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IMPACT OF ARCT-810 mRNA THERAPY ON DIETARY INTAKE AND BIOCHEMICAL DATA IN ADOLESCENTS AND ADULTS WITH ORNITHINE TRANSCARBAMYLASE DEFICIENCY

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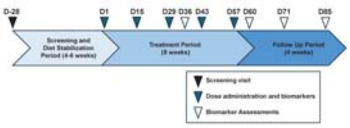
BACKGROUND

- Ornithine transcarbamylase deficiency (OTCD) is an X-linked urea cycle defect that can cause metabolic crises with neurotoxic elevated plasma ammonia and glutamine levels[1,2].
  - Hemizygous males and heterozygous females with post-natal onset OTCD can present from infancy to later childhood, adolescence, or adulthood.
  - Protein-restricted diets are used to reduce ammonia production; however, protein intake must remain adequate to prevent endogenous protein catabolism and support growth.These patients can show true (versus prescribed) protein avoidance.
  - Many post-natal onset OTCD patients still exhibit hyperammonemic crisis and neuropsychological complications despite protein-restricted diets and nitrogen scavenger medication.
- ARCT-810 is an investigational mRNA treatment intended to treat OTCD[3,4].
  - ARCT-810 has been formulated with a proprietary lipid nanoparticle (LNP), (LUNAR®) including an ionizable lipid that targets the mRNA to hepatocytes. The mRNA acts as a template for making functional OTC enzyme and is intended to restore urea cycle function.
  - Rapid plasma clearance of lipid (approximately 48 hours) has been shown with extended plasma mRNA exposure (approximately 2 to 4 weeks).
  - In prior Phase 1 and 2 studies, single doses of ARCT-810 in healthy volunteers and single and multiple doses of ARCT-810 in OTCD participants were safe and well tolerated.

METHODS

- ARCT-810-04 (US, NCT06488313) is an ongoing Phase 2, open-label, multiple ascending, repeat dose study to assess safety and pharmacodynamics of ARCT-810 in stable OTCD patients. The study was conducted at a single site in the US.
- 8 participants were enrolled across 2 dose cohorts (0.3 mg/kg and 0.5 mg/kg) for up to 5 IV infusions administered every 2 weeks (Figure 1).
  - 1 participant withdrew after a single dose and their data was only included in the safety results.
- Participants were 12 years or older with documented diagnosis of OTCD, a history of symptomatic hyperammonemia or elevated glutamine, on stable clinical management, with normal or impaired cognitive function.
- Laboratory data, including fasting plasma ammonia and amino acids, were monitored prior to each administration of study drug and at additional time points (Figure 1).
- Per protocol, subjects were counseled to maintain stable protein intakes and complete 3-day diet diaries prior to each laboratory assessment.
  - Participants maintained a stabilized diet and OTCD therapeutics regimen during a 4-6 week screening period.
  - Participants met regularly with experienced metabolic dietitians to help maintain dietary protein intake within 25% of baseline amounts.
- 7 female participants (5 adults and 2 adolescents) with OTCD completed the study.
  - One participant only received 4 doses of investigational medication due to elevated transaminases that subsequently resolved without treatment.
  - One participant received all doses of investigational medication but data from her final study visits are not yet available.
- All analyses are descriptive with no formal statistical analysis. Data presented is preliminary with continued analyses ongoing.

Figure 1: ARCT-810-04 Study Design



BASELINE CHARACTERISTICS

Table 1: Baseline Characteristics in Pharmacodynamic Analysis Set

	Total Participants (N=7)
Demographics	
Sex (n)	F (7)
Race (n)	White (7)
Ethnicity (n)	Hispanic (2)
Age (yrs) Median (Range)	38 (14 – 57)
Baseline Anthropometrics	
Weight (kg) Median (Range)	67.3 (47.6 – 75.5)
Height (cm) Median (Range)	166.0 (154.0 – 175.0)
BMI (kg/m²) Median (Range)	24.1 (17.0 – 30.7)
Baseline Medical Interventions	
Citrulline and/or arginine supplementation n (%)	5 (71%)
Nitrogen scavengers n (%)	6 (86%)
Medical food n (%)	0 (0%)

REFERENCES:

1. Lichter-Konecki U et al. (1993-2022) Ornithine transcarbamylase deficiency. Gene Reviews
2. Singh R et al. (2007) Nutritional management of patients with urea cycle disorders. J Inherit Metab Dis 30:880-7
3. Sablad, M et al. (2019, April 6-9). mRNA therapy for ornithine transcarbamylase deficiency. SIMD, Bellevue, WA.
4. McNutt, M et al. (2024, September 3-6). Safety and tolerability of ARCT-810 mRNA in early trials for ornithine transcarbamylase deficiency. SSIEM, Porto, Portugal

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RESULTS

DIETARY DATA AND BIOMARKERS

- Baseline energy intake adequately met estimated needs (Table 2).
- Average protein intake across all participants at baseline was 78.1 ± 24.9% of the Recommended Dietary Allowance (RDA) suggesting restriction of protein intake (Table 2).
- Essential amino acids, including the branched chain amino acids, remained stable throughout the study period without persistently low levels despite none of the subjects receiving essential amino acid medical food supplement.
- Due to citrulline and/or arginine supplementation, an effect on plasma levels of these amino acids after investigational drug treatment was not observed.
- Weight gain was observed in all participants over the 2-month treatment period.

Table 2: Dietary Summary

	Total Participants (N=7)
Baseline Nutrition Intake	
Avg kcal/kg body weight/day at baseline	26.6 ± 4.6
Avg protein (g)/kg body weight/day at baseline	0.64 ± 0.19
% Avg protein RDA/day at baseline	78.1 ± 24.9
Changes in Dietary Intake and Weight with ARCT-810	
Number of 3-day diet diaries >=25% of baseline protein intake	1.1 ± 1.4
% Change in protein from baseline to Day 60*	+18.4 ± 21.7
Weight change (kg)**	+2.6 ± 2.1
% Weight change**	+4.3 ± 3.2

Data are expressed as mean ± SD
*Day 60 was clinic visit after participants received their last dose of ARCT-810-04
**Weight change from baseline to last measurement obtained during treatment period at Day 57

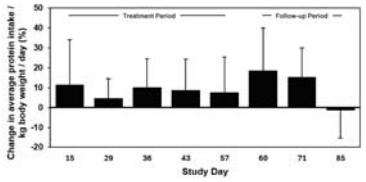

Figure 2: Change in mean (SD) average grams protein per kg body weight per day versus study day by dosing group. n=5-7 at individual timepoints.

- Despite ongoing counseling to maintain consistent protein intakes at baseline levels, protein intakes increased by a mean of 18.4 ± 21.7% from baseline to last dose of investigational drug. There was a consistent increase in protein intake across pooled participants during the treatment period (Figure 2).
- Despite increased protein consumption observed at the study visit after the last dose of investigational drug was received (Day 60), mean plasma ammonia, glutamine and glycine levels decreased by 44%, 22%, and 16%, respectively, from mean baseline.
- Three of seven participants had elevated first morning fasting ammonia levels at baseline. Following ARCT-810 administration, all participants had normal first morning fasting ammonia levels (Figure 3).
- Baseline plasma glutamine levels in all participants were above upper limits of normal. Following ARCT-810 administration, mean glutamine values were lower than mean baseline values (Figure 3).
- Baseline plasma glycine levels were elevated in 6 of 7 participants which can be associated with elevated glutamine levels and altered amino acid metabolism. Nominal decreases in glycine were observed over the course of the study (Figure 3).

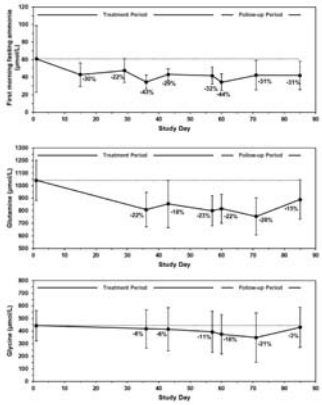

Figure 3: Mean (SD) first morning fasting plasma ammonia, plasma glutamine, and plasma glycine versus study day by dosing group. Dotted line represents mean baseline value. Percentages represent percent change in mean value from mean baseline. n=5-7 at individual timepoints.

SAFETY

- ARCT-810 was generally safe and well tolerated following multiple dose administrations (Table 3).
- No serious AEs were reported.
- No AESIs (hyperammonemia) were reported during the treatment and follow-up period.
- The most common TEAEs were headache (2/8), transaminitis (2/8), and IRRs (back pain) (2/8). Most treatment emergent adverse events (TEAE) were mild to moderate in severity.
- Two participants experienced Grade 3 non-serious asymptomatic transaminitis that resolved without intervention after stopping study drug.
- Two participants experienced infusion-related reactions (IRR) which were non-serious and mild to moderate in severity. There were no discontinuations due to IRRs.
- One participant discontinued after a single dose of ARCT-810 due to a non-serious Grade 2 AE of IV infiltration with a subsequent site injection reaction.

Table 3: Adverse Events in Safety Analysis Set

	Total Participants (N=8)
Participants with TEAE	8
TEAE events	25
Participants with related TEAE	7
Related or possibly related TEAE events	14
TEAE event severity	
Grade 1	7
Grade 2	5
Grade 3	2
Discontinued due to AE	1
Discontinued due to IRR	0
Serious AEs	0
AESIs (hyperammonemia)	0
Participants with IRR	2

CONCLUSIONS

- **This poster presents preliminary data. Evaluation of the safety and efficacy of ARCT-810 is ongoing. An expanded data analysis will be presented by webcast in September.**
- **ARCT-810 was generally safe and well tolerated throughout the study period.**
- **After ARCT-810 administration, all participants exhibited weight gain with increases in protein intake which may suggest improved dietary protein tolerance.**
- **The observed decreases in mean levels of first morning fasting plasma ammonia and glutamine despite increased dietary protein intake suggests possible improvements in urea cycle flux following ARCT-810 administration.**