4D-710 Phase 1/2 Interim Clinical Data Conference Call

Cohort 1 Results - Nov 3, 2022

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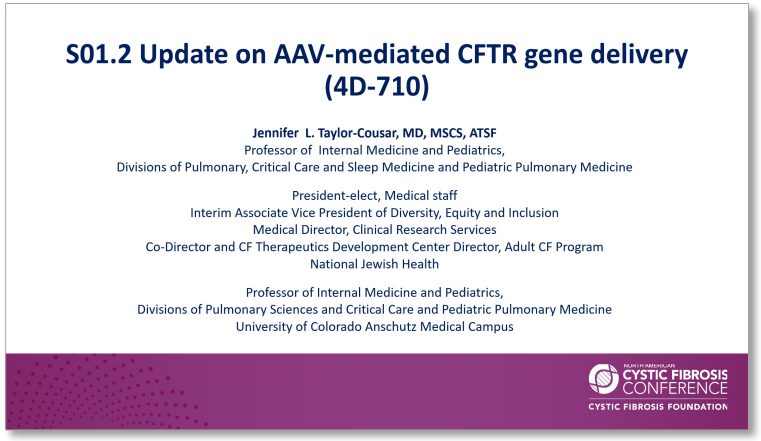
4D-710 Presentations

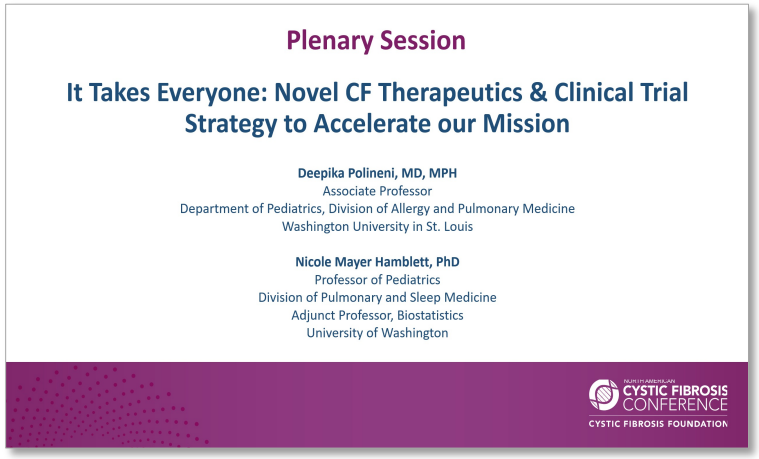
2022 NORTH AMERICAN CYSTIC FIBROSIS CONFERENCE



Session S01: Design of Clinical Trials to Evaluate Nucleotide-Based Interventions

S01.2 Update on AAV-mediated CFTR Gene Delivery (4D-710)

Jennifer L. Taylor-Cousar, MD, National Jewish Health
Thursday, November 3, 2022
9:45 AM – 11:45 AM ET
Location: 108 AB



Plenary Session

P2 It Takes Everyone: Novel CF Therapeutics & Clinical Trial Strategy to Accelerate our Mission

Deepika Polineni, MD, MPH, Washington University in St. Louis
Nicole Mayer Hamblett, PhD, University of Washington
Friday, November 4, 2022
2:00 PM – 3:15 PM ET
Location: Terrace Ballroom

Key Takeaways from NACFC 2022 Presentation

COHORT 1 CLINICAL DATA; DATA CUT-OFF: OCTOBER 7, 2022

- **Enrollment Details:**
  - Patients not amenable to CFTR modulators
  - Cohort 1 enrollment complete (n=3; 1E15vg dose)
- **Clinical Data Takeaways:**
  - Safe & well tolerated; no 4D-710 related AEs following aerosol delivery
  - Widespread ***delivery*** of the 4D-710 *CFTRΔR* transgene in all lung samples
  - Widespread ***expression*** of the 4D-710 *CFTRΔR* transgene in all lung samples
- **Next Steps:**
  - Cohort 2 enrollment underway (2E15 vg dose)
  - Assessment of clinical activity pending (e.g. ppFEV$_1$; QoL)

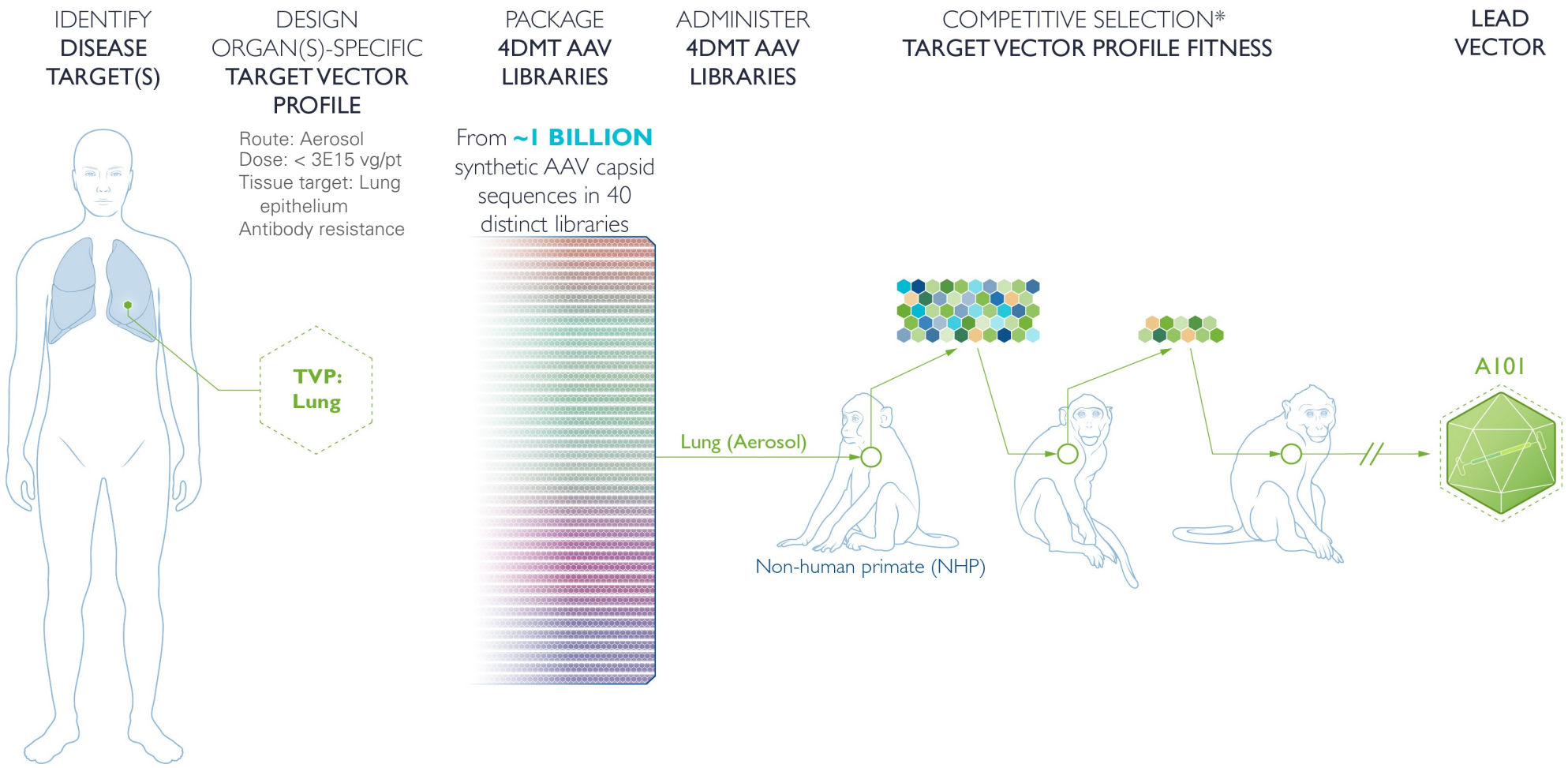
Limitations with Conventional AAV: Prior CF Lung Gene Therapy

PRIOR GENE THERAPY APPROACHES FAILED, INCLUDING WITH AAV2-BASED TGAAVCF

- **Prior AAV Gene Therapy Study Design:**
  - AAV2-based CFTR gene therapy (tgAAVCF)
  - Randomized Phase 2 trial
  - Aerosol administration day 1 & 30
  - 51 patients treated
- **Clinical Data Takeaways:**
  - Safe & well tolerated
  - Expression of CFTR transgene in lung was not reported
  - No FEV_1 benefit
- **Better AAV vector needed**

Therapeutic Vector Evolution: A101 Aerosol Delivered Synthetic AAV

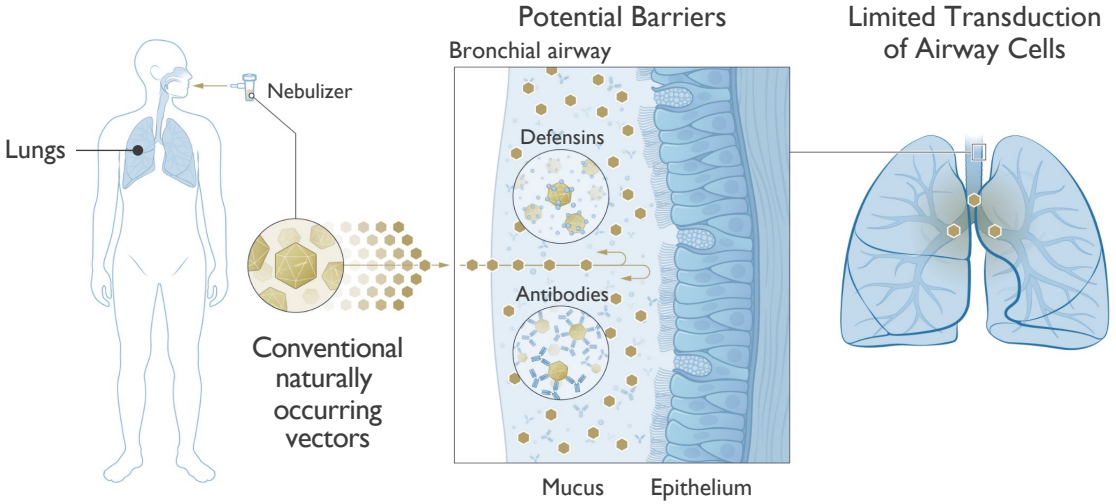
PROPRIETARY SYNTHETIC VECTOR DISCOVERY PLATFORM

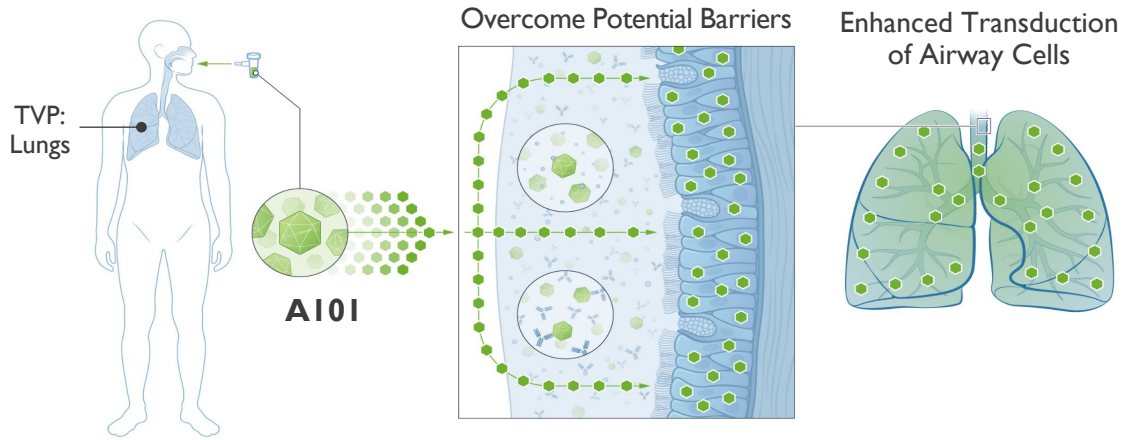


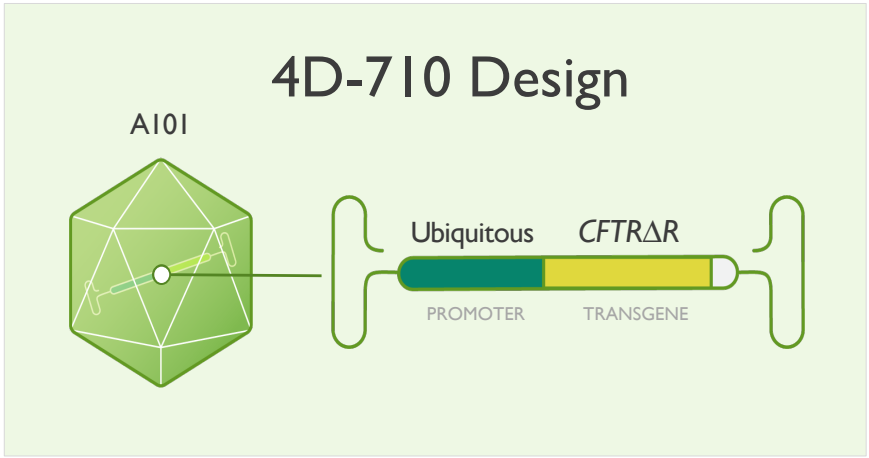
TVP, Therapeutic Vector Evolution.

4D-710: Next-Gen Aerosolized Genetic Medicine for Cystic Fibrosis Lung

A101 TARGET VECTOR PROFILE & 4D-710 PRODUCT DESIGN AND KEY ATTRIBUTES







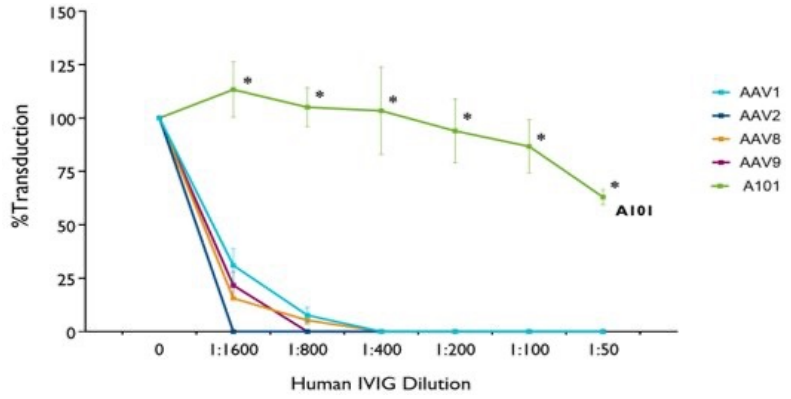
A101 KEY ATTRIBUTES

- Mucus penetration efficient
- Resistance to pre-existing human AAV antibodies
- Transgene expression efficient
- Specificity for lung (>99.9%)

Preclinical Characterization of A101 Vector & 4D-710 Product

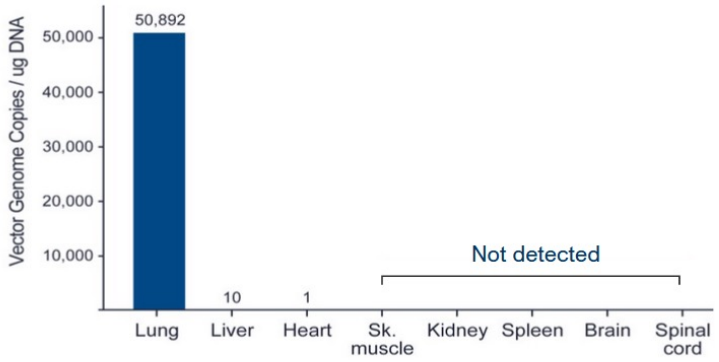
A101 RESISTANCE TO HUMAN ANTIBODIES; 4D-710 CFTR EXPRESSION IN PRIMATE LUNG

Human Antibody Resistance: IVIG



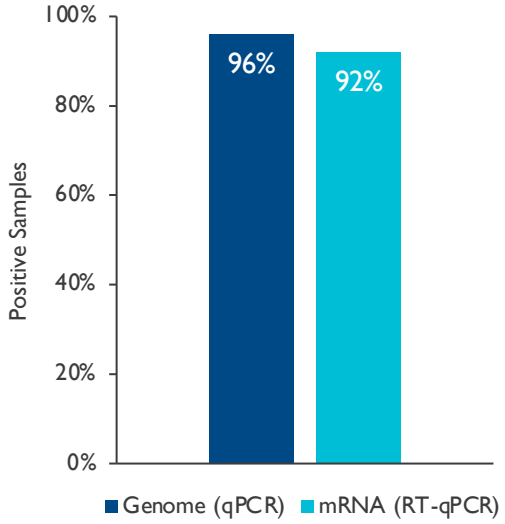
Human Hek2v6.11 cells. *p<0.05.

Lung-specific Delivery: Aerosol in Primate

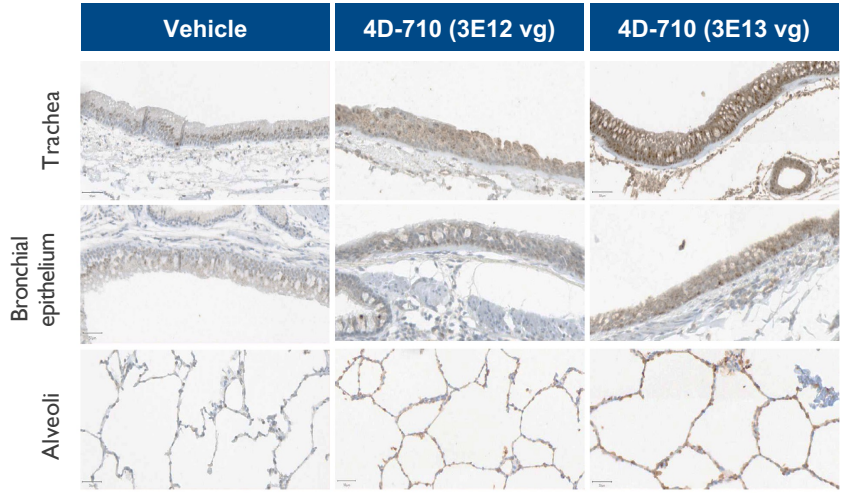


4D-710 CFTR DNA, RNA & Protein Expression: Primate Lung

% Samples (+) for DNA & RNA
(n=3 NHP; 48 samples)



CFTR IHC
(n=3 NHP/dose level)

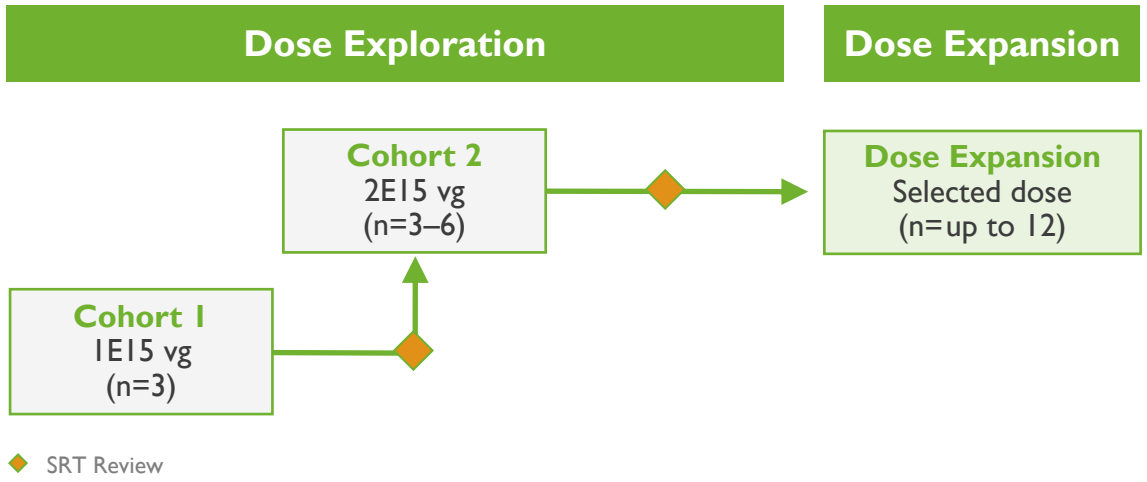


CFTR immunohistochemistry staining of lung tissue samples from nonhuman primates, representative images (10x).

Calton M. American Thoracic Society International Conference, May 14-19, 2021. Abbreviations: NHP, nonhuman primate.

Phase 1/2 Clinical Trial Study Design (4D-710-C001)

OPEN-LABEL PHASE 1/2 TRIAL IN MODULATOR-INELIGIBLE ADULTS WITH CYSTIC FIBROSIS

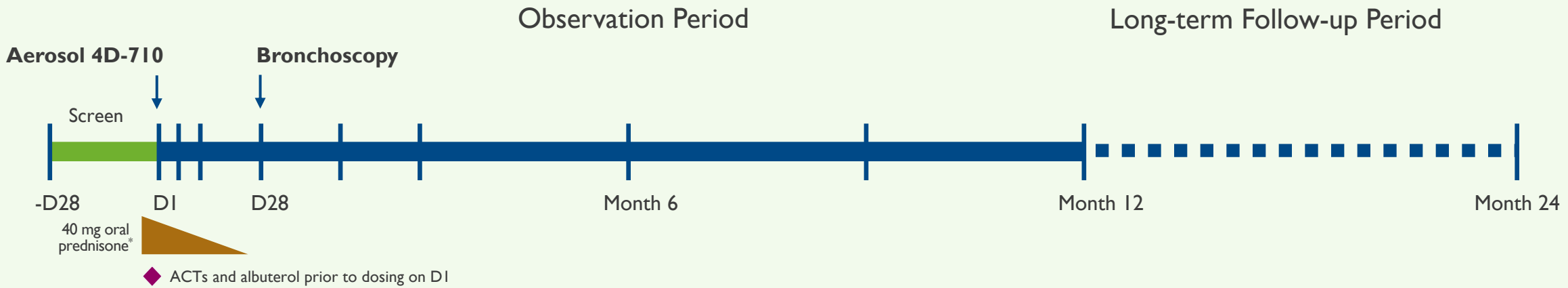


Key Inclusion Criteria

- Adults (≥18 years)
- Ineligible for CFTR modulator therapy
- ppFEV1 ≥50% and <100%
- Resting O2 sat ≥92%

Key Study Objectives

- Assess safety & tolerability
- Assess transgene delivery and expression in lung
- Assess 4D-710 clinical activity
  - Pulmonary function
  - Health-related QOL
- Identify Phase 2 dose



Vertical bars represent study clinic visits. *28-day taper (Day -1 to Day 27). ACTs, Airway Clearance Techniques; ppFEV1, percent predicted FEV_1; QOL, quality of life; SRT, Safety Review Team.

Phase 1/2 Clinical Trial: Cohort 1 Patients

BASELINE CHARACTERISTICS

Baseline Characteristic	Cohort 1 (1E15 vg dose)		
	Patient 1	Patient 2	Patient 3
Age, y	36	24	20
Sex	Male	Male	Female
CFTR modulator eligibility	Hypersensitivity	Ineligible mutation	Ineligible mutation
Historical sweat chloride, mmol/L	74	103	110
Percent predicted FEV_1 ($ppFEV_1$)	83	69	94

*As of 07 October 2022. CFTR, cystic fibrosis transmembrane conductance regulator.

4D-710 Phase 1/2 Clinical Trial: Cohort 1 Safety Summary

NO 4D-710–RELATED ADVERSE EVENTS AFTER COMPLETION OF DOSING

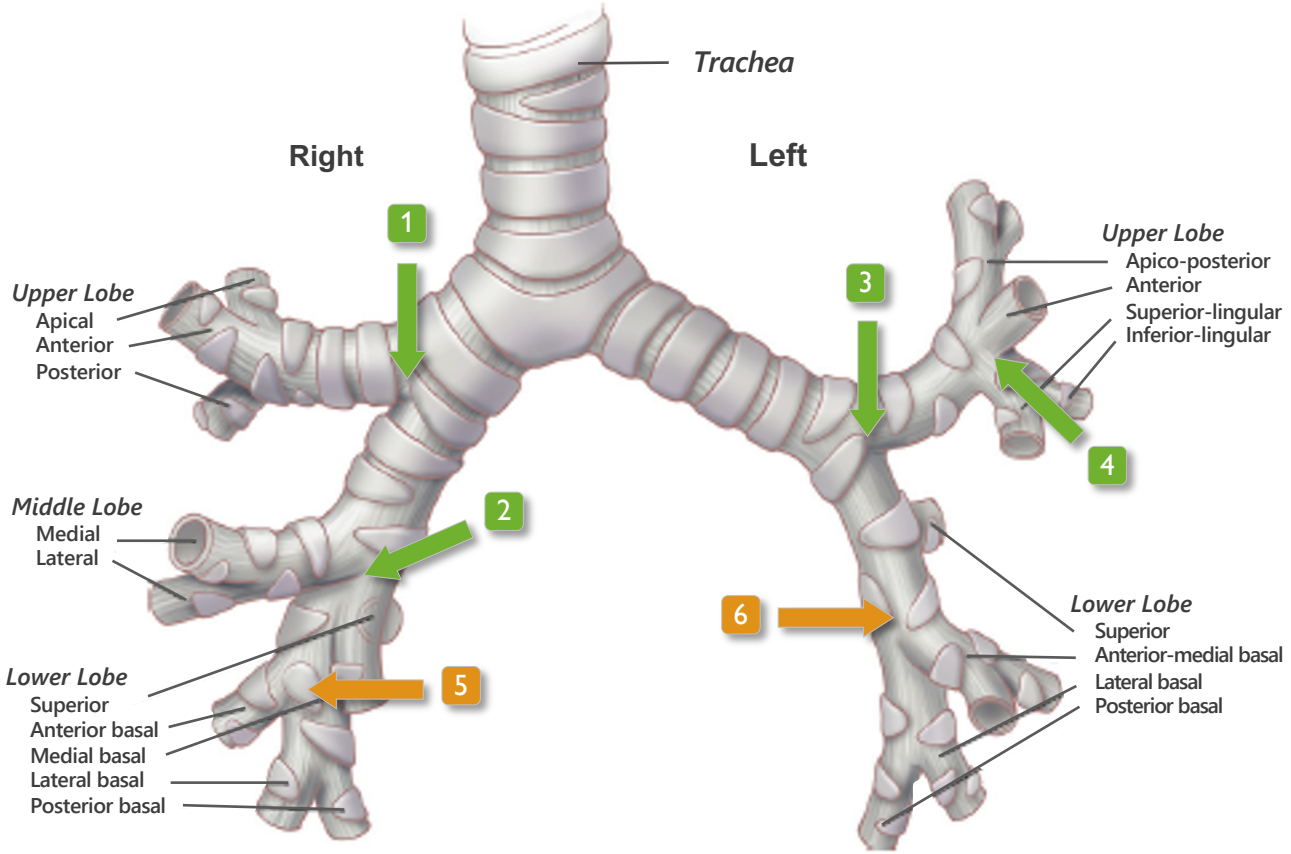
- No 4D-710–related adverse events following aerosol delivery
- During aerosol delivery: grade 1 dry mouth, fatigue (n=1)
- No 4D-710–related SAE

As of 07OCT2022.

Bronchoscopy Tissue Assessments: Transgene Delivery & Expression

BIOPSIES & BRUSHINGS PERFORMED WEEK 4 POST-DOSING*

Bronchoscopic Sampling Sites			Biomarker	
			ISH	PCR
Endobronchial biopsy				
	1	Right secondary carina		X
	2	Right middle lobe carina	X	
	3	Left secondary carina	X	
	4	Left upper lobe/lingula carina		X
Endobronchial brushing				
	5	Right lower lobe basal seg x 2	X	
	6	Left lower lobe basal seg x 2	X	



Minnich DJ, Mathisen DJ. Anatomy of the trachea, carina, and bronchi. *Thorac Surg Clin* 2007;17:571-85.

*Patient 3 bronchoscopy conducted at Week 8 due to pulmonary exacerbation (unrelated to study drug).

Summary of Delivery & Expression: 4D-710 CFTR Transgene

ENDOBRONCHIAL LUNG BIOPSIES & BRUSHINGS (WEEK 4 ASSESSMENT)

- **DNA delivery widespread (CFTR):**
  - All 3 patients positive
  - **100%** of biopsies (5 of 5) positive
- **RNA expression widespread (CFTR):**
  - All 3 patients positive
  - **100%** of endobronchial biopsies (5 of 5) positive
  - **100%** of brushings (6 of 6) positive
- **~40% of cells positive:**
  - Machine learning image analyses

As of 07OCT2022.

Widespread Transgene Delivery & Expression: Biopsies

CONSISTENT TRANSDUCTION ACROSS PATIENTS, LUNG REGIONS

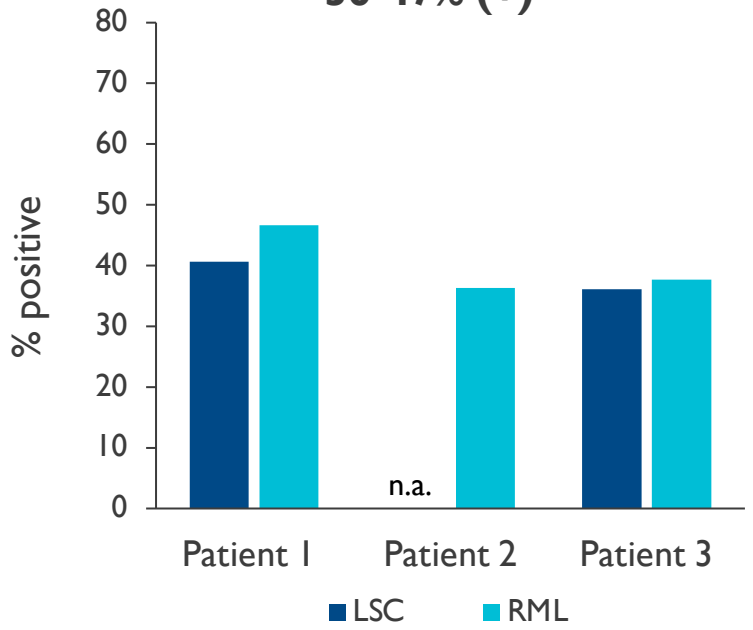
4D-710 DNA (+) Lung Biopsies

CFTRΔR DNA qPCR[1] Results
5 of 5 biopsies (+) (All 3 pts)

Patient	Left Upper Lobe/ Lingula Carina DNA	Right Secondary Carina DNA
1	**Positive**	**Positive**
2	n.a.	**Positive**
3	**Positive**	**Positive**

4D-710 RNA Expression (+) Lung Biopsies

CFTRΔR RNA ISH
% Positive Epithelial Cells[2]
36-47% (+)



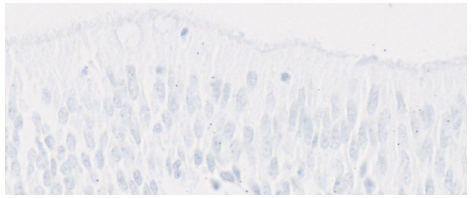
[1] qPCR assay range: 25 – 25,000,000 copies.
[2] Patient 2 LSC not sampled. Quantification by Visiopharm AI Machine Learning Analysis. SH, in situ hybridization; LSC, left secondary carina endobronchial biopsy; RML, right middle lobe endobronchial biopsy.

Widespread CFTR Expression in Lung: All 5 Biopsies (+)

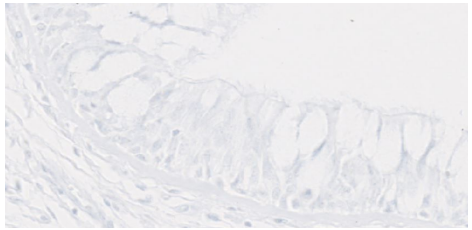
CFTRΔR RNA EXPRESSION BY ISH

Controls

DAPB ISH
(negative control probe)



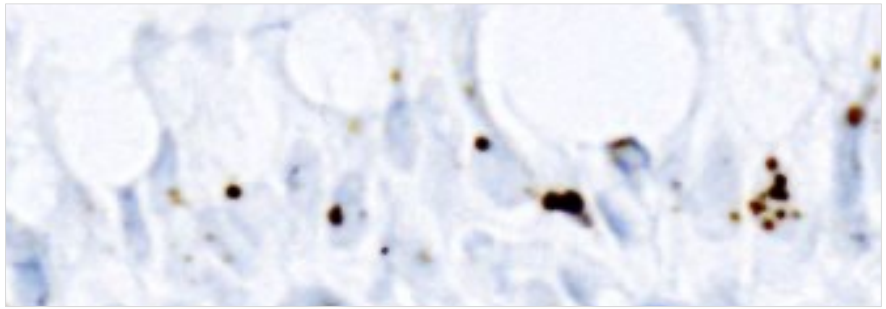
CFTRΔR ISH
Untreated lung tissue



4D-710–Treated *CFTRΔR* RNA probe*

Left Secondary Carina
Endobronchial Biopsy (40X)

Left Secondary Carina
Endobronchial Biopsy (80X)



*Representative images from Patient 1. *CFTRΔR* ISH signal observed in all evaluable biopsies from all 3 patients (Patient 2 LSC not sampled).
ISH, in situ hybridization; LSC, left secondary carina

All Major Bronchial Epithelial Cell Types Express CFTR Transgene

INDEPENDENT PATHOLOGISTS' REVIEW: *CFTRΔR* RNA ISH LOCALIZATION

Cell types expressing CFTR†

1. Basal cells
2. Goblet cells
3. Ciliated columnar cells

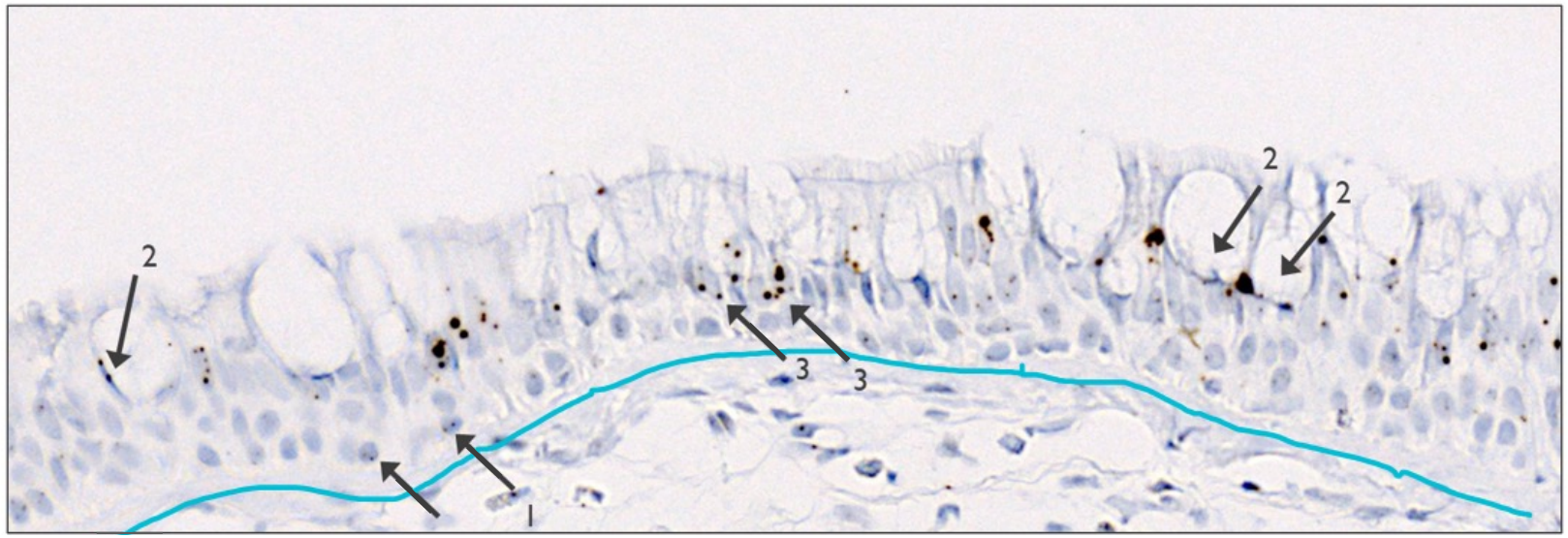


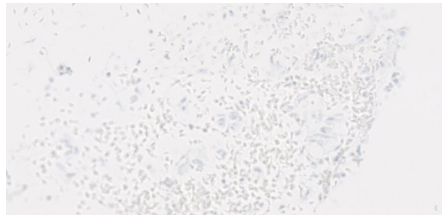
Image from Participant 1. †Assessed by 2 independent pathologists. ISH, in situ hybridization.

Widespread CFTR Expression in Lung: All 6 Brushings (+)

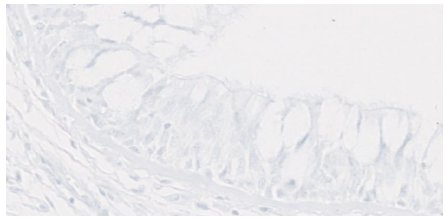
CFTRΔR RNA EXPRESSION BY ISH

Controls

DAPB ISH BRUSHING
(negative control probe)

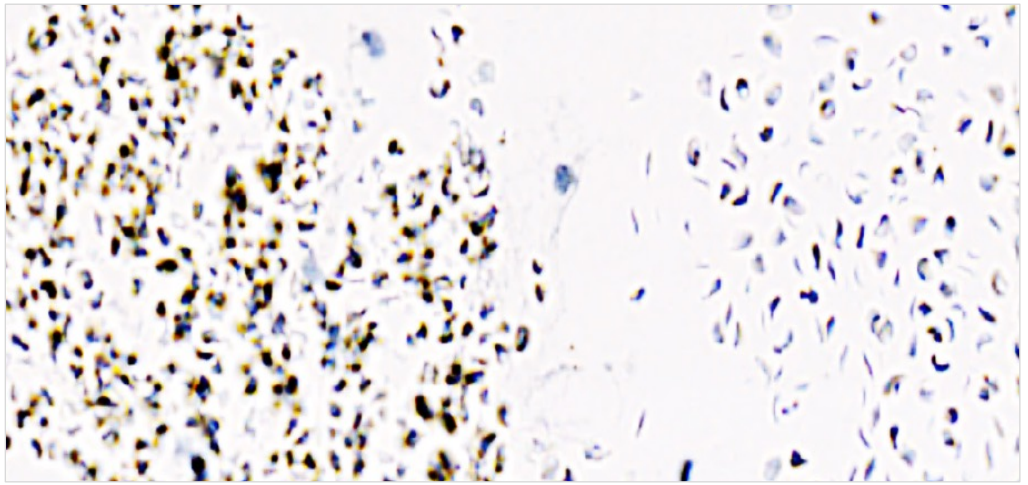


CFTRΔR ISH
Untreated lung tissue



4D-710 Treated
CFTRΔR RNA probe*

Right Lower Lobe



Left Lower Lobe

*Representative images from Patient 1. *CFTRΔR* ISH signal observed in brushings from 2/3 patients (Patient 2 brushings unevaluable). ISH, in situ hybridization.

4D-710 Clinical Data Summary, Implications & Next Steps

CLINICAL PROOF-OF-CONCEPT FOR SAFETY & WIDESPREAD TRANSGENE EXPRESSION

- **Clinical Data Summary:**
  - No 4D-710-related AEs following aerosol delivery
  - Widespread CFTR expression (All 11 lung samples)
  - ~40% of cells expressed CFTR (All major cell types)
- **Implications:**
  - Clinical proof-of-concept: 4D-710 transgene delivery & expression
  - A101 vector validation: Lung therapeutic area pipeline
  - Platform validation: Therapeutic Vector Evolution
- **Next Steps:**
  - Cohort 2 enrollment underway (2E15 vg dose); Assessment of clinical activity (e.g. ppFEV1; QoL)
  - Single agent & CFTR modulator combination development
  - Lung product pipeline: new markets tba

THANK YOU