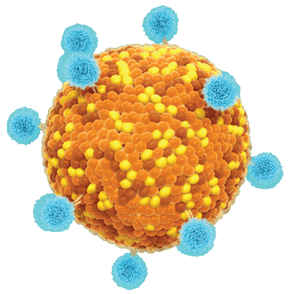
Poster #283

The Safety and Tolerability of Inhaled LUNAR®-CFTR mRNA (ARCT-032) Demonstrated in a Phase 1 Study

David E Geller[1], Constance Crowley[1], Juergen Froehlich[1], Christian Schwabe[2], Mark O'Carroll[3]

[1] Arcturus Therapeutics, San Diego, CA, USA; [2] New Zealand Clinical Research, Auckland, NZ; [3] Health New Zealand, Auckland, NZ

BACKGROUND



- Absent or reduced CFTR activity is the root cause of the pathophysiologic findings in people with cystic fibrosis (pwCF).
- Highly effective CFTR modulators (HEMT) have been transformational for many but not all pwCF.
- A significant unmet need remains for pwCF with ineligible CFTR variants or who do not tolerate nor respond to HEMT.
- LUNAR®-CFTR (a.k.a. ARCT-032) is an investigational, mutation agnostic therapy developed by Arcturus Therapeutics, comprised of CFTR-mRNA encapsulated in proprietary LUNAR lipid nanoparticles (LNP) and delivered by aerosol to restore functional CFTR protein to the lungs.
- Preclinical studies demonstrated effective transfection of LUNAR-mRNA in human bronchial epithelial cells (HBEC) and several animal species. Restoration of robust CFTR activity with LUNAR-CFTR has been demonstrated in HBEC and CF models of mice and ferrets (ECFC 2023, NACFC 2023), supporting advancement of LUNAR-CFTR (ARCT-032) to clinical studies.
- This Phase 1 first-in-human study was conducted at New Zealand Clinical Trials (Auckland, NZ) in 2023-4.

METHODS

Phase 1 study key objectives: assess safety, tolerability, and pharmacokinetics of ARCT-032. The study consisted of 2 parts:

Part 1: Randomized, DB, PC, SAD study in healthy volunteers (HV)

- 32 healthy adults randomized 3:1 to receive ARCT-032 or PBO.
- Four sequential dose-escalating cohorts (n=8 each).
- Single doses delivered by nebulizer: 3 mg (Cohort A), 9 mg (B), 18 mg (C), 27 mg (D).
- Assessments: AEs, vital signs, PEs, safety labs, ECGs, spirometry, oximetry, PK sampling; follow-up for 4 weeks.
- Safety review committee assessed safety after each cohort.

Part 2: Open-label, single cohort, 2-dose study in adults with CF

- Enrolled 7 pwCF aged ≥ 18 years with screening ppFEV1 ≥ 40%.
- No restrictions on genotype or sputum microbiology; or use of HEMT.
- Each subject received ARCT-032 9 mg on Day 1 and 18 mg on Day 3.
- Assessments and follow-up similar to Part 1.

RESULTS

Demographics:

- Part 1 (HV, n=32): mean age 30.6 years (range 21-45); 84% females; race 75% white, 22% Asian, 6% Maori. Baseline ppFEV1 >85%.
- Part 2: see **Table 1** for characteristics of pwCF.

Table 1: Demographics, Part 2 CF Subjects

Subject #	Age (yrs)	Sex	Genotype	Baseline ppFEV1	HEMT Use
1	24	F	F508del$^{+/+}$	83%	Y
2	43	M	F508/G85E	72%	Y
3	27	F	F508del$^{+/+}$	68%	Y
4	40	F	G542X$^{+/+}$	45%	N
5	19	F	F508del$^{+/+}$	93%	Y
6	34	M	F508del$^{+/+}$	86%	Y
7	23	M	F508del$^{+/+}$	46%	Y

Safety findings*:

- ARCT-03 generally safe and well tolerated.
- No serious or severe AEs or dose-limiting toxicities.
- No safety findings for vital signs, physical exams, ECG, safety labs.
- No evidence of complement activation (Part 1).
- Treatment-emergent adverse events (TEAE) more frequent at higher doses (**Table 2**).
  - All considered mild (except one event of moderate nausea).
- Part 1 (HV): at two highest doses, ↑ reports of fever (≥38° C) or feeling hot within hours of the dose, accompanied by nonspecific symptoms (e.g., headache, chills, nausea, myalgia; **Table 2**).
- Dose-related increase in transient, mild, respiratory symptoms and FEV1 ↓ after dosing (**Table 2** and **Figure 1**).
  - Part 1 Cohorts A, B and C (1st 5 subjects) received no albuterol pretreatment.
  - Part 1 Cohorts C (last 3 subjects) and D and Part 2 received albuterol pretreatment to mitigate the effects (per SRC recommendation).
- Part 2: Lack of pattern or safety concern for FEV1 change over 8 days in CF subjects after 2 doses of ARCT-032.

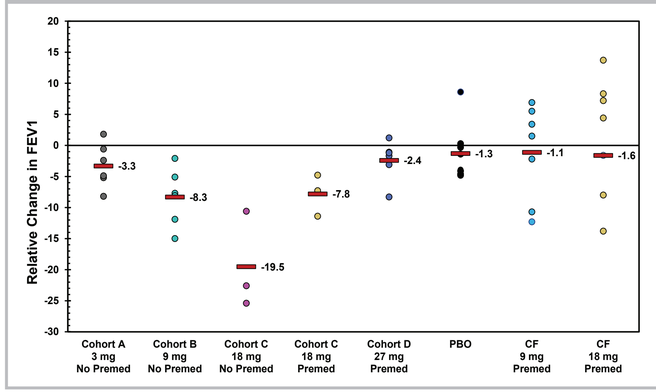
*Data from Part 2 are preliminary.

Table 2: Adverse Events

	Pooled PBO (n=8)	Cohort A (n=6)	Cohort B (n=6)	Cohort C (n=6)	Cohort D (n=6)	Part 2 CF (n=7)
n with ≥ 1 TEAE	5	3	4	6	6	6
n with ≥ 1 related TEAE	2	1	3	5	6	5
Total TEAE Events	8	5	9	22	25	13
Most frequent TEAE events						
Cough	1	0	3	5	2	2
Chest discomfort	0	0	1	0	1	1
Headache	4	1	1	3	4	3
Dizziness	0	0	1	1	1	1
Nausea	0	0	0	4	1	1
Fever or Feeling Hot	0	0	1	2	3	2
Myalgia/back pain	0	0	0	0	3	0

Figure 1: Acute Change in FEV1 15-Minutes Post-Dose

Red bars represent mean relative change in FEV1 across the cohort. Circles represent individual values



Pharmacokinetics (Part 1 only):

- Very low to no systemic exposure.
  - mRNA undetectable (BQL) in plasma.
  - LNP lipid components detected sporadically at low concentrations.
- Results expected; similar findings in nonclinical studies.

DISCUSSION AND CONCLUSIONS

- LUNAR-CFTR was generally safe and well tolerated.
- Post-dose mild respiratory symptoms and FEV1 decline was mitigated by albuterol pretreatment.
- The observed fever (objective or subjective) and nonspecific symptoms within a few hours of dosing were also reported with higher doses in a previous. mRNA-LNP CF program (Rowe 2023). In those studies, most of those AEs were considered moderate in severity; in this Phase 1 study they were mild.
- Encouraging Phase 1 safety results inform future studies (e.g., use doses below where most AEs were observed) and support clinical advancement of LUNAR-CFTR.
- The FDA has issued a 'study may proceed' letter for a Phase 2, multicenter, multiple-ascending-dose study of LUNAR-CFTR targeting pwCF who are not on HEMT. The study is planned for Q4 2024.

Reference: Rowe SM, et al. Inhaled mRNA therapy for treatment of cystic fibrosis: Interim results of a randomized, double-blind, placebo-controlled Phase 1/2 clinical study. J Cyst Fibros. 2023; 22(4):656-664.

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E-Mail for more information: clinicaltrials@arcturusrx.com or davidg@arcturusrx.com