Initial Findings from the First Four Patients Enrolled in OTC-HOPE Clinical Trial: No Hyperammonemic Events in First Participant to Complete 24-week Study

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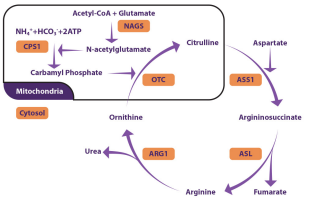
INTRODUCTION

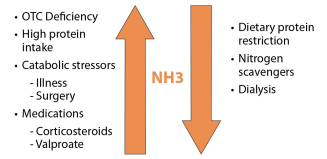
Ornithine transcarbamylase deficiency (OTCD) is a urea cycle (Figure 1) disorder that results in impaired ureagenesis and hyperammonemia. Males with severe neonatal onset OTCD typically become hyperammonemic within the first 48-72 hours of life. Clinical sequelae may include feeding difficulties, lethargy, respiratory distress, seizures, coma, and development delay. Current treatment includes nitrogen scavenger therapy and dietary protein restriction. Despite adherence to aggressive medical management, repeat life threatening hyperammonemic events (HAEs) and hyperammonemic crises (HACs) are common. Mortality rates up to 74% have been reported and long-term neurologic impairment and intellectual disability are expected.

Figure 1: The Urea Cycle



Current standard of care treatments, including nitrogen scavengers and protein restriction, are intended to be supportive and not curative in OTCD as they do not correct the underlying metabolic defect. The clinical effectiveness of these approaches is dependent upon a balance of nitrogen production/intake and scavenging capacity. Once this balance is disrupted, plasma ammonia accumulates leading to HAEs (NH3>100 umol/L) or HACs (NH3>100 with neurologic status change), and irreversible neurological damage is incurred. Several factors can increase nitrogen load and overwhelm the nitrogen scavenging pathway including stress, infections, fever, trauma, surgery, and dietary protein restriction non-adherence (Figure 2). Orthotopic liver transplant is a curative option for OTCD patients with recurrent decompensation episodes. However, pediatric liver transplantation still carries significant risk, including a 5-year 15% graft failure rate. There is a clear unmet therapeutic need for a potentially curative option that corrects the underlying metabolic defect in neonatal OTC deficiency.

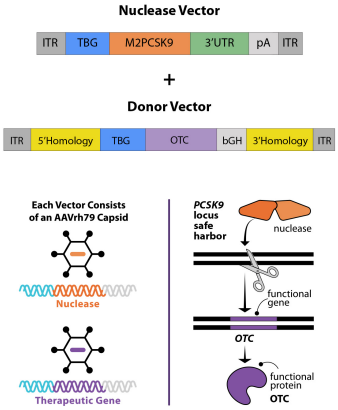
Figure 2: OTCD Management



ECUR-506 is a liver-directed, investigational gene insertion product being evaluated for the treatment of neonatal onset OTCD (ECUR-506-OTC-101; NCT06255782). Administered as a single intravenous dose, ECUR-506 comprises of a mixture of AAV vectors encoding either a meganuclease, M2PCSK9, for targeted editing of the human PCSK9 gene (safe harbor), or a codon-optimized human OTC donor gene at a ratio of 1:3, respectively. Dual vector administration is designed to guide OTC transgene integration into the hepatocyte genome (Figure 3). Gene integration is expected to result in the distribution of the integrated donor gene to daughter cells, thereby producing a more durable response when targeting rapidly dividing tissues, which may prove particularly beneficial in children.

A variant-agnostic gene insertion strategy is preferred to a variant-specific gene editing (e.g., base-editing or similar) approach because, like most monogenic diseases, OTCD is caused by multiple variants (>600) rather than a single predominant variant.

Figure 3: ECUR-506 Dual AAV Construct



METHODS

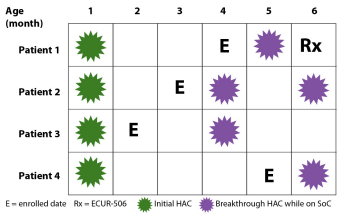
OTC-HOPE (NCT06255782) is a 24-week, first in human, single arm, open-label, global, multi-center trial designed to assess the safety and efficacy of ECUR-506 in male participants with genetically confirmed neonatal onset OTCD who are <9 months of age at the time of dosing.

The initial dose in the OTC-HOPE trial was the minimally effective dose identified in a murine model of OTCD. Subsequent doses will be based on an assessment of the totality of the safety and efficacy data accumulating in the trial. A 14.5-year follow-up study (ECUR-LTFU; NCT06805695) will evaluate the long-term safety and efficacy of OTC-HOPE participants. Pre-dose observations of all enrolled participants through 08Apr2025 are reported along with post-dose observations of the first participant to complete the OTC-HOPE trial and transition to LTFU.

RESULTS

All four participants enrolled in the OTC-HOPE clinical trial to date experienced an initial HAC within the first week of life and then stabilized. All participants were transitioned to standard of care (SOC) therapy (oral nitrogen scavenger and dietary protein restriction) but subsequently experienced HACs despite SOC therapy. Following their initial HAC, and after enrolling in the clinical trial, the four participants have thus far experienced a total of five additional HACs over a combined duration of 11.5 months, thereby averaging one HAC every 2.3 months while on SOC therapy and prior to receiving ECUR-506 (Figure 4).

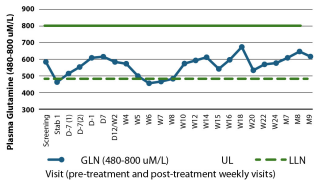
Figure 4: HACs Experienced by Participants



Prior to receiving ECUR-506, the first participant in the study experienced a hyperammonemic crisis (HAC) shortly after birth with ammonia levels reaching 16X ULN. The infant underwent dialysis and standard of care treatment was initiated. A known OTC pathogenic variant, c.77G>C (p.Arg26Pro), was identified. The participant experienced a second HAC at 5.5 months of age. The participant underwent ECUR-506 (1.3 x 10^{13} GC/kg) infusion at 6.5 months of age. The infusion was generally well-tolerated. Four weeks post dose, the participant experienced Grade 3 asymptomatic transaminitis which resolved over the ensuing four weeks following the addition of immunosuppressive therapy.

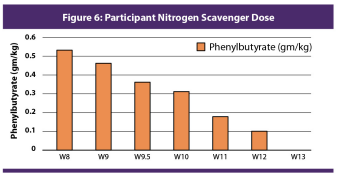
Despite being administered corticosteroids, which have been known to induce hyperammonemia in UCD participants, ammonia and glutamine levels remained controlled during this time.

Figure 5: Participant Glutamine Levels



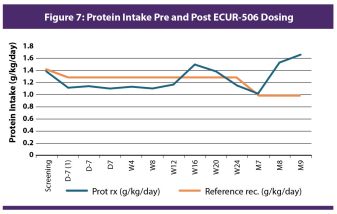
A reduction in glutamine levels in weeks 6 & 7 post-ECUR-506 (Figure 5) prompted the weaning of nitrogen scavenger therapy starting week 8 post-ECUR-506. Discontinuation of nitrogen scavenger therapy was achieved12 weeks post ECUR-506 administration (Figure 6).

Figure 6: Participant Nitrogen Scavenger Dose



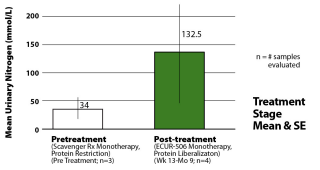
Ammonia and glutamine levels remained in normal range post discontinuation of nitrogen scavenger therapy which allowed for complete protein intake liberalization (Figure 7).

Figure 7: Protein Intake Pre and Post ECUR-506 Dosing



The mean urinary nitrogen following treatment with ECUR-506 and discontinuation of SOC medical management was increased relative to the pre-treatment levels (Figure 8).

Figure 8: Mean Urinary Nitrogen



Mean ammonia remained within normal limits during the 6-month clinical trial and have remained within normal limits during LTFU (Figure 9). The participant remained off standard of care therapy (nitrogen scavenger + protein restriction) beginning at week 16 through the end of study visit (week 24) and into LTFU. The participant did not experience an HAC following treatment with ECUR-506. Mean BUN levels have increased approximately 2.5-fold (Figure 10).

Figure 9: Mean Plasma NH3 Levels

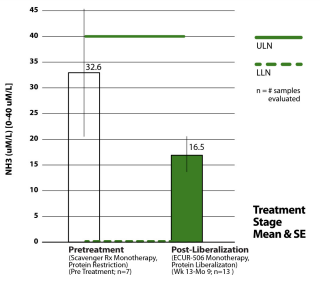
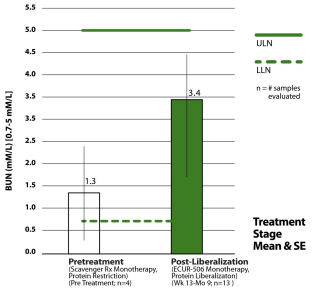
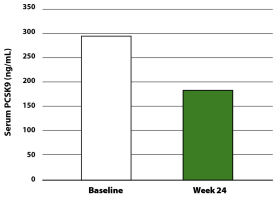


Figure 10: Mean BUN Levels



Serum PCSK9 levels decreased by 37% at 24 weeks compared to baseline, suggesting editing of the PCSK9 gene (Figure 11).

Figure 11: PCSK9 Serum Levels



Conclusion

These data represent initial findings of the first four participants enrolled in the OTC-HOPE trial and the 9-month data on the first participant dosed with ECUR-506. These observations support the continued evaluation of *in vivo* gene insertion as a possible treatment option for neonatal onset OTC deficiency.

COI Statement

Gabriel Cohn, Matthew Hall, Karen Kuhn, Thomas White and George A. Diaz are employees of iECURE.