Aerosolized 4D-710 for the Treatment of Cystic Fibrosis (CF) Lung Disease

AEROW

Interim Phase 1/2 Safety & Efficacy Data and Program Update

June 6, 2024

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Positive New Data Supports Aerosolized 4D-710's Potential as a Durable Genetic Medicine for Cystic Fibrosis Lung Disease

Wholly-Owned Pulmonology Franchise

- **Next-generation aerosolized A101 vector for large-market lung diseases:** 4D-710 for CF & 4D-725 for A1AT deficiency lung diseases

Interim Data from 4D-710 AEROW Phase 1 Dose Exploration Stage (Single aerosolized dose, Four dose levels ranging from 2.5E14 to 2E15 vg dosed in 10 participants)

Lung Function ($ppFEV_1$):

Improved (+5% & +6%) in 2 of 3 participants with >6 months of follow up and baseline $ppFEV_1$ ≤80%

Safety & Tolerability:

Well tolerated at dose levels up to 1E15 vg

Lung Biopsy:

Dose-dependent 4D-710 transgene expression

Widespread CFTR protein expression in all doses & all participants studied

Pre-existing A101 Immunity:

No effect on:

Transgene Expression

Clinical Activity

Safety

Next Steps

Cleared to Begin Phase 2 Expansion Stage (n= up to 9; begin dosing H2 2024):

Expect to evaluate **1E15 vg**; *inclusion of 5E14 vg dose pending enrollment & follow-up from 3rd participant in Phase 1 5E14 vg cohort*

Next interim data update expected mid-2025 after completing enrollment and f/u of Phase 2

Best available data as of May 24, 2024.

A101 Lung Vector is Among Three Proprietary, Highly Targeted Next-Generation AAV Vectors Invented at 4DMT & in Clinical Development

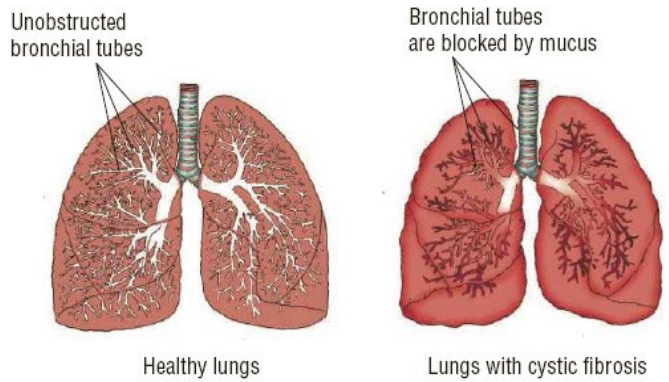
VECTOR / DELIVERY	PRODUCT CANDIDATE	INDICATION	ESTIMATED PREVALENCE	RESEARCH CANDIDATE	IND-ENABLING	PHASE 1/2	PHASE 3	PRODUCT RIGHTS
OPHTHALMOLOGY **R100** Intravitreal	4D-150	Wet AMD	*~3M U.S./EUMM*					4DMT
		DME	*~5M U.S./EUMM*					
	4D-125	XLRP	*~24K U.S./EUMM*					4DMT
	4D-110	Choroideremia	*~13K U.S./EUMM*					4DMT
	4D-175	Geographic Atrophy	*~2.5M U.S./EUMM*					4DMT
	Undisc. *Vector licensed to Astellas*	Undisclosed Rare Disease	*Undisc.*					astellas
PULMONOLOGY **A101** Aerosol	4D-710	**CF Lung Disease (mod. ineligible/intol)**	*~15K WW*					4DMT
		CF Lung Disease (combo w/ mods)	*~90K WW*					
	4D-725	**A1ATD Lung Disease**	*~200K U.S./EUMM*					4DMT
CARDIOLOGY **C102** IV	4D-310*	Fabry Disease Cardiomyopathy	*~50-70K U.S./EUMM*					4DMT
CNS **B SERIES** Multiple	Unnamed *Led by Arbor*	Amyotrophic Lateral Sclerosis	*~79k U.S./EU/UK*					arbor biotech 50/50 WW

*Currently on clinical hold.

CF Lung Disease Has High Unmet Medical Need Despite Modulators

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
- **Lung function** ($ppFEV_1$) **annual decline:** –1 to –2.3%[1*,2]
- **Median survival (Pre-modulators):** ~40 years[3]



Epidemiology

- **~105,000[4,5] prevalence worldwide:**
  - ~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:**
  - **$9.9 billion** annually (2023)[6]

Illustration by Frank Forney. © 2016 Cengage Learning *Estimate based on *DF508* homozygous population, which appears to have a similar rate of decline as Class I (null) variant population. 1. Konstan MW et al. *Lancet Respir Med* 2017; 5:107–18. 2. Caley et al. Journal of Cystic Fibrosis 2021;20:86–90. 3. Ramsey & Welsh. *Am J Respir Crit Care Med* 2017;195(9):1092–9. 4. Guo J et al. *Journal of Cystic Fibrosis* 2022; 21:456-62. 5. Cystic Fibrosis Foundation. 6. Vertex Pharmaceuticals FY 2023 financial results.
ppFEV1, percent predicted forced expiratory volume in 1 second.

A101: Next-Gen Aerosolized Genetic Medicine Vector for Pulmonology

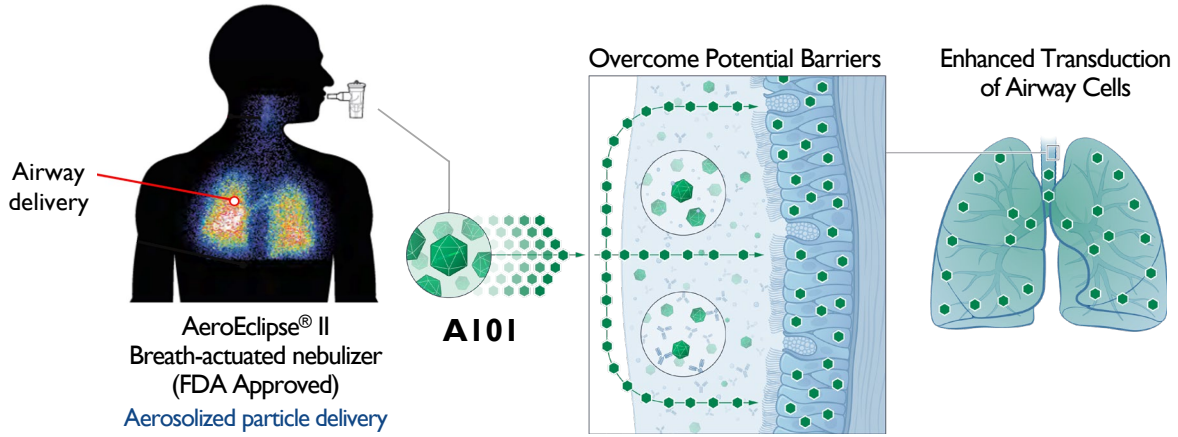
Prior aerosol gene therapy trials failed to achieve transgene expression in lung[1,2]; potential limitations:

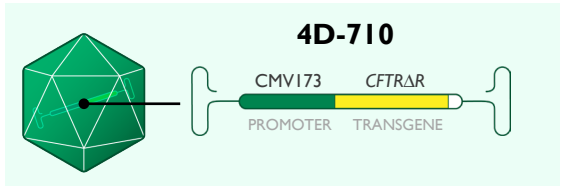
- ✕ Poor mucus penetration
- ✕ Inefficient airway cell transduction
- ✕ Suboptimal tissue tropism
- ✕ Susceptibility to clearance by human AAV immunity

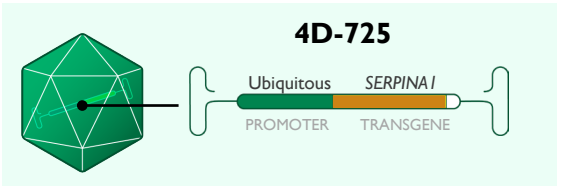
A101 invented at 4DMT to overcome these limitations:

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

Aerosolized A101-Based Genetic Medicines





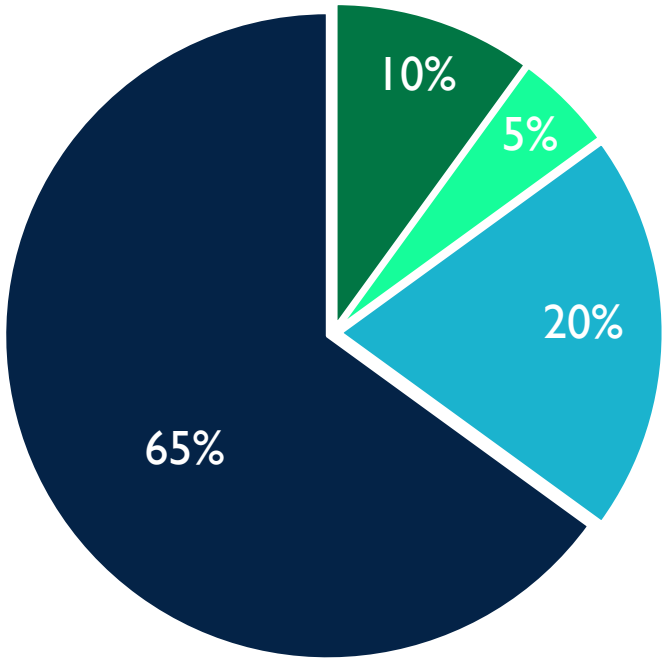


Product	Indication	Prevalence	Preclinical	Phase 1/2	Phase 3
4D-710	CF Lung Disease (monotherapy)	*~15K WW*			
	CF Lung Disease (w/ modulators)	*~90K WW*			
4D-725	A1AT Deficiency Lung Disease	*~200K U.S./EU*			

1. Aitken ML et al. Hum Gene Ther 2001; 12:1907–16. 2. Moss RB et al. Chest 2004;125:509–21.

Highest Unmet Need in ~35K People with Cystic Fibrosis

4D-710 has the Potential to Treat Cystic Fibrosis Lung Disease Regardless of Genetic Variant

Cystic Fibrosis Population WW	Population Segment	Estimated People	
 ~105k	**Ineligible** for CFTR modulators	~10k	AEROW study population evaluating 4D-710 as **monotherapy**
	Intolerant to CFTR modulators	~5k	
	Suboptimal response to CFTR modulators[1]	~20k	Potential future 4D-710 study population
	Responsive to CFTR modulators	~70k	*Upside if superior dosing, efficacy, and/or safety is demonstrated*

~35k

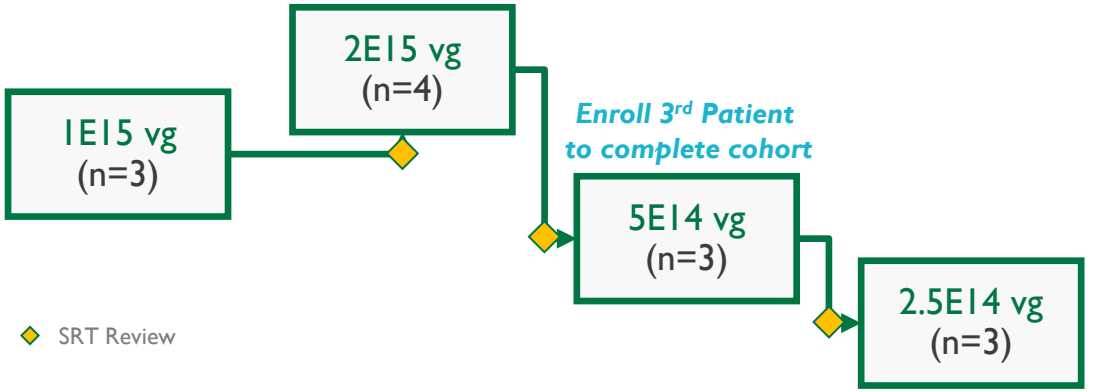
CFTR, cystic fibrosis transmembrane conductance regulator. 1. Based on assumptions derived from Middleton, 2019 and CFF registry analysis.

Phase 1/2 Designed to Identify Doses for Late-Stage Development

Generate Safety, Biomarker & Clinical Activity Data to Determine & Confirm Phase 2 & 3 Dose

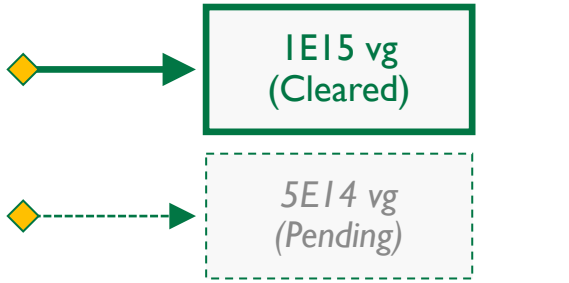
Phase 1 (Dose Exploration)

$ppFEV_1$ Eligibility Criteria: 50% to 100%



Phase 2 (Dose Expansion)

$ppFEV_1$ Eligibility Criteria:
50% to 90%



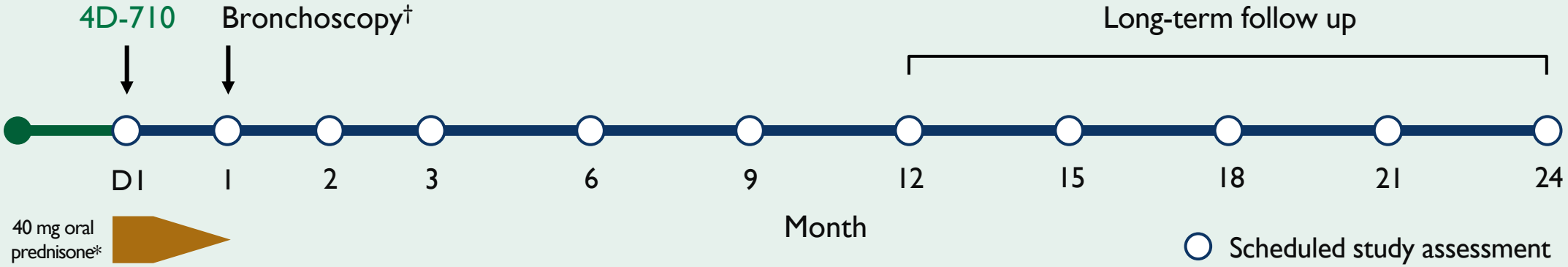
Expect to begin dosing (n= up to 9) H2 2024

Primary Objectives:

- **Phase 1:** Dose ranging to characterize safety & biomarkers
- **Phase 2:** Expand in selected dose to confirm clinical activity for Phase 3

Key Endpoints:

- Safety & tolerability
- Lung biomarkers
- Clinical activity



*28-day taper. †Endobronchial biopsy (4D-710 transgene and protein expression), pending protocol amendment to allow for 2nd biopsy beyond 12 months. ppFEV1, percent predicted forced expiratory volume in 1 second; SRT, Safety Review Team.

AEROW To-Date Enrolled pwCF Ineligible or Intolerant to Modulators with a Broad Range of Disease Activity, 5 with Pre-Existing Immunity to A101

	2E15 vg				1E15 vg			5E14 vg		2.5E14 vg
Participant #	1	2	3	4	1	2	3	1	2	1
Age, y	37	27	32	69	36	24	20	42	39	25
Sex	Female	Male	Female	Female	Male	Male	Female	Female	Female	Male
Race/Ethnicity	Non-Hispanic White	Non-Hispanic White	Non-Hispanic White	Non-Hispanic White	Non-Hispanic White	Non-Hispanic White	Non-Hispanic White	Non-Hispanic White	Non-Hispanic Black	Non-Hispanic White
CFTR modulator status	Ineligible	Ineligible	Ineligible	Intolerant	Intolerant	Ineligible	Ineligible	Intolerant	Ineligible	Ineligible
Historical Sweat chloride, mmol/L†	84	96	103	114	74	103	110	107	134	120
$ppFEV_1$	90	56	80	86	83	69	95	100	77	58
CFQ-R-R score	78	72	89	78	72	61	83	72	78	28
Anti-A101 Ab	Negative	Negative	Negative	Negative	Positive	Negative	Positive	Positive	*Pending*	Negative
A101-specific T cells	Positive	Negative	Negative	Negative	Negative	Positive	Positive	*Pending*	*Pending*	*Pending*

Best available data as of May 24, 2024. †Sweat chloride normal range ≤29 mmol/L, Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation (2017). pwCF = people with cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFQ-R-R, Cystic Fibrosis Questionnaire–revised respiratory domain; NAb, neutralizing antibodies.

4D-710 Safety & Tolerability: Results with Highest Dose Studied (2E15 vg)

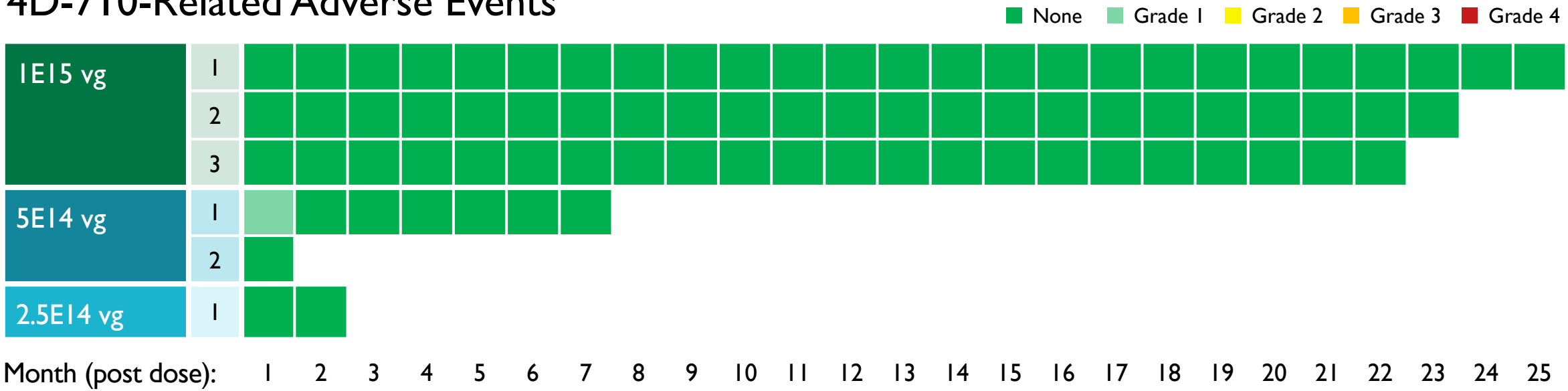
Duration of Follow Up: 13–17 Months (n=4)

- Treatment-related adverse events:
  - Transient pneumonitis & FEV_1 decline (n=1 participant)*; both resolved
  - No new SAE
  - Complete resolution of previously reported SAE (pneumonitis NOS, n=1 participant)
    - $ppFEV_1$ improved from baseline (+6% at month 12; last timepoint assessed)
- Lung biopsy biomarkers (weeks 4–8):
  - No inflammation or toxicity
  - CFTR protein expression
    - Significant over-expression: ~400% higher in epithelium compared to normal (non-CF) lung samples
    - No increase in expression: vs. 1E15 vg dose
    - Widespread expression in interstitium: negative in normal lung controls
- **1E15 vg selected as highest dose for dose exploration; no further evaluation of 2E15**

Best available data as of May 24, 2024. *Both events reported by one study participant (Participant 2). ppFEV1, % predicted forced expiratory volume in 1 second; SAE, serious adverse event; NOS, not otherwise specified.

Aerosolized 4D-710 (Up to 1E15 vg) Was Well Tolerated

4D-710-Related Adverse Events



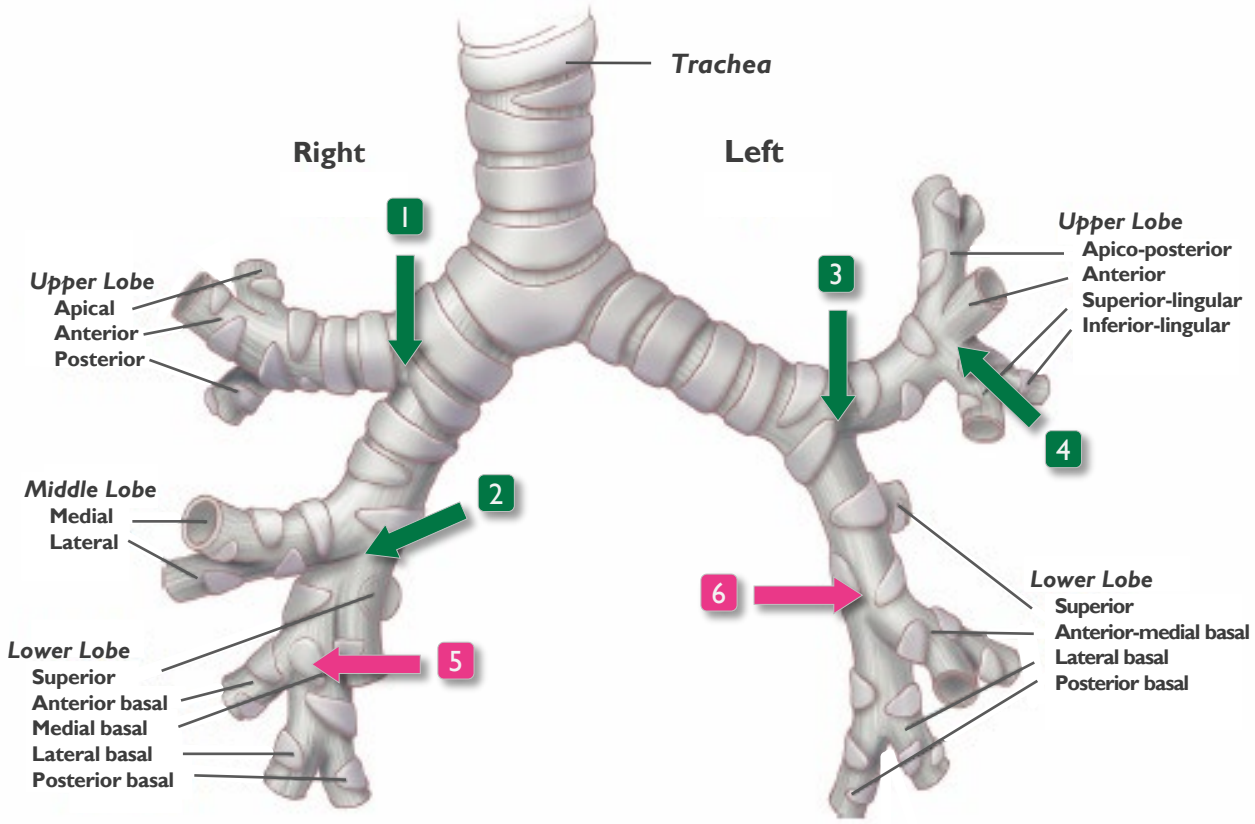
- Administration of aerosolized 4D-710 well tolerated
  - No dose-limiting toxicities
  - No 4D-710–related SAEs
  - No clinically significant 4D-710-related adverse events after administration
- No inflammation or toxicity in lung biopsies samples

Best available data as of May 24, 2024.

Biopsies & Brushings Collected 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	

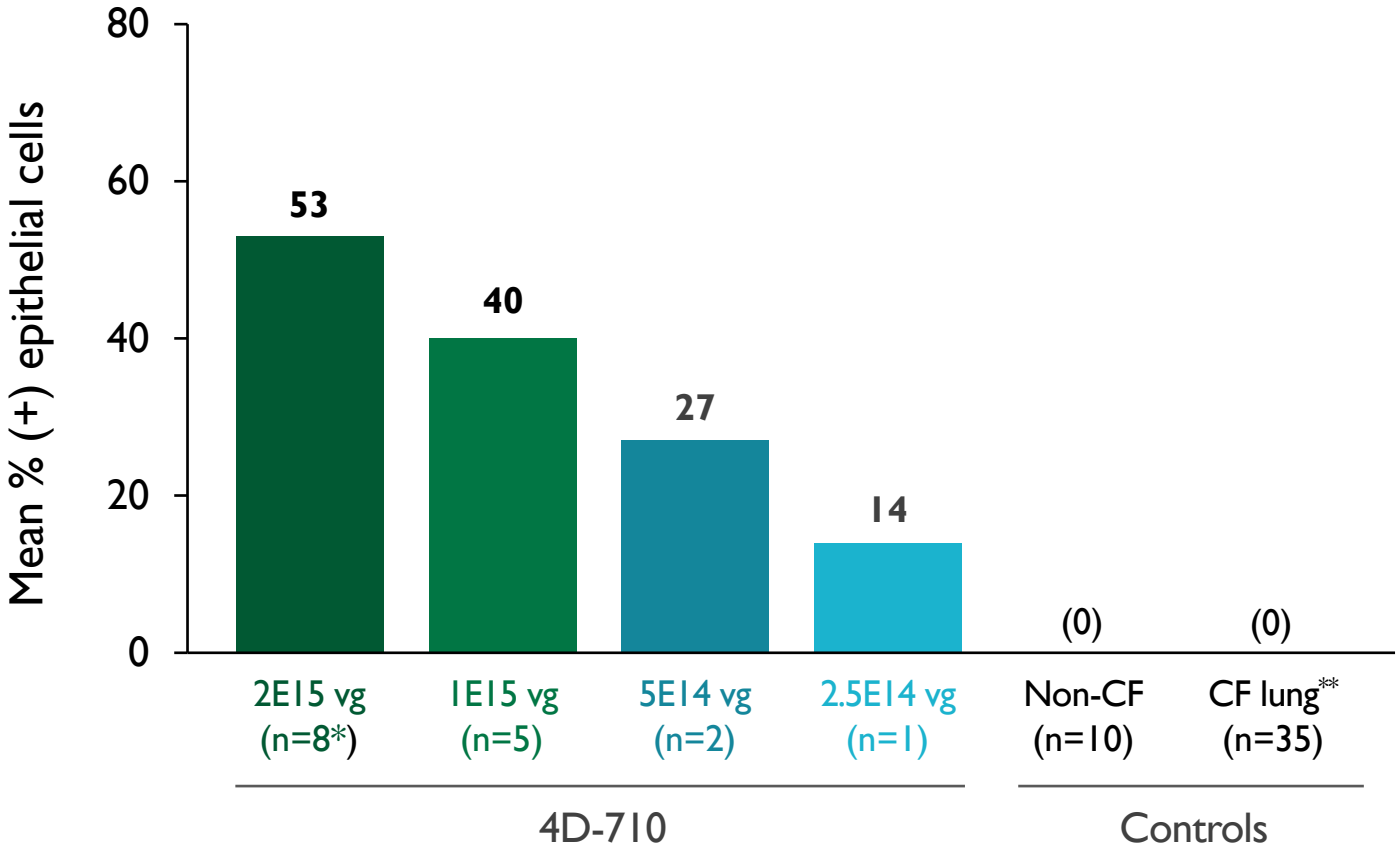


*Participant 3 bronchoscopy conducted at Week 8 due to pulmonary exacerbation (unrelated to study drug).
†Assessed by *in situ* hybridization. ‡Assessed by immunohistochemistry. ¶Assessed by quantitative PCR.

Minnich DJ, Mathisen DJ. *Thorac Surg Clin* 2007;17:571-85.

Dose-dependent *CFTRΔR* RNA Expression Following 4D-710 Administration

CFTRΔR RNA (ISH): mean % (+) airway epithelial cells

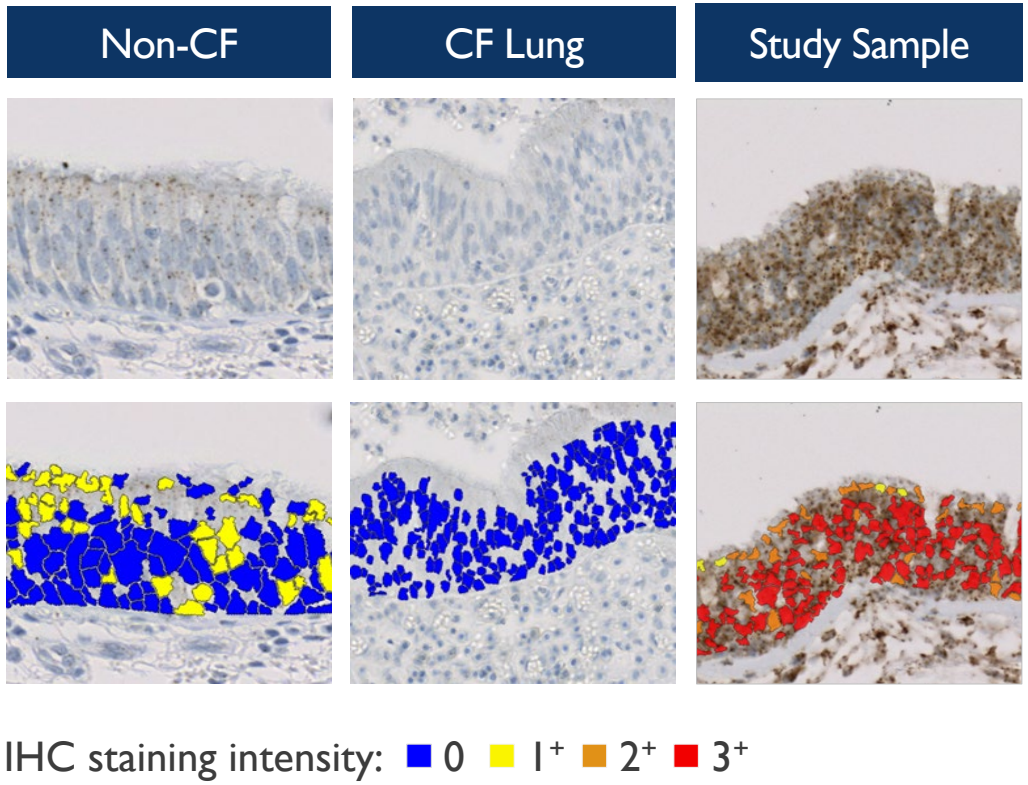


- Dose-dependent *CFTRΔR* mRNA expression in bronchial epithelial cells
- No *CFTRΔR* mRNA expression observed in commercial non-CF and CF lung samples
- Commercial non-CF samples positive for endogenous *CFTR* mRNA expression

Best available data as of May 24, 2024. Quantification by Visiopharm® AI Machine Learning Analysis. *Number shown below each group indicates the number of lung samples. **Attempts to genotype commercial CF samples yielded results for 13/35 samples; of these, a majority were ΔF508 homozygous mutations. CFTR, cystic fibrosis transmembrane conductance regulator; ISH, in situ hybridization.

CFTR Protein Expression: Machine Learning-Assisted Image Analysis (Quantitative & Qualitative Analyses)

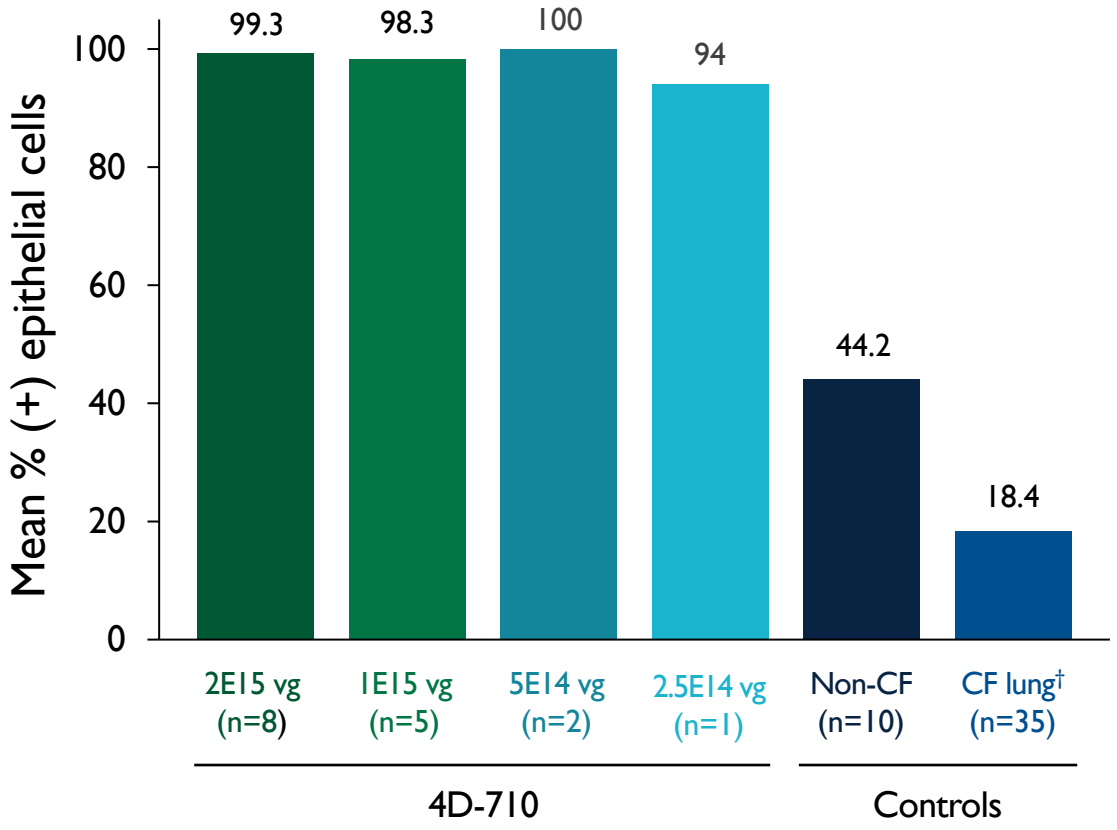
- Clinical-grade image analysis software*
- Holistic & objective whole-slide analysis:
  - 100% of airway epithelial cells analyzed
  - 100% manual QC to confirm accuracy
- Percent (+) cells & H-score automatically calculated by software algorithm
- H-score (range, 0–300):
  - measure of staining intensity & distribution
  - higher scores: increased signal intensity & distribution



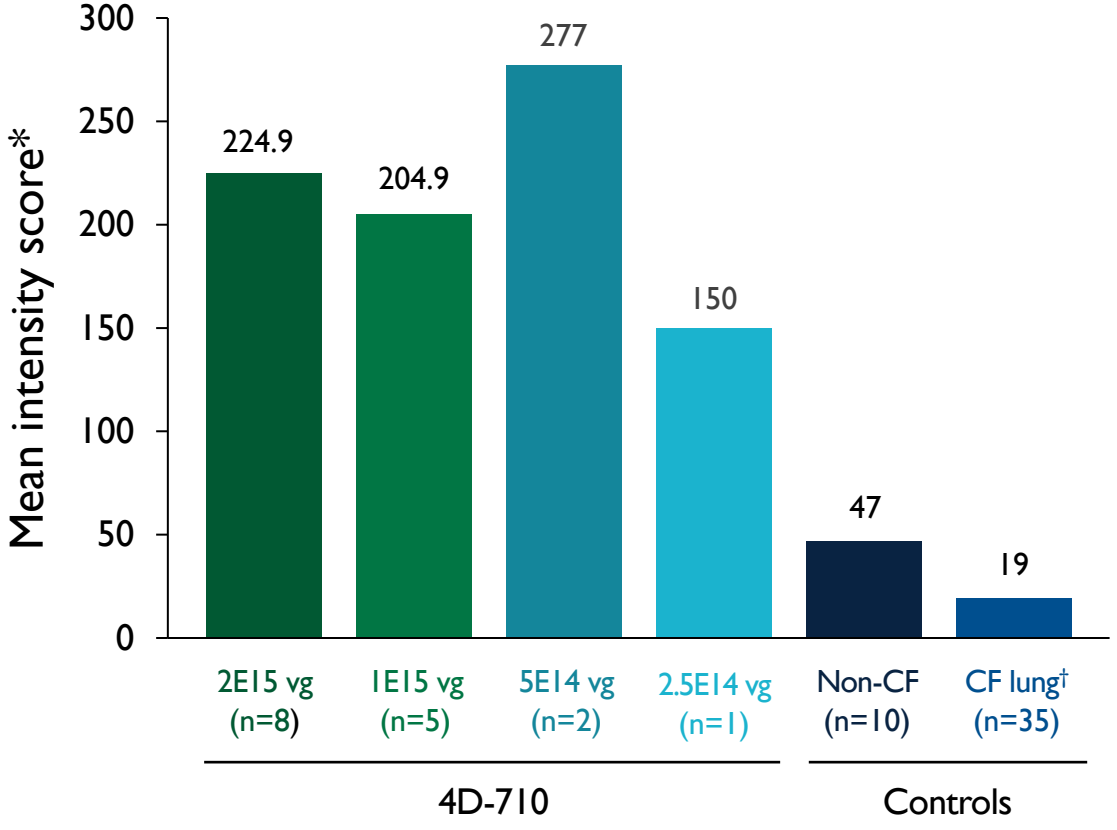
*Visiopharm® image analysis software. CFTR, cystic fibrosis transmembrane conductance regulator; IHC, immunohistochemistry.

Widespread 4D-710–Mediated CFTR Protein Expression at All Doses and in All Participants

CFTR (+) Epithelial Cells (IHC)



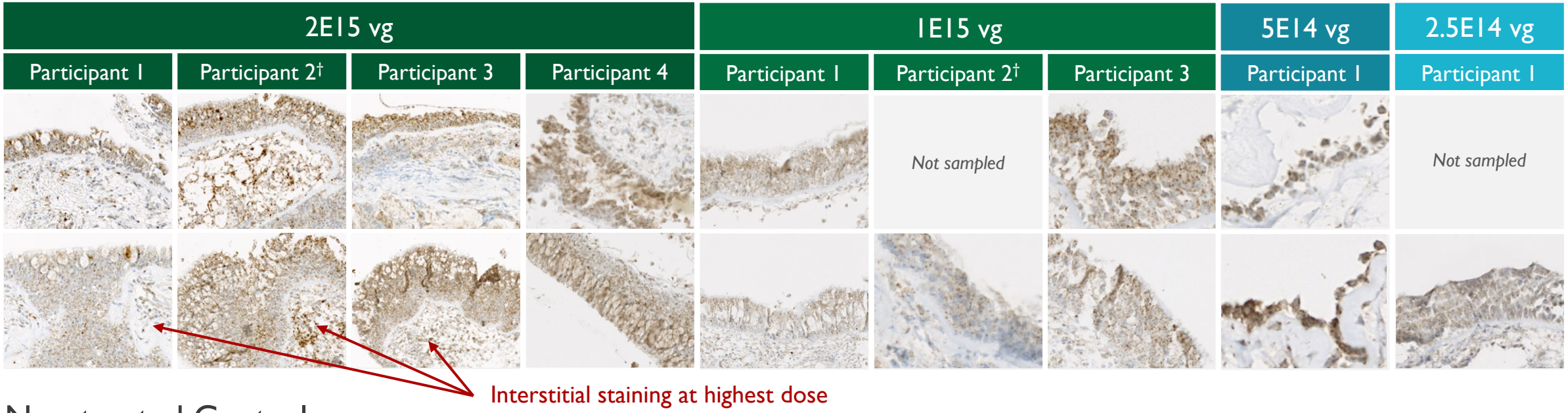
CFTR Staining Intensity (IHC)*



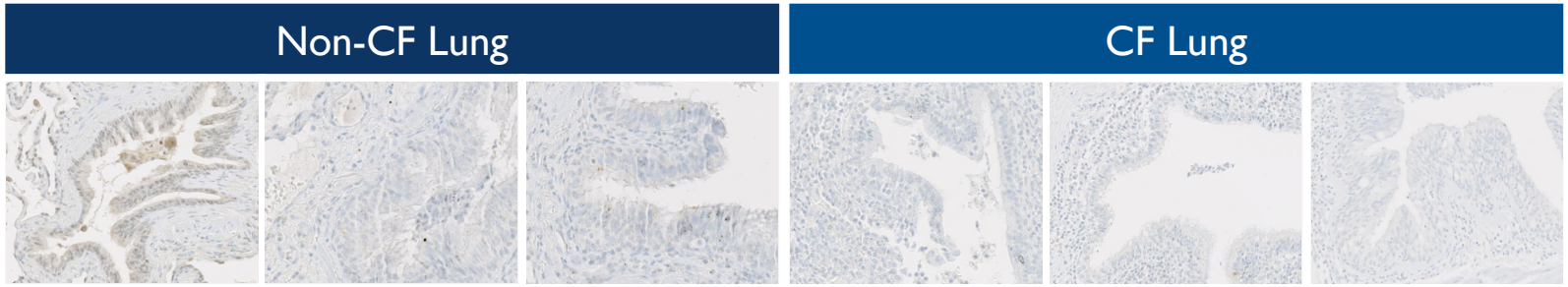
Best available data as of May 24, 2024. Quantification by Visiopharm AI Machine Learning Analysis. Number shown below each group indicates the number of lung samples. *H-score. †Attempts to genotype commercial CF samples yielded results for 13/35 samples; of these, a majority were ΔF508 homozygous mutations. IHC, immunohistochemistry.

Widespread & Consistent CFTR Protein Expression: 100% of Samples

4D-710 Treated



Non-treated Controls

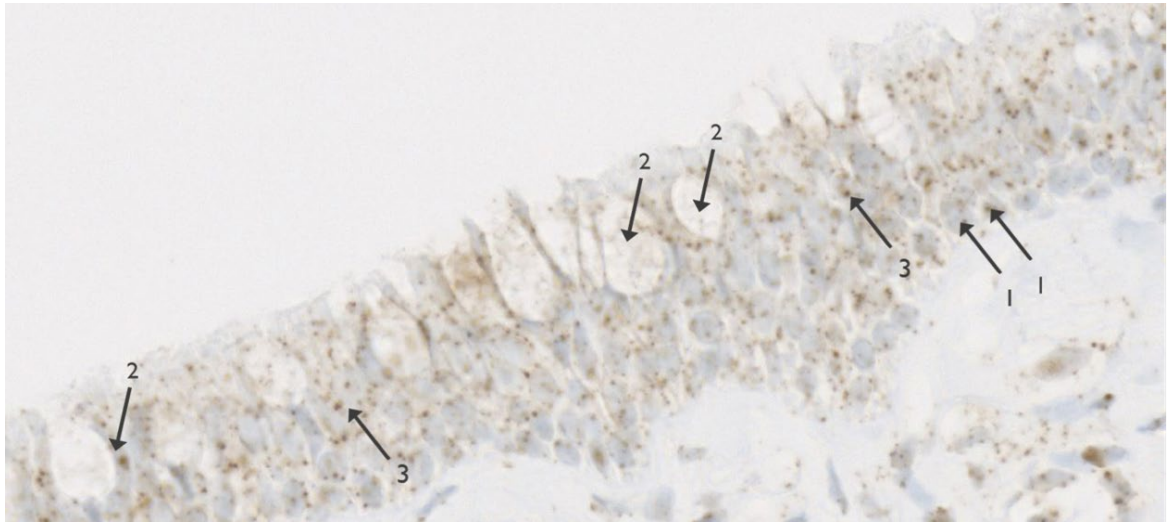


Best available data as of May 24, 2024. *Representative images, endobronchial biopsy samples obtained from the left secondary carina (row 1) and right middle lobe (row 2). †Endobronchial biopsy performed at Week 8.

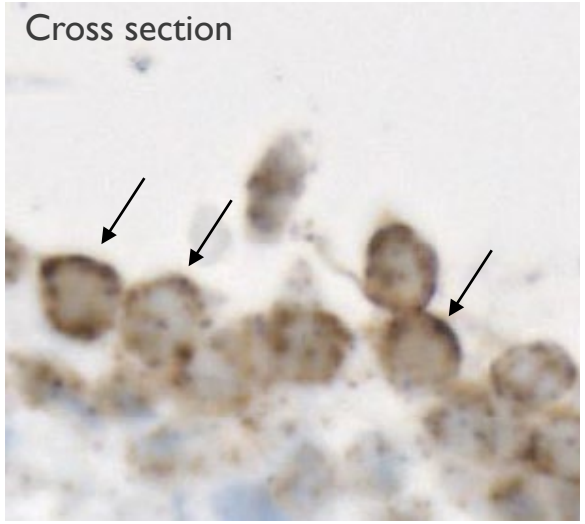
CFTR Protein Expression Observed in Multiple Airway Cell Types

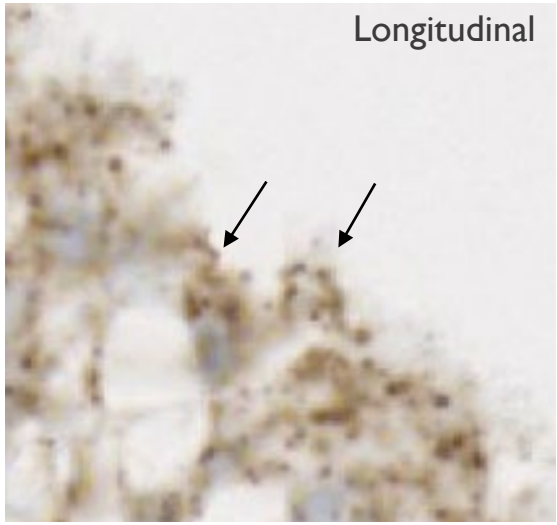
CFTR Protein Localization (IHC) Following Administration of 4D-710: Secretory, Ciliated & Basal Cells

CFTR Protein Expressed in Multiple Cell Types*



Localization to Apical Region†





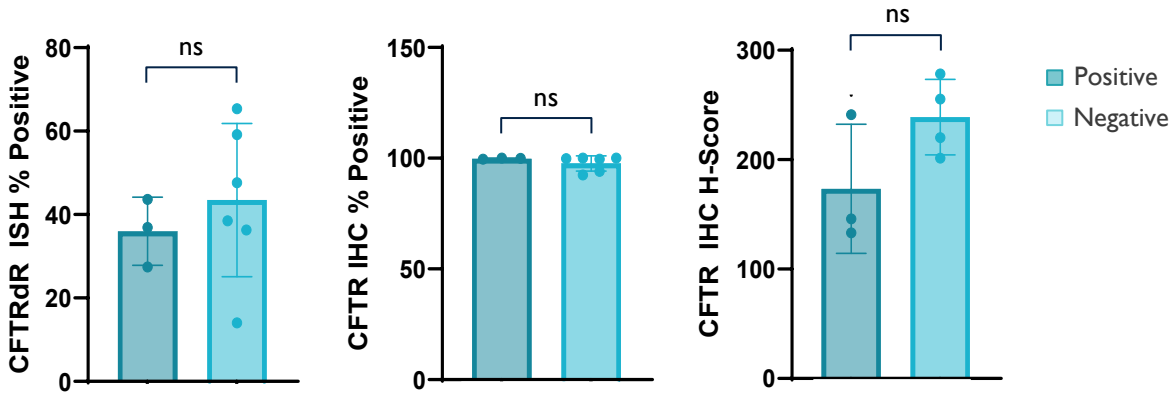
(**1**) Basal cells (**2**) Goblet cells (**3**) Columnar ciliated cells

Best available data as of May 24, 2024. *Image from 1E15 vg participant. †Images from 2E15 vg participants. CFTR, cystic fibrosis transmembrane conductance regulator. IHC, immunohistochemistry.

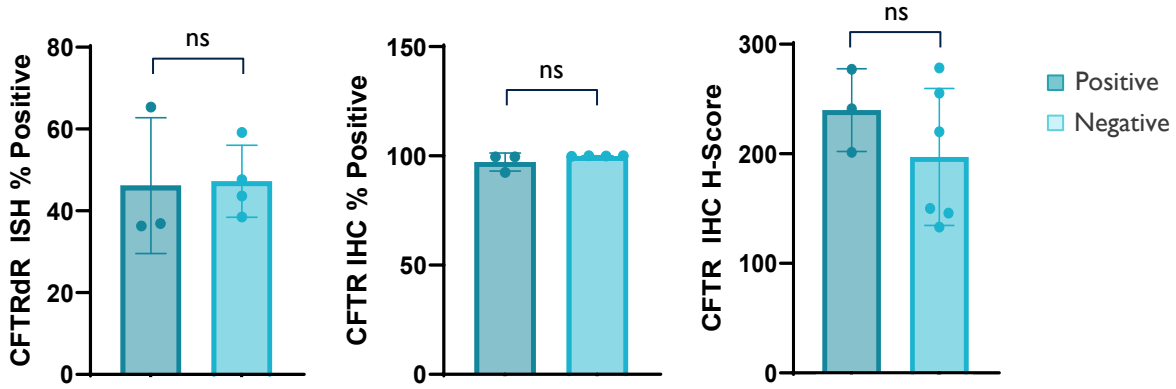
Pre-existing A101 Immunity and Transgene-mediated Protein Expression

Pre-existing A101 Immunity Did **NOT** Affect *CFTRΔR* RNA or CFTR Protein Expression

CFTR Expression According to Baseline Anti-A101 Antibodies



CFTR Expression According to Baseline A101-specific T Cells



Pre-existing Anti-A101 Capsid Antibodies

- 3/9 positive for pre-existing A101 capsid antibodies*
- **No significant difference in mRNA/protein expression** between participants with (n=3) and without (n=6) pre-existing A101 antibodies
- No observed effect of pre-existing antibodies on safety

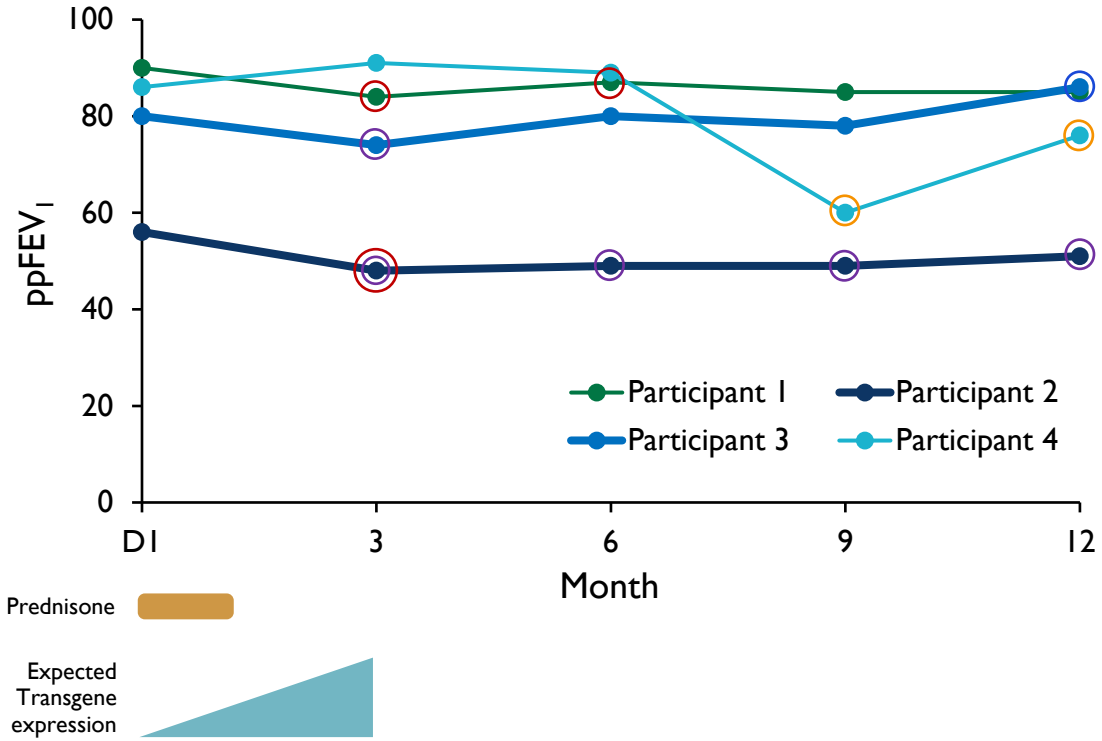
Pre-existing A101-specific T cells

- 3/7 positive for pre-existing A101-specific T cells†
- **No significant difference in mRNA/protein expression** between participants with (n=3) and without (n=4) pre-existing A101-specific T cells

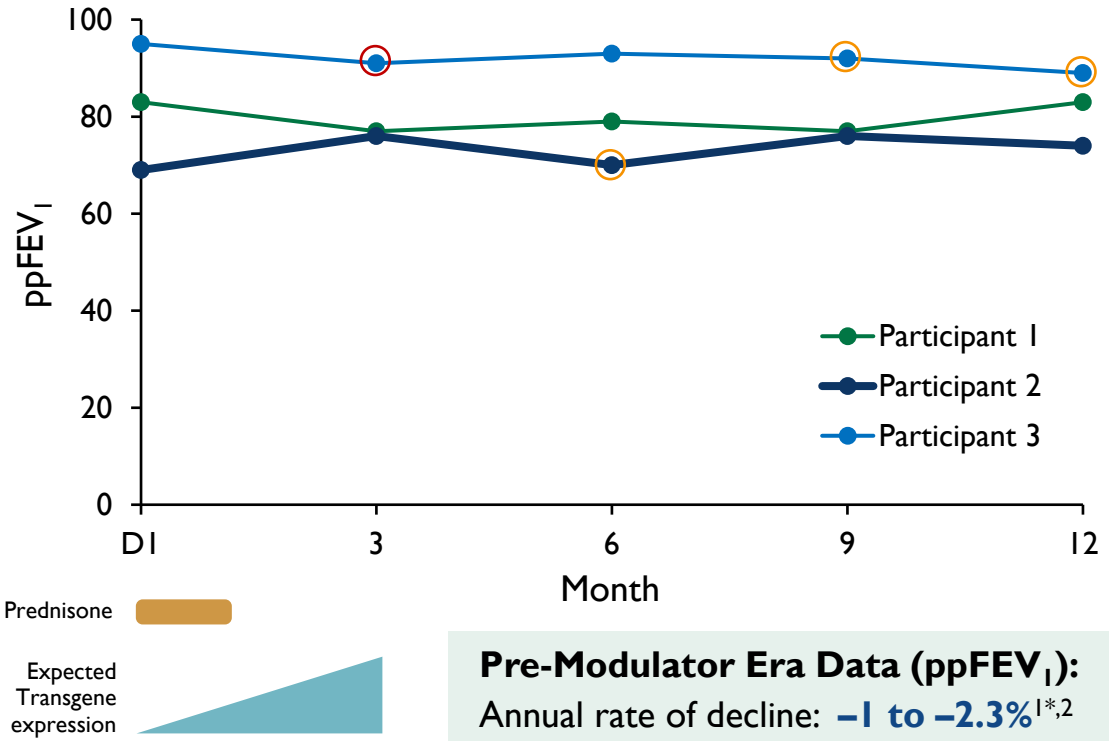
Best available data as of May 24, 2024. *Results pending for n=1 participant (5E14 vg group). †Results pending for n=2 and n=1 in the 5E14 vg and 2.5E14 vg cohorts, respectively.

Generally **Stable or Improved** $ppFEV_1$ through 12 Months (Maximum $ppFEV_1$ Follow-up per Original Protocol), Despite Non-4D-710 Respiratory-Related Adverse Events

4D-710 (2E15 vg)



4D-710 (1E15 vg)

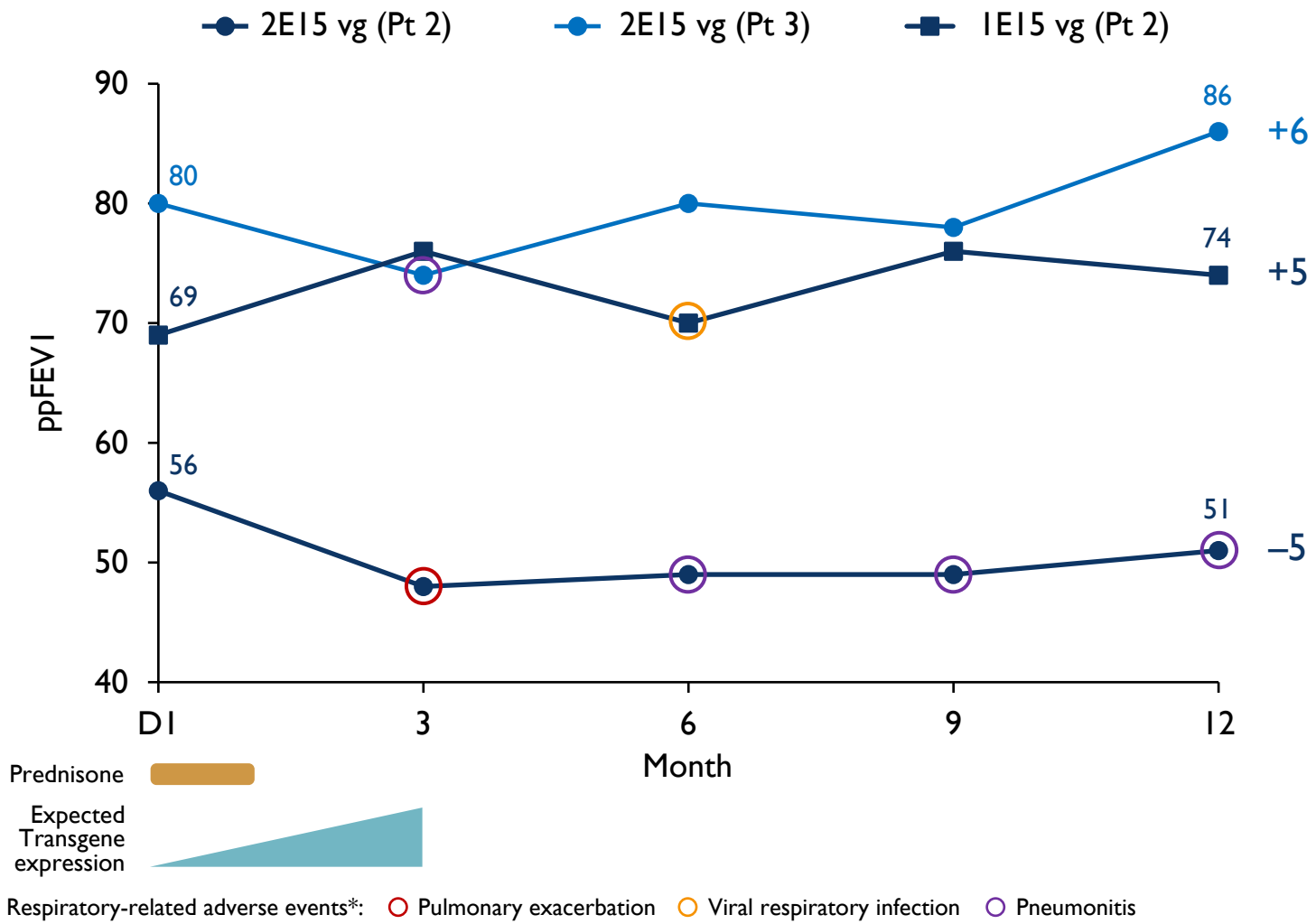


Pre-Modulator Era Data ($ppFEV_1$):
Annual rate of decline: **–1 to –2.3%**[1*,2]
Within-subject variability: **SD ±4.5%**[3]

Respiratory-related adverse events*: ○ Pulmonary exacerbation ○ Viral respiratory infection ○ Pneumonitis ○ Hemoptysis

Best available data as of May 24, 2024. *Occurring within 21 days of pulmonary function assessment. †Estimate based on *DF508* homozygous population, which appears to have a similar rate of decline as Class I (null) variant population. 1. Konstan MW et al. *Lancet Respir Med* 2017; 5:107–18. 2. Caley et al. Journal of Cystic Fibrosis 2021;20:86–90. 3. Stanbrook MB et al. *Chest* 2004; 125:150–5.

Two of Three Participants with Mild to Moderate ppFEV$_1$ Impairment at Baseline Showed Improvement at 12 Months

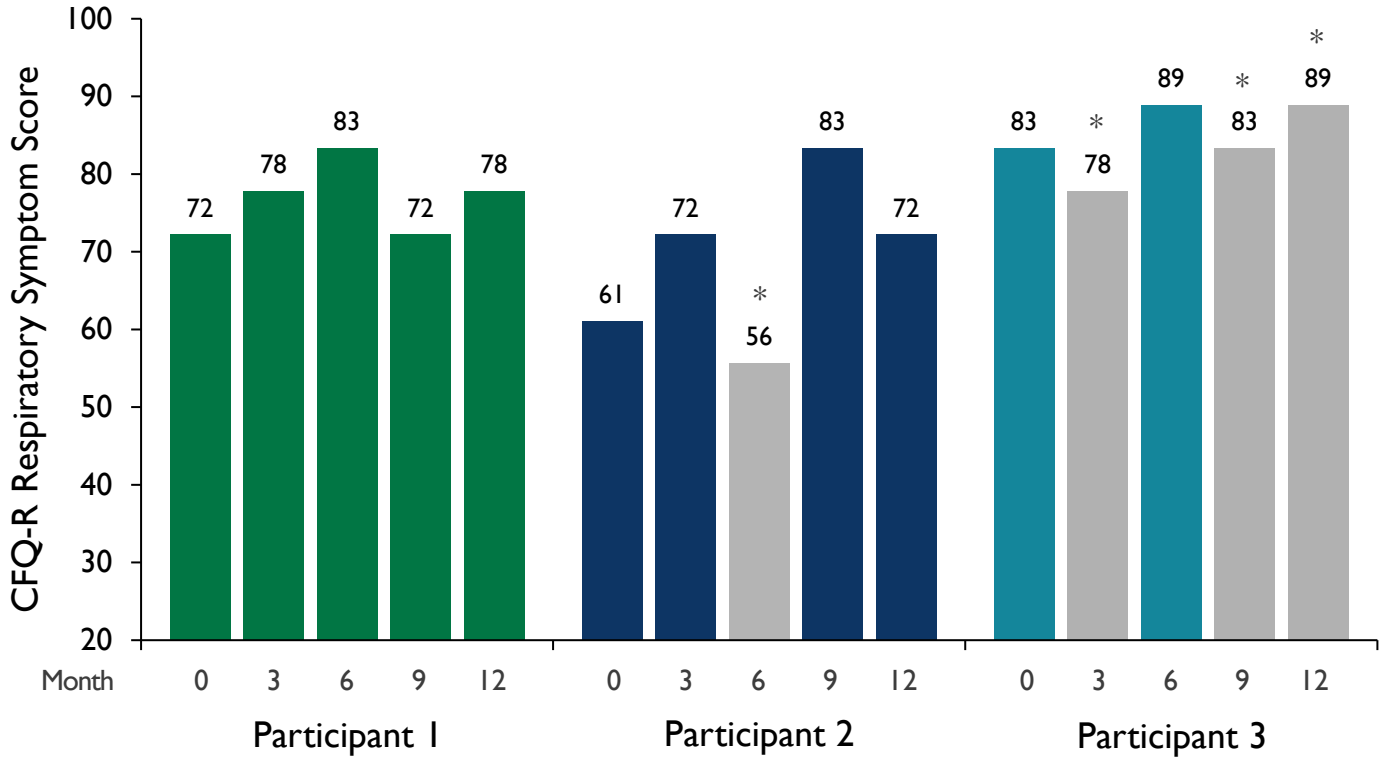


- Three participants had a baseline ppFEV$_1$ ≤80% and >6 months of follow up
- Two showed improvement in ppFEV$_1$ at 12 months
  - 2E15 vg (n=1): +6%
  - 1E15 vg (n=1): +5%

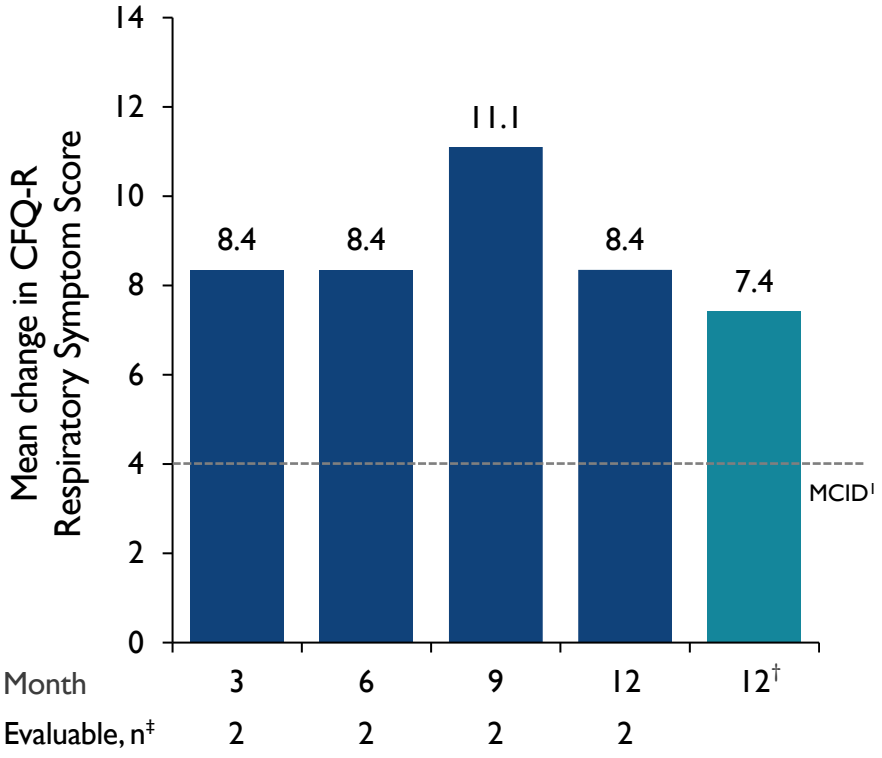
Best available data as of May 24, 2024.

4D-710 (1E15 vg): Durable Improvement in CFQ-R-R Score

CFQ-R Respiratory Symptom Score



Mean Change in CFQ-R-R Score



Best available data as of May 24, 2024. *Respiratory-related adverse event within 21 days of assessment. †All enrolled participants (n=3). ‡Excludes participants with a respiratory-related event within 21 days of assessment. CFQ-R-R, Cystic Fibrosis Questionnaire-Revised (respiratory symptoms scale). Scores range from 0 to 100, with higher scores indicating better health. MCID=4 points [1]. 1. Quittner AL et al. Chest 2009;135:1610–18.

Totality of Clinical & Biomarker Data To-date Supports **1E15 vg** as Intended Phase 2 Expansion Dose, 5E14 vg Dose Pending Additional Follow-Up

Dose Selection Criteria:		Target Profile
Expression	*CFTRΔR* RNA expression (ISH)	**≥15% cells**[1,2]
	CFTR protein expression (IHC)	**≥15% cells**[1,2]
	Cell types transduced	**Basal cells & secretory cells**
		No/limited expression in interstitial cells
	Pre-existing A101 Immunity	**No effect on expression**
Safety & Tolerability	Safety & tolerability	**No ≥Grade 3 related AEs, no SAEs**
Clinical Activity	$ppFEV_1$ (at 6-12 months)	**>4.5% change from baseline**
	CFQ-R-R (at 6-12 months)	**>4 points change from baseline**

Best available data as of May 24, 2024.
*Both events reported by one study participant (Participant 2) 1. Dannhoffer L et al. Am J Respir Cell Mol Biol 2009; 40:717–23. 2. Bell S et al. Lancet Resp Med 2020; 8:65–124.

Totality of Clinical & Biomarker Data To-date Supports **1E15 vg** as Intended Phase 2 Expansion Dose, 5E14 vg Dose Pending Additional Follow-Up

Dose Selection Criteria:		Target Profile	2E15 vg (n=4)	1E15 vg (n=3)	5E14 vg (n=1)	2.5E14 vg (n=1)
Expression	*CFTRΔR* RNA expression (ISH)	**≥15% cells**[1,2]		✓		
	CFTR protein expression (IHC)	**≥15% cells**[1,2]		✓		
	Cell types transduced	**Basal cells & secretory cells**		✓		
		No/limited expression in interstitial cells		✓		
	Pre-existing A101 Immunity	**No effect on expression**		✓		
Safety & Tolerability	Safety & tolerability	**No ≥Grade 3 related AEs, no SAEs**		✓		
Clinical Activity	$ppFEV_1$ (at 6-12 months)	**>4.5% change from baseline**		✓		
	CFQ-R-R (at 6-12 months)	**>4 points change from baseline**		✓		

Best available data as of May 24, 2024.
*Both events reported by one study participant (Participant 2) 1. Dannhoffer L et al. Am J Respir Cell Mol Biol 2009; 40:717–23. 2. Bell S et al. Lancet Resp Med 2020; 8:65–124.

Totality of Clinical & Biomarker Data To-date Supports **1E15 vg** as Intended Phase 2 Expansion Dose, 5E14 vg Dose Pending Additional Follow-Up

Dose Selection Criteria:		Target Profile	2E15 vg (n=4)	1E15 vg (n=3)	5E14 vg (n=1)	2.5E14 vg (n=1)
Expression	*CFTRΔR* RNA expression (ISH)	**≥15% cells**[1,2]		✓	✓	
	CFTR protein expression (IHC)	**≥15% cells**[1,2]		✓	✓	
	Cell types transduced	**Basal cells & secretory cells**		✓	✓	
		No/limited expression in interstitial cells		✓	✓	
	Pre-existing A101 Immunity	**No effect on expression**		✓	✓	
Safety & Tolerability	Safety & tolerability	**No ≥Grade 3 related AEs, no SAEs**		✓	✓	
Clinical Activity	$ppFEV_1$ (at 6-12 months)	**>4.5% change from baseline**		✓	*Pending*	
	CFQ-R-R (at 6-12 months)	**>4 points change from baseline**		✓	*Pending*	

Best available data as of May 24, 2024.
*Both events reported by one study participant (Participant 2) 1. Dannhoffer L et al. Am J Respir Cell Mol Biol 2009; 40:717–23. 2. Bell S et al. Lancet Resp Med 2020; 8:65–124.

Totality of Clinical & Biomarker Data To-date Supports **1E15 vg** as Intended Phase 2 Expansion Dose, 5E14 vg Dose Pending Additional Follow-Up

Dose Selection Criteria:		Target Profile	2E15 vg (n=4)	1E15 vg (n=3)	5E14 vg (n=1)	2.5E14 vg (n=1)
Expression	*CFTRΔR* RNA expression (ISH)	**≥15% cells**[1,2]	✓	✓	✓	✗
	CFTR protein expression (IHC)	**≥15% cells**[1,2]	✓	✓	✓	✓
	Cell types transduced	**Basal cells & secretory cells**	✓	✓	✓	✓
		No/limited expression in interstitial cells	✗	✓	✓	✓
	Pre-existing A101 Immunity	**No effect on expression**	✓	✓	✓	*Pending*
Safety & Tolerability	Safety & tolerability	**No ≥Grade 3 related AEs, no SAEs**	✗	✓	✓	✓
Clinical Activity	$ppFEV_1$ (at 6-12 months)	**>4.5% change from baseline**	✓	✓	*Pending*	*Pending*
	CFQ-R-R (at 6-12 months)	**>4 points change from baseline**	*Not interpretable*	✓	*Pending*	*Pending*
				Cleared	*Pending*	

Best available data as of May 24, 2024.
*Both events reported by one study participant (Participant 2) 1. Dannhoffer L et al. Am J Respir Cell Mol Biol 2009; 40:717–23. 2. Bell S et al. Lancet Resp Med 2020; 8:65–124.

Robust Safety, Biomarker, and Clinical Activity Profile Generated To-date Supports Advancement into Phase 2 Dose Expansion

- Expect to **begin enrollment in Phase 2 Expansion stage in H2 2024** starting with 1E15 vg (anticipate enrolling n= up to 9)
  - In parallel, complete evaluation of 5E14 vg as a potential 2nd Phase 2 dose by completing enrollment & follow-up of a 3rd participant in the 5E14 vg cohort in Phase 1 Dose Exploration
  - Amendment to AEROW submitted to the Cystic Fibrosis Therapeutics Development Network (TDN):
    1. Enroll pwCF with lower baseline $ppFEV_1$ (50-90%)
    2. Introduce 2nd lung biopsy procedure at 12 months
    3. Open cohort for 4D-710 in participants on CFTR modulators with persistent moderate to severe lung disease; expect to begin enrollment **in H2 2024**
  - Anticipate sharing interim data from AEROW in **mid-2025** after completing enrollment and f/u of Phase 2
- Initial GMP-ready suspension manufacturing process **completed in-house at 500-liter scale**; technology transfer initiation to commercial CDMO anticipated H1 2025

pwCF = people with cystic fibrosis; ppFEV1, percent predicted forced expiratory volume in 1 second

Preliminary Registration Path for 4D-710 for Treatment of People with CF Who are Modulator-Ineligible/-Intolerant

Preliminary Phase 3 Design	
N=	~60-80
Population	pwCF with low baseline ppFEV$_1$ (planned ~40-80%)
Design	Randomized, placebo-controlled (with opportunity for cross-over)
Endpoints	Δ in: ppFEV$_1$, quality-of-life (CFQ-R-R), frequency of pulmonary exacerbations

Accelerated Approval

Additional FDA/EMA discussions to follow additional AEROW clinical and lung biomarker data in pwCF with lower baseline ppFEV$_1$ (50-90%) to evaluate correlation between clinical and biomarker endpoints

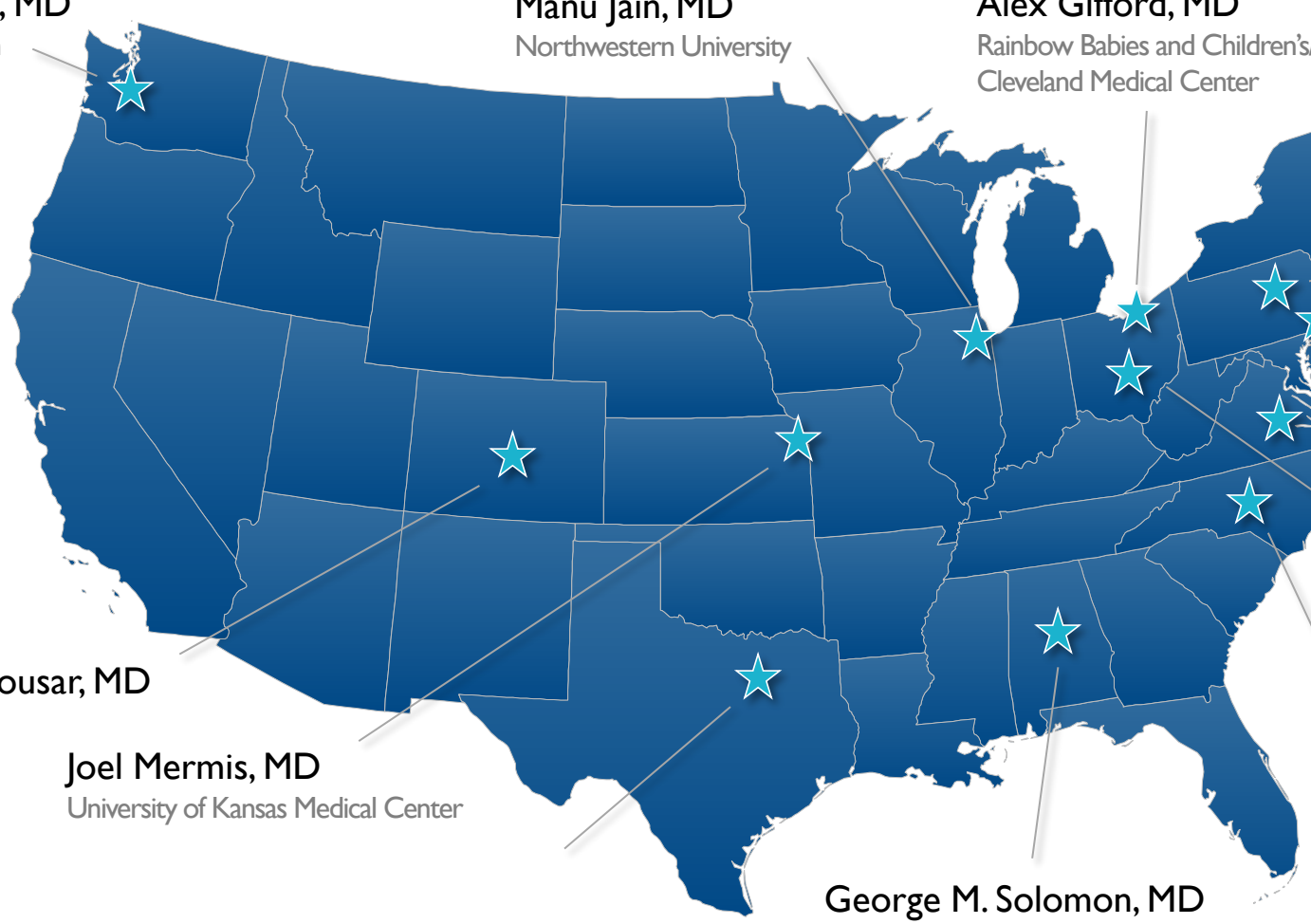
Initiation planned in **H2 2025**

pwCF = people with cystic fibrosis; CFQ-R-R: Cystic Fibrosis Questionnaire Revised Respiratory Domain

Pulmonology Pipeline Key Expected Milestones

VECTOR DELIVERY	PRODUCT CANDIDATE	INDICATION	EPIDEMIOLOGY (PREVALENCE)	RESEARCH CANDIDATE	IND-ENABLING	PHASE 1/2	PHASE 3	EXPECTED UPCOMING MILESTONES
PULMONOLOGY **AAT** **Aerosol** 	4D-710	Cystic Fibrosis Lung Disease (modulator ineligible / intolerant)	*~15K WW*			AEROW		▪ **Mid-2025** Interim data update from Phase 1/2 AEROW clinical trial ▪ **H2 2025** Pivotal trial initiation
		Cystic Fibrosis Lung Disease (combo with modulators)	*~90K WW*			AEROW		▪ **H2 2024** Initiation of enrollment of modulator combination cohort
	4D-725	A1AT Deficiency Lung Disease	*~200K U.S./EUMM*					▪ **H2 2024** Program update

Acknowledgments: Participants and Their Families, Principal Investigators and Study Staff, CFF



Christopher Goss, MD
University of Washington

Manu Jain, MD
Northwestern University

Alex Gifford, MD
Rainbow Babies and Children's/
Cleveland Medical Center

Allen Lapey, MD
Massachusetts General Hospital

Henry Dorkin, MD
Boston Children's Hospital

Daniel Dorgan, MD
The Hospital of the University of Pennsylvania

Nauman A. Chaudary, MD
Virginia Commonwealth University Health

Karen S. McCoy, MD
Nationwide Children's Hospital

Scott Donaldson, MD
University of North Carolina at Chapel Hill

Jennifer Taylor-Cousar, MD
National Jewish Health

Joel Mermis, MD
University of Kansas Medical Center

George M. Solomon, MD
University of Alabama Child Health

CYSTIC FIBROSIS FOUNDATION THERAPEUTICS DEVELOPMENT NETWORK

CYSTIC FIBROSIS FOUNDATION®

Strong Cash Balance to Execute Through Key Near-Term Expected Milestones

Large Market Ophthalmology	4D-150 for **Wet AMD**	Initial interim 24-week analysis for Phase 2 Population Extension cohort (N=32) at ASRS: **July 2024**
		Update on Phase 3 clinical trial design: **Q3 2024**
		Initiation of first Phase 3 study: **Q1 2025**
	4D-150 for **DME**	Initial interim 24-week analysis for Phase 2 Dose Confirmation cohort (N=22): **Q4 2024**
	4D-175 for **GA**	IND filing: **Q2 2024** Phase 1 initiation: **H2 2024**
Pulmonology	4D-710 for **CF**	Interim data update from Phase 1/2 AEROW clinical trial: **Mid-2025** Pivotal trial initiation: **H2 2025**
Cash Balance		**$589M cash as of end Q1 2024; Runway into H1 2027**

4DMT

THANK YOU

5858 Horton Street, Suite 455 | Emeryville, California 94608

(510) 505-2680 | Investor.Relations@4DMT.com

IR.4DMT.com | LinkedIn

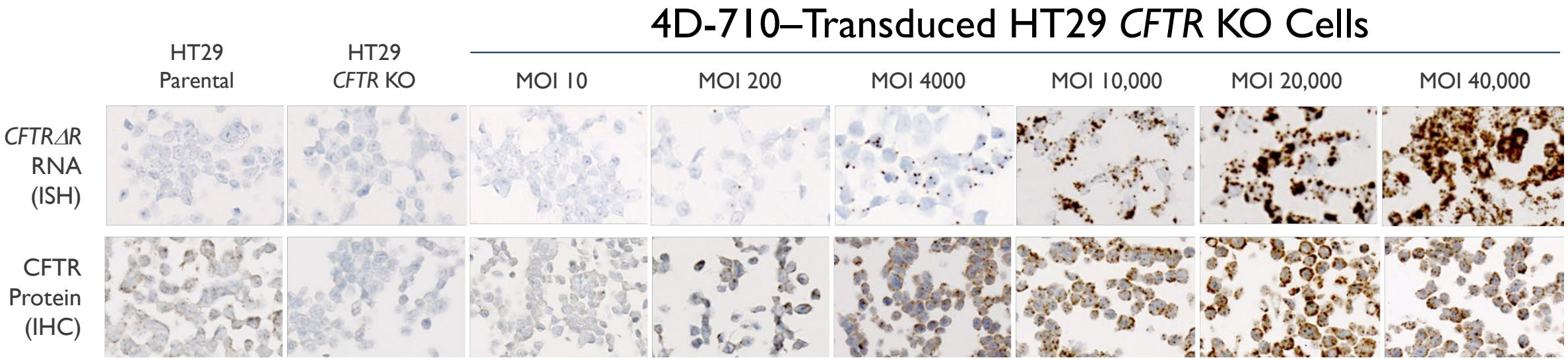
4DMT CFTR IHC Assay Development

Validated by Extensive Control Testing to Ensure Specificity to CFTR Epitope

Test	Control Cell/Tissue	Result
Specificity and Signal Differential	Transfected vs. un-transfected HEK293T cells	Confirmed
	Untreated HT29 vs. CFTR CRISPR-modified knockout HT29 cell lines	Confirmed
	Vehicle-treated vs. 4D-710–treated NHP lung tissue	Confirmed
	Commercial lung samples: normal lung (n=10); genotyped CF lung (n=35)	Confirmed
	Transduced CRISPR-modified knockout HT29 cell lines	Confirmed
	Western blotting using IHC antibody (M3A7)	Confirmed
Sensitivity	Transduced CRISPR-modified knockout HT29 cell lines (transduction across range of MOIs)	Confirmed
Negative Control	*CFTR* null lung samples (CF Foundation)	Confirmed
	NHP lung tissue treated with vehicle & A101 carrying alternate transgene	Confirmed
	Mouse IgG1-matched isotype controls (all tested lung samples)	Confirmed

IHC & ISH Assay Specificity and Sensitivity

Superior Sensitivity of IHC Compared to ISH Confirmed in 4D-710–Transduced HT29 *CFTR* CRISPR KO Cells



CFTR IHC and ISH % (+) vs 710 MOI in HT29 KO Cells

- IHC is more sensitive and has a different dynamic range compared to ISH

HT29 cells: human-derived intestinal epithelial cells expressing endogenous CFTR protein [1]. 1. Sood et al. *EMBO J* 1992;11:2487–94.

Historical & 4DMT Data Demonstrate Feasibility of Repeat Dosing for Aerosolized 4D-710

Rationale

- Repeat dosing desirable for this population
- **Historical data demonstrates feasibility of redosing:**
  - **NHP[1]:** Repeat dose **safe and well-tolerated**, transgene **expression levels for repeat dose similar to single dose**
  - **Rabbit[2] and ferret[3]:** **Similar transgene expression results** for repeat dose **in the presence of treatment emergent serum & anti-capsid NAbs**
  - **Human[4]:** 70 patients with aerosol AAV.CFTR – **3 doses over 2 months well tolerated**

4DMT Results

- **4DMT data demonstrates initial feasibility:**
  - **NHP pre-existing anti-A101 immunity** (cross-reactivity)**:** Safe & equivalent transduction vs immune (-) NHP
  - **4D-710 AEROW in 5 pwCF with pre-existing anti-A101 immunity:** Safe & equivalent transduction vs immune (-) pwCF

Next Steps: AEROW study results will inform timing

- Plan to implement lung biopsies **at Month 12** post-dosing to understand long term expression kinetics
- Observe durability of clinical activity: CFQ-R-R & $ppFEV_1$

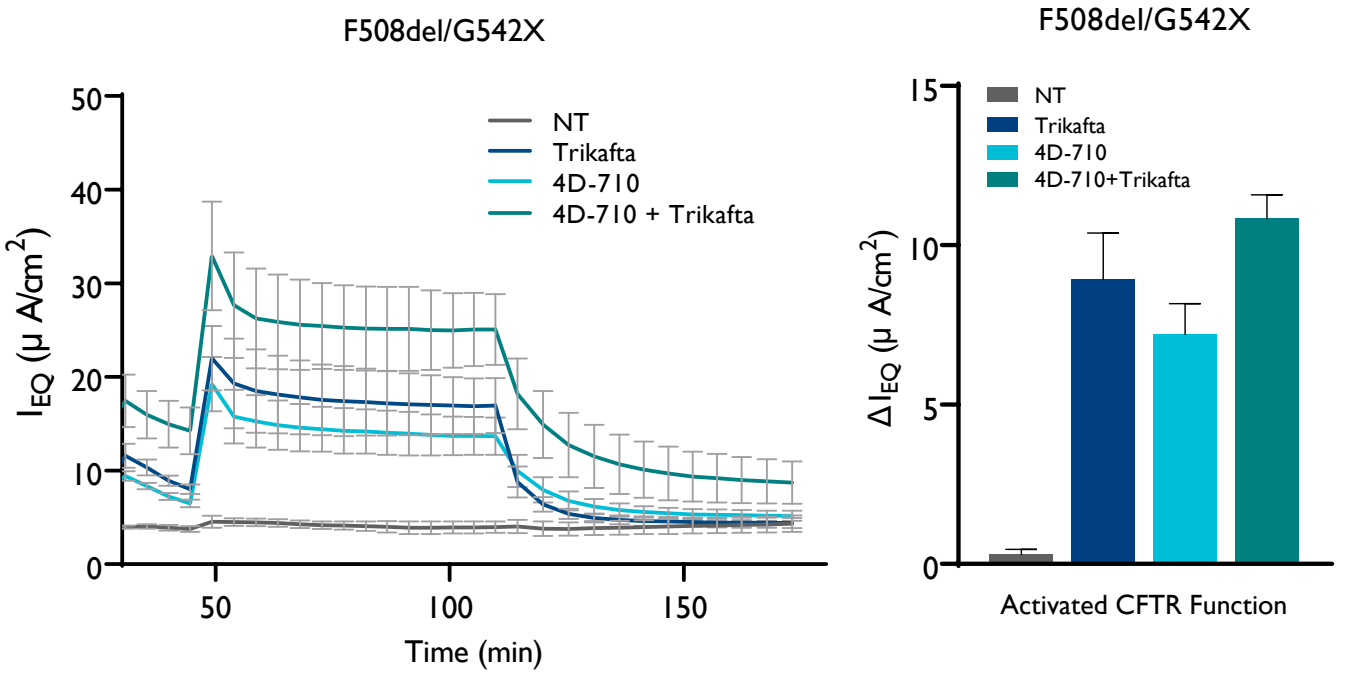
1. Fischer AC et al., *Mol Ther* 2003; 8:918-26 2. Beck SE et al. *J Virol* 1999; 73:9446-55 3. Tang Y et al., *Mol Ther Methods Clin Dev* 2020;19:186-200; Tang Y. et al., *Mol Ther Methods Clin Dev* 2023;29:70-80 4. Moss RB et al., *Chest* 2004;125:509-21; Moss RB et al., *Hum Gene Ther* 2007;18:726-32. CFQ-R-R, Cystic Fibrosis Questionnaire-Revised (respiratory symptoms scale); pwCF = people with cystic fibrosis; $ppFEV_1$, percent predicted forced expiratory volume in 1 second.

Strong Rationale for 4D-710 + Trikafta Combination

Rationale

- **Unmet need remains**
  - Trikafta Ph 3 results suggest population with suboptimal response, remaining unmet need
- **Scientific rationale: additive effects**
  - Different MOAs
  - Different cells & cell types may be targeted
  - Modulators treat extra-pulmonary tissues
- **Scientific rationale: synergistic effects**
  - 4D-710 transduction increased by modulators (mucus thinning)
  - Modulators predicted to bind/improve CFTRΔR function
  - Targeting different cell types & distribution

In vitro: 4D-710+Trikafta = **CFTR Function Improvement**



Next Steps:
Plan to begin enrolling combination cohort in H2 2024

CFTR activity in CFhBE ALI airway epithelial cultures transduced with 4D-710 (1x10^6) for 7 days and/or Trikafta (2 μM VX-445, 3 μM VX-661, 0.1 μM VX-770) for 24hr; n=3 different experiments; error bars, ±SEM. F508del/F508del Donor ID#: KKCFFT006f; F508del/G542X Donor ID#: KKD017K. CFhBE, cystic fibrosis primary human bronchial epithelial celsl; ALI, air-liquid interface; CFTR, cystic fibrosis transmembrane conductance regulator; NT, not treated.