Phase 1/2 Clinical Trial of Aerosolized 4D-710 for Treatment of Cystic Fibrosis Lung Disease

Interim Safety & Efficacy Data

June 7, 2023

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4DMT Pipeline

GROWING PULMONOLOGY THERAPEUTIC AREA WITH AEROSOLIZED A101 VECTOR

VECTOR *Delivery*	PRODUCT CANDIDATE	INDICATION	EPIDEMIOLOGY (PREVALENCE)	RESEARCH CANDIDATE	IND-ENABLING	PHASE 1 / 2	PHASE 3	PRODUCT RIGHTS
R100 *Intravitreal*	**OPHTHALMOLOGY**							
	4D-150	Wet AMD	*~3M U.S./EUMM*					4DMT
	4D-150	Diabetic Macular Edema	*~1.2M U.S.*					4DMT
	4D-125	XLRP	*~24K U.S./EUMM*					4DMT
	4D-110	CHM	*~13K U.S./EUMM*					4DMT
	4D-175	Geographic Atrophy	*~1M U.S.*					4DMT
A101 *Aerosol*	**PULMONOLOGY**							
	4D-710	**CF Lung Disease (not modulator-amenable)**	*~6K U.S.*					4DMT
	4D-710	**CF Lung Disease (modulator-amenable)**	*~34K U.S.*					4DMT
	4D-725	A1AT Deficiency Lung Disease	*~200K U.S./EUMM*					4DMT
C102 *IV*	**CARDIOLOGY**							
	4D-310*	Fabry Disease Cardiomyopathy	*~50-70K U.S./EUMM*					4DMT

*Currently on clinical hold.

Key Takeaways: Aerosol-Delivered 4D-710 Phase 1/2 Cohort 1 (1E15, n=3) Results

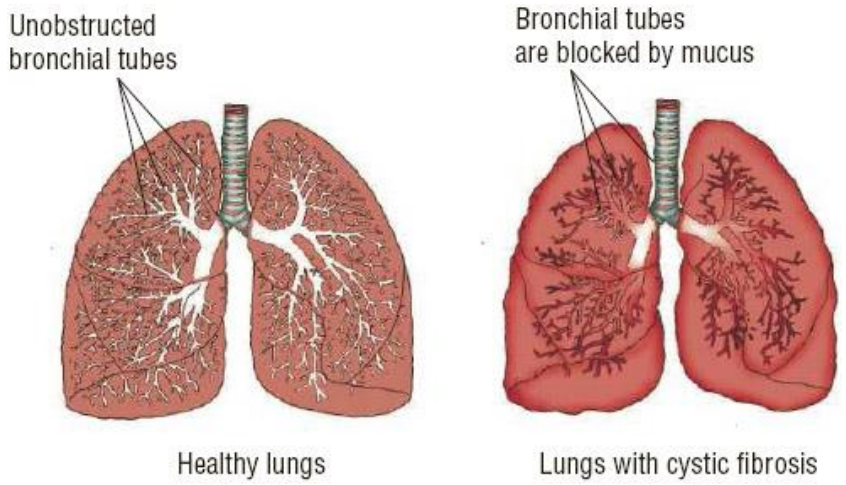
- Aerosol Delivery: **Routine & outpatient** nebulizer; **widespread** airway delivery
- CF Patient Population: **Most severe** variants; **highest** unmet need; **no** disease-modifying meds
- Safety Data (9–12 mo f/u): **Well tolerated** & no post-dosing 4D-710–related AEs
- Lung Biomarker Data (4–8 weeks):
  - **Widespread & reproducible** CFTR expression at levels **significantly above normal**
  - Pre-existing antibodies in blood: delivery & expression **feasible**
- Efficacy Data (9–12 mo f/u):
  - Moderate impairment in baseline $ppFEV_1$ (n=1): **clinically meaningful improvement**
  - Normal or mildly impaired baseline $ppFEV_1$: **maintained stable**
  - QoL (CFQ-R-Respiratory): clinically meaningful **improvement in all 3 participants**; **6 of 7** timepoints

CFTR, cystic fibrosis transmembrane conductance regulator; $ppFEV_1$, percent of predicted forced expiratory volume in 1 second; AE, adverse advent; QoL, Quality of Life; CFQ-R-Respiratory, respiratory domain of the Cystic Fibrosis Questionnaire–revised.

Cystic Fibrosis Lung Disease Market Background & Market Size

Disease Burden

- **Dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR) protein** → inability to transport chloride at the apical membrane → thickened mucus
- **Lung disease:** inflammation, infections, respiratory failure



Epidemiology

- **~105,000[1] prevalence WW:**
  - ~40,000 prevalence in U.S. alone
  - ~1,000 incidence in U.S. alone

Standard of Care

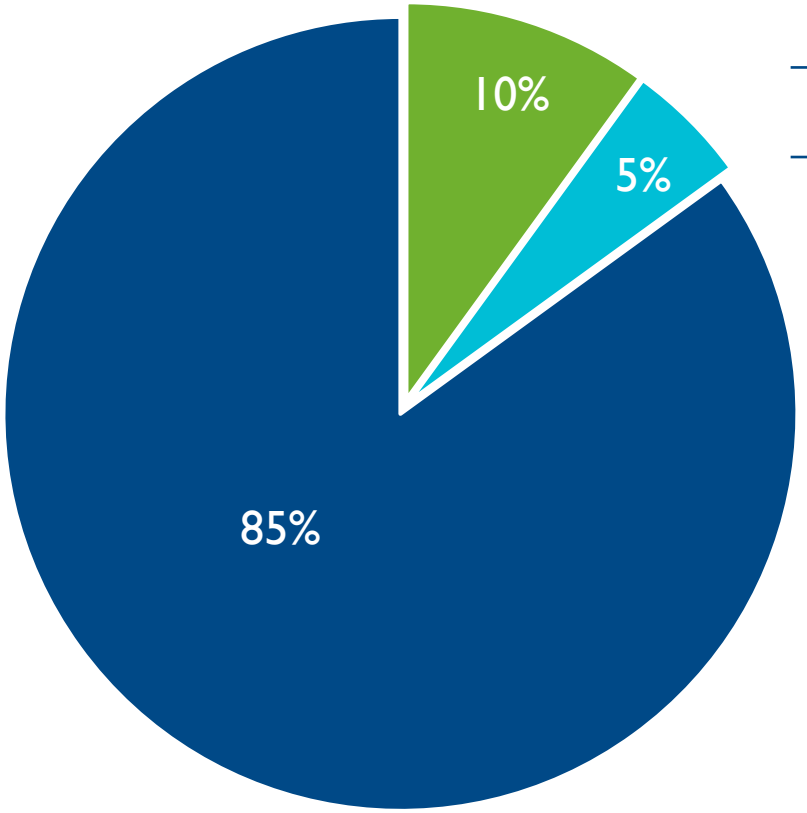
- **Daily Supportive Care:**
  - Airway clearance (~100 mins)
  - Inhaled antibiotics & bronchodilators
- **Disease modifying CFTR modulators**
  - **$8.9 billion** annually (2022)[2]

Illustration by Frank Forney. © 2016 Cengage Learning 1. Guo, J. et al. *Journal of Cystic Fibrosis* 2022, 21, 456-462 and Cystic Fibrosis Foundation. 2. Vertex Pharmaceuticals FY 2022 financial results. CFTR, cystic fibrosis transmembrane conductance regulator.

4D-710: Mutation Agnostic Therapy for CF Lung Disease

POTENTIAL TO TREAT CYSTIC FIBROSIS LUNG DISEASE REGARDLESS OF VARIANT

Cystic Fibrosis Population



- Modulator ineligible
- Modulator intolerant

AEROW study population

- Modulator eligible

Potentially treatable population

CFTR Modulators: Notable Adverse Events

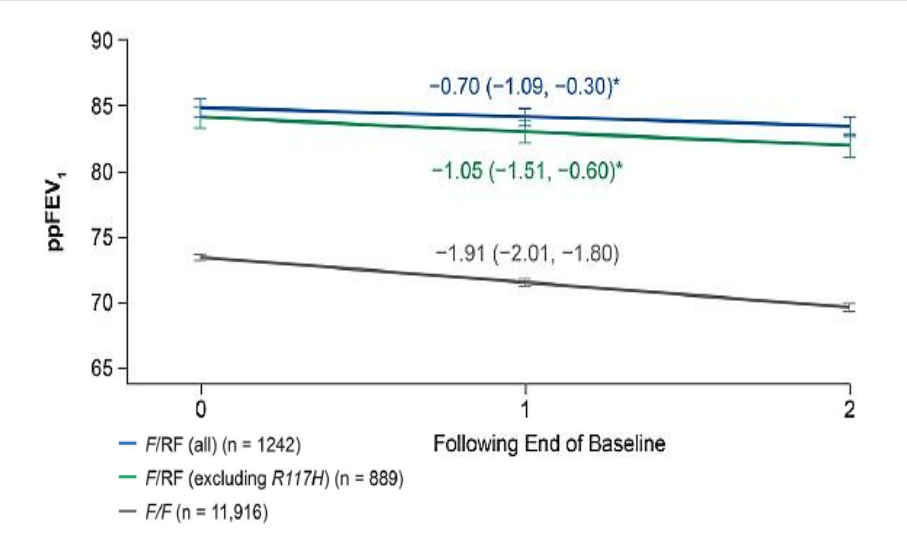
- Hypersensitivity (rash, swelling, itching)[1,2]
- Neuropsychiatric (depression, anxiety, brain fog, insomnia)[3]

1. De Boeck et al. *Lancet Resp Med* 2016. 2. Hubert D et al, *Cyst Fibros* 2017. 3. Zhang L et al. *Ther Adv Respir Dis* 2022.

$ppFEV_1$ Decline Correlates with Variant & Modulator Treatment Status

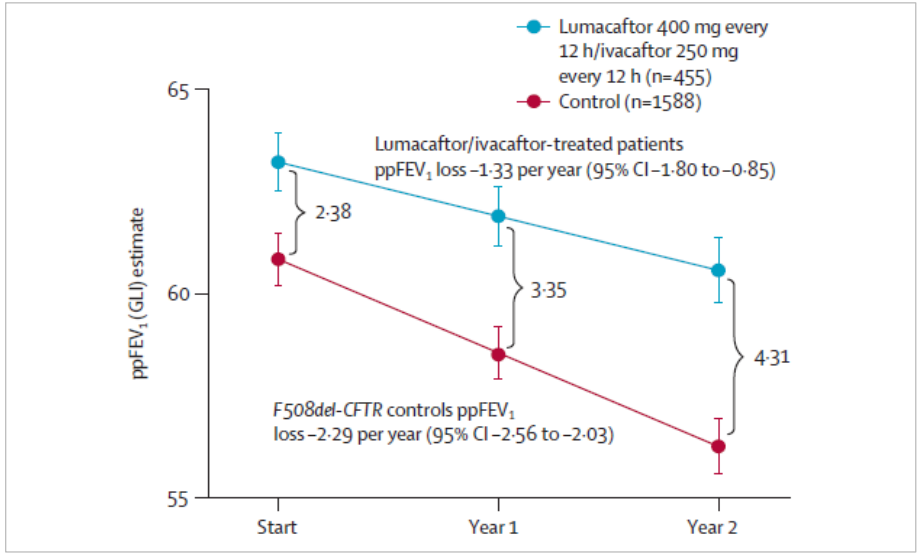
DECLINE ~75% MORE RAPID FOR SUBJECTS WITH SEVERE CFTR VARIANTS

Minimal Function Variants Associated with More Rapid Decline[1]



CFTR modulator-untreated homozygous ΔF508 (*F/F*) associated with **steeper rate of decline** compared to residual function (RF) mutations

Rapid Decline in Untreated Patients Compared to Modulator Treated[2]



CFTR modulator-untreated ΔF508 individuals exhibit a more rapid decline in $ppFEV_1$ than modulator-treated patients:

-2.3/yr vs. -1.3/yr

1. Sawicki GS et al. *Pulm Ther* 2022. 2. Konstan et al. *Lancet Respir Med* 2017.

Limitations with Conventional AAV: Prior CF Lung Gene Therapy

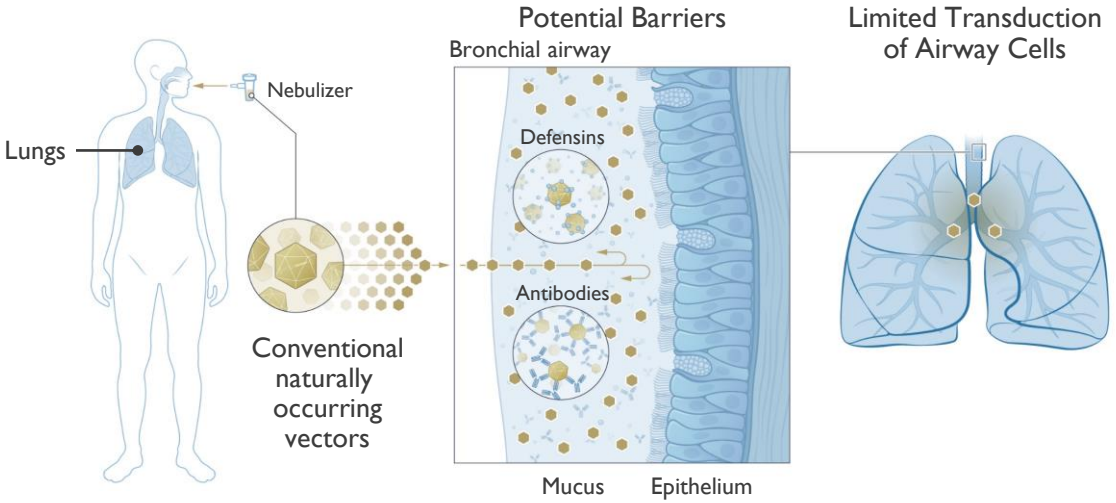
PRIOR GENE THERAPY APPROACHES FAILED, INCLUDING WITH AAV2-BASED TGAAVCF

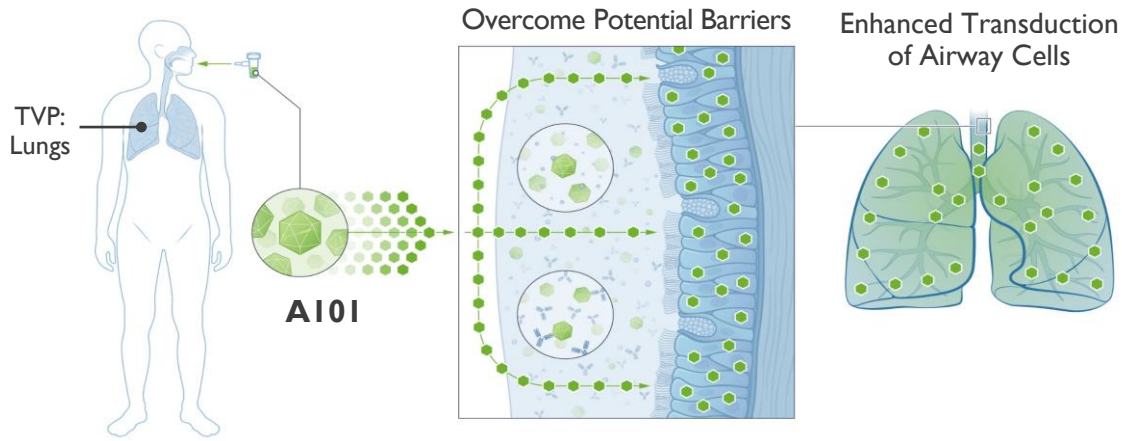
- **Prior AAV Gene Therapy Study Design**[1,2]
  - AAV2-based CFTR gene therapy (tgAAVCF)
  - Randomized Phase 2 trial (n=51)
  - Aerosol administration on days 1 & 30
- **Clinical Data Takeaways**
  - Safe & well tolerated
  - Expression of CFTR transgene in lung was not reported
  - No FEV_1 benefit
- **Effective AAV vector needed**

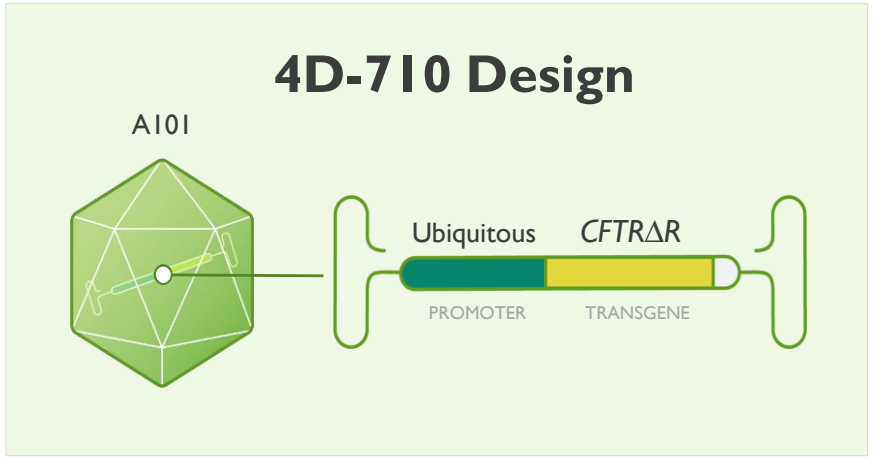
1. Moss RB et al. *Chest* 2004;125:509-21. 2. Moss RB et al. *Hum Gene Ther* 2007;18:726-32.

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

A101 TARGET VECTOR PROFILE & 4D-710 PRODUCT DESIGN







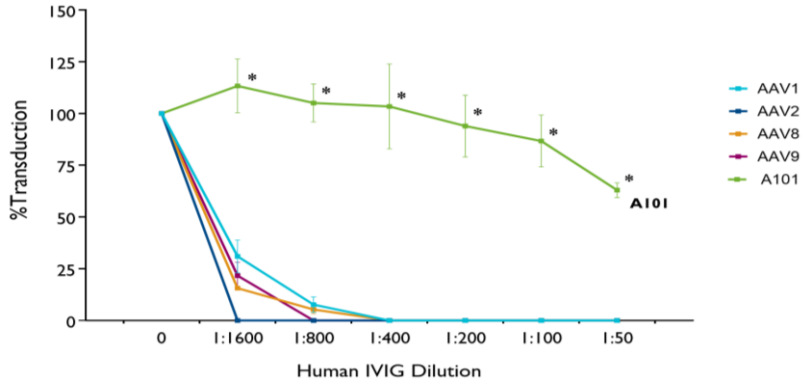
A101 KEY ATTRIBUTES

- Mucus penetration efficient
- Transgene expression efficient
- Transduction of multiple airway cell types
- Specificity for lung (>99.9%)
- Resistance to pre-existing human AAV antibodies

4D-710 Characterization in Primates (NHP) & Human IVIG

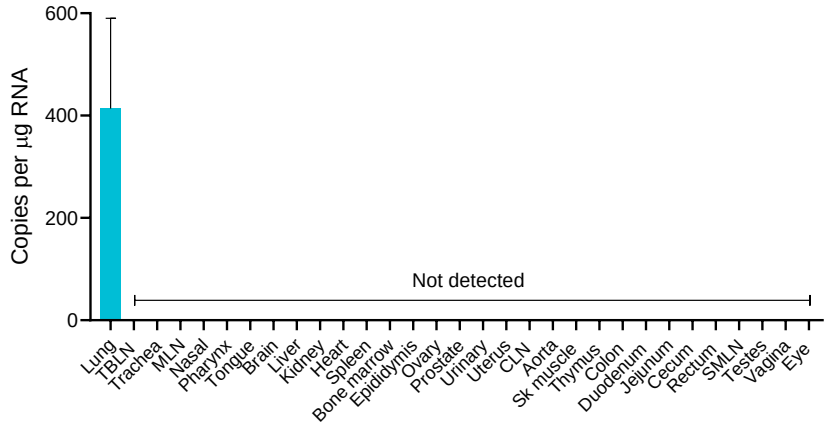
A101 VECTOR RESISTANCE TO HUMAN IVIG; WIDESPREAD 4D-710 DISTRIBUTION & CFTRΔR EXPRESSION IN NHP AIRWAYS

Human Antibody Resistance: IVIG



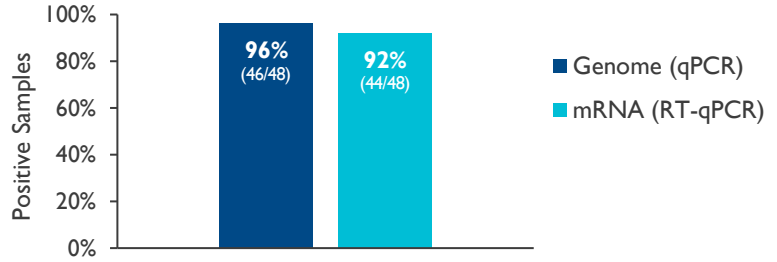
Human Hek2v6.11 cells. *p<0.05.

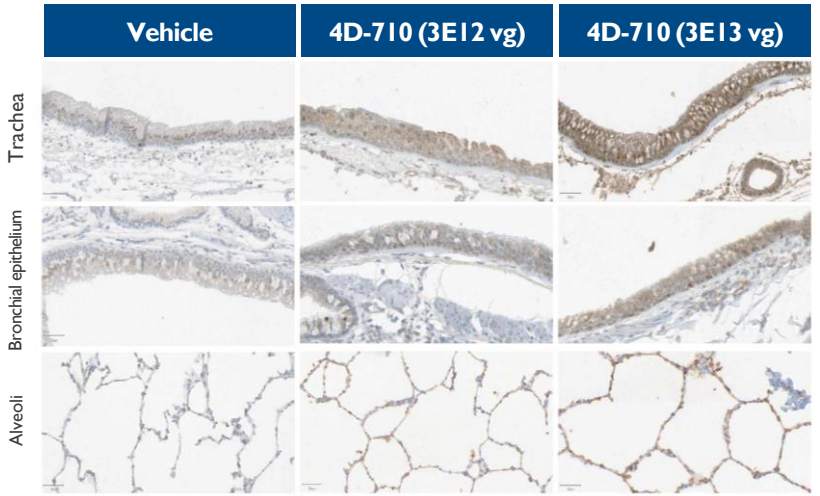
Lung-Specific *CFTRΔR* Expression in NHP



Delivery and Transduction: Aerosol NHP

4D-710 Biodistribution in NHP Lung (n=3 NHP; 48 samples)





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

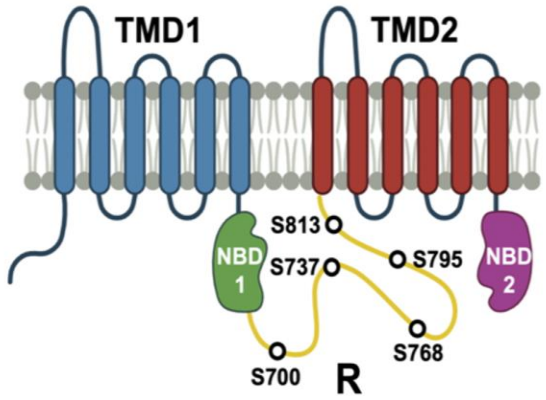
Calton M. American Thoracic Society International Conference, May 14-19, 2021. Abbreviations: NHP, nonhuman primate.

4D-710 *CFTR* Transgene Payload: Normal Function & Regulation

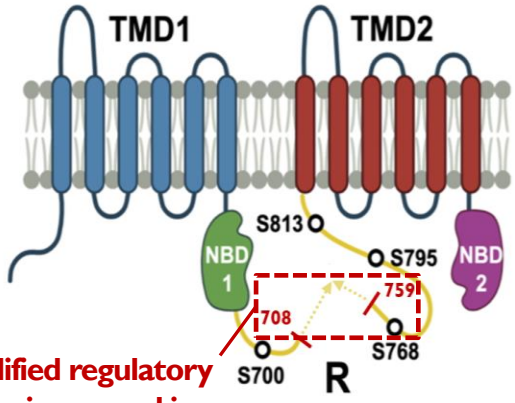
CFTRΔR STRUCTURE & FUNCTION

- Human *CFTR* gene, partial deletion in the regulatory domain (*CFTRΔR; Δ708–759*)
  - 4/5 serine residues remain
  - Normal ion channel structure & function
- *CFTRΔR* transgene protein product function demonstrated in multiple *in vitro* & *in vivo* models
  - **CF patient-derived ALI**: Function comparable to wild-type CFTR[1]
  - **CF mice**: Corrected nasal epithelium voltage defect[1]
  - **CF pig model aerosol delivery**: CFTR protein expression & corrected multiple phenotypes[2]

Wild-type CFTR



CFTRΔR$_{708–759}$



Modified regulatory domain, normal ion channel

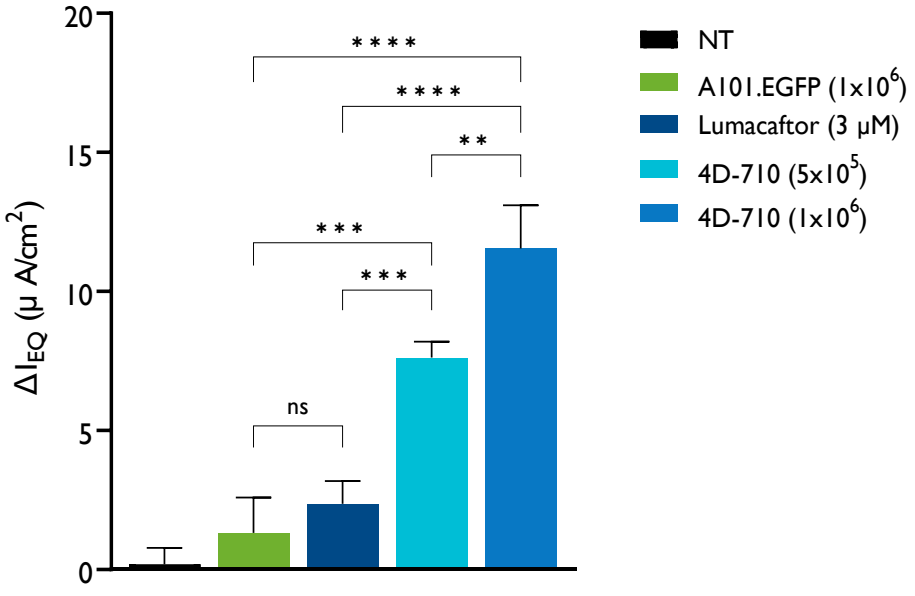
Adapted from Infield et al. *J Gen Physiol* 2023;155(4):e202213216.

1. Ostedgaard et al. PNAS 2002;99:3093-8. 2. Steines et al. *JCI Insight* 2016;1:e88728. ALI, air-liquid interface; CFTR, cystic fibrosis transmembrane conductance regulator; TMD, transmembrane domain.

CFTR Function Assays: 4D-710 Function Equivalent to Trikafta

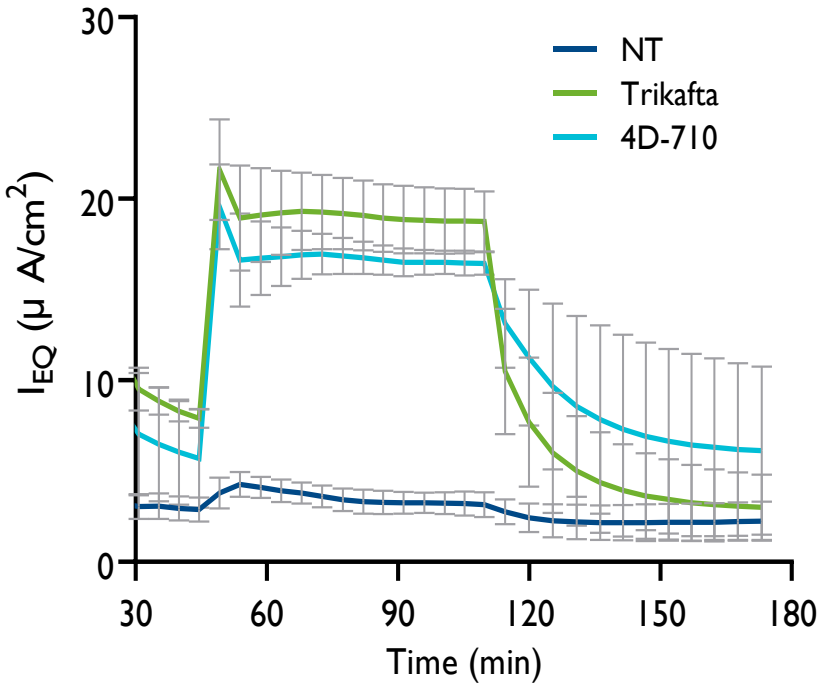
DOSE-RELATED 4D-710–MEDIATED CFTR FUNCTION; REGULATION PATTERN AS EXPECTED

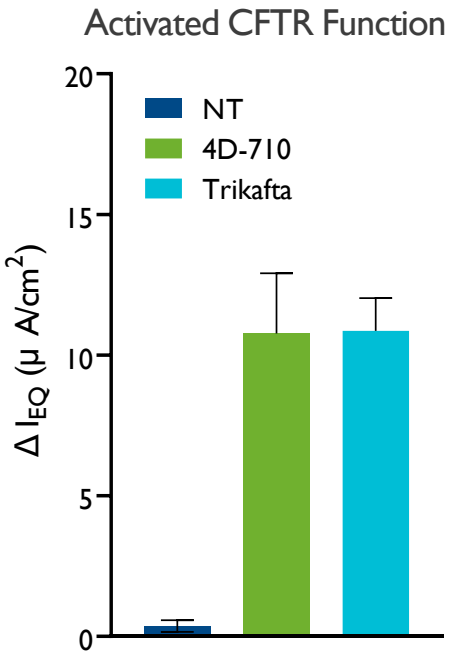
Dose-dependent CFTR Activity > Lumacaftor*



**p<0.01; ***p<0.001; ****p<0.0001.

4D-710 CFTR Function = Trikafta†



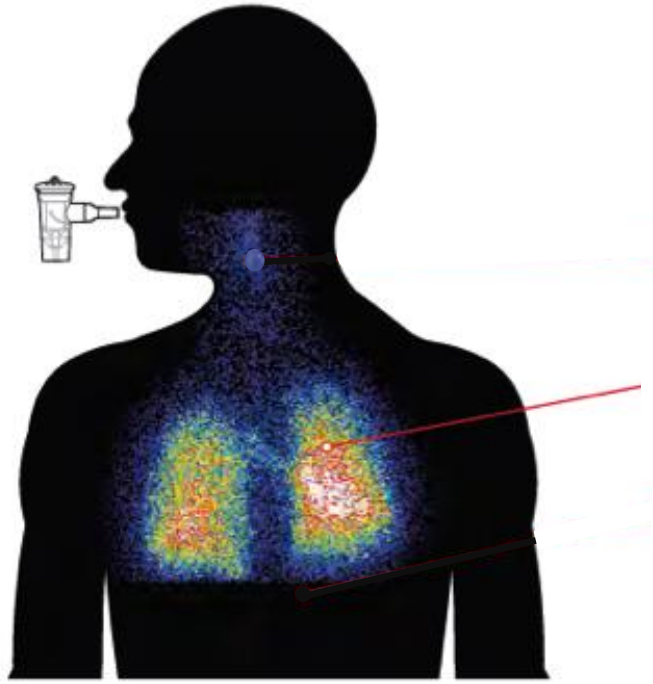


*Activated CFTR function in CF *ΔF508* ALI airway epithelial cultures (n=3 different experiments). †CFTR activity in CF *ΔF508* ALI airway epithelial cultures transduced with 4D-710 (1x10⁶) or Trikafta (2 μM VX-445, 3 μM VX-661, 0.1 μM VX-770); n=3 different experiments; error bars, ±SD. ALI, air-liquid interface; CFTR, cystic fibrosis transmembrane conductance regulator; EGFP, enhanced green fluorescent protein; NT, not treated.

4D-710 Delivery via Routine Aerosolization: AeroEclipse® II Device

APPROVED DEVICE PERFORMANCE ASSESSMENT INCORPORATED EARLY IN 4D-710 DEVELOPMENT

- 4D-710 developed for aerosol delivery
- Commercially available breath-actuated jet nebulizer (AeroEclipse® II):
  - Reproducible particle sizes in respirable range (≤5μm)[1]
  - No product shearing
- Used in preclinical & clinical studies
- Drug–device compatibility & airway delivery confirmed



AeroEclipse® II
Breath-actuated nebulizer

Aerosolized particles delivered to lungs

1. Data on file, 4DMT.

Aerosolized 4D-710 in Patients with Cystic Fibrosis Lung Disease Not Amenable to Modulators

Phase 1/2 Clinical Trial Design & Baseline Characteristics

AEROW

4D-710 Phase I/2 AEROW Clinical Trial Design

STUDY OBJECTIVES & ELIGIBILITY CRITERIA

Study Objectives

- Evaluate a single aerosol dose of 4D-710 (1E15 or 2E15 vg)
  - Safety, tolerability & immunogenicity
  - Transduction & transgene expression in lung (bronchoscopy samples)
  - Impact on pulmonary function ($ppFEV_1$)
  - Impact on CF lung-related QoL (CFQ-R-R)
- Identify recommended Phase 2 dose

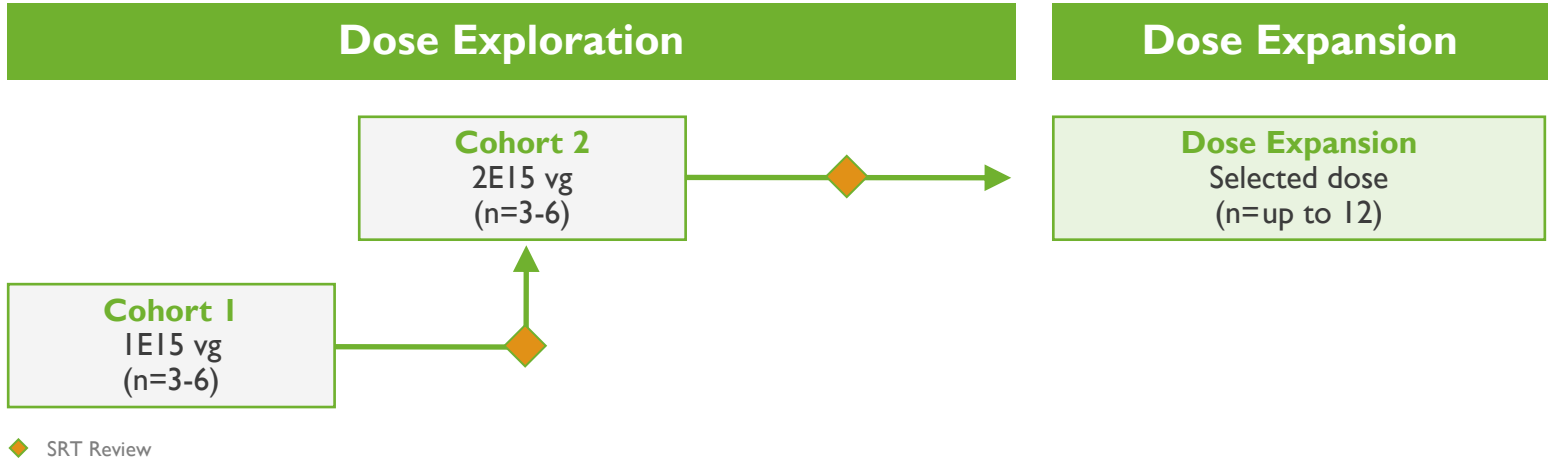
Key Inclusion Criteria

- Confirmed diagnosis: CF lung disease
- Ineligible for CFTR modulator therapy (per USPI) OR discontinued due to adverse effects
- % predicted FEV_1 ≥50% and ≤100%
- Resting O_2 sat ≥92% on room air
- Age ≥18 years

CFTR, cystic fibrosis transmembrane conductance regulator; $ppFEV_1$, forced expiratory volume in 1 second; QoL, Quality of Life; CFQ-R-R, respiratory domain of the Cystic Fibrosis Questionnaire–revised. USPI, U.S. prescribing information.

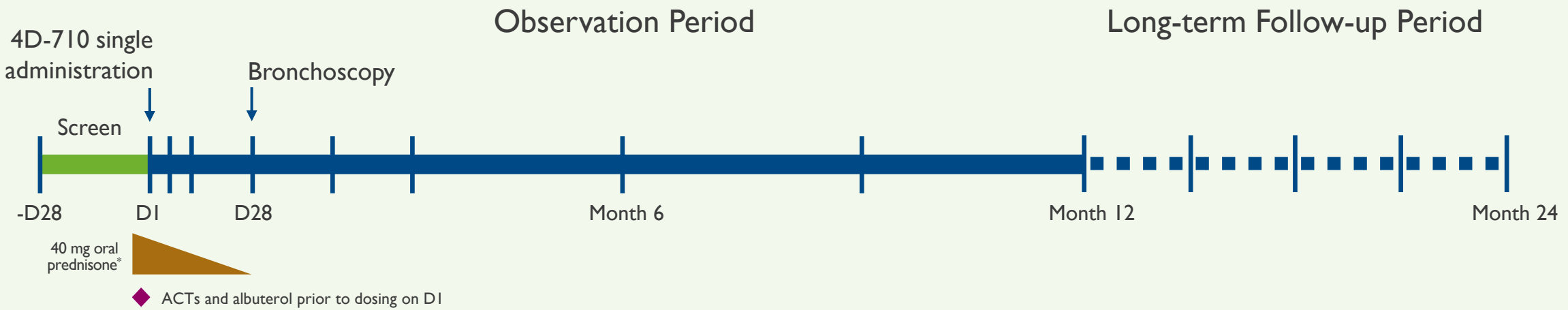
4D-710 Phase 1/2 AEROW Clinical Trial Study Design

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



4D-710 Administration

- Pre-dose procedures (Day 1):
  - Airway clearance technique
  - Aerosol bronchodilator (albuterol)
  - Pre- & post-bronchodilator spirometry
- 4D-710 administered via AeroEclipse® II breath-actuated nebulizer



Vertical bars represent study clinic visits. *28-day taper (Day -1 to Day 27). ACTs, Airway Clearance Techniques; SRT, Safety Review Team.

Phase 1/2 AEROW Clinical Trial: Cohort 1

BASELINE CHARACTERISTICS

Characteristic	Cohort 1 (1E15 vg)		
	Participant 1	Participant 2	Participant 3
Age, y	36	24	20
Sex	Male	Male	Female
Race/ethnicity	Non-Hispanic white	Non-Hispanic white	Non-Hispanic white
CFTR modulator eligibility	**Tolerability**	**Ineligible variant**	**Ineligible variant**
CFTR variant (class)	II/V	I/I* (minimal function)	I/II (minimal function)
Historical sweat chloride, mmol/L	74 (High)	103 (High)	110 (High)
Percent predicted FEV_1	**83 (Mild)**	**69 (Moderate)**	**95 (Normal)**
Pre-dose NAb titer to A101 capsid†	Low	Negative	Moderate
Pre-dose anti-capsid antibody titer†	Low	Negative	Moderate

*Large gene deletion projected to result in a null variant profile. †Nab and antibody titer categories defined as negative (0), low (1:1–1:999), moderate (1:1000–1:14,999,) and high (≥1:15,000).
Sweat chloride normal range ≤29 mmol/L, *Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation* (2017). CFTR, cystic fibrosis transmembrane conductance regulator; NAb, neutralizing antibodies.

Aerosolized 4D-710 in Patients with Cystic Fibrosis Lung Disease Not Amenable to Modulators

Phase 1/2 Clinical Trial: Safety & Tolerability

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Interim Safety Summary: Cohort 1 Participants (9–12 Months)

WELL TOLERATED WITH NO 4D-710–RELATED ADVERSE EVENTS POST DOSING

- No dose-limiting toxicities
- No 4D-710–related serious adverse events
- **No 4D-710–related adverse events after dosing**
- Dosing procedure well tolerated:
  - No decrease in FEV_1
  - Single episode of mild dry throat

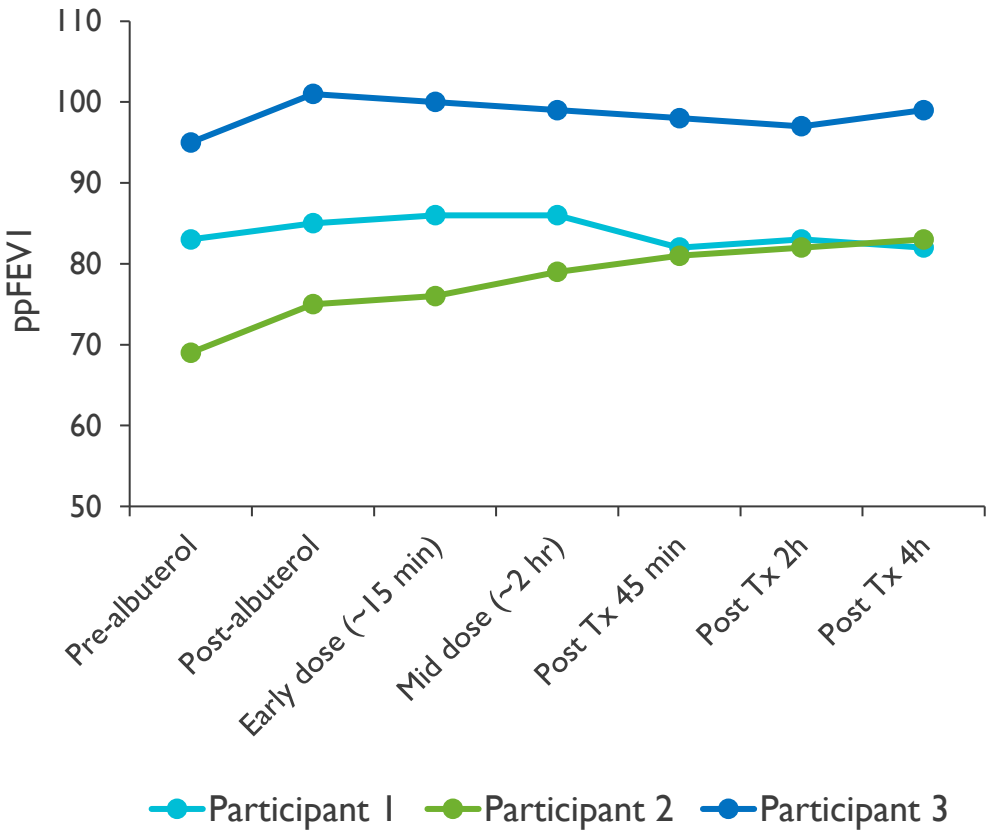
Data cutoff date, April 12, 2023.

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

SERIAL SPIROMETRY & ADVERSE EVENTS DURING NEBULIZATION OF 4D-710

- Full dose administered (1E15 vg)
- No significant AEs
- No bronchospasm
- Participant 1: mild, self-limited dry throat during nebulized dosing

Serial Spirometry During 4D-710 Dosing: Through 4 Hours Post Nebulization

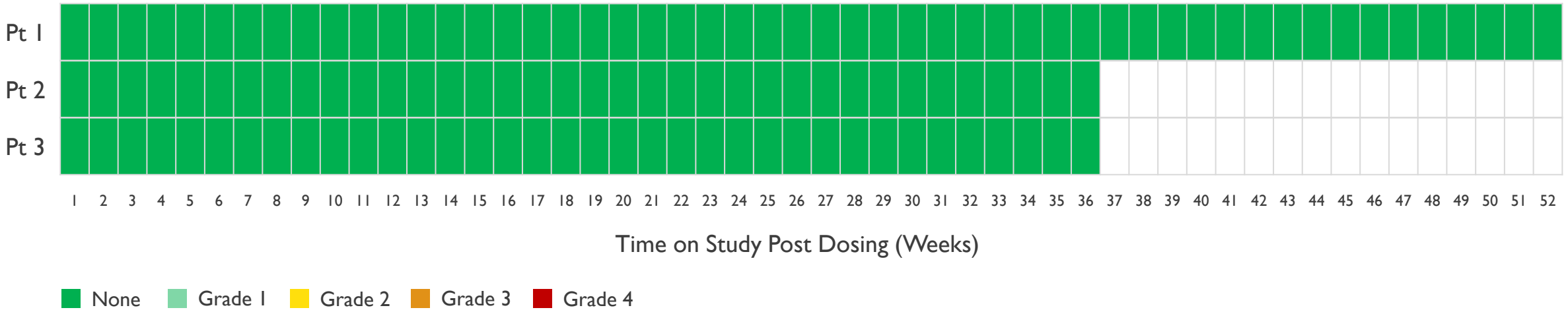


AE, adverse event; $ppFEV_1$, percent predicted forced expiratory volume in 1 second.

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

NO 4D-710–RELATED ADVERSE EVENTS UP TO 12 MONTHS AFTER COMPLETION OF DOSING

4D-710–Related Adverse Events



- **No 4D-710–related adverse events**
- No 4D-710–related serious adverse events
- No dose-limiting toxicities

Duration of Cohort 1 safety follow-up as of 12 April 2023: 12 months (Participant 1), 9 months (Participants 2 and 3).

Aerosolized 4D-710 in Patients with Cystic Fibrosis Lung Disease Not Amenable to Modulators

Phase 1/2 Clinical Trial: Lung Biomarkers

AEROW

Aerosol 4D-710: CFTR Target Transgene Expression Profile

CFTR Function & Disease Severity

- ≥10% correction in *in vitro* monolayer corrects mucus layer[1]
- ≥15% residual CFTR function in CF subjects correlated with less severe disease[2]

4D-710 Target Expression Profile:

Reproducible, consistent distribution & transgene expression in airways

- Widespread & consistent distribution throughout airways
- Reproducibility between individuals
- All major epithelial cell types (including basal cells & secretory cells)
- Robust expression regardless of pre-treatment antibody titers
- ≥15% cells transduced
- CFTR protein expression ≥ observed normal levels

1. Dannhoffer et al. *Am J Respir Cell Mol Biol* 2009;40:717–23. 2. Bell et al. *Lancet Resp Med* 2020;8:65–124.

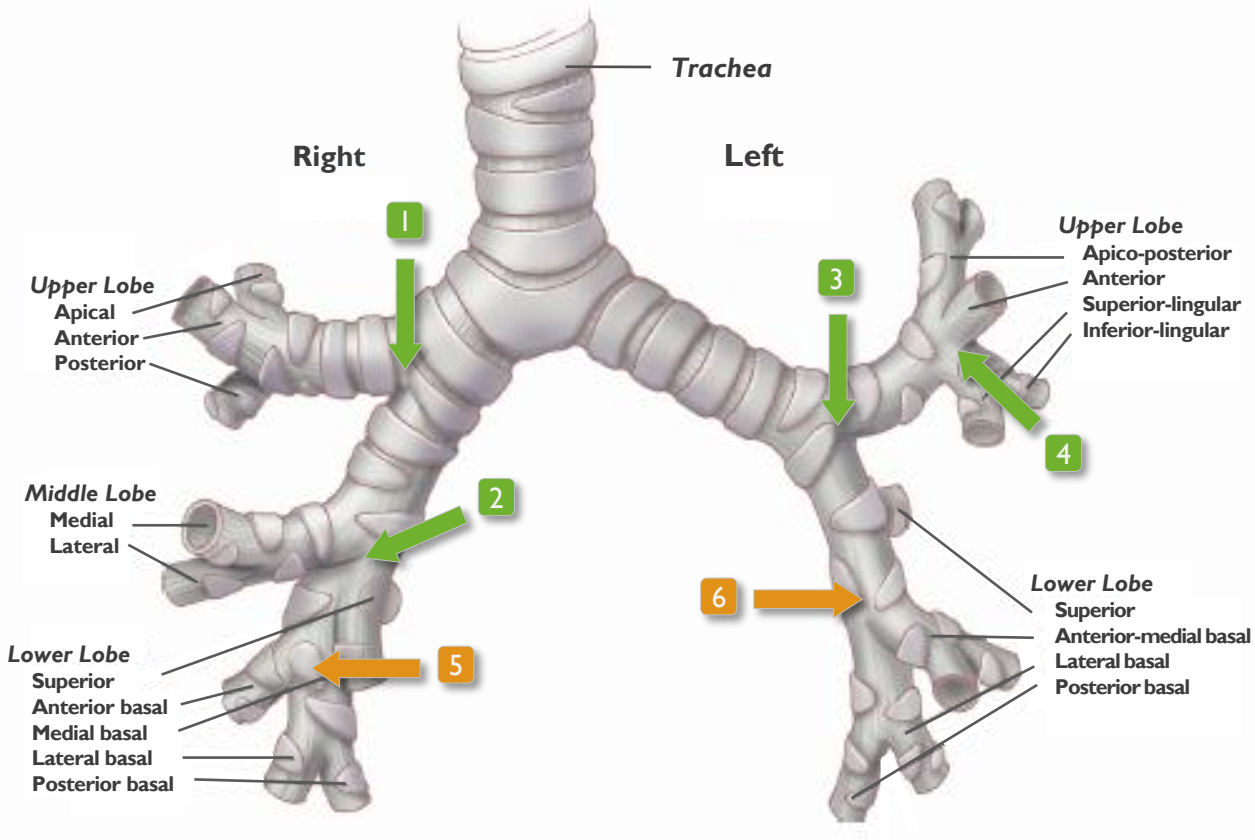
4D-710 Phase 1/2 Clinical Trial: Bronchoscopy Sampling Plan

BIOPSIES & BRUSHINGS IN MULTIPLE LUNG LOBES BILATERALLY FOR DNA, RNA & PROTEIN

Bronchoscopy: Week 4–8*

Bronchoscopic Sampling Sites			Biomarker	
			RNA† Protein‡	DNA¶
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	

*Participant 3 bronchoscopy conducted at Week 8 due to pulmonary exacerbation (unrelated to study drug).
†Assessed by in situ hybridization. ‡Assessed by immunohistochemistry. ¶Assessed by quantitative PCR.



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

Widespread Transgene Delivery & RNA Expression: Cohort 1

CONSISTENT TRANSDUCTION ACROSS PARTICIPANTS & LUNG REGIONS; ML-GUIDED IMAGE ANALYSES

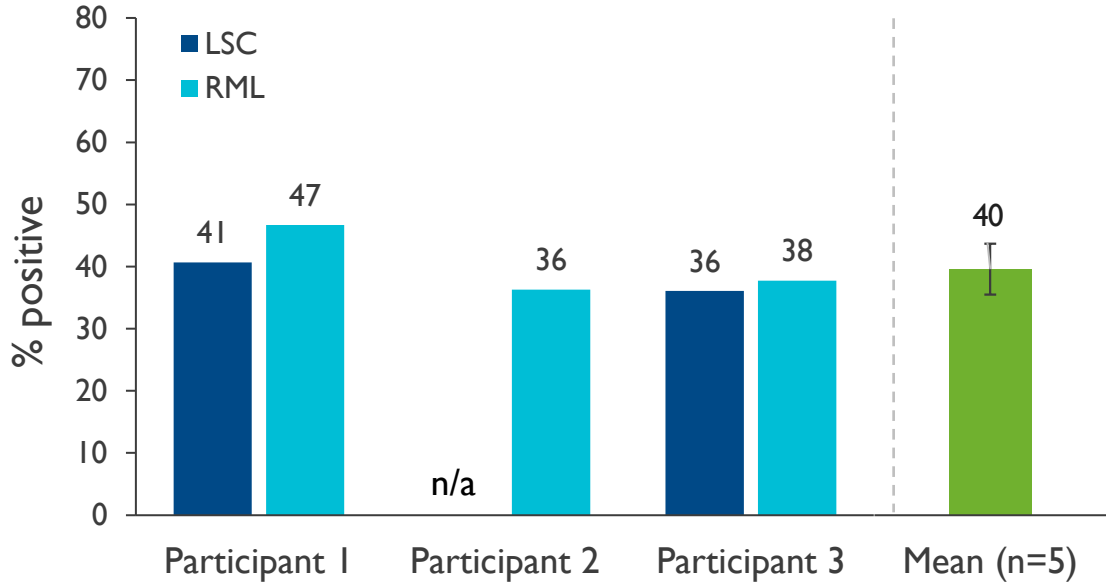
4D-710 DNA (+) Lung Biopsies

CFTRΔR DNA qPCR*
5 of 5 biopsies (+)
All 3 participants

Participant	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

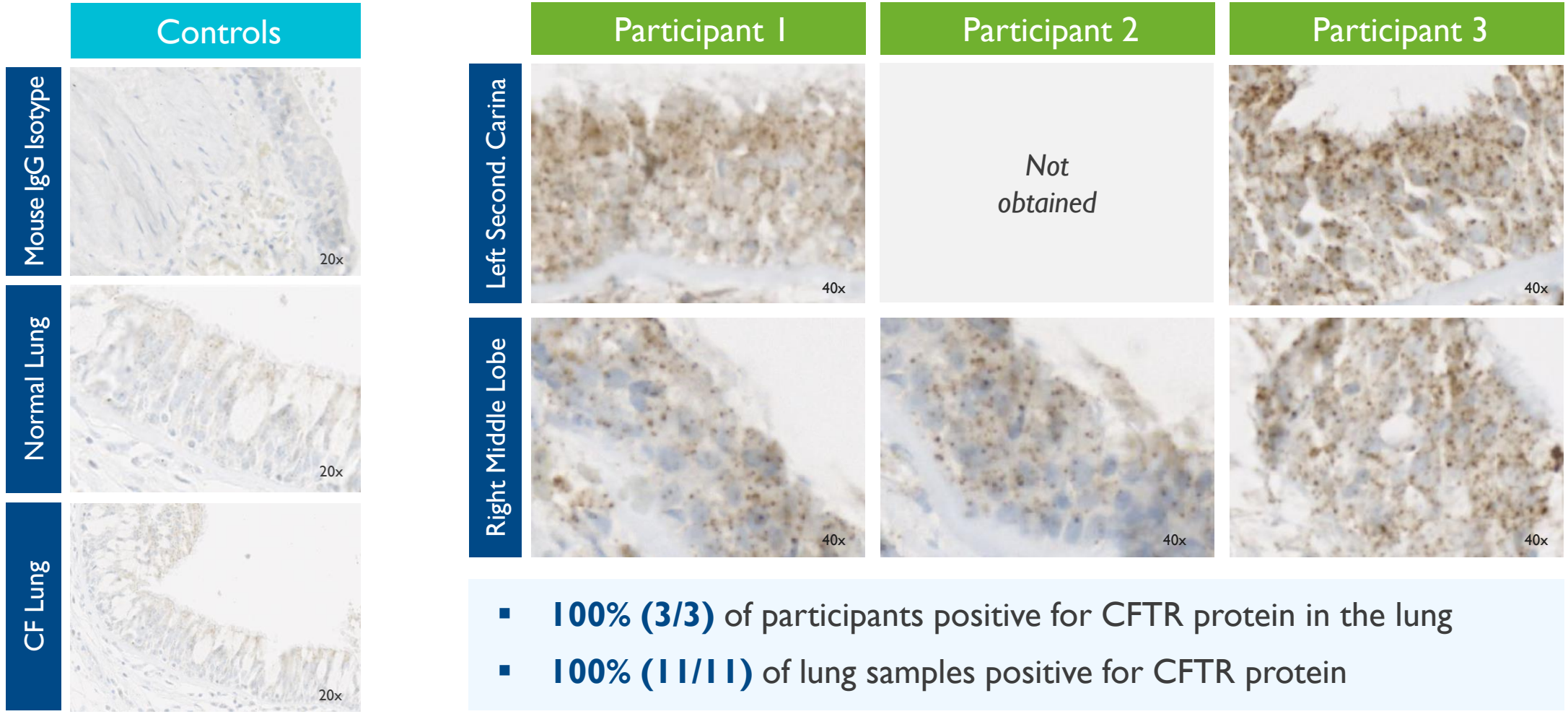
CFTRΔR RNA ISH
% Positive Epithelial Cells†
36–47% (+)



qPCR assay range: 25 – 25,000,000 copies.
†Participant 2 LSC not sampled. Quantification by Visiopharm AI Machine Learning Analysis. ISH, *in situ* hybridization; LSC, left secondary carina endobronchial biopsy; ML, machine learning; RML, right middle lobe endobronchial biopsy.

Widespread CFTR Protein Expression in Airways After 4D-710

CFTR PROTEIN EXPRESSION BY IHC 4–8 WEEKS AFTER 4D-710 DOSING



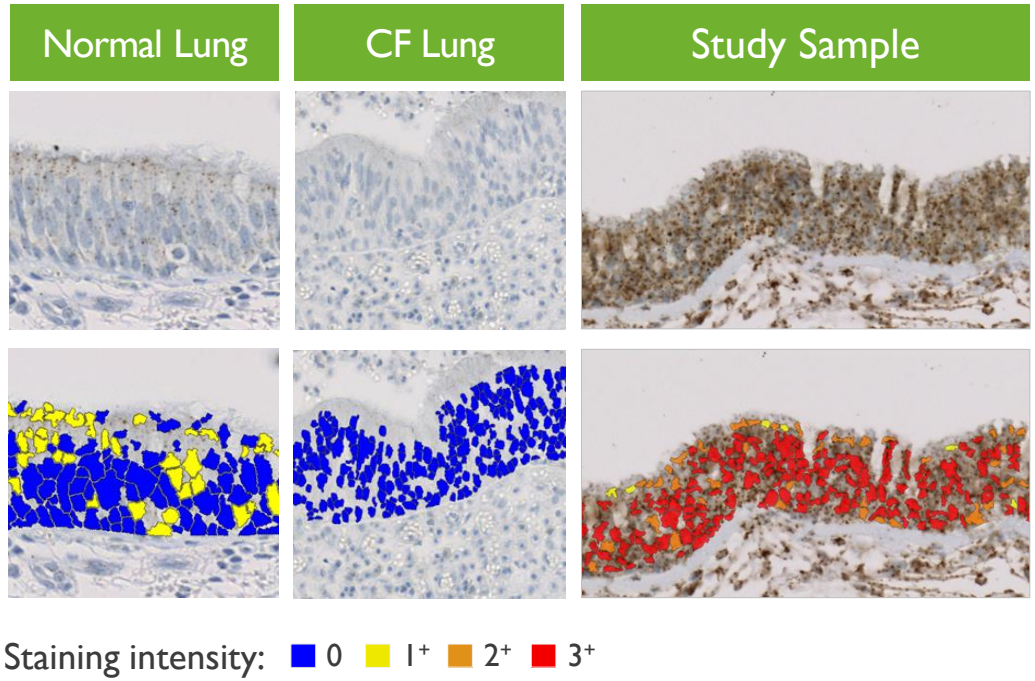
- **100% (3/3)** of participants positive for CFTR protein in the lung
- **100% (11/11)** of lung samples positive for CFTR protein

*Endobronchial biopsy samples collected at Week 4 (Participants 1 and 2) or Week 8 (Participant 3). CFTR, cystic fibrosis transmembrane conductance regulator; IHC, immunohistochemistry.

CFTR Protein IHC: Machine Learning Assisted Analytic Methods

QUALITATIVE & QUANTITATIVE ANALYSES

- **Immunohistochemistry (IHC):**
  - Tissue samples tested for CFTR protein
  - Control: normal lung (n=7) and CF lung (n=10)
- **Quantitative Analyses: % Cells (+) & Intensity**
  - Visiopharm® machine learning image analysis
  - Cell evaluation: 1^+, 2^+, 3^+ based on CFTR IHC signal intensity
  - H-score (range, 0–300): intensity & % cells staining

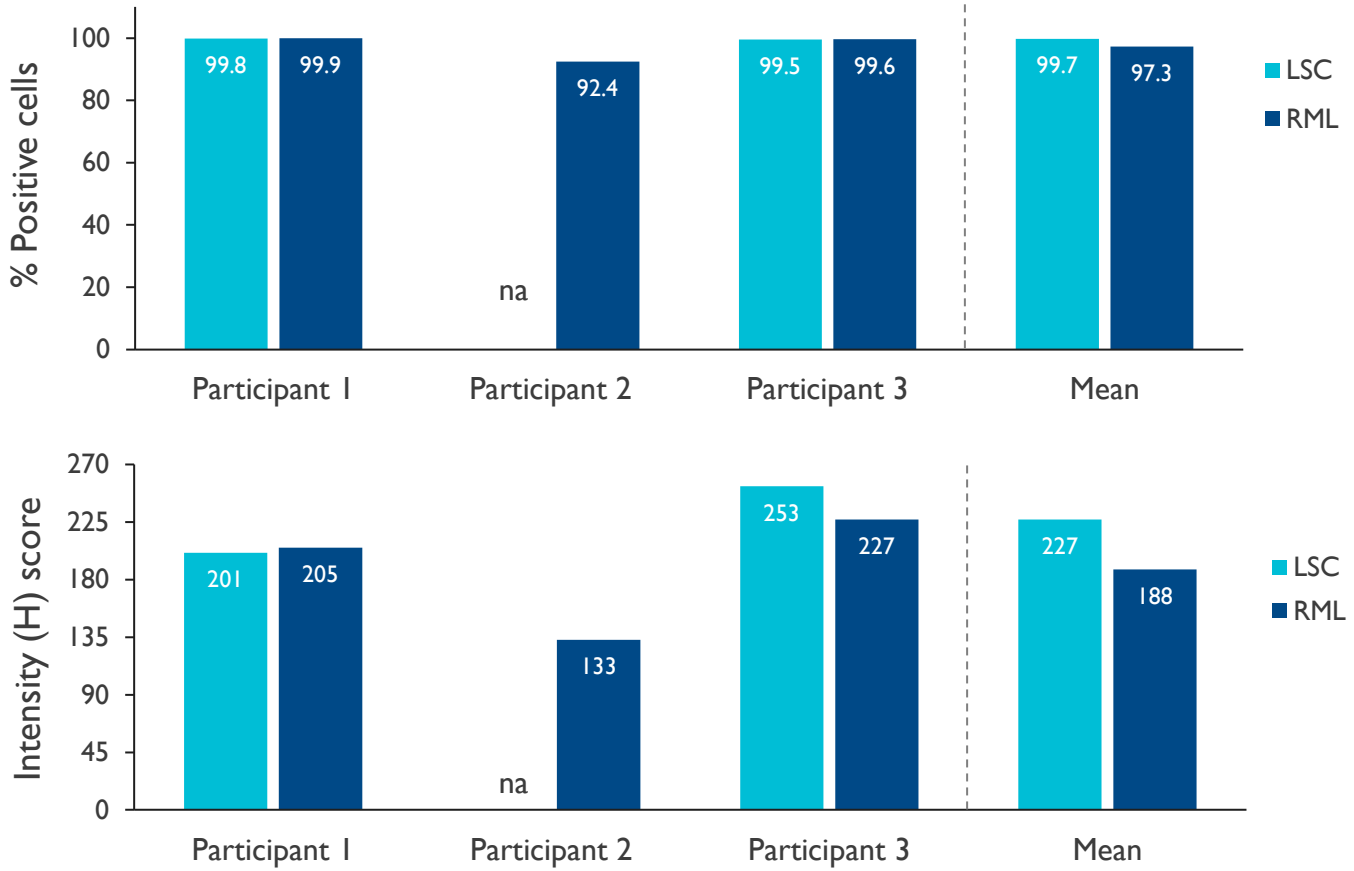


CFTR, cystic fibrosis transmembrane conductance regulator; IHC, immunohistochemistry.

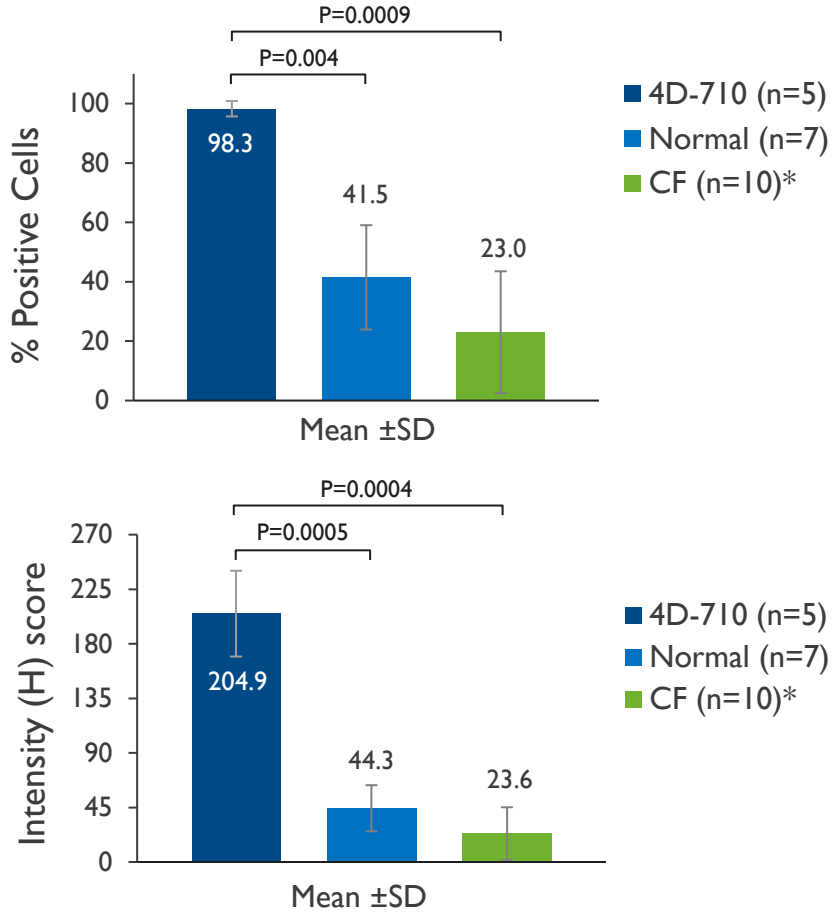
Widespread CFTR Protein Expression in Airways

CFTR PROTEIN EXPRESSION BY IHC 4–8 WEEKS AFTER 4D-710 DOSING

Cohort 1 (1E15 vg)



4D-710 vs. Control Lung Samples

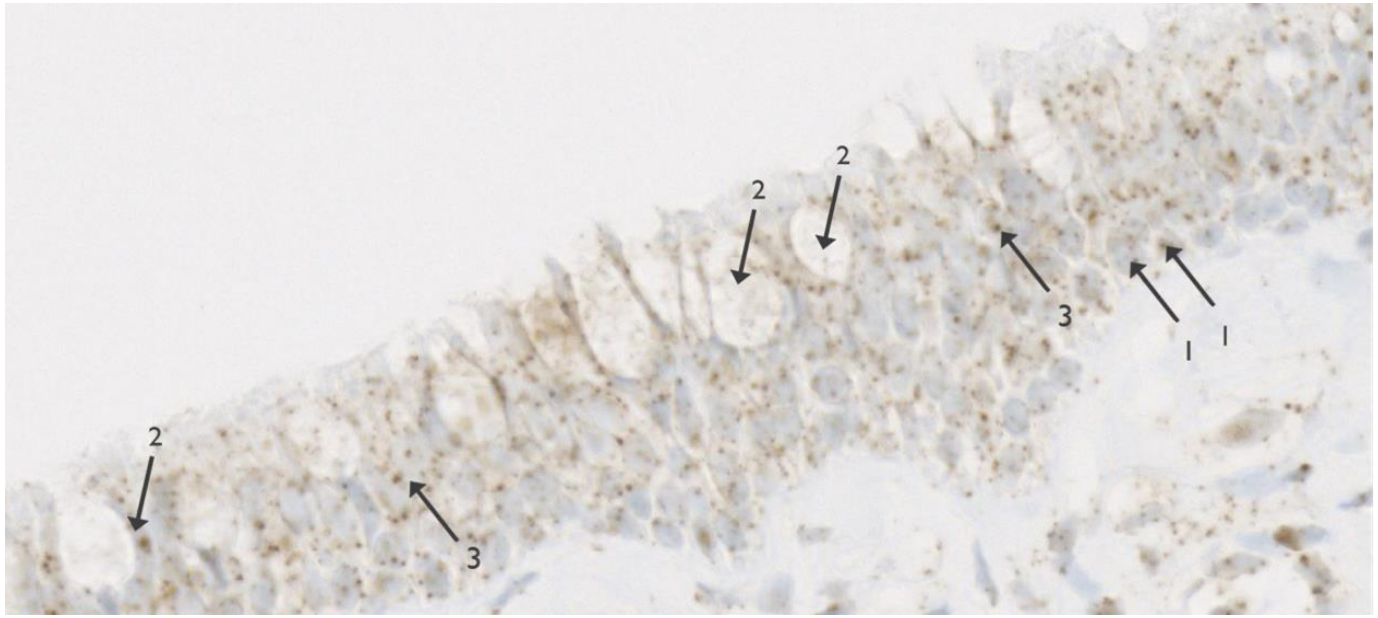


Visiopharm® machine learning image analysis quantification of CFTR IHC staining. *Variant and modulator treatment status unspecified. IHC, immunohistochemistry LSC, left secondary carina; RML, right middle lobe.

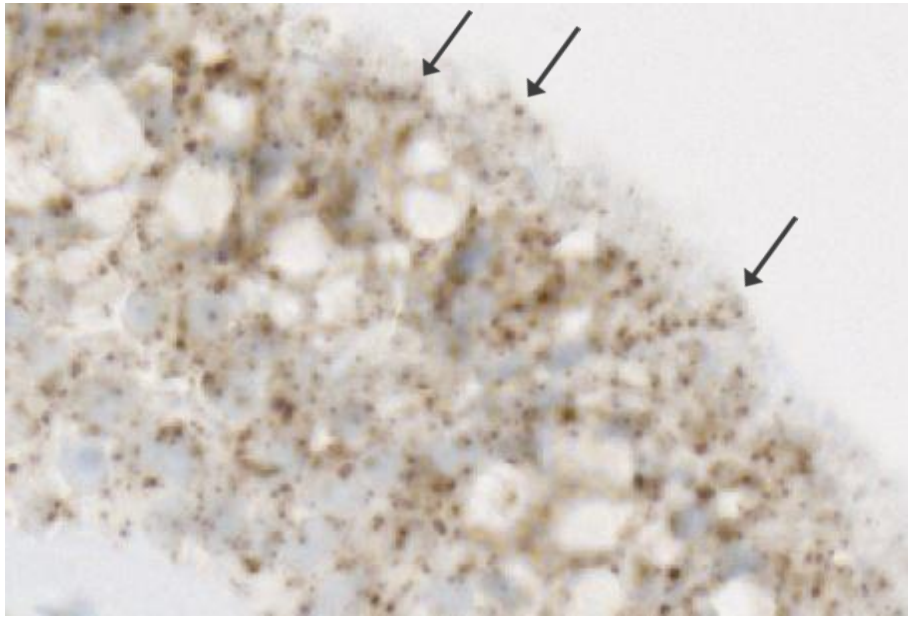
CFTR Protein Expression Observed in Multiple Bronchial Epithelial Cell Types

CFTR PROTEIN LOCALIZATION (IHC) FOLLOWING 4D-710 AEROSOL TREATMENT

CFTR Protein Expressed in Multiple Cell Types



Localization to Apical Membrane



(**1**) Basal cells (**2**) Goblet cells (**3**) Columnar ciliated cells

Images from Participants 1 and 3. IHC, immunohistochemistry.

Target 4D-710 CFTR Transgene Expression Profile Achieved (Cohort 1)

4D-710 Target Expression Profile:

Reproducible, consistent distribution & transgene expression in airways

Program Objectives	Initial Results
✓ Widespread distribution throughout airways	**100%** of tissue samples positive (11 of 11)
✓ Reproducibility between individuals	**Confirmed:** 3 of 3 participants
✓ All major epithelial cell types (including basal cells & secretory cells)	**Confirmed:** 3 of 3 participants and in all biopsy samples (n=5)
✓ Robust expression regardless of baseline antibody titer	**Confirmed:** 2 of 2 participants with pre-treatment anti-capsid antibodies
✓ ≥15% cells transduced	**92-100%** of airway cells (+) for CFTR
✓ CFTR protein expression ≥ normal observed levels	**Above normal** CFTR levels observed

Aerosolized 4D-710 in Patients with Cystic Fibrosis Lung Disease Not Amenable to Modulators

Phase 1/2 Clinical Trial: Interim Efficacy Endpoint Data

AEROW

Historical Data for Untreated Minimal Function CFTR CF Patients

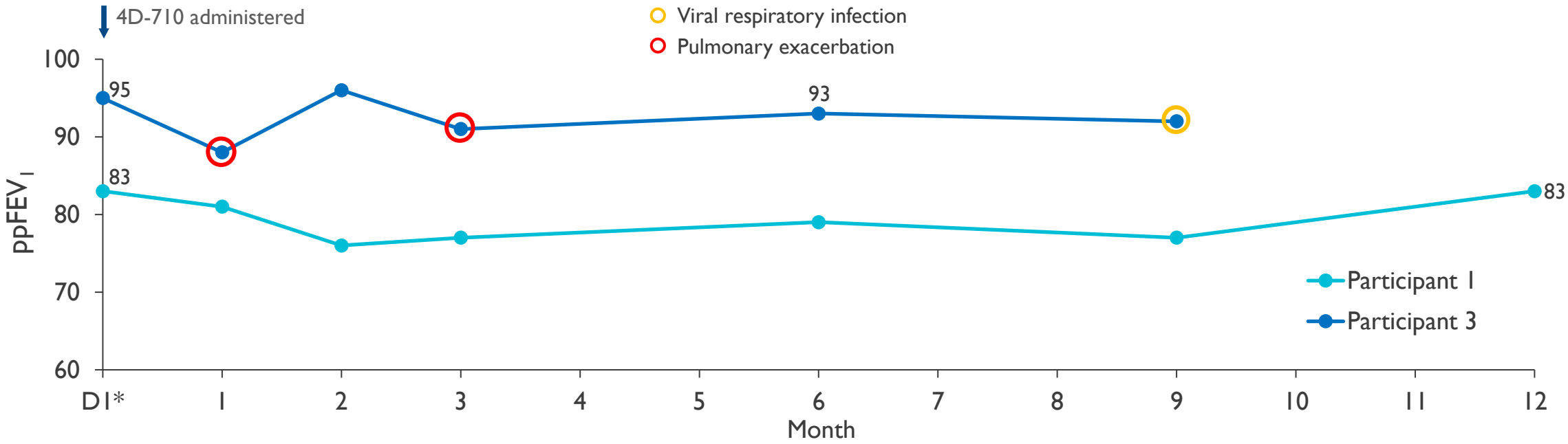
DECLINE EVIDENT IN SPIROMETRY ASSESSMENTS AT ~1 YEAR

Assessment	Instrument	Historical Data
Spirometry	% Predicted FEV_1	Annual rate of decline: **-2.3**[1*] Within-subject variability: **SD ±4.5**[2†]

*Estimate based on *DF508* homozygous population, which appears to have a similar rate of decline as Class I (null) variant population. †*CFTR* variants not reported.
FEV_1, forced expiratory volume in 1 second. SD, standard deviation.
1. Konstan et al. *Lancet Respir Med* 2017;5:107–18. 2. Stanbrook MB et al. *Chest* 2004;125:150–5.

$ppFEV_1$ Change From Baseline

STABLE IN PARTICIPANTS WITH MILD/NORMAL LUNG FUNCTION IMPAIRMENT



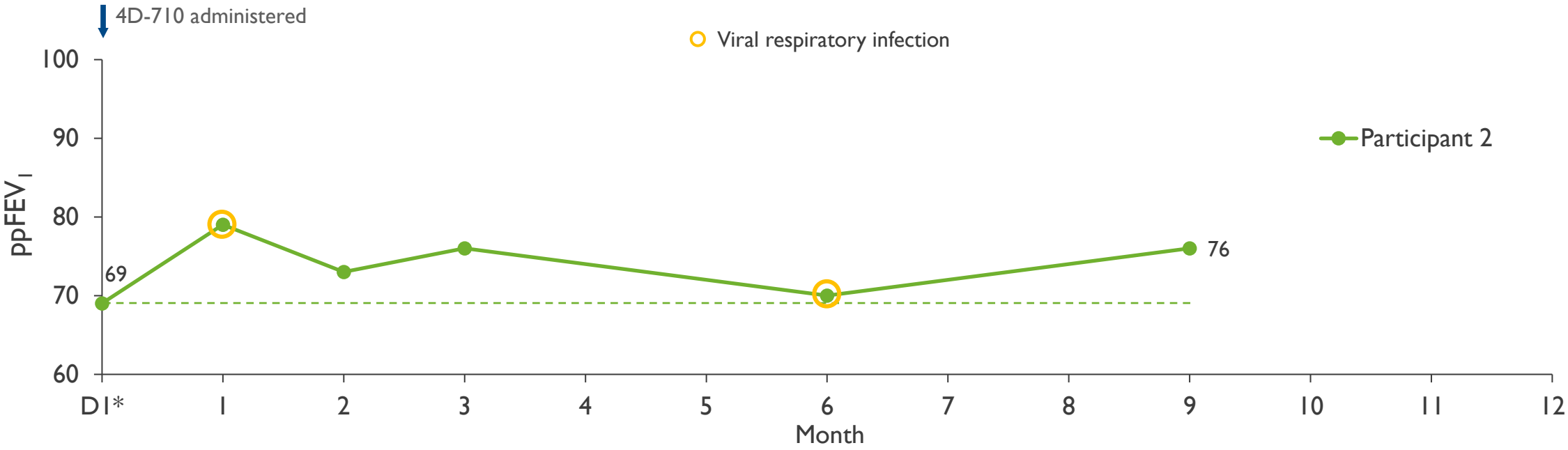
Pulmonary Exacerbations/Viral Respiratory Infections (not related to 4D-710):

Cohort 1	Month 1	Month 3	Month 6	Month 9	Month 12
Participant 1	**none**	**none**	**none**	**none**	**none**
Participant 3	Day 28: Grade 2 Infective PE	Day 88: Grade 1 Infective PE	**none**	Day 266: Grade 1 COVID-19	*pending*

*Pre-dose spirometry assessment. $ppFEV_1$, percent predicted forced expiratory volume in 1 second

$ppFEV_1$ Change From Baseline

IMPROVED IN PARTICIPANT WITH MODERATE LUNG FUNCTION IMPAIRMENT



Pulmonary Exacerbations/Viral Respiratory Infections (not related to 4D-710):

Cohort 1	Month 1	Month 3	Month 6	Month 9	Month 12
Participant 2	Day 8: Grade 3 COVID-19, dyspnea	**none**	Day 176: Grade 1 rhinovirus	**none**	*pending*

*Pre-dose spirometry assessment. $ppFEV_1$, percent predicted forced expiratory volume in 1 second.

Historical Data for Untreated Minimal Function CFTR CF Patients

DECLINE EVIDENT IN BOTH CLINICAL ASSESSMENTS AT ~1 YEAR

Assessment	Instrument	Historical Data
Spirometry	% Predicted FEV_1	Annual rate of decline: **-2.3**[1*] Within-subject variability: **SD ±4.5**[2†]
Health-related Quality of Life: Respiratory Symptoms	Cystic Fibrosis Questionnaire-Revised (CFQ-R-R)	48 week change from baseline: **Est. -4 points** (placebo)[3]

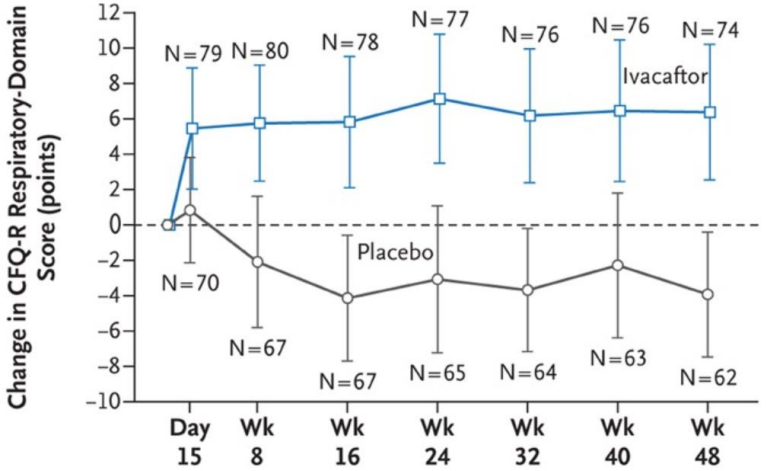
*Estimate based on *DF508* homozygous population, which appears to have a similar rate of decline as Class I (null) variant population. †*CFTR* variants not reported.
CFQ-R-R, Cystic Fibrosis Questionnaire-Revised (respiratory symptoms scale); MCID, minimal clinically important difference; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SD, standard deviation.
1. Konstan et al. *Lancet Respir Med* 2017;5:107–18. 2. Stanbrook MB et al. *Chest* 2004;125(1):150-5. 3. Ramsey et al. *N Engl J Med* 2011;365:1663-72.

Cystic Fibrosis Questionnaire-Revised Respiratory Symptom Scale

INSTRUMENT OVERVIEW

- Most common PRO instrument for CF[1]
- CFQ-R Respiratory Symptom Scale (CFQ-R-R): recognized by FDA (clinical efficacy endpoint)
- Reliability: Strong internal consistency
  - Cronbach alpha, 0.67–0.94[2]
- Validity: Correlation with exacerbations and FEV_1[3,4]
- Responsiveness: Sensitive to change with treatment[5]
  - Est. mean change from baseline (Week 48):
    - **Ivacaftor: est. +6 points**
    - **Placebo: est. -4 points**
  - No evidence of placebo effect[6]

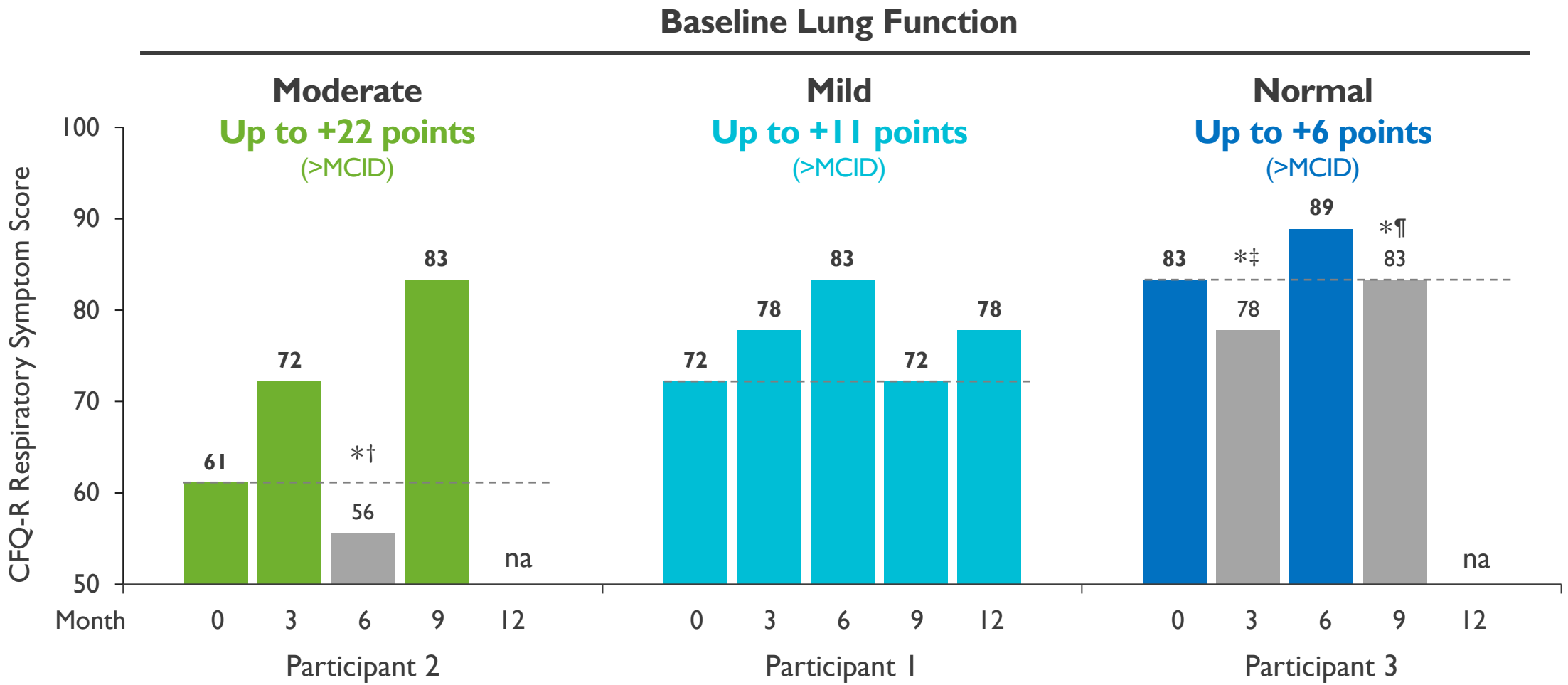
CFQ-R Respiratory Symptom Scale[5]
(Mean Change from Baseline)



1. Ratnayake et al. *BMJ Open* 2020;10:e033867. 2. Quittner et al. *Chest* 2005;128:2347-54. 3. Quittner et al. *Qual Life Res* 2012;21:1267-78. 4. Borawska-Kowalczyk et al. *Dev Period Med* 2015;19:127-36.
5. Ramsey et al. *N Engl J Med* 2011;365:1663-72. 6. Colton et al. *J Cystic Fibrosis* 2019;18:461-7. BMI, body mass index; FEV1, forced expiratory volume in 1 second; PRO, patient reported outcome.

CFQ-R-R Improved in All 3 Pts & at 6 of 7 Timepoints

CONSISTENT IMPROVEMENTS IN QOL >MCID (4 POINTS)



7 timepoints from 3 months post-dosing through last observation evaluable (no respiratory-related AE within 21 days).

*Respiratory-related adverse event within 21 days of assessment. †Grade 1 rhinovirus (D176). ‡Grade 1 infective pulmonary exacerbation (D88). ¶Grade 1 COVID-19. QoL, Quality of Life; CFQ-R-R, respiratory domain of the Cystic Fibrosis Questionnaire–revised. Scores range from 0 to 100, with higher scores indicating better health. MCID=4 points (individuals with CF and stable respiratory disease) [1]. 1. Quittner AL et al. *Chest* 2009;135:1610–18.

Interim Cohort 1 Efficacy Data: Change in ppFEV$_1$ & CFQ-R-R QoL

IMPROVED AND/OR STABLE IN 3 PARTICIPANTS TREATED WITH 4D-710

Assessment	Instrument	Historical Data	4D-710 Outcomes (n=3)*
Spirometry	% Predicted FEV$_1$	Annual rate of decline: **-2.3**[1*] Within-subject variability: **SD ±4.5**[2†]	**Baseline Moderate: Improved (+7pp)** Baseline Mild: Stable (0pp) Baseline Normal: Stable (-2pp)
Health-related Quality of Life: Respiratory Symptoms	Cystic Fibrosis Questionnaire-Revised (CFQ-R-R)	48 week change from baseline: **Est. -4 points** placebo[3]	**Clinically meaningful improvement** (≥4 points; MCID): ▪ **3 of 3 participants** (last evaluable measurement; **+6 to +22 points**) ▪ **+ at 6 of 7 evaluable timepoints**

*Estimate based on *DF508* homozygous population, which appears to have a similar rate of decline as Class I (null) variant population. †*CFTR* variants not reported.
CFQ-R-R, Cystic Fibrosis Questionnaire-Revised (respiratory symptoms scale); MCID, minimal clinically important difference; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; QoL, quality of life; SD, standard deviation.
1. Konstan et al. *Lancet Respir Med* 2017;5:107–18. 2. Stanbrook MB et al. *Chest* 2004;125:150–5. 3. Ramsey et al. *N Engl J Med* 2011;365:1663–72.

Participant 2: Moderate Baseline ppFEV$_1$ & CFQ-R-R; Minimal Function Variant

24-YEAR-OLD MALE, INELIGIBLE FOR CFTR MODULATOR THERAPY

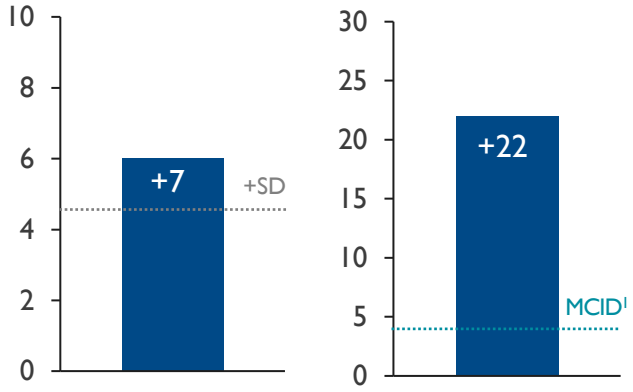
Baseline

ppFEV1	CFQ-R-R
69 (low)	61 (low)

CFTR Variant Class

I/I*
minimal function variant; modulator ineligible

Change from Baseline (Mo 9)



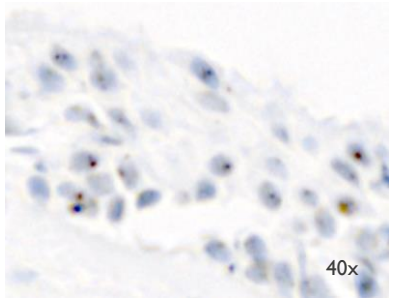
Lung Biomarkers

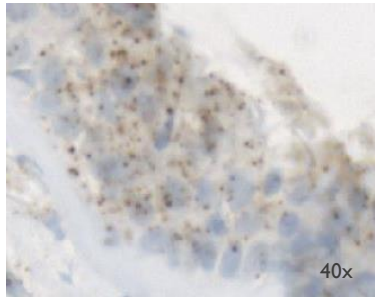
CFTRΔR Transgene

CFTR Protein Expression (IHC)

CFTRDR RNA (ISH)

Endobronchial Biopsy





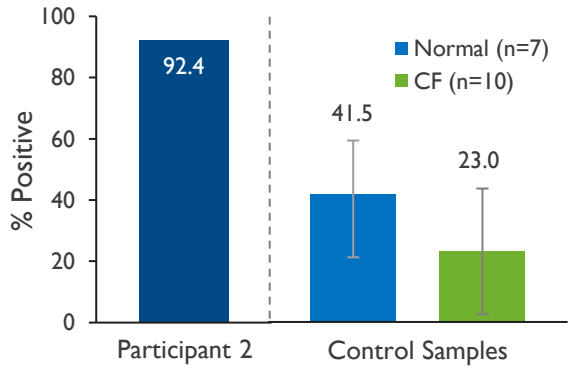
- Widespread CFTR protein expression
- Localization to apical surface membrane
- Expression detected in basal cells, goblet cells, ciliated columnar cells

Summary

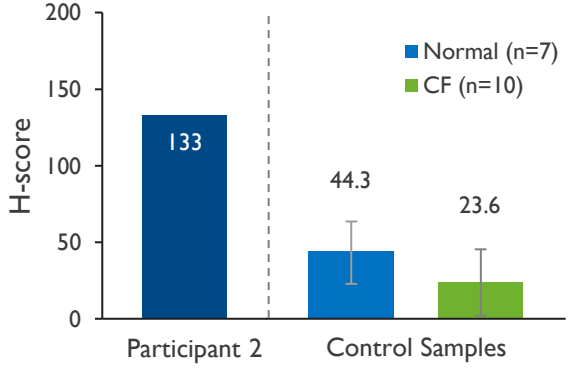
- 24-year-old male with moderate baseline ppFEV$_1$ and CFQ-R respiratory symptom score
- Widespread transgene and protein expression in airways
- Evaluation of outcomes at 9 months: Improvement in ppFEV$_1$ and CFQ-R respiratory symptom score

*Large gene deletion projected to result in a null variant profile. 1. Quittner AL et al. *Chest* 2009;135:1610–18.

CFTR (+) Cells



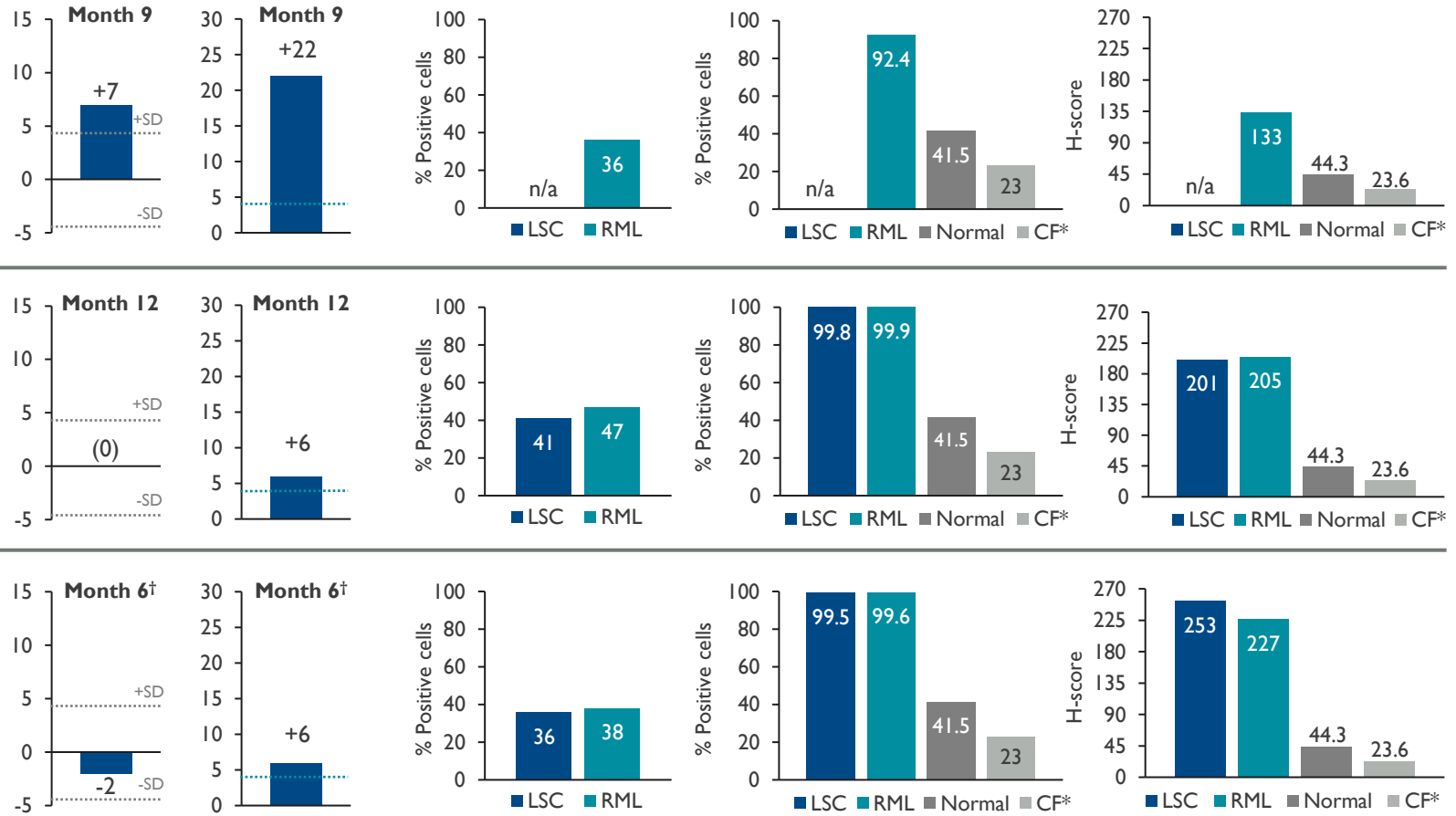
Staining Intensity (H-score)



Cohort 1 Biomarkers (4–8 Weeks) & Clinical Activity (9–12 Months)

ROBUST EXPRESSION, STABLE LUNG FUNCTION, IMPROVING QUALITY OF LIFE

Participant	Baseline		Δ from Baseline		Lung Biomarkers	
	ppFEV$_1$	CFQ-R-R	ppFEV$_1$	CFQ-R-R	*CFTRΔR* RNA (ISH)	CFTR Protein (IHC)
Participant 2	69 (moderate)	61	Month 9: +7	Month 9: +22	n/a; 36	n/a; 92.4; 41.5; 23 / n/a; 133; 44.3; 23.6
Participant 1	83 (mild)	72	Month 12: (0)	Month 12: +6	41; 47	99.8; 99.9; 41.5; 23 / 201; 205; 44.3; 23.6
Participant 3	95 (normal)	83	Month 6†: -2	Month 6†: +6	36; 38	99.5; 99.6; 41.5; 23 / 253; 227; 44.3; 23.6



Data cutoff, April 12, 2023. *Mean value, commercial and normal CF lung samples (N=10 and N=7). †Respiratory-related adverse event within 21 days of Month 9 assessment.
IHC, immunohistochemistry; ISH, in situ hybridization LSC, left secondary carina; RML, right middle lobe.

Aerosolized 4D-710 in Patients with Cystic Fibrosis Lung Disease Not Amenable to Modulators

Summary & Next Steps

AEROW

Interim Data Summary: Cohort 1 Participants (9–12 Mo Follow-Up)

Phase 1 Cohort 1 (n=3)

- Dose Cohort: 1E15 vg (**low**; n=3)
- Highest-need patients: **Most severe** disease; **not amenable** to CFTR modulators

Tolerability

- **Well tolerated:** No post-dosing 4D-710–related AEs, DLTs, SAEs

Lung Biomarker: CFTR Protein Expression

- CFTR protein expression in lung samples (n=11):
  - **All lung samples (+)** (biopsies & brushings; n=11); **92-99% of cells (+)**
  - Staining intensity and % of airway cells (+) **both significantly above normal and CF controls**
  - **Expression in ciliated, goblet & basal cells** & **correct localization** at apical membrane

Clinical Activity

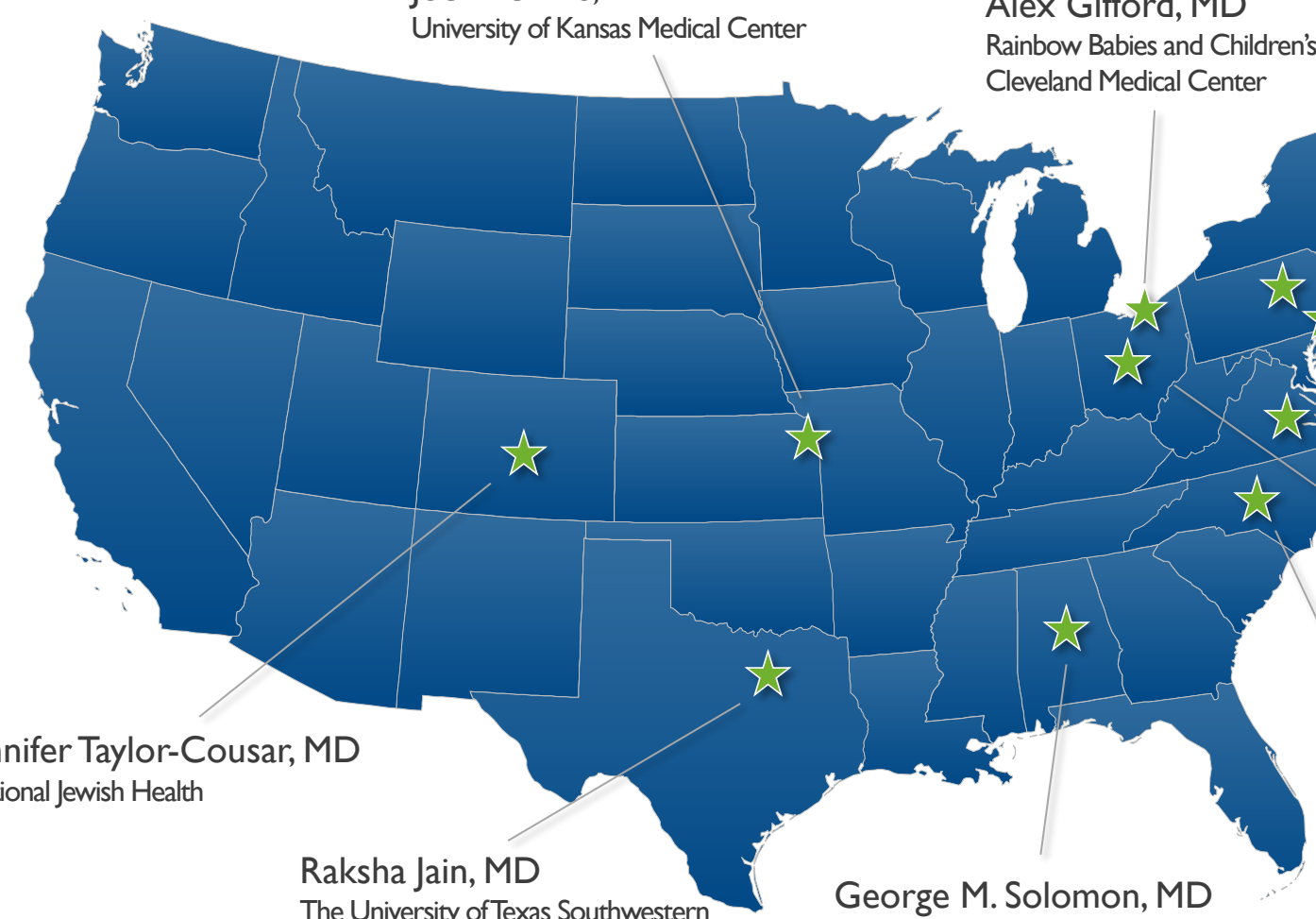
- ppFEV1: historical controls: ~2.3% mean annual decline
  - Moderate impairment in ppFEV1 at baseline (n=1): **7pp increase**
  - Normal or mild impairment in ppFEV1 at baseline (n=2): **both maintained stable**
- CFQ-R-R (QoL): historical ~4 point mean decline
  - Clinically meaningful **improvement in all 3 participants (+6 to +22)**; **6 of 7** timepoints

4D-710 Clinical Development: Planned Next Steps

CFTR MODULATOR INELIGIBLE AND COMBINATION WITH CFTR MODULATORS

	Milestone	Target Completion
AEROW **Phase 1/2:** **Modulator Ineligible / Intolerant**	▪ Phase 1 Dose Exploration stage (Cohort 1 & 2) interim data expected at the North American Cystic Fibrosis Conference	Nov 2023
	▪ Dose selection for and initiation of Phase 2 Dose Expansion stage	H2 2023
	▪ FDA discussion on pivotal endpoints	Q4 2023
Non-clinical: **Combination with Modulators**	▪ Development plan update	Q4 2023

Acknowledgments:
Participants & Their Families, Principal Investigators & Study Staff, CFF/TDN



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PROGRAM EXPECTATIONS & CASH POSITION

Multiple 2023-24 Clinical Catalysts: Cash Runway into H1 2026

LARGE MARKET OPHTHALMOLOGY

4D-150

- Wet AMD Ph 2 enrollment complete: **Q3 2023**
- Wet AMD Ph 3 discussion with FDA: **Q4 2023**
- Wet AMD Ph 2 interim data: **H1 2024**
- DME Ph 2 FPI: **Q3 2023**

4D-175

- Program update: **Q4 2023**
- File IND: **2024**

PULMONOLOGY

4D-710

- Ph 1/2 Dose Exploration interim data (Cohort 1 & 2) at NACFC: **Nov 2023**
- Dose selection for and initiation of Phase 2 Dose Expansion stage: **H2 2023**
- Update development plan for mod combo: **Q4 2023**

$331M

Cash, cash equivalents & marketable securities as of the end of Q1 2023[1]

Expected to fund operations into H1 2026

1. Pro forma net proceeds from May 2023 Offering ($129M)

THANK YOU

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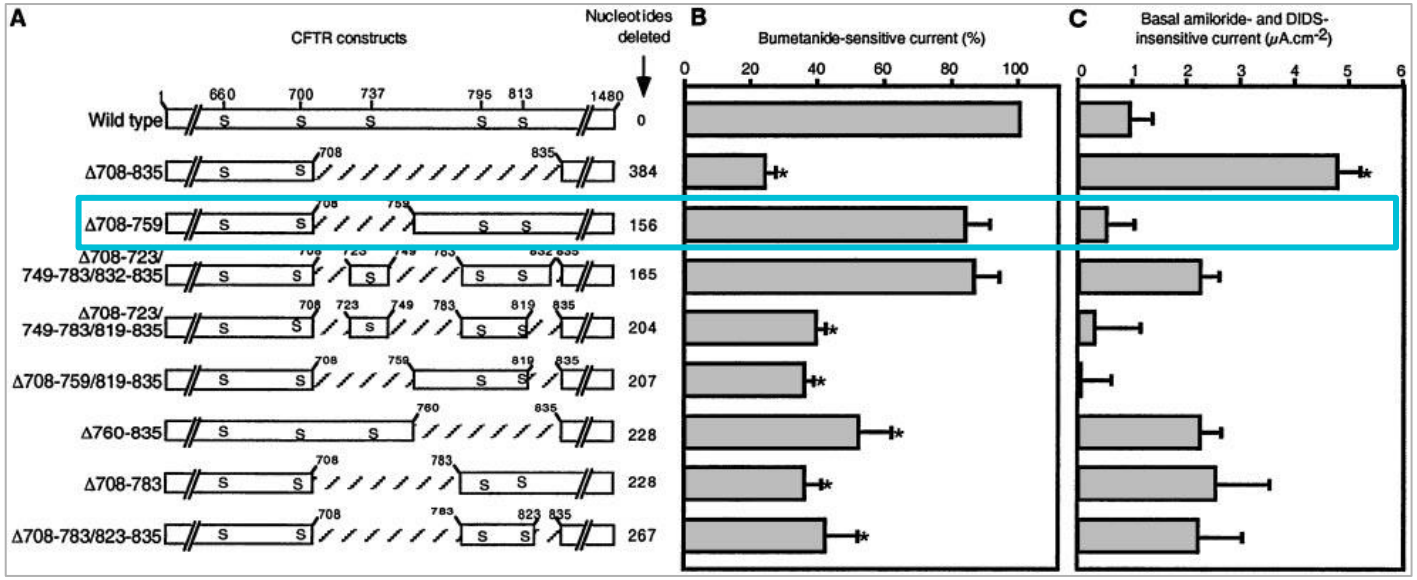
Supplementary Materials

Selection of Optimal CFTR Transgene: Maximal Function & Regulation

IDENTIFICATION OF OPTIMAL DELETION SITE WITHIN CFTR PROTEIN

Δ708-759 Selected to Maximize Function and Regulation



Δ708-759 is Highly Functional

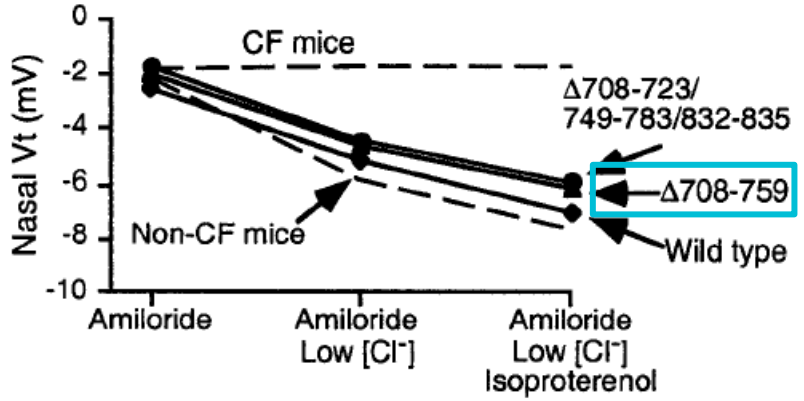


Fig. 6. Voltage across nasal epithelium (Vt) in CF mice expressing indicated constructs in the nasal mucosa. Values of Vt obtained from untreated CF and wild-type mice are indicated by dashed lines (33). The three interventions are indicated at the bottom. $n = 3$ for wild type and 4 for the deleted variants.

Ostedgaard et al. PNAS 2002;99:3093-8