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GLASGOW, UNITED KINGDOM

47th EUROPEAN CYSTIC FIBROSIS CONFERENCE

WS10: Inhaled LUNAR®-CFTR mRNA (ARCT-032) is safe and well tolerated: 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 and [3] Health New Zealand; Auckland NZ

Conflict of interest(s):

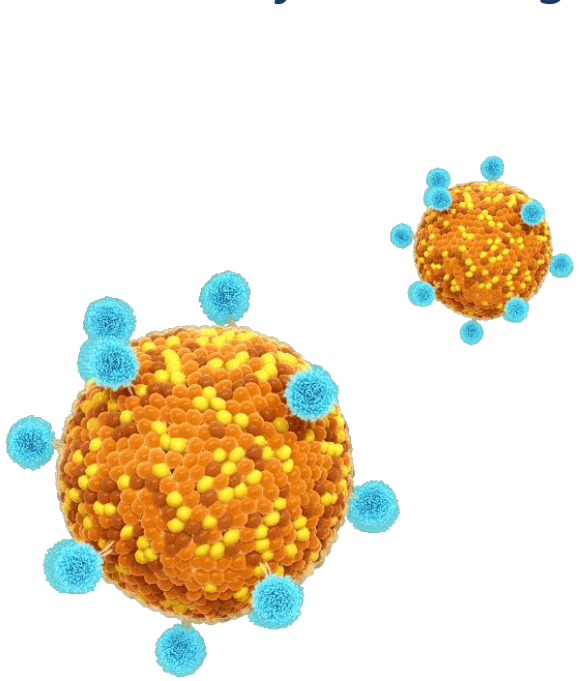
D Geller, C Crowley and J Froehlich are employees and stockholders of Arcturus Therapeutics, Inc.

C Schwabe and M O'Carroll received research funding from Arcturus for the conduct of this trial.

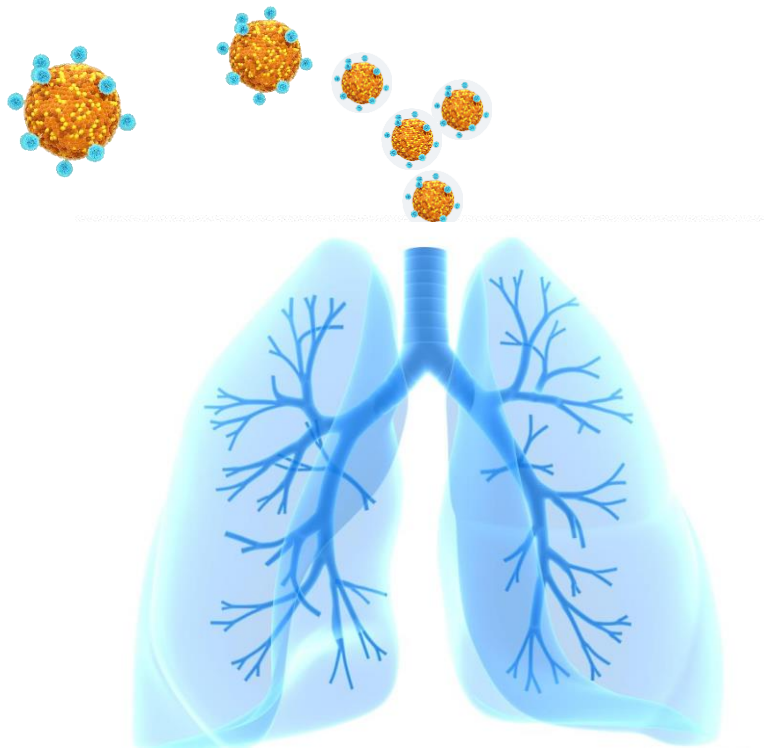
LUNAR®- CFTR (ARCT-032)

Investigational inhaled mRNA-LNP treatment for CF Lung Disease

Cargo: Codon-Optimized CFTR mRNA



Delivery vehicle: LUNAR® Lipid Nanoparticle Platform



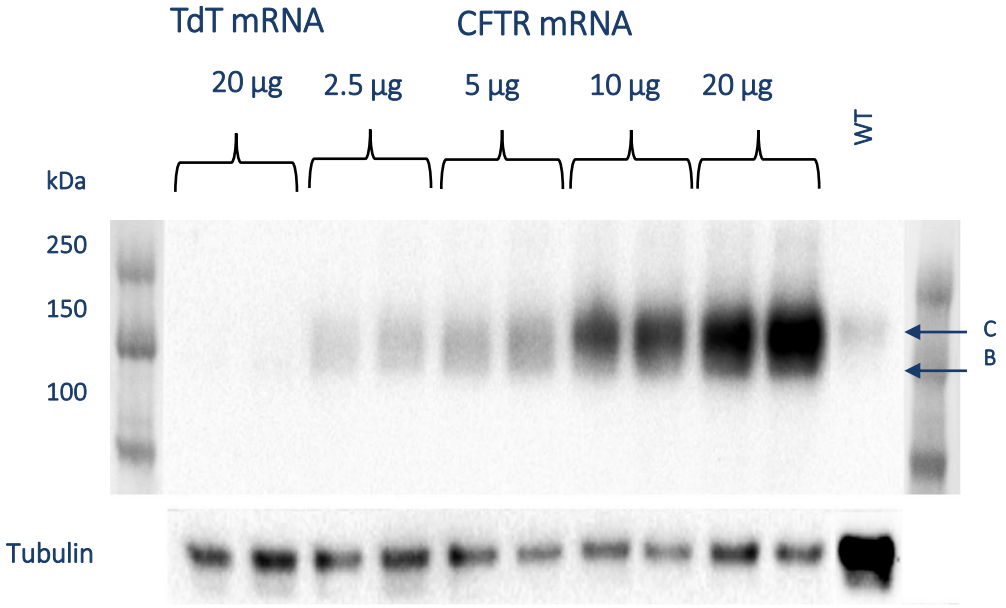
Delivery format: Aerosol

LUNAR-CFTR is a variant-agnostic mRNA treatment for CF lung disease for pwCF

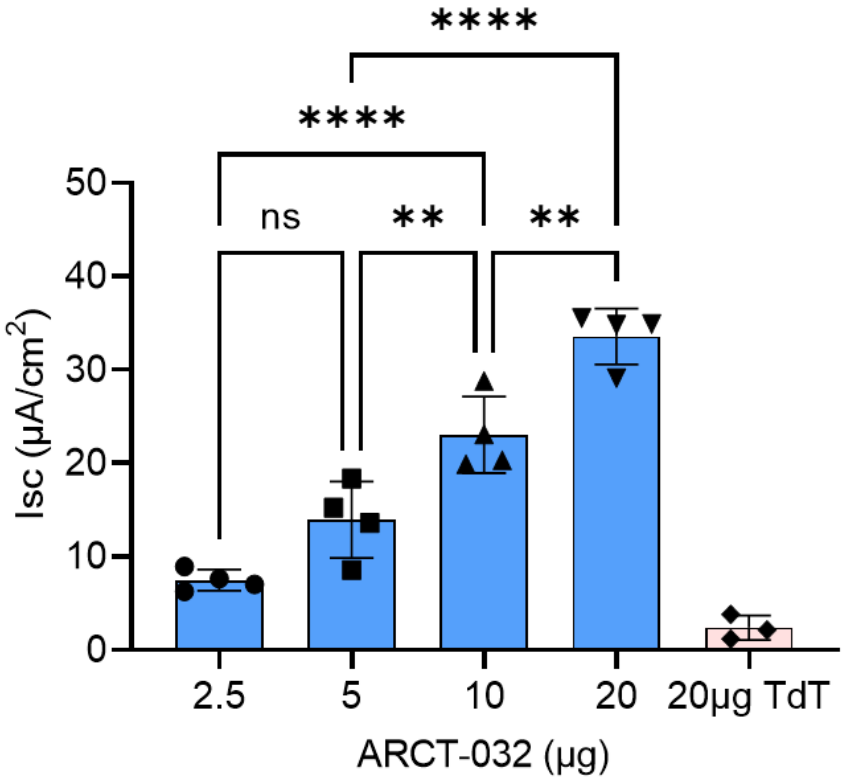
Expression & Functional Restoration of CFTR in vitro

Dose response in F508del HBE cells

CFTR Expression: Western Blot



Cl^- Conductance in HBE cells

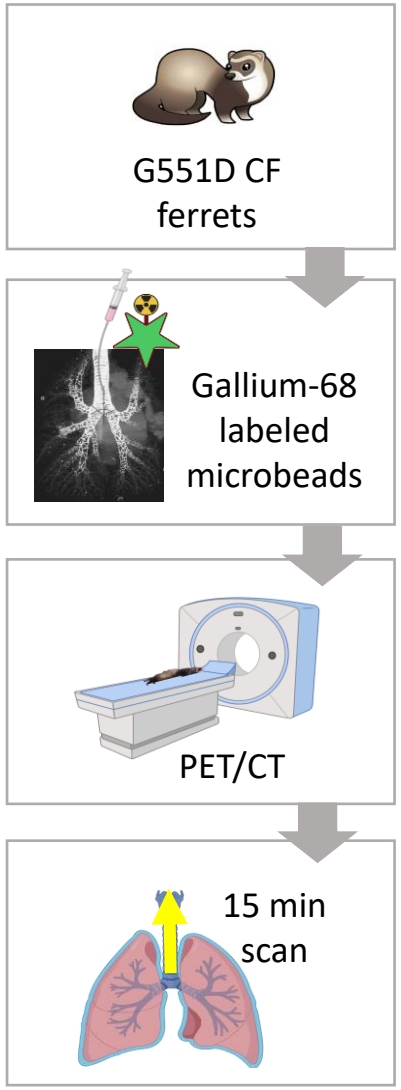


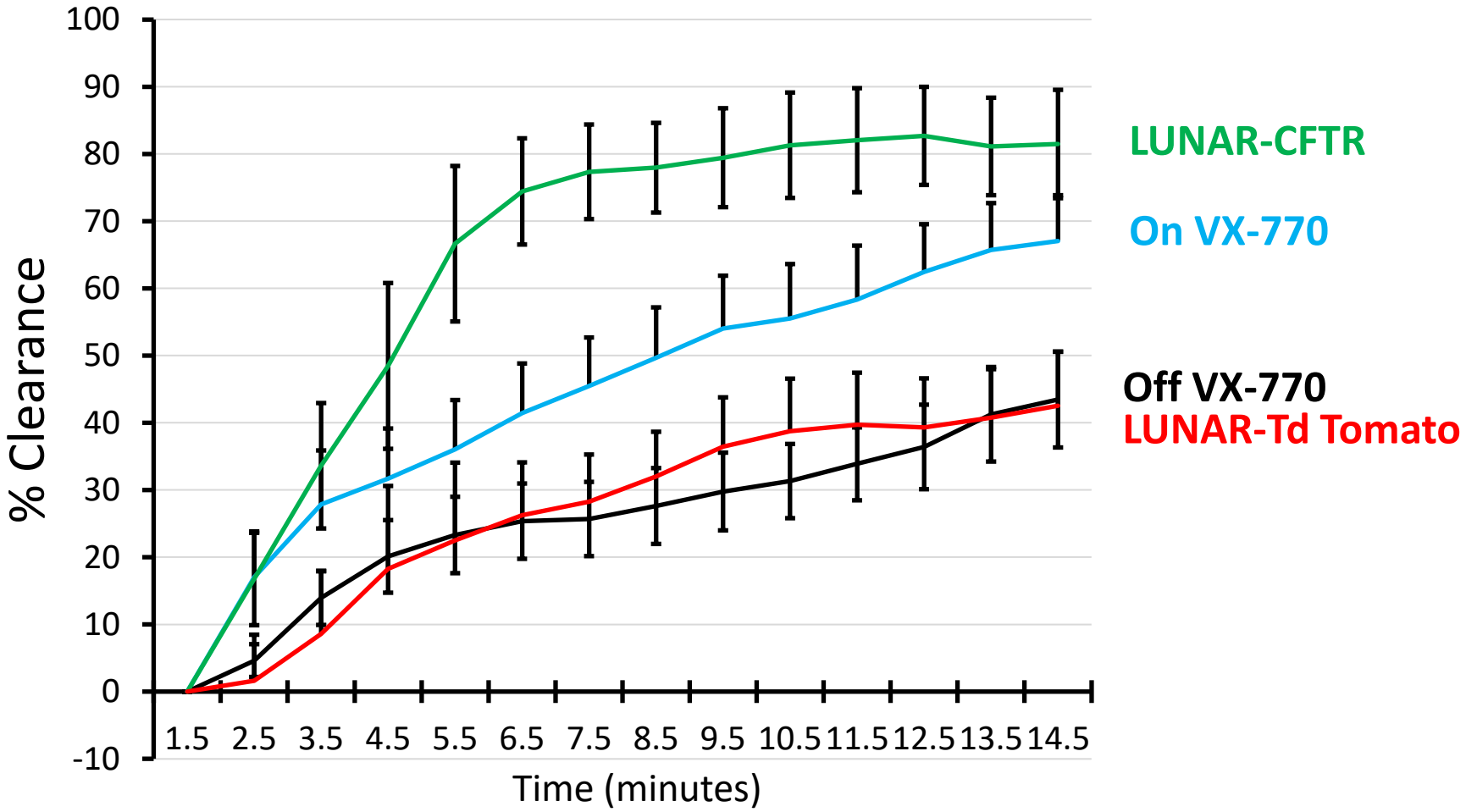
** P<0.001
**** P<0.00001
Unpaired t test

Campos-Gomez, Univ. of Alabama in Birmingham
NACFC 2023

Functional Restoration with LUNAR®-hCFTR *in vivo*

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





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/m^2, 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
    - Cohorts A, B, and C (5 subjects) received no pretreatment
    - 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

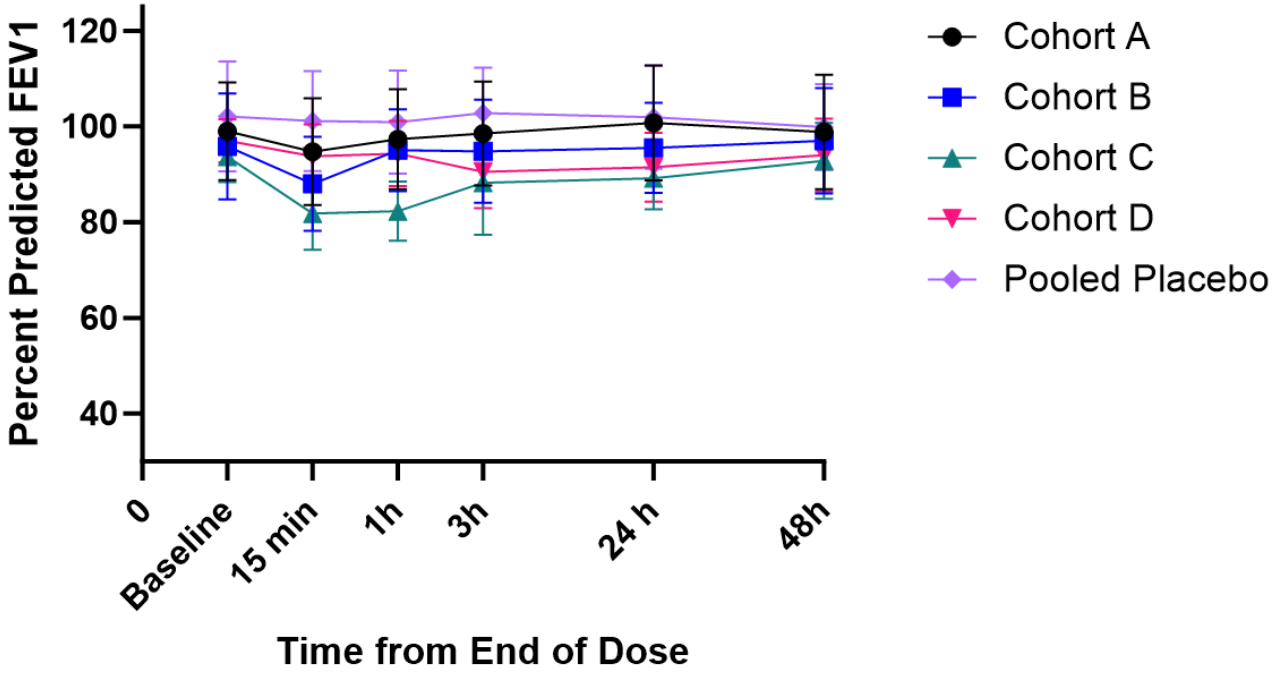
	Cohort A (n=6)	Cohort B (n=6)	Cohort C (n=6)	Cohort D (n=6)	Pooled PBO (n=8)
n with ≥ 1 TEAE	3	4	6	6	5
n with ≥ 1 related TEAE	1	3	5	6	2
Total TEAE Events	5	9	22	25	8
Most frequent TEAE events in Part 1					
Cough	0	3	5	2	1
Chest discomfort	0	1	0	1	0
Headache	1	1	3	4	4
Dizziness	0	1	1	1	0
Nausea	0	0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

All AEs graded ‘mild’ except for 2 moderate unrelated infections (PBO, Cohort D) and 1 moderate pyrexia (Cohort D)

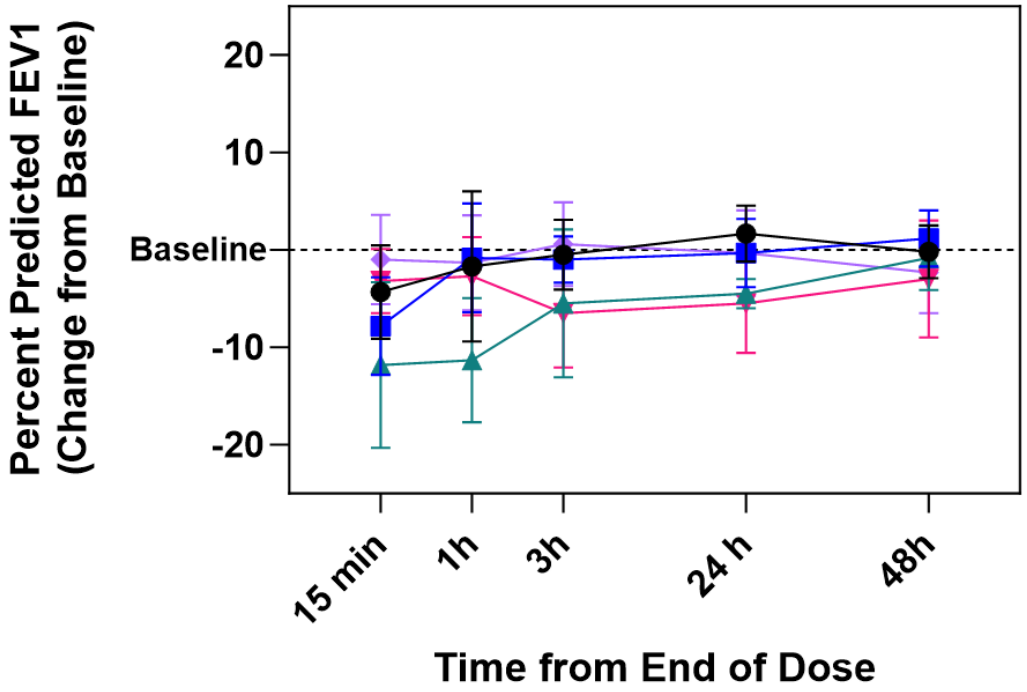
Part 1 HV: Spirometry (safety)

Dose-related transient FEV_1 decline

ppFEV1



Δ ppFEV1



Pretreatment with salbutamol mitigated acute FEV_1 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
    - Premedication with salbutamol 2-4 puffs
  - Key eligibility criteria:
    - CF adults 18-65 years old; screening ppFEV1 ≥ 40%
    - No restrictions on sputum microbiology or genotype
    - May be taking CFTR modulators
  - Enrolling 6-8 subjects
    - ARCT-032 delivered by nebulizer in single doses on Day 1 and Day 3
    - Follow up D2, D4, D8, D15, D29 (PC)
  - Assessments:
    - AEs, vital signs, PEs, safety labs, ECGs, oximetry, PK sampling at various time points
    - Spirometry at various times through Day 8

ARCT-032 Phase 1 Part 2

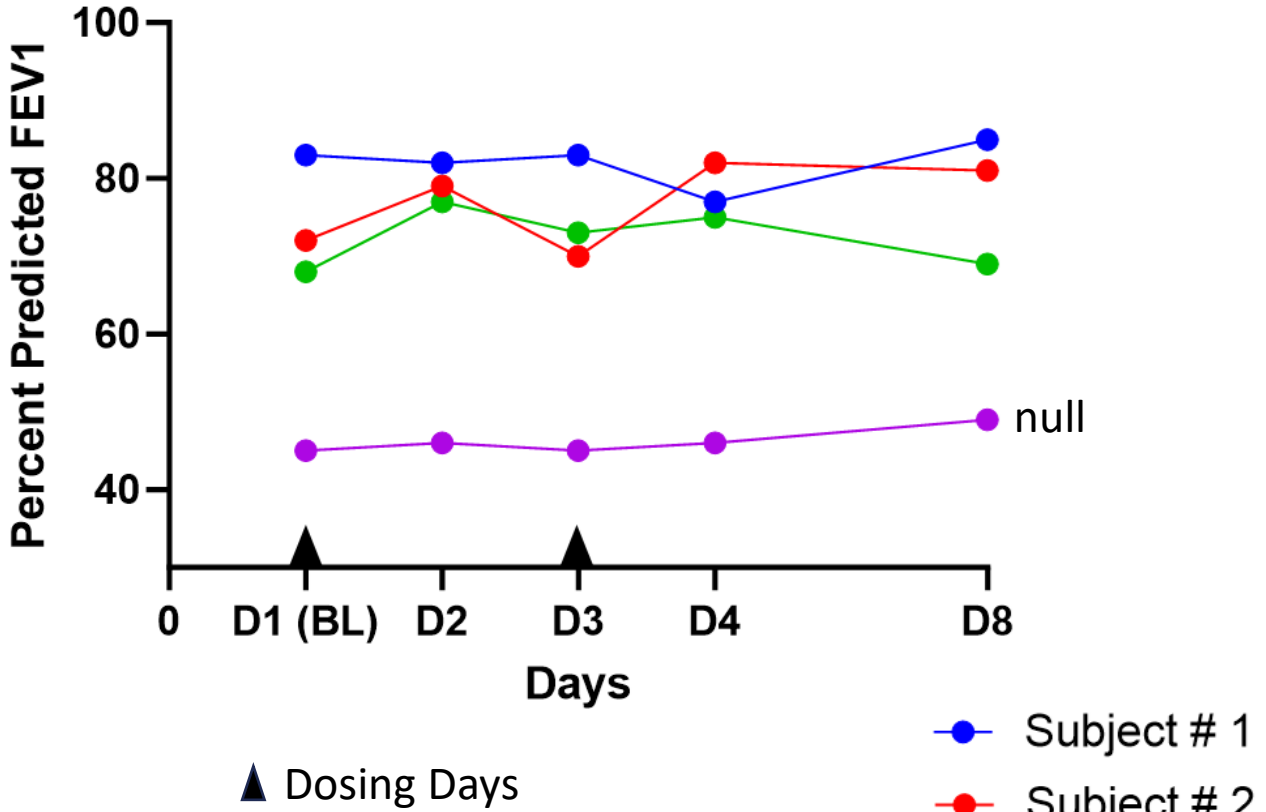
First 4 subjects

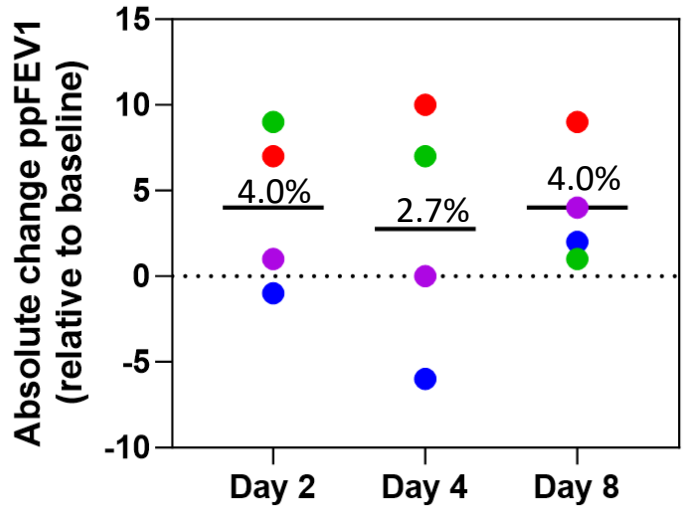
Demographics					
Subject #	**Age (yrs)**	**Sex**	**Genotype**	**Baseline ppFEV1**	**Kaftrio?**
1	24	F	F508del$^{+/+}$	83%	Y
2	43	M	F508/G85E	72%	Y
3	27	F	F508del$^{+/+}$	68%	Y
4	40	F	G542X$^{+/+}$	45%	N

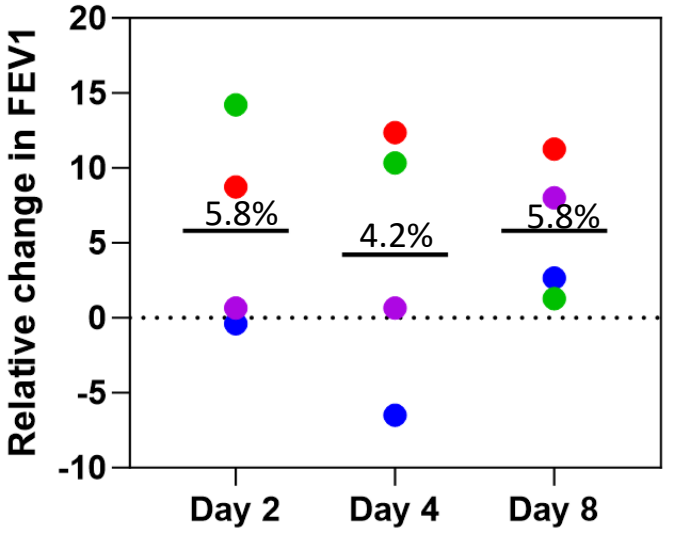
- ARCT-032 tolerated well at both dose levels
  - No SAE or severe AE
    - Subject 1 reported mild HA (D1) and mod. nausea (D3), mild cough and unpleasant taste (both)
    - Subject 2 reported mild unpleasant taste
  - No significant changes in oximetry or FEV_1 on dosing days
  - No febrile reactions

Part 2 Preliminary Spirometry Results

Positive Trend in FEV_1 after 2 doses of ARCT-032 in first 4 subjects







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 FEV_1 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