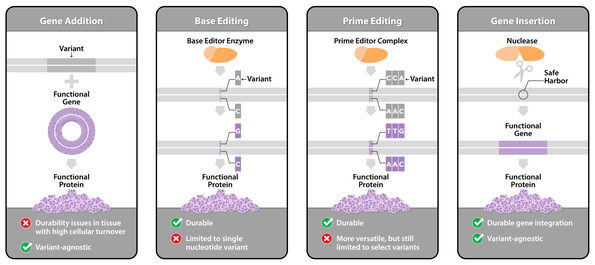
INTRODUCTION

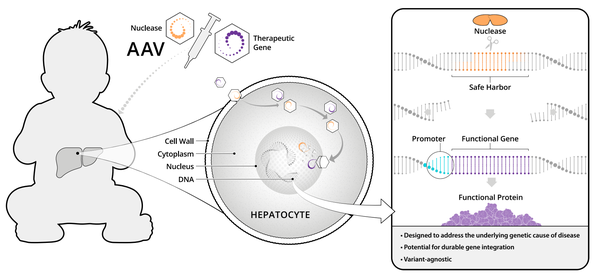
Neonatal-onset ornithine transcarbamylase deficiency (OTCD) is an X-linked urea cycle disorder characterized by hyperammonemia due to impaired OTC activity. Recurrent hyperammonemic events (HAEs; NH_3 >100 umol/L) and hyperammonemic crises (HACs; NH_3 >100 umol/L with neurologic status change) may occur despite standard-of-care (SoC) management with protein restriction and nitrogen scavengers. HACs are associated with irreversible neurologic injury and can progress to coma and/or death. Metabolic instability, as indicated by recurrent HACs, is a key driver for liver transplantation. Traditional gene addition approaches using adeno-associated virus (AAV) to treat murine OTCD models in infancy have shown limited success due hepatocyte proliferation-associated episomal dilution. Genome editing (Fig. 1), specifically targeted gene insertion, offers a promising alternative with the potential for durable clinical response.

Figure 1: Gene Addition and Genome Editing Approaches



ECUR-506 (Fig 2) is an in vivo, liver-directed, investigational genome editing product being developed for the treatment of neonatal-onset OTCD. ECUR-506 is a one-time intravenous therapy comprised of two populations of AAVrh79 delivering either a meganuclease, M2PCSK9, targeting the PCSK9 gene, or a codon-optimized OTC donor gene. Co-expression of these cassettes permits OTC transgene integration into the hepatocyte genome.

Figure 2: ECUR-506 Mechanism of Action

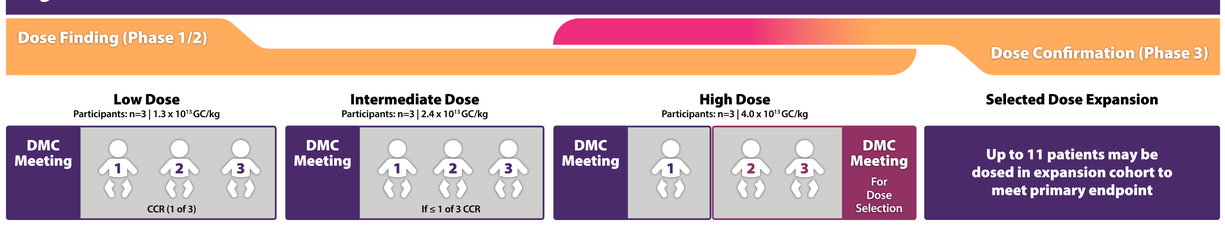


METHODS

OTC-HOPE (NCT06255782) is a 24-week, first in human, single arm, open-label, global, multi-center trial designed to assess the safety and efficacy of ECUR-506 in male participants with genetically confirmed neonatal-onset OTCD who are <9 months of age and 3.5 kg to 13.5 kg at the time of dosing. Dose levels were informed by nonclinical studies.

The initial dose in the OTC-HOPE trial (1.3 x 10^{13} gc/kg) was the minimally effective dose in a murine model of OTCD. Subsequent dose escalations to intermediate (2.4 x 10^{13} gc/kg) and high dose (4.0 x 10^{13} gc/kg) levels were based on an assessment of the totality of the accumulated safety and efficacy data. A 14.5-year follow-up study will evaluate the long-term safety and efficacy of OTC-HOPE participants (ECUR-LTFU; NCT06805695). LTFU data from the first participant dosed (data cut 11FEB2026) and from the first cohort to complete dosing and end of study visits (data cut 20APR2026) are shared herein.

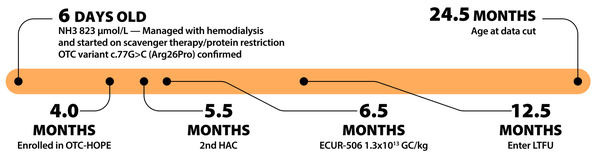
Figure 3: OTC-HOPE Clinical Trial Schema



RESULTS

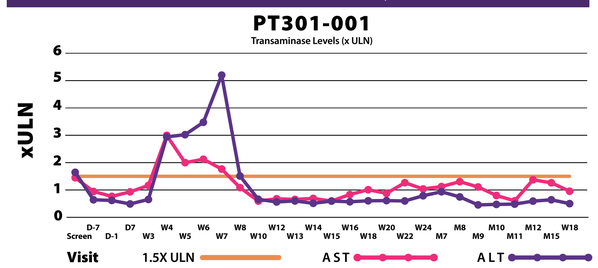
The first participant presented at six days of age with plasma ammonia of 840 µmol/L, consistent with severe neonatal-onset OTCD. Acute metabolic stabilization required hemodialysis alongside initiation of nitrogen scavenger therapy and dietary protein restriction. A second HAC occurred at five and a half months of age (Fig. 4). The participant received ECUR-506 at 6.5 months of age and the infusion was generally, well tolerated.

Figure 4: Participant Timeline on Study



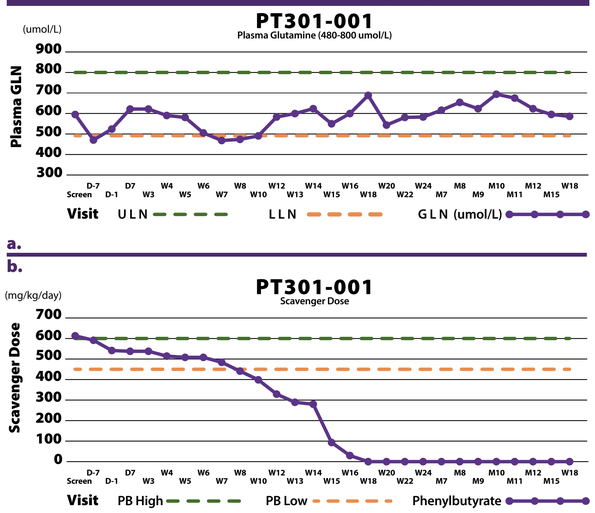
A grade 3 elevation in alanine aminotransferase (ALT) occurred at week 4 post-dose (ALT 3× ULN) and resolved with a reactive immunosuppression protocol without subsequent elevations (Fig. 5).

Figure 5: Timelines for: **a.** Transaminase **b.** Immunomodulation



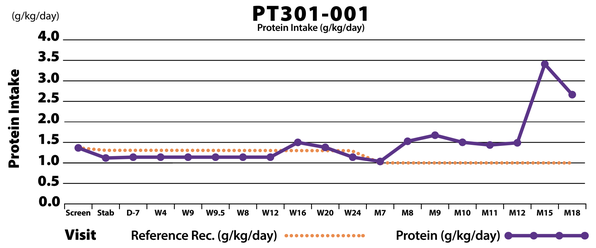
Plasma glutamine declined below the lower limit of normal between Weeks 6–8 post-dosing , despite ongoing high-dose corticosteroid administration for the transaminitis episode. Weaning of nitrogen scavenger was initiated and completed at Week 13 post-dose (Fig. 6).

Figure 6: Timelines for: **a.** Plasma Glutamine **b.** Glycerol phenylbutyrate



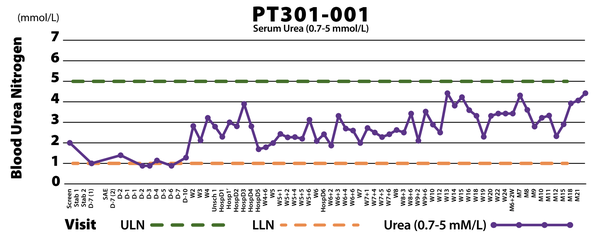
Following scavenger discontinuation, dietary protein intake was progressively liberalized. Sustained age-appropriate protein intake was achieved with no biochemical or clinical evidence of hyperammonemia (Fig. 7). At 18 months post-dose, no episodes of hyperammonemia have been triggered by dietary challenge or intercurrent illness.

Figure 7: Dietary Protein Intake Timeline



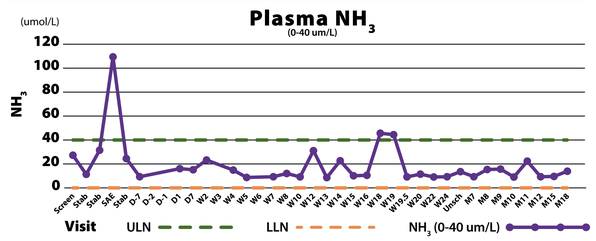
Serum urea increased by Day 10 post-dose and has been maintained within the normal reference range throughout follow-up, consistent with increased ureagenesis (Fig. 8).

Figure 8: Serum Urea Timeline



Plasma ammonia levels have generally remained within the normal reference range (0–40 µmol/L) throughout the entirety of post-ECUR-506 dosing (Fig. 9), including during a febrile viral illness, which is historically associated with metabolic decompensation and risk for hyperammonemic crisis in neonatal-onset OTCD. The described sustained clinical response in absence of SoC in the first participant has not been previously reported in patients with neonatal-onset OTCD.

Figure 9: Plasma NH_3 Timeline



ADDITIONAL PARTICIPANT DOSING

Seven infants with neonatal-onset OTCD have been dosed across three dose levels (low, intermediate, and high). The low-dose cohort (n=3) has completed the 6-month study, while intermediate (n=3) and high-dose (n=1) cohort assessments are ongoing. Enrollment and dosing for the high-dose cohort is ongoing (Table 1).

Table 1: Participant Baseline Characteristics

Cohort	Peak Plasma NH_3 (µmol/L)	OTC Variant
Low Dose	840	c.77G>C p.(Arg26Pro)
Low Dose	2106	ChrX(GRCh38):g.38401291G>C
Low Dose	1600	c.533C>T p.(Thr178Met)
Intermediate Dose	1238	c.890A>C p.(Asp297Ala)
Intermediate Dose	2750	c.986A>G p.(Asn329Ser)
Intermediate Dose	1542	c.274C>T p.(Arg92Ter)
High Dose	2800	c.299-2A>G

PRELIMINARY SAFETY OBSERVATIONS

Preliminary safety observations are provided for all dose cohorts, even as they continue to undergo safety and efficacy evaluations. ECUR-506 was generally well tolerated across all dose cohorts.

- No unexpected safety events
- No infusion reactions
- No cases of thrombotic microangiopathy (TMA)
- Asymptomatic transaminitis (Grade 2-3) in 5/7 participants
- Effectively managed with reactive immunosuppression (IS)
- No recurrence following IS taper
- One death (intermediate dose cohort) deemed unrelated to study drug

PRELIMINARY EFFICACY OBSERVATIONS

Preliminary efficacy analyses were conducted on the clinically relevant measures of HAEs and HACs in the low dose cohort which has completed the OTC-HOPE study (Table 2). Breakthrough HAEs and HACs that may have occurred prior to enrollment were not captured. The presenting hyperammonemia was excluded from analysis as SoC was not initiated.

Post OTC-HOPE enrollment and prior to dosing, 6 breakthrough HAEs and 3 HACs occurred, corresponding to an annualized rate of 8.43 and 4.21 breakthrough HAEs and HACs per year, respectively.

ECUR-506 treatment was associated with a reduction in HAE and HAC events to 5 and 2, respectively, yielding annualized HAE and HAC rates of 3.65 and 1.46, respectively, corresponding to a risk reduction of 57% and 65%. The observed rate changes were statistically significant (p=0.0181 and 0.0111 respectively). Two of 3 participants in the low dose cohorts experienced no HAEs or HACs post treatment. The participant with post-dose events had a reduction in annualized rates of HAC (8.49 to 4.32) and HAEs (16.98 to 10.80). Participant 1 was removed from the transplant waiting list and participant 3 went on to liver transplant during ECUR-LTFU.

Table 2: Pre- and Post-Dose HAE and HAC Analysis in Low Dose Cohort

Endpoint	Period	Statistic	Low Dose Level (N=3)
HAE	Pre Dose	Number of Events	6
		Number of Person-Years	0.712
		Rate	8.43
	Post Dose	Number of Events	5
		Number of Person-Years	1.369
		Rate	3.65
		Rate Ratio vs Pre Dose	0.43
		95% CI	0.20, 0.95
		p-value	0.0181
HAC	Pre Dose	Number of Events	3
		Number of Person-Years	0.712
		Rate	4.21
	Post Dose	Number of Events	2
		Number of Person-Years	1.369
		Rate	1.46
		Rate Ratio vs Pre Dose	0.35
		95% CI	0.14, 0.86
		p-value	0.0111

CI, confidence interval; **HAC**, hyperammonemic crisis; **HAE**, hyperammonemic episode

HAC/HAE events were captured from electronic data capture and adverse event reports to generate HAC rates. Rate ratios, CIs, and p-values were calculated using generalized estimating equations with correlated count data. For groups with 0 events in the post-dose period, a conditional exact test was used. P-values are for one-sided tests (significance levels = 0.025).

CONCLUSION:

Neonatal-onset OTCD is a life-threatening condition in which breakthrough HAEs and HACs occur despite standard of care, contributing to significant morbidity and mortality. In this highly vulnerable population, ECUR-506 demonstrated an encouraging safety profile and preliminary evidence of clinical efficacy. We report here the observations of a durable clinical response in the first participant dosed at the low dose level and statistically significant reductions in HAEs and HACs in the low dose cohort that has completed the OTC-HOPE study. While a limitation of these findings include a small sample size, they support early proof of concept and continued evaluation in the ongoing study.