WS10: Inhaled LUNAR®-CFTR mRNA (ARCT-032) is safe and well tolerated: A Phase 1 Study

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Conflict of interest(s):

D Geller, C Crowley and J Froehlich are employees and stockholders of Arcturus Therapeutics, Inc.

C Schwabe and M O’Carroll received research funding from Arcturus for the conduct of this trial.
LUNAR®- CFTR (ARCT-032)

*Investigational inhaled mRNA-LNP treatment for CF Lung Disease*

**Cargo:** Codon-Optimized CFTR mRNA

**Delivery vehicle:** LUNAR® Lipid Nanoparticle Platform

**Delivery format:** Aerosol

LUNAR-CFTR is a variant-agnostic mRNA treatment for CF lung disease for pwCF
Expression & Functional Restoration of CFTR in vitro

Dose response in F508del HBE cells

CFTR Expression: Western Blot

- TdT mRNA
- CFTR mRNA

<table>
<thead>
<tr>
<th>Dose (µg)</th>
<th>20</th>
<th>2.5</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>WT</th>
</tr>
</thead>
<tbody>
<tr>
<td>kDa</td>
<td>250</td>
<td>150</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tubulin

Cl⁻ Conductance in HBE cells

- ** P<0.001
- **** P<0.00001

Unpaired t test

Campos-Gomez, Univ. of Alabama in Birmingham
NACFC 2023
Functional Restoration with LUNAR®-hCFTR \textit{in vivo}

Mucociliary clearance improves in G551D CF Ferrets after Single ARCT-032 dose

G551D CF ferrets

Gallium-68 labeled microbeads

PET/CT

15 min scan

J Engelhardt, Univ. of Iowa
NACFC 2023
ARCT-032 Phase 1 Study (New Zealand)
Part 1: Healthy volunteers single ascending dose (SAD)

- Objectives: Safety, tolerability and PK of ARCT-032
- Design and Methods
  - Randomized, double blinded, placebo-controlled, SAD
  - Key eligibility criteria: healthy adults 18-65 years old; BMI 16-35 kg/m², screening ppFEV1 >85% (mild intermittent asthma allowed)
  - 4 sequential dose-escalating cohorts (8 per cohort, randomized 3 active:1 placebo)
    - Sentinel subjects for each cohort (1 active : 1 placebo)
    - Single doses delivered by nebulizer: 3 mg (Cohort A), 9 mg (B), 18 mg (C) and 27 mg (D)
    - SRC reviewed safety data after each cohort before dose escalation
  - Assessments: AEs, vital signs, PEs, safety labs, ECGs, spirometry, oximetry, PK sampling at various time points; follow up visits on D2, D3, D8, D15, D29 (Phone Call)

NCT05712538
ARCT-032 Phase 1 Study
Part 1 HV: Overall Results

• Safety findings
  ▪ No SAEs, severe AEs, or dose-limiting toxicities
  ▪ No safety findings for VS, PE, ECG, serum chemistry/hematology, coags, or complement
  ▪ Dose-related increase in transient, mild, post-dose respiratory symptoms
    o Cohorts A, B, and C (5 subjects) received no pretreatment
    o Cohort C (last 3 subjects) and D: pretreatment with salbutamol mitigated response
  ▪ Dose-related incidence of 1 or more: elevated temp, headache, chills, myalgias – starting 2-6 hours post-dose

• PK findings: Very low systemic exposure
  ▪ mRNA: all plasma specimens BLQ
  ▪ LNP lipid components sporadically detected in low concentrations (<1.0 ng/mL)
ARCT-032 Phase 1, Part 1: Adverse Events

All AEs graded ‘mild’ except for 2 moderate unrelated infections (PBO, Cohort D) and 1 moderate pyrexia (Cohort D)
Pretreatment with salbutamol mitigated acute FEV₁ decline
ARCT-032 Phase 1 Study (New Zealand)
Part 2: CF Adults - Ongoing

• Objectives: Safety, tolerability, PK and PD (exploratory) of ARCT-032

• Design and Methods
  ▪ Open-label, single cohort, 2 doses of ARCT-032 per subject
    o Premedication with salbutamol 2-4 puffs
  ▪ Key eligibility criteria:
    o CF adults 18-65 years old; screening ppFEV1 ≥ 40%
    o No restrictions on sputum microbiology or genotype
    o May be taking CFTR modulators
  ▪ Enrolling 6-8 subjects
    o ARCT-032 delivered by nebulizer in single doses on Day 1 and Day 3
    o Follow up D2, D4, D8, D15, D29 (PC)
  ▪ Assessments:
    o AEs, vital signs, PEs, safety labs, ECGs, oximetry, PK sampling at various time points
    o Spirometry at various times through Day 8
ARCT-032 Phase 1 Part 2
First 4 subjects

Demographics

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Genotype</th>
<th>Baseline ppFEV1</th>
<th>Kaftrio?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>F</td>
<td>F508del+/+</td>
<td>83%</td>
<td>Y</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>M</td>
<td>F508/G85E</td>
<td>72%</td>
<td>Y</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>F</td>
<td>F508del+/+</td>
<td>68%</td>
<td>Y</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>F</td>
<td>G542X+/+</td>
<td>45%</td>
<td>N</td>
</tr>
</tbody>
</table>

- ARCT-032 tolerated well at both dose levels
  - No SAE or severe AE
    - Subject 1 reported mild HA (D1) and mod. nausea (D3), mild cough and unpleasant taste (both)
    - Subject 2 reported mild unpleasant taste
  - No significant changes in oximetry or FEV₁ on dosing days
  - No febrile reactions
Part 2 Preliminary Spirometry Results

Positive Trend in \( \text{FEV}_1 \), after 2 doses of ARCT-032 in first 4 subjects

- Subject # 1
- Subject # 2
- Subject # 3
- Subject # 4

![Graph showing percent predicted FEV1 over days](image1)

![Bar chart showing absolute change ppFEV1](image2)

![Line chart showing relative change in FEV1](image3)
Conclusions

• ARCT-032 is generally safe and well tolerated
• Salbutamol pretreatment mitigates transient post-dose respiratory AEs in HVs
• Higher doses in HVs associated with pyrexia; not in pwCF (yet)
• Early trend of improved FEV₁ in pwCF after 2 doses of ARCT-032 is encouraging and correlates with CF ferret MCC data after single dose
  ▪ Only 4 CF subjects
  ▪ Needs validation in a multi-dose study in pwCF

Phase 1 results and the preclinical package support the advancement of ARCT-032 into a multi-dose Phase 2 study in pwCF
Thank you

- John Engelhardt
- Xiaoming Liu
- Steven Rowe
- Javier Campos Gomez
- Cystic Fibrosis Foundation