Initial clinical results from OTC-HOPE, the first *in vivo*, liver directed, AAV-mediated gene insertion study in neonatal OTC deficiency; complete clinical response observed in first male infant to receive ECUR-506: 10-month data

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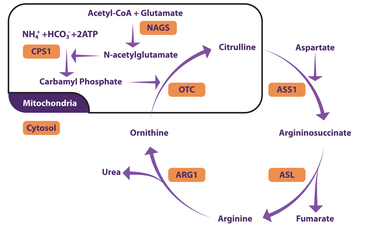
INTRODUCTION

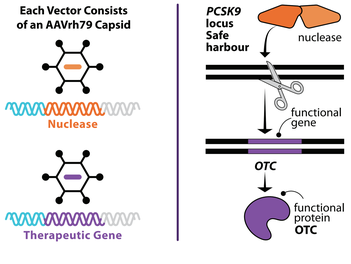
Urea cycle disorders (UCDs) are a group of biochemical diseases caused by deficiency of one of six enzymes necessary to convert toxic ammonia into urea. As a result, UCD patients are prone to developing hyperammonemia and progressive encephalopathy leading to lethargy, seizures, coma and/or death. Developmental delay is common among survivors.

Figure 1: The Urea Cycle



Ornithine transcarbamylase deficiency (OTCD) is an X-linked disorder and the most common UCD with an incidence rate of 1:56,500.[1] Neonatal onset represents the most severe form of the disease with symptoms typically presenting in the first 48-72 hours of life. Management may include renal replacement therapy acutely, and nitrogen scavengers and protein restriction both acutely and long-term. Orthotopic liver transplantation is the only curative option.

Figure 2: ECUR-506 Dual AAV Construct



ECUR-506 is a liver-directed, investigational targeted gene insertion product being evaluated for the treatment of neonatal onset OTCD. The therapy comprises of two vectors, an ARCUS® (Precision BioSciences, Durham, NC) nuclease vector which encodes a meganuclease responsible for targeted gene editing of the well characterized PCSK9 gene locus and a donor vector that inserts the desired functional OTC gene. ARCUS® is a single component protein containing both a site-specific DNA recognition interface and endonuclease activity.

The nuclease vector and donor gene vector that comprise ECUR-506 are co-administered intravenously in a 1:3 ratio respectively. ECUR-506 is designed to allow for integration of the OTC transgene into exon 7 of the PCSK9 locus of the hepatocyte genome for long-term expression of OTC in transduced hepatocytes and their progeny.

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 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 will evaluate the long-term safety and efficacy of OTC-HOPE participants (ECUR-LTFU; NCT06805695).

Figure 4: Three Treatment Stages

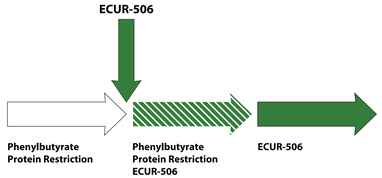


Figure 3: Participant Clinical Journey

Participant 1 History: The male infant was born to a family with no prior history of OTCD. Participant received ECUR-506 at 6.5 months of age.

Pre Dose	Day 1 Dosing	Weeks 4-8	Weeks 8-12	Weeks 12-16	Weeks 16-24	Months 7-10
After birth, developed symptomatic encephalopathy with ammonia levels of 16x ULN (HAC#1). Underwent dialysis to manage hyperammonemia and was transitioned to oral treatment and placed on a protein restricted diet. OTC pathogenic variant c.77G>C (Arg26Pro) identified. Experienced HACs at 5.5 months of age	Infusion at 6.5 months of age was generally well tolerated.	Grade 3 transaminitis, ALT 3-5x ULN, prompting Safety Review Team (SRT), voluntary Clinical Halt, and DMC meeting. Treated with oral and IV corticosteroid and tacrolimus, hospitalized for monitoring (Grade 3, SUSAR). Liver biopsy showed acute inflammation with T lymphocyte infiltration.	Normal plasma ammonia concentrations. Increased blood urea nitrogen (BUN). Stable protein intake, and consistent weight gain. Reduced plasma glutamine levels below LLN. Tapering of daily scavenger medicine dose completed. Remained clinically stable.	Normal plasma ammonia concentrations. Discontinued corticosteroids and weaning tacrolimus. Normal blood urea nitrogen (BUN). Increased protein intake, and consistent weight gain. Normal plasma glutamine levels. Remained clinically stable.	Normal plasma ammonia concentrations Weaning tacrolimus Normal blood urea nitrogen (BUN). Unrestricted protein intake, and consistent weight gain. Normal plasma glutamine levels. Remains clinically stable. Completed Ph1/2 Study.	Normal plasma ammonia concentrations. Discontinued tacrolimus. Normal blood urea nitrogen (BUN). Unrestricted protein intake, and consistent weight gain. Normal plasma glutamine levels. Remains clinically stable.

Current data and observations are indicative of enhanced urea cycle activity, suggestive of investigational product activity.

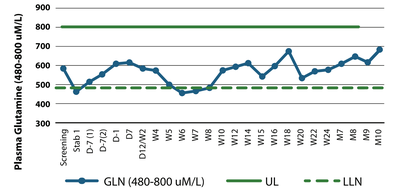
ECUR-LTFU

RESULTS

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.

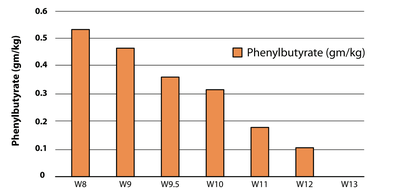
Despite being administered corticosteroids, which have been known to induce hyperammonemia in UCD participants, ammonia and glutamine levels remained controlled during this time.

Figure 5: Participant Glutamine Levels



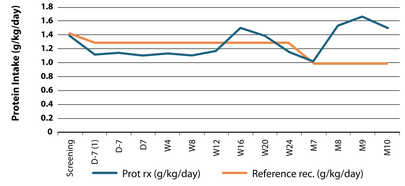
A reduction in glutamine levels in weeks 6 & 7 post-ECUR-506 (Figure 5) prompted the weaning of nitrogen scavenger therapy starting week 8 post-ECUR-506. Discontinuation of nitrogen scavenger therapy was achieved 12 weeks post ECUR-506 administration (Figure 6).

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



Mean ammonia levels remained within normal limits during the 6-month clinical trial and have remained within normal limits during LTFU (Figure 8). 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.

Figure 8: Mean Plasma NH3 Levels

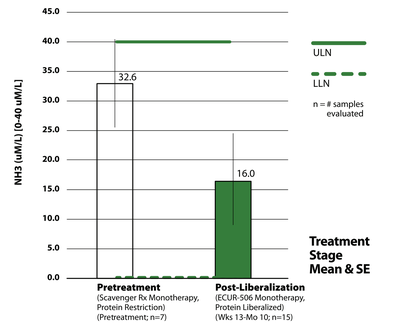
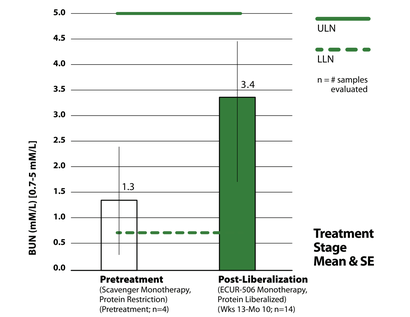


Figure 9: Mean BUN Levels



Serum PCSK9 levels decreased by 37% at 24 weeks compared to baseline, suggesting editing within the PCSK9 gene.

The subject has experienced consistent weight gain and remained above the 50th percentile for weight during the 6-month study and into LTFU .

Figure 10: Weight-for-age Boys (Birth to 2 Years)

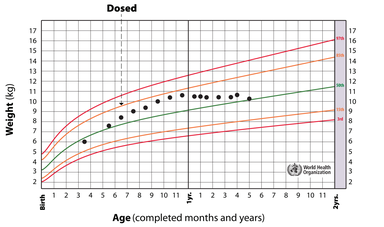
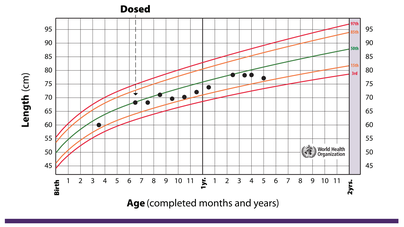


Figure 11: Length-for-age Boys (Birth to 2 Years)



CONCLUSION

These are data from the first infant to undergo *in vivo*, liver directed, AAV-mediated gene insertion and to complete the OTC-HOPE clinical trial. The observed increase in BUN along with normal mean ammonia levels and increased protein intake following ECUR-506 administration in conjunction with scavenger medication discontinuation are suggestive of increased nitrogen flux through the urea cycle and restoration of at least partial functional hepatic OTC enzyme activity. As protocol defined, complete clinical response was observed, continued evaluation of the low dose of ECUR-506 (1.3 x10^{13} GC/kg) in the OTC-HOPE study has been supported by the Data Monitoring Committee.

REFERENCES

1. Ah Mew N, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. 2003 Apr 29 [Updated 2017 Jun 22]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm. nih.gov/books/NBK1217/