It Translates: An Update on the ARCT-810 mRNA for OTC Deficiency

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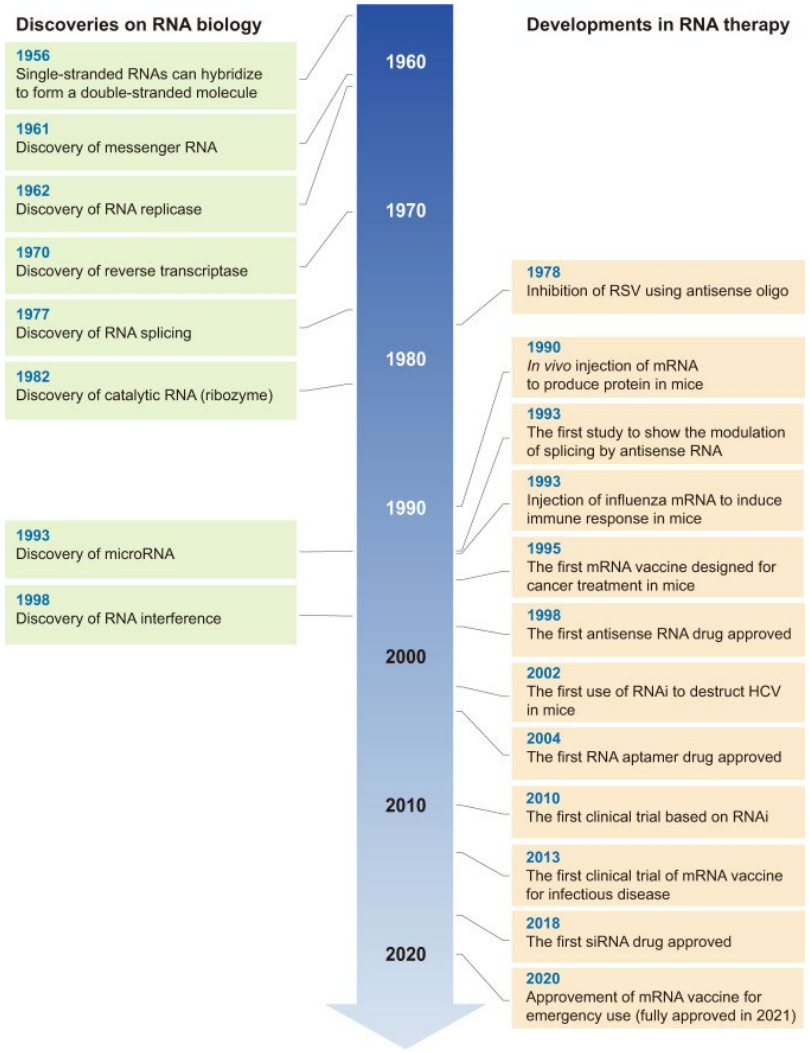
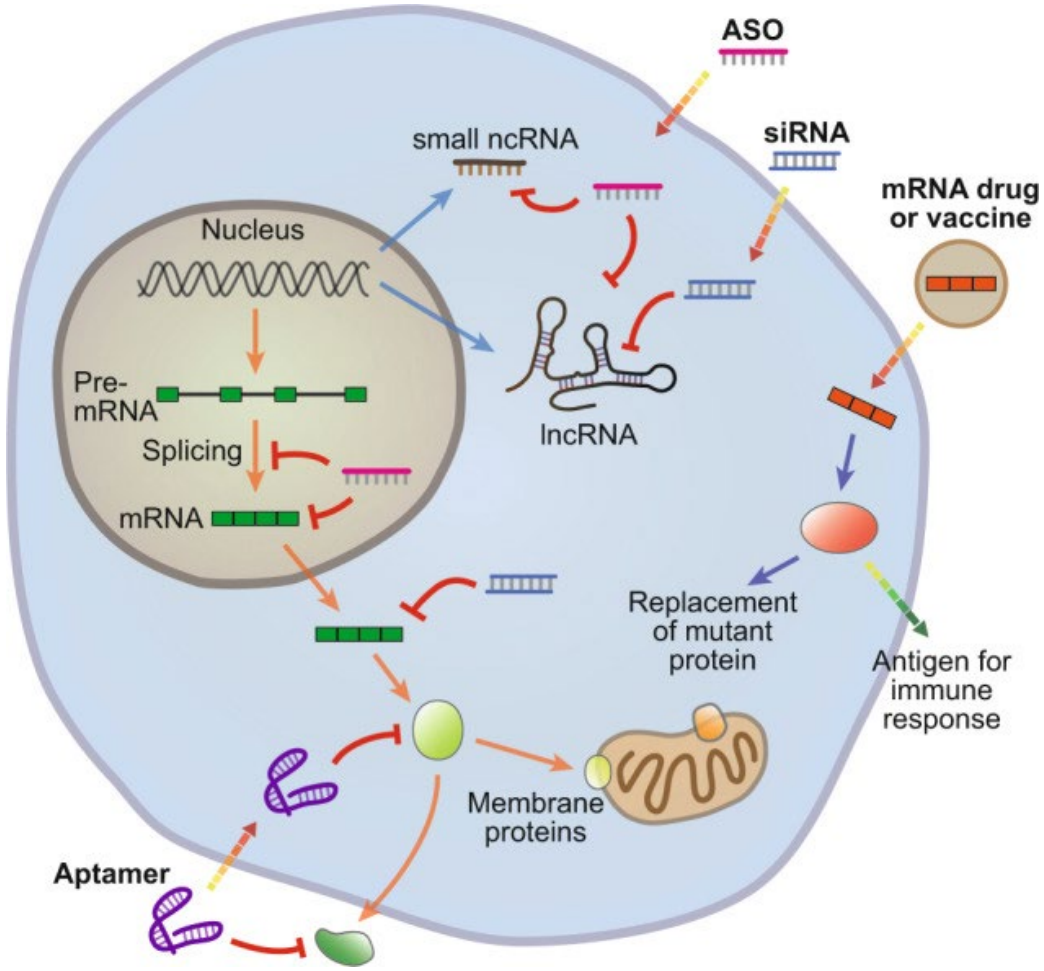
Disclosures

- Grant/Research Support: Aeglea Biotherapeutics, Reneo Pharmaceuticals, PTC Therapeutics, Homology Medicines, Horizon Therapeutics, Arcturus Therapeutics, Jnana Therapeutics, Synlogic Therapeutics, and Biomarin Pharmaceutical, and Moderna.
- Consultant: Horizon Therapeutics, Biomarin Pharmaceuticals, Eton Pharmaceuticals, Acer Therapeutics, Ultragenyx, Alexion Pharmaceuticals, and Chiesi USA.
- Arcturus Therapeutics sponsored the clinical trial presented and provided content for trial related slides.

RNA Therapeutics Past and Present





Exp Mol Med. 2022 Apr; 54(4): 455–465. doi: 10.1038/s12276-022-00757-5 PMCID: PMC9016686 PMID: 35440755

Current RNA Therapeutics

RNA drug	Brand name	Approved year	Action mechanism	Target disease
Antisense oligonucleotides				
Fomivirsen	Vitravene	1998	Inhibition of the translation of viral mRNA encoding IE2 protein	CMV retinitis
Mipomersen	Kynamro	2013	Induction of the degradation of APOB mRNA	Familial hypercholesterolemia
Nusinersen	Spinraza	2016	Induction of exon inclusion in SMN2 mRNA	Spinal muscular atrophy
Eteplirsen	Exondys 51	2016	Induction of exon skipping in DMD mRNA	Duchenne muscular dystrophy
Inotersen	Tegsedi	2018	Induction of the degradation of TTR mRNA	Hereditary transthyretin amyloidosis
Golodirsen	Vyondys 53	2019	Induction of exon skipping in DMD mRNA	Duchenne muscular dystrophy
Casimersen	Amondys 45	2021	Induction of exon skipping in DMD mRNA	Duchenne muscular dystrophy
Small interfering RNAs				
Patisiran	Onpattro	2018	RNA interference-mediated cleavage of TTR mRNA	Hereditary transthyretin amyloidosis
Givosiran	Givlaari	2019	RNA interference-mediated cleavage of ALAS1 mRNA	Acute hepatic porphyria
Lumasiran	Oxlumo	2020	RNA interference-mediated cleavage of HAO1 mRNA	Primary hyperoxaluria type 1
Inclisiran	Leqvio	2021	RNA interference-mediated cleavage of PCSK9 mRNA	Hypercholesterolemia
RNA aptamers				
Pegaptanib	Macugen	2004	Antagonistic binding to VEGF protein	Age-related macular degeneration
Defibrotide	Defitelio	2020	Activating Adenosine A1/A2 receptor	Veno-occlusive disease in liver
Messenger RNAs				
Tozinameran	Comirnaty	2020	Induction of immune response by producing the spike protein of SARS-CoV-2	COVID-19
Elasomeran	Spikevax	2020	Induction of immune response by producing the spike protein of SARS-CoV-2	COVID-19

Adapted from Exp Mol Med. 2022 Apr; 54(4): 455–465. doi: 10.1038/s12276-022-00757-5 PMCID: PMC9016686 PMID: 35440755

Kim, YK. RNA therapy: rich history, various applications and unlimited future prospects. *Exp Mol Med* **54**, 455–465 (2022). https://doi.org/10.1038/s12276-022-00757-5

Drug Development in Inborn Errors and OTC

- Enzyme/Protein replacement therapy
  - Limited location of action
- Synthetic biology (Pre/Probiotics)
- New targeted oral medication
- Gene Replacement/Editing
  - Delivery
  - Off target effects
  - Irreversible
  - Repeat dosing
- mRNA delivery
  - Transient
  - Titratable
  - Usable throughout development

Where does mRNA fit?

- Stand-alone therapy
- Bridge to transplant
- Bridge to gene therapy

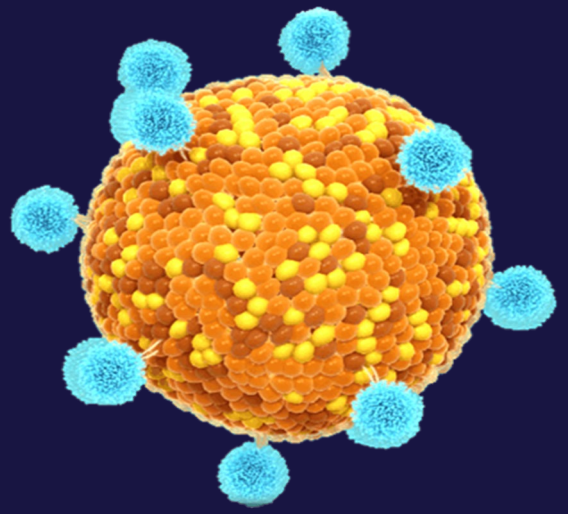
mRNA Trials in IEMs

- MMA (phase 2, Moderna)
- PA (phase 2, Moderna)
- GSD1A (phase 1, Moderna)
- PKU (phase 1 expected soon, Moderna)
- OTC (phase 2, Arcturus)

ARCT-810 Consists of OTC-mRNA in a proprietary LNP

3 amino acid changes from WT

- Increase OTC half-life
- Increase fraction directed to mitochondria



- Lipid nanoparticles encase the mRNA, protecting it from being broken down in the circulation.
- Proprietary ionizable lipid enables mRNA release into the cell
- mRNA is translated into functional OTC

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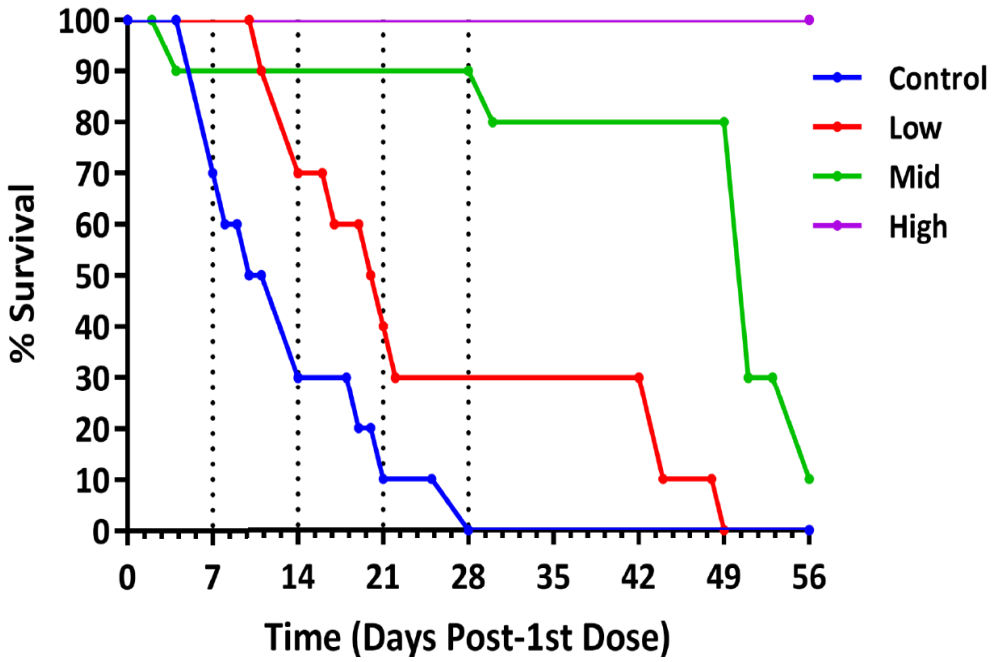
ARCT-810 Effective in spf/ash Mouse Model of OTCD

spf/ash Mice treated with ARCT-810 demonstrated improved biochemical markers of urea cycle function and improved survival

- Reduced plasma ammonia
- Reduced plasma glutamine
- Reduced urine orotic acid
- Improved ureagenesis
- Improved survival (mice fed high protein diet)
- Minimal anticipated biologic effect = 0.1



Weekly administration improved survival in spf/ash Mice fed a high-protein diet

Phase I (ARCT-810-01) Single-Ascending-Dose (SAD) Study in Healthy Adult Volunteers

Completed in 2020 in New Zealand

- 30 healthy volunteers randomized 2:1 to a single IV dose of ARCT-810 or saline placebo
- Dose cohorts ranged from 0.1 to 0.4 mg/kg IV; infused over 90 minutes
- Premedication with ibuprofen, H1 and H2 blockers

- **Findings**
  - ARCT-810 was generally safe and well tolerated
  - AEs were graded as mild and non-serious; usual AE types for a Phase 1 study
  - No safety concerns for vitals, physical exams, ECG, labs
  - PK: dose-related increase in exposure; mRNA detectable in plasma 15 days after dose; ionizable lipid detectable <48 hours
  - PD: Ureagenesis assay and plasma OTC activity unchanged (as expected in healthy subjects)
  - Infusion reactions (IRR; moderate) in sentinel subject receiving 0.4 mg/kg
    - Infusion protocol modified to 2-step, 90-minute procedure (same as Onpattro, an LNP-siRNA)
    - No further IRR in remaining 7 subjects receiving 0.4 mg/kg
    - 2-step, 90-minute infusion procedure carried over into the Phase 1b study

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Phase Ib ARCT-810-02 SAD Study in Stable OTCD Adults

Study Design:

- Subjects randomized 3:1 to single IV dose of ARCT-810 or saline placebo
- Ascending-dose cohorts 0.2, 0.3, 0.4 & 0.5 mg/kg; n = 4 per cohort
- Premedication with ibuprofen, H1 and H2 blockers

Objectives:

- Primary: safety & tolerability of ARCT-810
- Secondary: pharmacokinetics of ARCT-810 mRNA and ionizable lipid components
- Exploratory: changes in ureagenesis biomarkers after single dose ARCT-810 (on Day 1)
  - Plasma ammonia and amino acids*
  - Urine orotic acid**
  - Plasma OTC activity**
  - Ureagenesis assay (^{13}C acetate) †

*Assessed predose BL, D2, D8, D15, D29
**Assessed predose BL, D2, D3, D8, D15, D29
† Assessed predose BL and D2

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ARCT-810-02 US Study Sites

Principal Investigator	Site
Markey McNutt	University of Texas Southwestern Medical Center
Jerry Vockley	Children’s Hospital of Pittsburgh
Nicolo Longo	University of Utah
George Diaz / Margo Breilyn	Icahn School of Medicine at Mount Sinai
Donald Basel	Children’s Hospital of Wisconsin
Reid Sutton	Baylor College of Medicine & Texas Children's Hospital
Roberto Zori	University of Florida
Susan Berry	University of Minnesota

Key Eligibility Criteria

- Ages ≥18 years with documented diagnosis of OTC deficiency confirmed with genetic testing.
- Good cognitive function (able to understand study procedures, sign consent)
- Stable OTC deficiency as evidenced by no clinical symptoms of hyperammonemia AND an ammonia level <100 µmol/L at Screening
- Stable treatment regimen (e.g., protein restriction, NH_4 scavengers if applicable)
- Good general health with no conditions that would make participation unsuitable or jeopardize safety or data integrity

Mild Disease and Female Carriers

ARCT-810-02 Demographics & Disposition

- Age range: 22 - 68 years
- Gender: 5 Male, 11 Female
- Race: 14 Caucasian, 2 Asian
  - Ethnicity: 5 Hispanic/Latino, 11 not Hispanic/Latino
- Weight range: 52 to 106 kg
- Height range (cm):151 to 181 cm
- BMI: 19-42 kg/m^2
- Treatment: 9/16 on NH_4 scavengers, all on various levels of protein restriction
- 16 subjects enrolled
  - 15 completed
  - 1 early termination (PI decision due to IRR)

ARCT-810-02 Findings: Safety

- ARCT-810 was generally safe and well tolerated
  - No serious or severe AEs or dose-limiting toxicity
  - No safety concerns for vitals, physical exams, ECG, safety labs
  - Infusion reactions (IRR) in 3 subjects; 1 withdrawal

	0.20 mg/kg ARCT-810 N=3 (%)	0.30 mg/kg ARCT-810 N=3 (%)	0.40 mg/kg ARCT-810 N=2 (%)	0.50 mg/kg ARCT-810 N=3 (%)	Pooled Placebo N=5 (%)	Pooled ARCT-810 N=11 (%)
Any TEAE	2 (66.7)	2 (66.7)	2 (100.0)	3 (100.0)	3 (60.0)	9 (81.8)
Any Treatment-Related TEAE	1 (33.3)	2 (66.7)	1 (50.0)	2 (66.7)	0	6 (54.5)
Trtmt-Related TEAE by severity						
Mild	1 (33.3)	1 (33.3)	1 (50.0)	2 (66.7)	0	5 (45.5)
Moderate	1 (33.3)	1 (33.3)	0	0	0	2 (18.2)
Any IRR TEAE	1 (33.3)	1 (33.3)	0	1 (33.3)	0	3 (27.3)
IRR Severity						
Mild	0	0	0	1 (33.3)	0	1 (9.1)
Moderate	1 (33.3)	1 (33.3)	0	0	0	2 (18.2)

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ARCT-810: Summary of IRRs

Initial IRRs within a few minutes of starting infusion

Study	Age/ Sex	Dose/ Inf. Time	IRR Description	Notes / Contributing factors
810-01	21/M (HV)	0.4 mg/kg 90-min. flat rate	#1-Back pain, SOB, feeling hot on face. Paused 25 min. & restarted at 1/2 rate. #2- After 45 min. N/V, abd pain, HA, feeling hot (T=37.7°C); rx with diphenhydramine, acetaminophen, ibuprofen.	• Infusion d/c-ed
810-02	32/F	0.2 mg/kg 90-min. 2-step	Infusion started via **central IV port**: chest pain, tachycardia, mild O2 desat. Recovered in 24 min. and restarted via peripheral IV with no further issues.	• Uncertain if central infusion contributed
810-02	45/F	0.3 mg/kg 90-min. 2-step	Nausea, abd cramps, flushing, leg pain, transient low HR (42). Paused 2.5 hr and fed, restarted at lower rate and stepped up but symptoms recurred	• Had been fasting prior • Obese (i.e. high total dose) • Infusion d/c-ed
810-02	35/F	0.5 mg/kg 3-hour 3-step	Initial mild flushing/chest pain; later had N/V, chest pain, transient hypotension. Ate crackers & treated with IV solumedrol, was able to restart at lower rate and finish infusion with no further problems.	• Initial infusion rate 4x too fast (nursing error) • Had been fasting, received IV diphenhydramine, sat up quickly (orthostatic changes?)

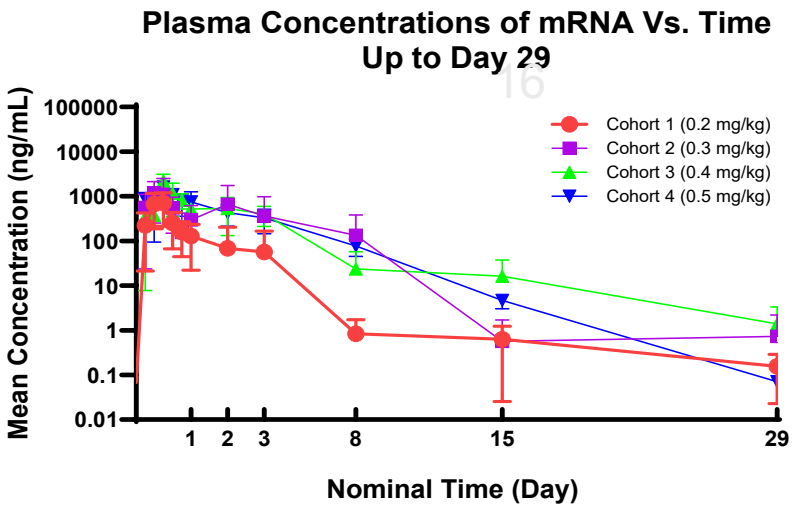
IRR Takeaways

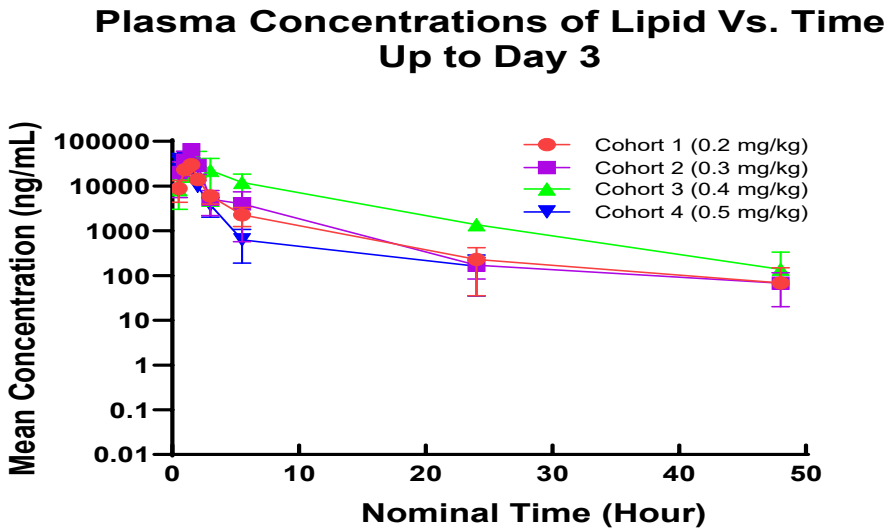
- IRRs were associated with transient perturbations in complement, hsCRP and cytokines
- Lower infusion rates may reduce the frequence and severity of IRRs
  - Need more clinical experience with a 3-step, 3-hour dosing regimen
  - Investigate the tolerability of infusions in central venous lines
- How to optimize the premedication regimen with limited options for OTCD patients
  - Corticosteroids have relative contraindication for OTCD, especially if given repeatedly
  - Acetaminophen 500 mg seems to be well tolerated; alternative for ibuprofen?
  - Use high potency H1 blockers
  - H2 blockers historically used; scientific evidence is scant

IRRs informed infusion procedure modifications

ARCT-810-02 Findings: PK

- PK: similar to Phase I HV study
  - C_{max} occurred at end of infusion
  - mRNA t½ 52-62 hrs (detectable at 2-4 wks after dose)
  - Ionizable lipid not detected >48 hrs after dose





mRNA persists and lipid clears rapidly

Pharmacodynamic overview (exploratory)

- No trends were identified for changes from baseline in any of the PD biomarkers (NH_4, glutamine, urine orotic acid, plasma OTC activity, ureagenesis assay)
- Rationale:
  - Primary objective was safety; efficacy was not anticipated after a single dose of ARCT-810
  - Most subjects had mild OTCD, some with no history of hyperammonemia
  - Subjects were compliant with their protein-restricted diet and NH_4 scavengers when applicable.
  - Ureagenesis assay may have been performed too soon after dosing (24 hrs) to detect a change

Proof of activity will depend on multiple-dose studies in more severe OTCD

Summary and Conclusions

- Single doses of IV ARCT-810 are well tolerated at doses ranging from 0.1-0.5 mg/kg
  - No severe adverse events observed
  - Sporadic IRRs could be managed with symptomatic treatment and appear to be less frequent with slower infusion rates
- mRNA could be detected up to 4 weeks; terminal half-life of 52-62 hours supports dosing interval of 2 weeks for ARCT-810 in multiple-dose studies
- A Phase 2 multi-dose clinical trial in adolescents and adults with controlled mild-moderate OTCD is ongoing in Europe (ARCT-810-03)
- An additional multiple-dose safety and efficacy study is warranted in more severe and younger OTCD patients, including assessment of disease-related biomarkers that demonstrate the effect of ARCT-810 on OTC activity
- Biomarkers of interest will require validation in a clinical trial
  - Ammonia: 24-hr profile vs. fasting morning ammonia
  - Ureagenesis assay: which stabile isotope label is more meaningful (^{13}C or ^{15}N)?
  - Serum glutamine, urine orotic acid, others

Thank you

Patients and families

ARCT-810-02 Investigators & clinical research teams

SOCIETY FOR INHERITED METABOLIC DISORDERS

ARCTURUS® therapeutics

LUNAR-OTC website: OTCmRNAstudy.com

Information about OTC studies: ClinicalTrials@Arcturusrx.com