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

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

November 1, 2023

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This Presentation discusses our product candidates that are under preclinical study and in clinical trials, and which have not yet been approved for marketing by the U.S. Food and Drug Administration. No representation is made as to the safety or effectiveness of our product candidates for the therapeutic use for which they are being studied.

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Presentations Featuring 4D-710: 2nd Consecutive Year in Plenary

2023 North American Cystic Fibrosis Conference (NACFC)

Plenary

PL1- Genetic Therapies for All: Harnessing Cross-Disease Knowledge for Breakthroughs in Cystic Fibrosis

Thursday, November 2, 2023 | 4:30 PM – 6:00 PM MST | Location: North Ballroom A-D

Speaker(s)

Paul B. McCray, Jr., MD (he/him/his)

University of Iowa

Symposium

S14--Restoration of CFTR Ion Transport for All People With CF

S14.2- Building the Path to the Cure: the role of AAV therapy

Friday, November 3, 2023 | 3:30 PM – 5:30 PM MST | Location: 102 AB (West)

Speaker(s)

Jennifer L. Taylor-Cousar, MD, MSCS

National Jewish Health

Plenary Session

PL1 Genetic Therapies for All: Harnessing Cross-Disease Knowledge for Breakthroughs in Cystic Fibrosis

Paul McCray, Jr., M.D.,
University of Iowa
Thursday November 2, 2023
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Session S14

Restoration of CFTR Ion Transport for All People with CF

S14.2 Building a Path to the Cure: the Role of AAV Therapy

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National Jewish Health
Friday, November 3, 2023
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Positive 4D-710 Data Strengthens 4DMT's Commitment to Pulmonology

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

4D-710 Clinical Update
(Phase 1/2 AEROW study n=7, 1E15 and 2E15 vg)

- **Well tolerated generally:** acute dosing & long-term f/u (up to 17 months)
- **Promising & reproducible** CFTR transgene expression: **all 7** participants
  - ✓ **100% (34 of 34)** of lung samples positive (+)
  - ✓ **Significantly higher than normal**: **98%** in airway tissue samples & **~450%** of normal
- **Durable** clinical activity through **12 months in Cohort 1** (Cohort 2 pending)

Next Steps

- Cohort 1 dose level (1E15 vg) **to continue into Phase 2**
- **Dose ranging continues** (5E14 – 2E15 vg): expression profile enables lower doses; first participant dosed in Cohort 3 (5E14 vg)
- **FDA feedback for monotherapy & modulator combination regimens** expected to be shared in Q1 2024

Wholly-Owned Pulmonology Franchise is a Key Value Driver

A101 Lung Vector Among Three Novel, Highly Targeted Next-Generation AAV Vectors Currently in the Clinic

VECTOR/ DELIVERY	PRODUCT CANDIDATE	INDICATION	RESEARCH CANDIDATE	IND-ENABLING	PHASE 1/2	PHASE 3	PRODUCT RIGHTS
OPHTHALMOLOGY R100 Intravitreal	4D-150	Wet AMD					4DMT
		Diabetic Macular Edema					
	4D-125	XLRP					4DMT
	4D-110	Choroideremia					4DMT
	4D-175	Geographic Atrophy					4DMT
	Undisclosed *Vector licensed to Astellas Pharma*	Undisclosed Rare Monogenic Ophthalmic Disease					astellas
PULMONOLOGY A101 Aerosol	4D-710	Cystic Fibrosis Lung Disease (monotherapy)					4DMT
		Cystic Fibrosis Lung Disease (combo with modulators)					
	4D-725	A1AT Deficiency Lung Disease					4DMT
CARDIOLOGY C102 IV	4D-310	Fabry Disease Cardiomyopathy					4DMT

A101: Next-Gen Aerosolized Genetic Medicine Vector for Pulmonology

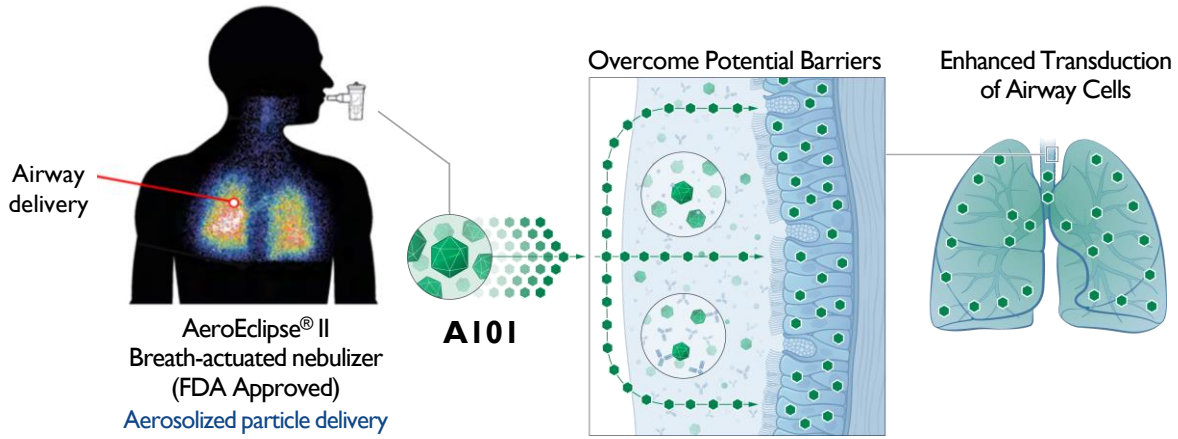
Prior aerosol gene therapy trials failed to achieve transgene expression in lung[1-3]; potential limitations:

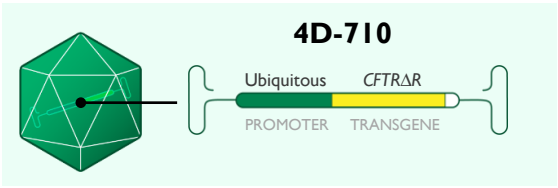
- ✕ Poor mucus penetration
- ✕ Inefficient airway cell transduction
- ✕ Suboptimal tissue tropism
- ✕ Susceptibility to clearance by antibodies

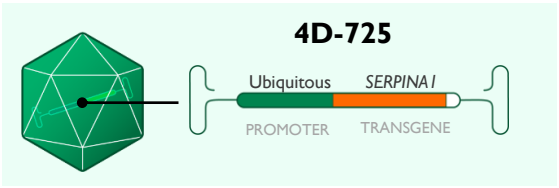
A101 invented at 4DMT to overcome these limitations:

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

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. 3. Moss RB et al. *Hum Gene Ther* 2007; 18:726–32.

Alan Cohen, M.D. Joins 4DMT as SVP, Therapeutic Area Head, Pulmonology

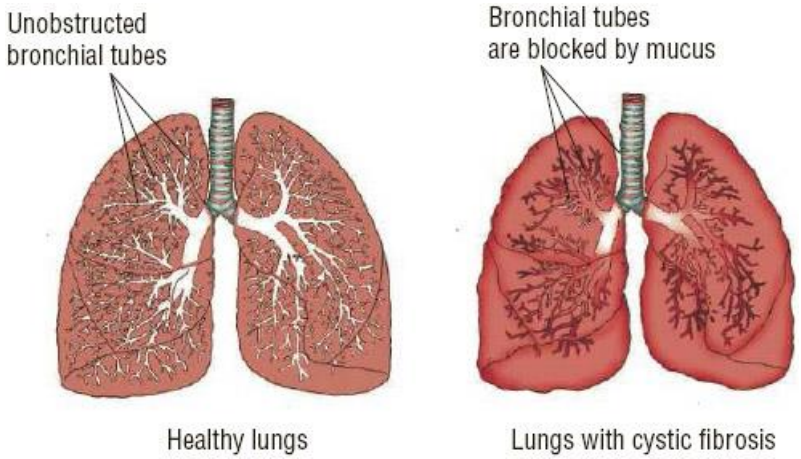
30+ Years of Extensive Pulmonology Expertise Including Cystic Fibrosis

- Board Certified **Pediatric Pulmonologist, Lung Transplant & Cystic Fibrosis Physician**
- Residency and Fellowship: **National Jewish Center/University of Colorado**
- Faculty positions:
  - **Stanford** (14 years): Adjunct Clinical/Teaching Faculty
  - **Johns Hopkins** (4 years): Adjunct Asst. Professor
  - **Washington University School of Med** (4 years): Asst. Professor/Director of Lung Transplant
- 20+ years in big pharma & biotech companies; leadership in Global Clinical Dev & Medical Affairs:
  - **Bayer**: Global Clinical Leader, Orphan Drug/Ped Clinical
  - **InterMune** (acquired by Roche/Genentech): SVP Global Medical Affairs
  - **Metagenomi**: SVP/CMO Clinical Development, Gene Editing
  - **BridgeBio/Eidos**: VP Global Medical Affairs
  - **Jazz Pharma**: CMO/VP, Clinical Development, Global Safety & Pharmacovigilance
- 100+ peer reviewed medical/scientific publications, incl CF, IPF & other lung diseases

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
- **Median survival (Pre-modulators):** ~40 years[1]



Epidemiology

- **~105,000[2,3] prevalence worldwide:**
  - ~40,000 prevalence in U.S. alone
  - ~1,000 incidence in U.S. alone

Standard of Care

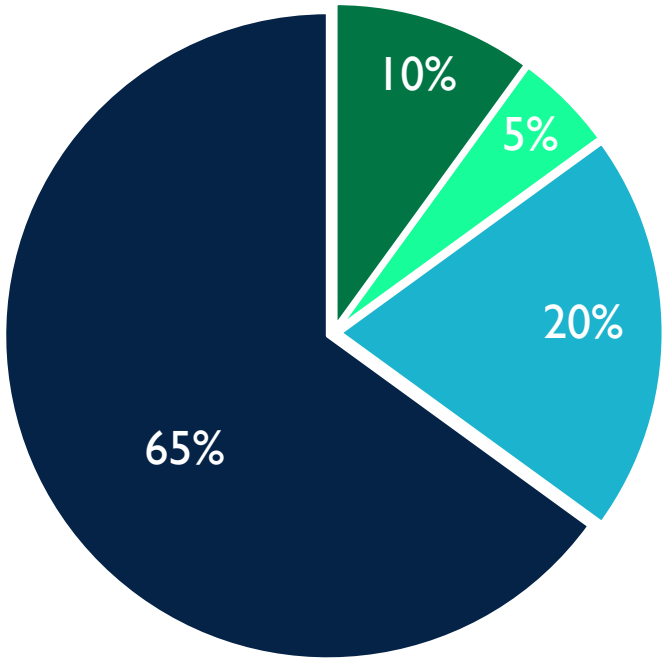
- **Daily Supportive Care:**
  - Airway clearance (~100 mins)
  - Inhaled antibiotics & bronchodilators
- **Disease modifying CFTR modulators:**
  - **$8.9 billion** annually (2022)[4]

Illustration by Frank Forney. © 2016 Cengage Learning 1. Ramsey & Welsh. *Am J Respir Crit Care Med* 2017;195:1092–9. 2. Guo J et al. *Journal of Cystic Fibrosis* 2022; 21:456-62. 3. Cystic Fibrosis Foundation. 4. Vertex Pharmaceuticals FY 2022 financial results. CFTR, cystic fibrosis transmembrane conductance regulator.

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**
- **Intolerant** to CFTR modulators — **~5k**

AEROW study population evaluating 4D-710 as **monotherapy**

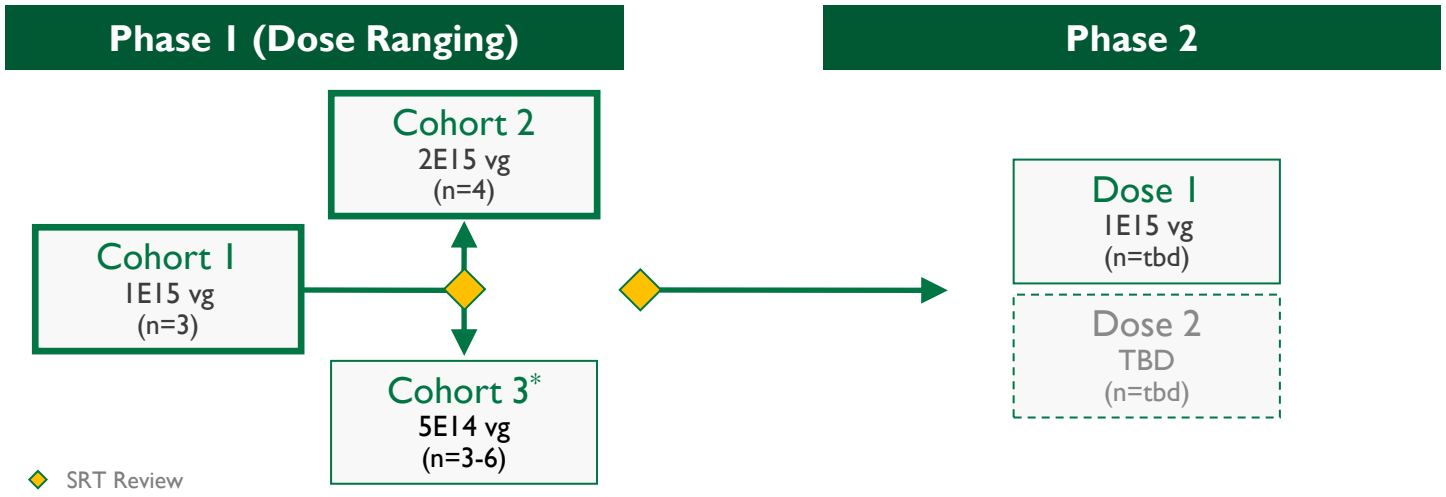
- **Suboptimal response** to CFTR modulators[1] — **~20k** Potential future 4D-710 study population
- Responsive to CFTR modulators — **~70k** *Upside if superior dosing, efficacy, and/or safety is demonstrated*

~35k

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

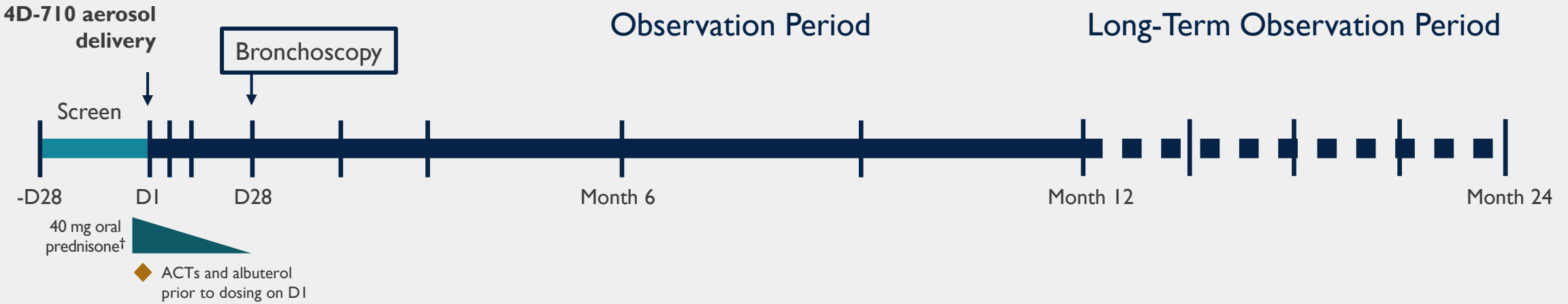
Phase 1/2 Designed to Identify Doses for Late-Stage Development

Generate Safety, Biomarker & Clinical Activity Data to Determine 2 Doses Incl Minimal Effective Dose



Key Endpoints:

- Safety & tolerability
- Lung biomarkers
- Clinical activity



Vertical bars represent study clinic visits. * Protocol allows for additional lower doses to be explored. † 28-day taper (Day -1 to Day 27). ACTs, Airway Clearance Techniques; SRT, Safety Review Team.

AEROW Enrolled Individuals with Generally Mild Baseline ppFEV$_1$ Impairment

2 Participants with Pre-Dosing NAbs to A101 Capsid

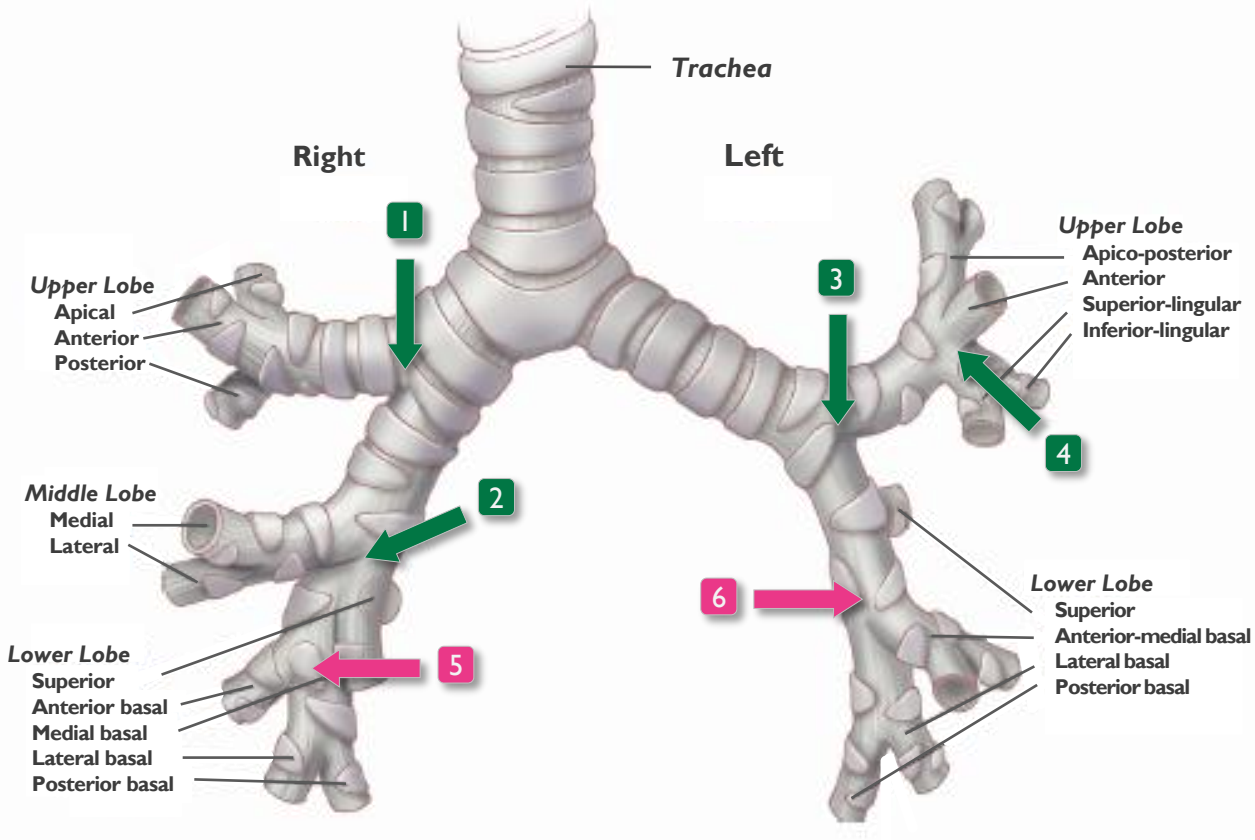
Characteristic	Cohort 1 (1E15 vg)			Cohort 2 (2E15 vg)			
	Participant 1	Participant 2	Participant 3	Participant 1	Participant 2	Participant 3	Participant 4
Age, y	36	24	20	37	27	32	69
Sex	Male	Male	Female	Female	Male	Female	Female
Race/ethnicity	Non-Hispanic white	Non-Hispanic white	Non-Hispanic white	Non-Hispanic white	Non-Hispanic white	Non-Hispanic white	Non-Hispanic white
CFTR modulator eligibility	Intolerable	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible	Intolerant
CFTR variant (class)	II/V	I/I*	I/II	I/I	I/I	I/I	II/II
Historical sweat chloride, mmol/L	74	103	110	84	96	103	114
Percent predicted FEV$_1$	**83**	69	**95**	**90**	56	**80**	**86**
Quality of Life (CFQ-R-RD)	72	61	83	78	72	89	78
Pre-dose NAb to A101 capsid	**Positive**	Negative	**Positive**	Negative	Negative	Negative	Negative

*Large gene deletion projected to result in a null variant profile. 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; CFQ-R-RD, Cystic Fibrosis Questionnaire–revised respiratory domain; NAb, neutralizing antibodies.

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.

4D-710 Significantly Exceeded Target CFTR Expression Profile in Airways

Target CFTR Expression Profile	Biomarker Results from Cohorts 1 & 2
✓ **Widespread** distribution throughout airways	**Confirmed: 100%** of bronchoscopy samples (+) (34 of 34)*
✓ **Reproducibility** between individuals	**Confirmed: 7 of 7** participants
✓ **All major epithelial cell types** (incl. basal cells & secretory cells)	**Confirmed: 7 of 7** participants
✓ Robust expression **regardless of baseline antibody titer** (initial redosing feasibility)	**Confirmed: 2 of 2** participants with pre-treatment anti-capsid antibodies, **no decrease in transduction efficiency observed**
✓ **≥15% of airway cells transduced with CFTR**[1,2]	**Significantly Exceeded: >98%** of airway cells CFTR (+)
✓ **≥15% of normal CFTR protein levels**[1,2]	**Significantly Exceeded: ~450% of normal** CFTR protein levels

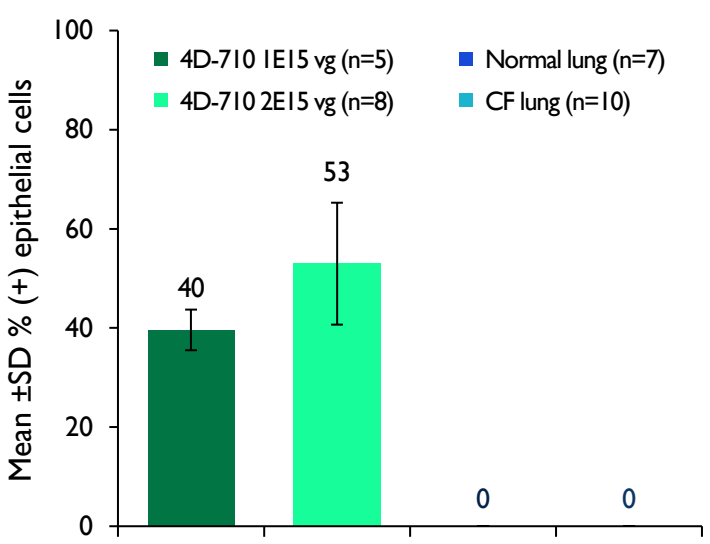
1. Dannhoffer L et al. *Am J Respir Cell Mol Biol* 2009; 40:717–23. 2. Bell S et al. *Lancet Resp Med* 2020; 8:65–124. *13/13 biopsy samples and 21/21 bronchial brushing samples. CFTR, cystic fibrosis transmembrane conductance regulator.

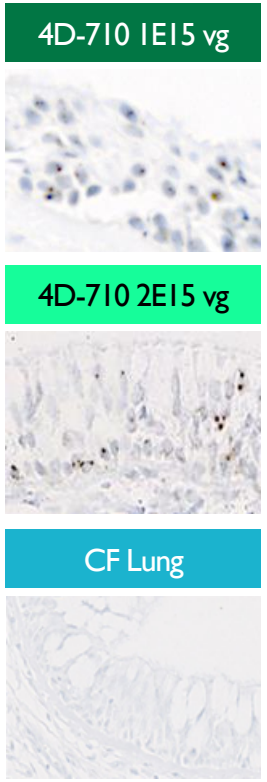
High-Level CFTR Expression in All 34 Lung Samples*

Robust 4D-710 Transgene Expression in Airway Epithelium Post Aerosol Delivery (7 Participants)

CFTRΔR RNA (ISH)

100% of samples (+) for *CFTRΔR* RNA

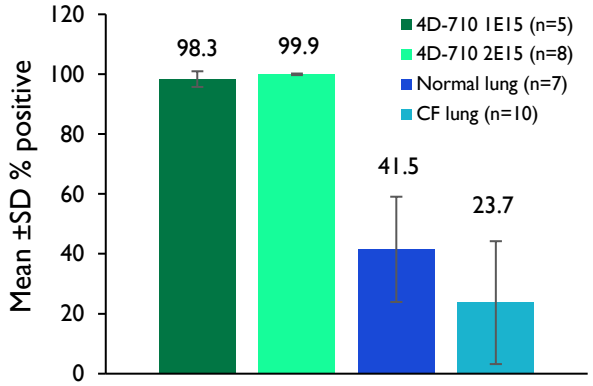


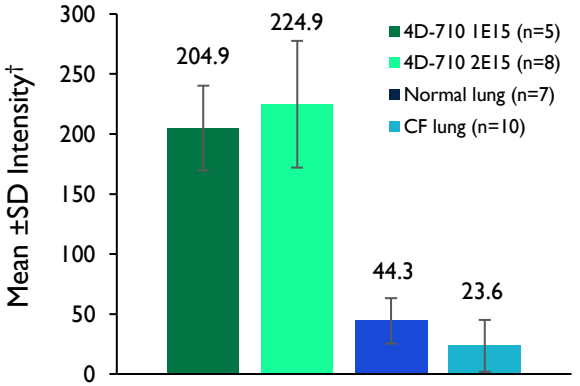


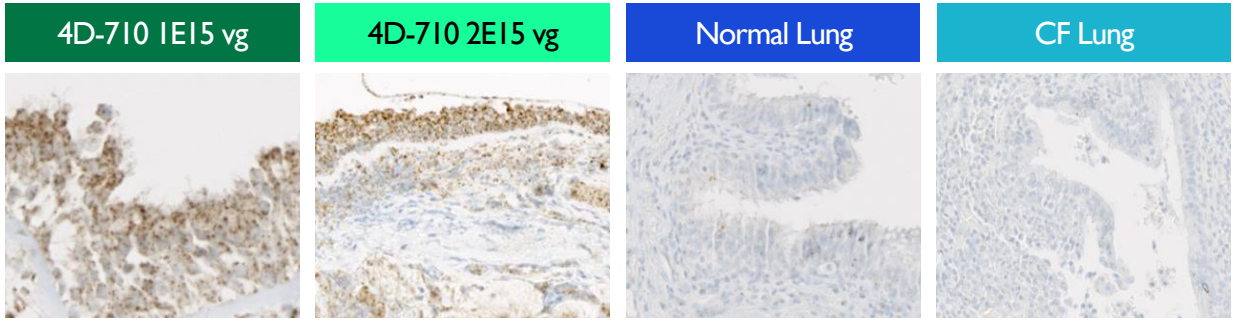
Robust levels of *CFTRΔR* RNA observed throughout the airway epithelium in biopsy samples from 4D-710–treated participants

CFTR Protein (IHC)

~100% of samples (+) for CFTR protein, **~450% of normal**





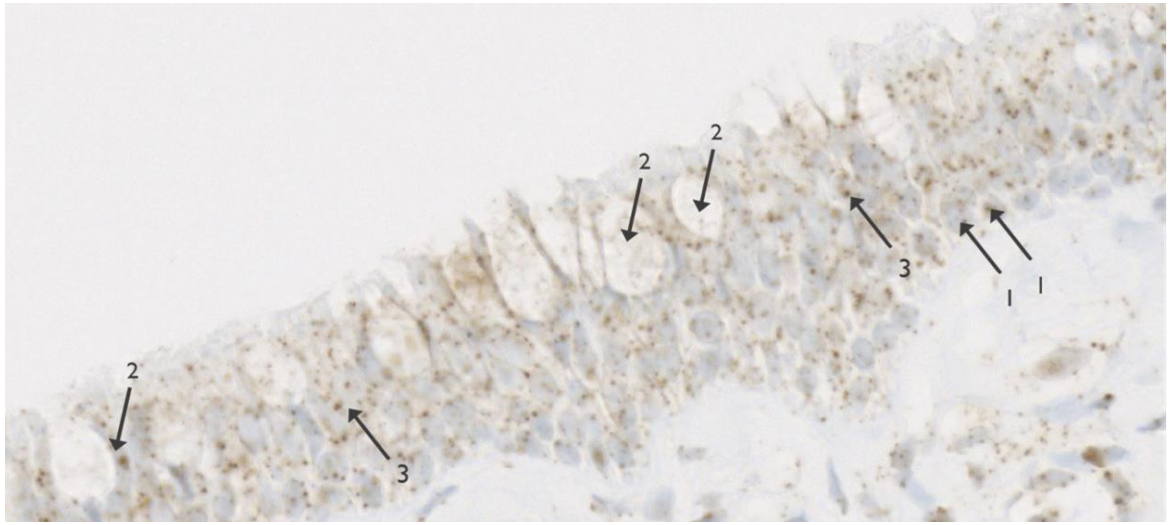


*13/13 biopsy samples and 21/21 bronchial brushing samples. †H-score. Quantification by Visiopharm AI Machine Learning Analysis. CFTR, cystic fibrosis transmembrane conductance regulator. IHC, immunohistochemistry; ISH, *in situ* hybridization; SD, standard deviation.

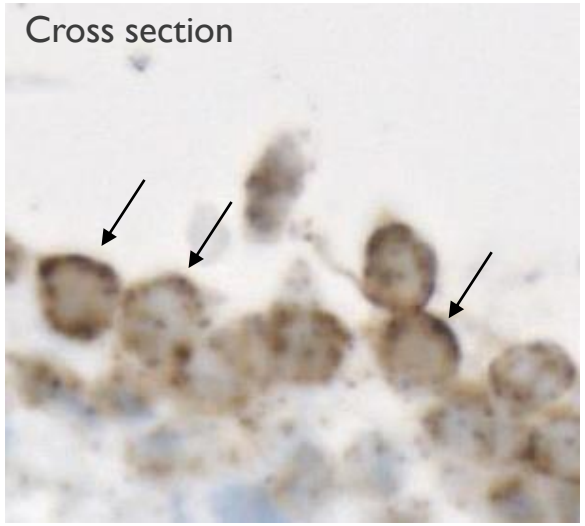
CFTR Protein Expression Observed in Multiple Bronchial Epithelial Cell Types

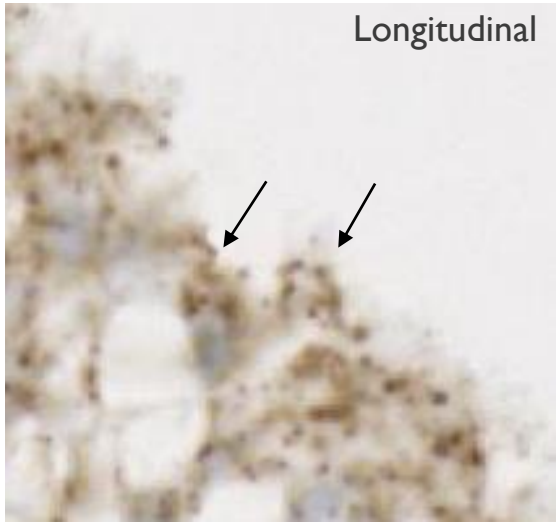
CFTR Protein Localization (IHC) Following 4D-710 Aerosol Treatment

CFTR Protein Expressed in Multiple Cell Types*



Localization to Apical Membrane†





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

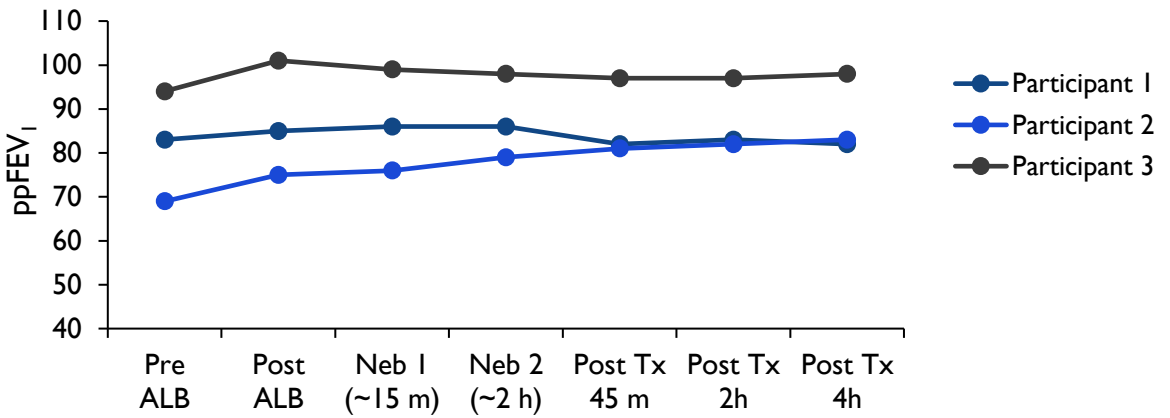
*Image from Cohort 1 participant. †Images from Cohort 2 participants. CFTR, cystic fibrosis transmembrane conductance regulator. IHC, immunohistochemistry.

No Clinically Significant AEs During Aerosol Administration of 4D-710

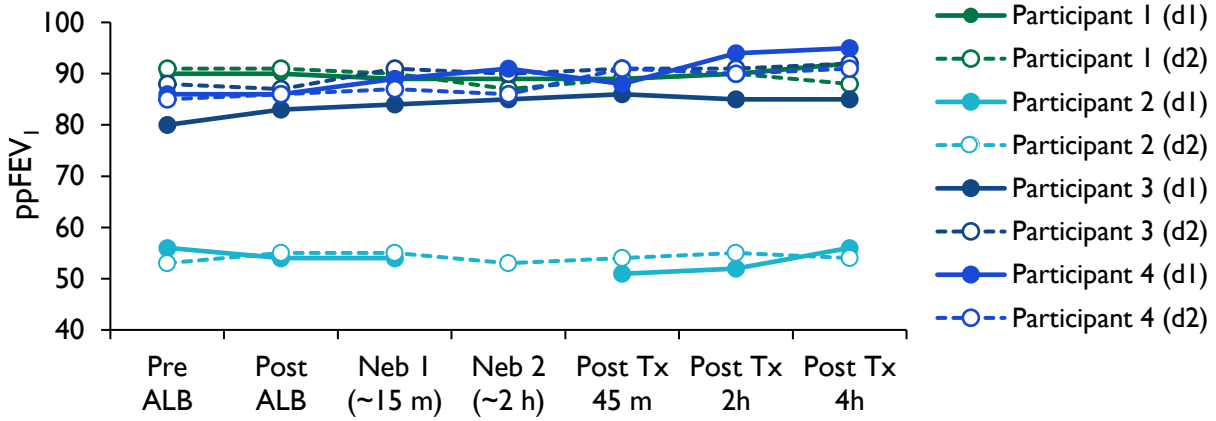
- Safety and spirometry monitored during and up to 4 h post dosing
- Generally well tolerated
- No bronchospasm
- Adverse events (n=3)
  - Cohort 1: mild dry throat (n=1)
  - Cohort 2: rhinorrhea (n=1), cough (n=1)

Serial Spirometry During 4D-710 Dosing

Cohort 1



Cohort 2

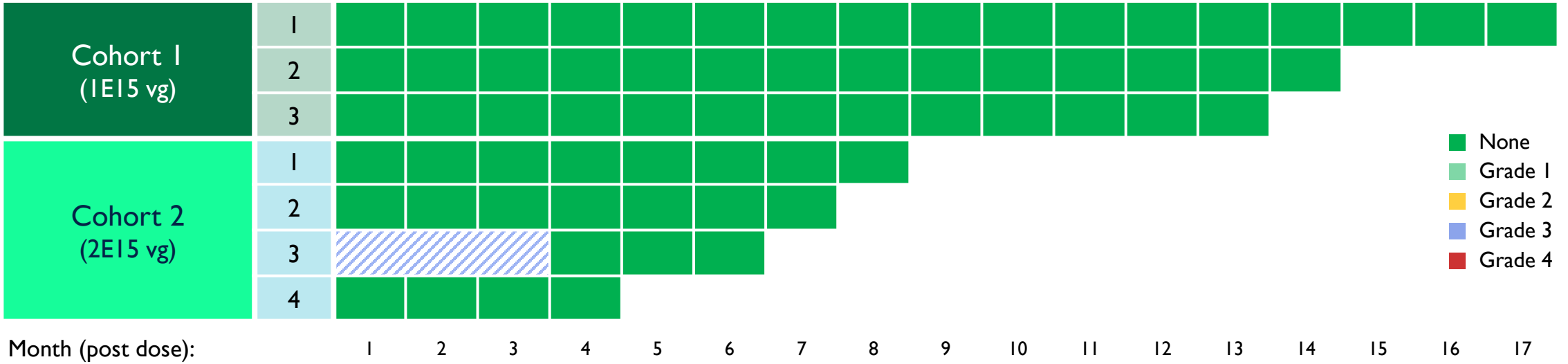


AE, adverse event; $ppFEV_1$, % predicted forced expiratory volume in 1 second; ALB, albuterol; NEB, nebulization. Tx, treatment

Generally Well Tolerated in 6 Participants with Up To 17 Months of Follow-Up

No Inflammation Observed in Airway Biopsies 4-8 Weeks Following 4D-710 Dosing

4D-710-Related Adverse Events Post-Dosing



- Background: In NHP GLP Tox studies, no inflammation or toxicity observed at dose ~5-fold[1] higher than Cohort 2 dose
- No inflammation observed in any lung biopsy samples via 3rd party pathologist evaluation
- Cohort 1: no related AEs in 3 of 3 participants
- Cohort 2: no related AEs in 3 of 4 participants
  - Single SAE (hospitalization <72 hours; pneumonitis NOS) at week 3: Consistent with bacterial pneumonia (next slide)

1. Human lung equivalent. NHP, non-human primate; GLP, good laboratory practices; AE, adverse event; SAE, severe adverse event; NOS, not otherwise specified.

Single SAE (Pneumonitis NOS): Consistent with Bacterial Pneumonia (*Inquilinus limosus*)

- **33 y.o. female, baseline ppFEV$_1$ of 80, history of chronic bacterial infection (including *I. limosus)* requiring IV/oral antibiotics 1-2 x/year, alternating monthly Tobi, and daily azithromycin**
- **Observation, antibiotic treatment course, and resolution**
  - Week 3 onset of dyspnea, ppFEV$_1$ decline (18 pp)
  - Hospitalized (<72 hours) & treated with O_2 & increased prednisone & released
  - After discharge, BALF culture results received (below), **prescribed 2-week course of IV antibiotics and prolonged steroid taper**
  - **Completely resolved over ~10 weeks, including ppFEV$_1$ returning to baseline value**
- **Clinical/BALF/Chest CT findings consistent with bacterial pneumonia (*I. limosus)*[1,2]**
  - WBC: 14,600 / µL (differential, 84% neutrophils, 9% lymphocytes, 5% monocytes)
  - HRCT (hospital radiologist): centrilobular nodularity, ground glass opacity; differential diagnosis incl. "atypical infection, cryptogenic organizing pneumonia"
  - BALF: *I. limosus,* 700,000 CFU / mL
  - Lung biopsy (Week 5): normal & no inflammation or toxicity
- **Relatedness assessment:** PI reported as possibly related

SAE, severe adverse event; NOS, not otherwise specified; IV, intravenous; ppFEV$_1$, % predicted forced expiratory volume in 1 second; BALF, bronchoalveolar lavage fluid; WBC, white blood cell; HRCT, high resolution computed tomography; PI, principal investigator. CT, computed tomography. WBC, white blood cell. 1. Farfour E et al. *Emerg Infect Dis* 2023;29:642–4. 2. McHugh KE et al. *Diagnostic Microbiol Infect Dis* 2016;86:446–9.

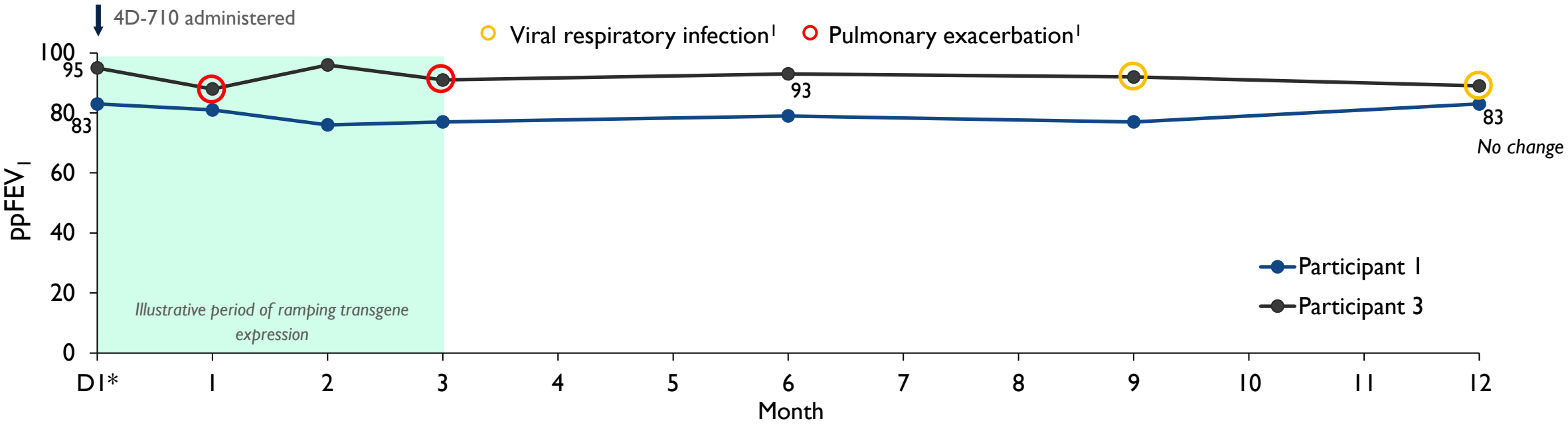
Decline Evident in Both ppFEV$_1$ and CFQ-R-RD at ~1 Year for Untreated People with Cystic Fibrosis

Assessment	Instrument	Historical Data
Spirometry	% Predicted FEV$_1$	Annual rate of decline: **-1 to -2.3%**[1*,2] Within-subject variability: **SD ±4.5%**[3†]
Health-related Quality of Life: Respiratory Symptoms	Cystic Fibrosis Questionnaire-Revised Resp. Domain (CFQ-R-RD)	48 week change from baseline: **Est. -4 points** placebo[4] MCID: **4 points**[5]

*-2.3% 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-RD, 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 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. 4. Ramsey et al. *N Engl J Med* 2011;365:1663–72. 5. Quittner AL et al. *Chest* 2009;135:1610–18.

Cohort 1: Durable ppFEV$_1$ Stabilization in Participants with **Mild/No** Lung Impairment

Stable Despite Pulmonary Exacerbations/Viral Respiratory Infections Not Related to 4D-710



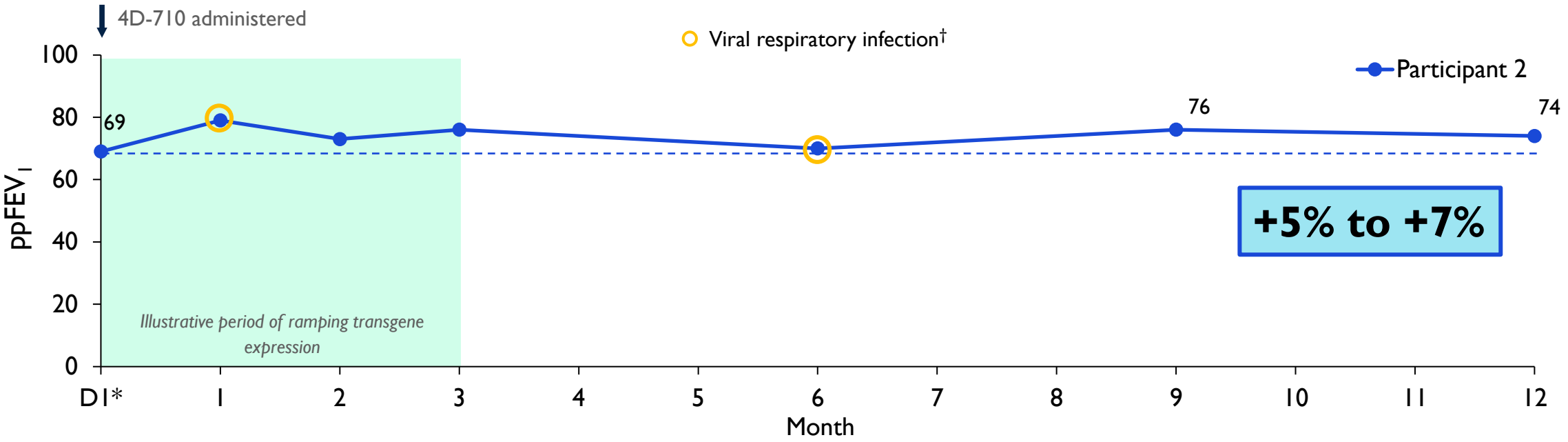
Start Day, Pulmonary Exacerbations/Viral Respiratory Infections (not related to 4D-710):

Cohort 1	Month 1	Month 3	Month 6	Month 9	Month 12	**Beyond Month 12**
Participant 1	**none**	**none**	**none**	**none**	**none**	**none** (through month 17)
Participant 3	Day 29: Grade 2 Infective PE	Day 81: Grade 1 Infective PE (*S. aureus*+)	**none**	Day 266: Grade 1 COVID-19	Day 329: Grade 1 Upper respiratory infection	**none** (through month 13)

1. Within 21 days of assessment. *Pre-dose spirometry assessment. ppFEV$_1$, percent predicted forced expiratory volume in 1 second; PE, pulmonary exacerbation.

Cohort 1: Durable ppFEV$_1$ Improvement in Participant with **Moderate** Lung Impairment

Range +1 To +10 Over 12 Months



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

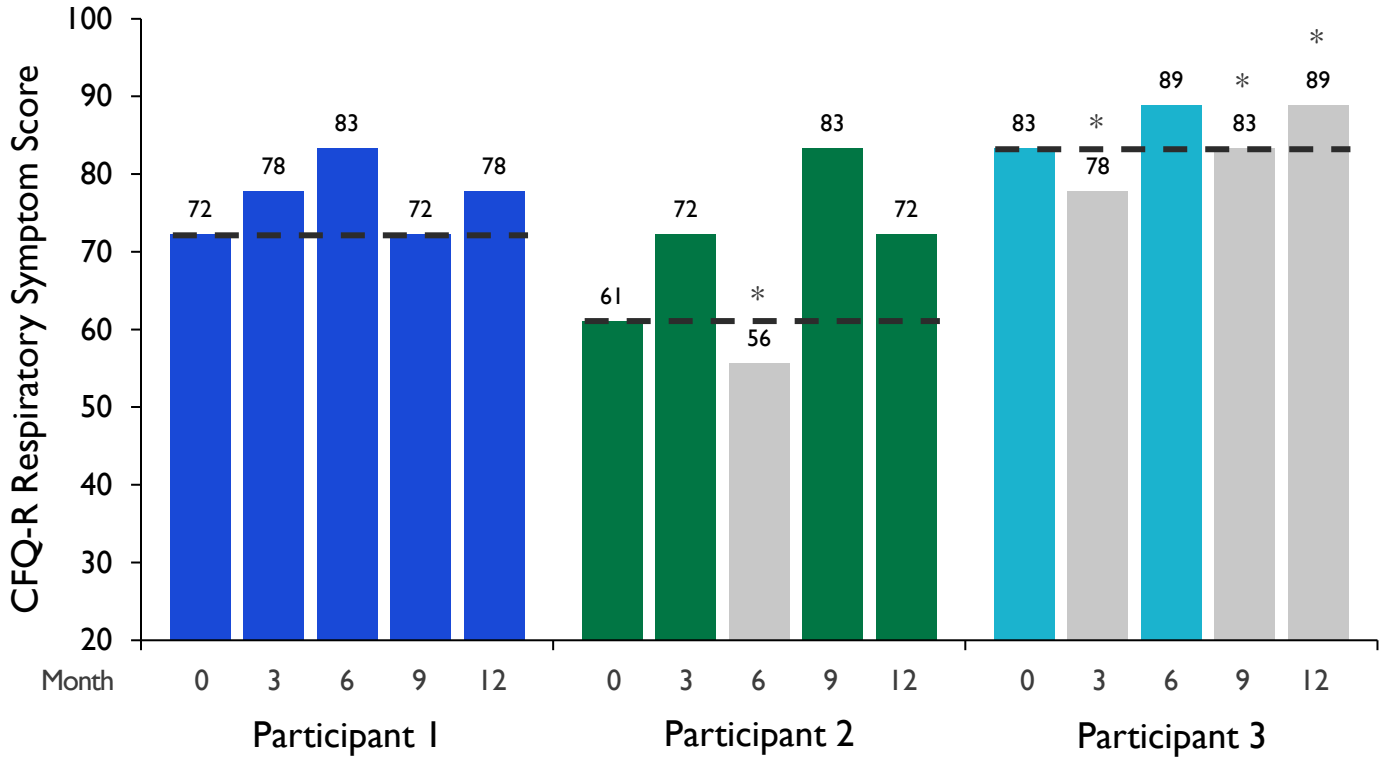
Cohort 1	Month 1	Month 3	Month 6	Month 9	Month 12	**Beyond Month 12**
Participant 2	Day 8: Grade 3 COVID-19, dyspnea	**none**	Day 176: Grade 1 rhinovirus	**none**	**none**	**none** (through month 14)

*Pre-dose spirometry assessment. ppFEV$_1$, percent predicted forced expiratory volume in 1 second. †Within 21 days of assessment.

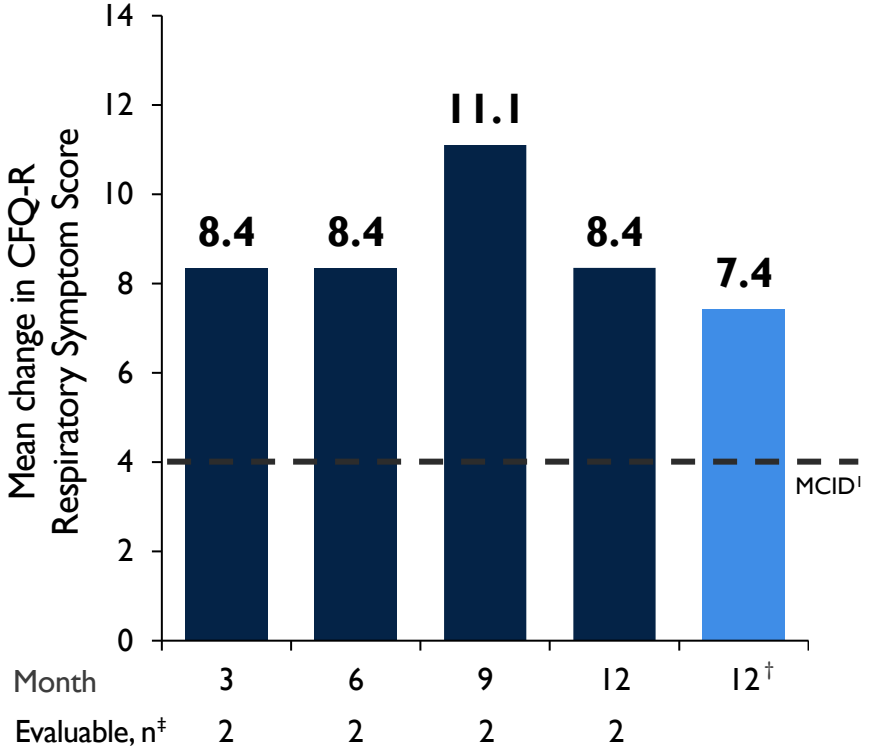
Cohort 1: Durable Improvement in CFQ-R-RD Quality of Life in All 3 Participants

Mean Increase of 8.4–11.1 Points Over 12 Months Consistently Above MCID

CFQ-R Respiratory Symptom Score



Mean Change in CFQ-R Score



*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-RD, 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.

Cohort 1: Improved and/or Stable in 3 Participants Treated with 4D-710

Assessment	Instrument	Historical Data	4D-710 Outcomes Through 12 Months (n=3)
Spirometry	% Predicted FEV_1	Annual rate of decline: **-1 to -2.3%**[1*,2] Within-subject variability: **SD ±4.5%**[3]	**BL Moderate: Improved (+5-7%)** BL Mild: Stable (0%) BL Normal: Stable (-2%)†
Health-related Quality of Life: Respiratory Symptoms	Cystic Fibrosis Questionnaire-Revised Resp. Domain (CFQ-R-RD)	48 week change from baseline: **Est. -4 points** placebo[4] MCID: **4 points**[5]	**Clinically meaningful improvement** (≥4 points; MCID): ▪ **3 of 3 participants** ▪ **Mean Increase of 8.4–11.1** and up to **+22 points**

*Estimate based on *DF508* homozygous population, which appears to have a similar rate of decline as Class I (null) variant population. †Based on last evaluable time point.
CFQ-R-RD, 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 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. 4. Ramsey et al. *N Engl J Med* 2011;365:1663–72. 5. Quittner AL et al. *Chest* 2009;135:1610–18.

Strong Clinical POC Further Advances 4D-710 Program

4D-710 Clinical Update
(Phase 1/2 AEROW study
n=7, 1E15 and 2E15 vg)

- **Well tolerated generally:** acute dosing & long-term f/u (up to 17 months)
- **Promising & reproducible** CFTR transgene expression: **all 7** participants
  - ✓ **100% (34 of 34)** of lung samples positive (+)
  - ✓ **Significantly higher than normal**: **98%** in airway tissue samples & **~450%** of normal
- **Durable** clinical activity through **12 months in Cohort 1** (Cohort 2 pending)

Next Steps

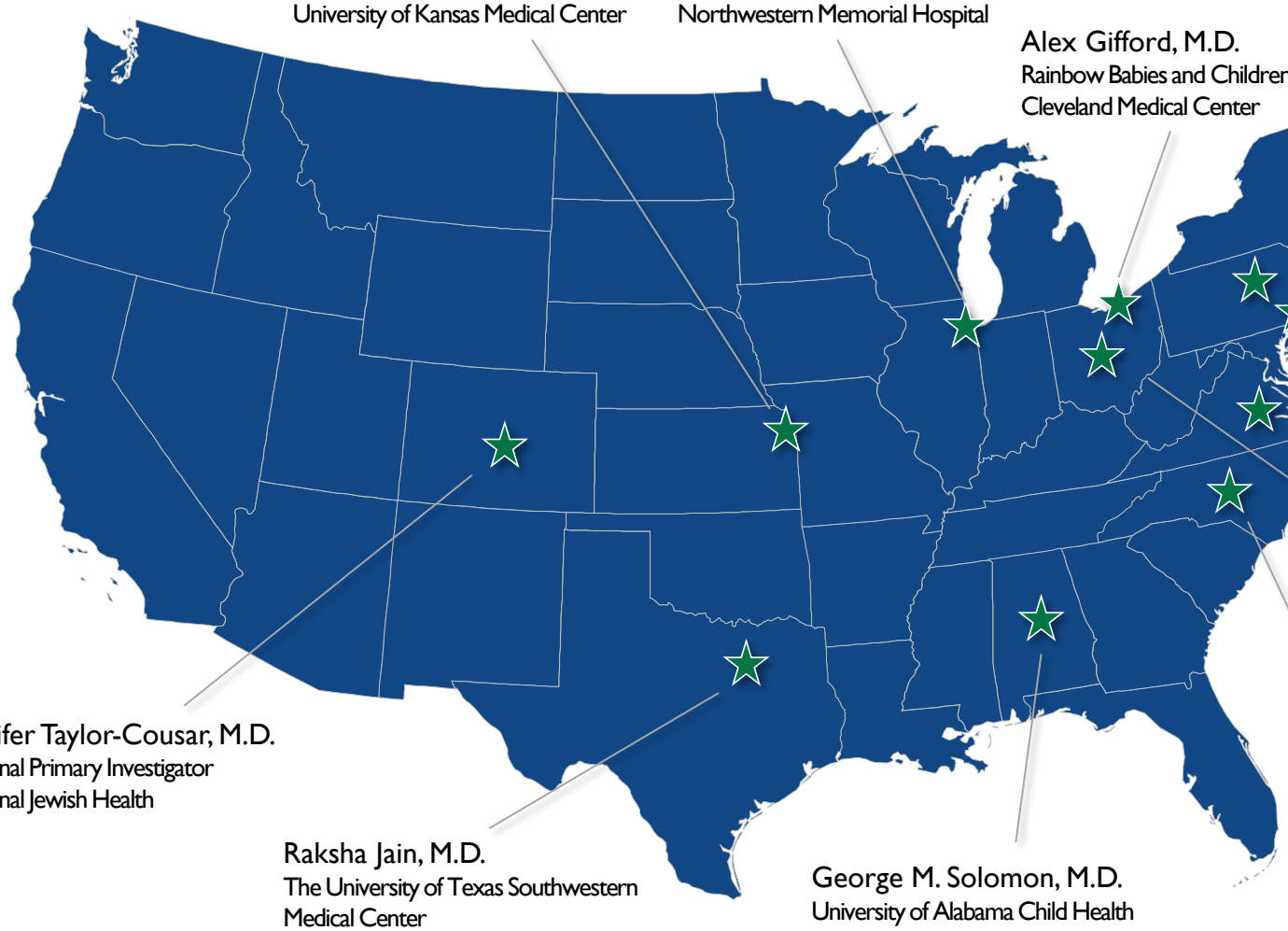
- Cohort 1 dose level (1E15 vg) **selected to continue into Phase 2**
- **Dose ranging continues** (5E14 – 2E15 vg): expression profile enables lower doses; first participant dosed in Cohort 3 (5E14 vg)
- **Opportunity to demonstrate functional benefit via additional measures:** HRCT, LCI, MCC, # & severity of bacterial PEs
- Opportunities for **redosing** and **modulator combination**
- **FDA feedback for monotherapy & modulator combination regimens** expected to be shared in Q1 2024

HRCT, high resolution computed tomography; LC, Lung Clearance Index; MCC, mucociliary clearance; PE, pulmonary exacerbation.

Significant Progress in Pulmonology Pipeline Expected in Next 12 Months

VECTOR DELIVERY	PRODUCT CANDIDATE	INDICATION	EPIDEMIOLOGY (PREVALENCE)	RESEARCH CANDIDATE	IND-ENABLING	PHASE 1/2	PHASE 3	UPCOMING MILESTONES
PULMONOLOGY **AAV** **Aerosol** 	4D-710	Cystic Fibrosis Lung Disease (monotherapy)	*~15K WW*					▪ **Q1:24** Share FDA feedback on development plan ▪ **Mid 24** Interim Ph 1 data
		Cystic Fibrosis Lung Disease (combo with modulators)	*~90K WW*					▪ **Q1:24** Share FDA feedback on development plan
	4D-725	A1AT Deficiency Lung Disease	*~200K U.S./EUMM*					▪ **2024** Program update

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



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CYSTIC FIBROSIS FOUNDATION THERAPEUTICS DEVELOPMENT NETWORK

CYSTIC FIBROSIS FOUNDATION®

7+ Year Collaboration & ~$20M in Financial Support From CFF to Accelerate Development of 4DMT Lung Vectors and Product Candidates for People with CF

	Mechanism	CFF Expertise	Financials
CYSTIC FIBROSIS FOUNDATION®	Research Grant *(2016)*	**Gain access to:** ▪ CFF scientists & specialists ▪ *In vitro* assays ▪ Animal models ▪ World renowned research lab ▪ CF patient samples ▪ Patient registry including data from >32k people with CF	***$6.3M*** *(recently increased by $2.8M)*
	Equity Investment *(2020-21)*		***$14M***
CYSTIC FIBROSIS FOUNDATION THERAPEUTICS DEVELOPMENT NETWORK	Phase 1/2 Trial AEROW *(Sanctioned by TDN in 2022)*	▪ Deep development experience conducting >150 clinical studies for CF ▪ Access to >90 accredited care centers with demonstrated expertise in clinical research	*N/A*

Thank You

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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 2 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 later timepoint(s) post-dosing
- Observe durability of clinical activity: CFQ-R-RD & $ppFEV_1$

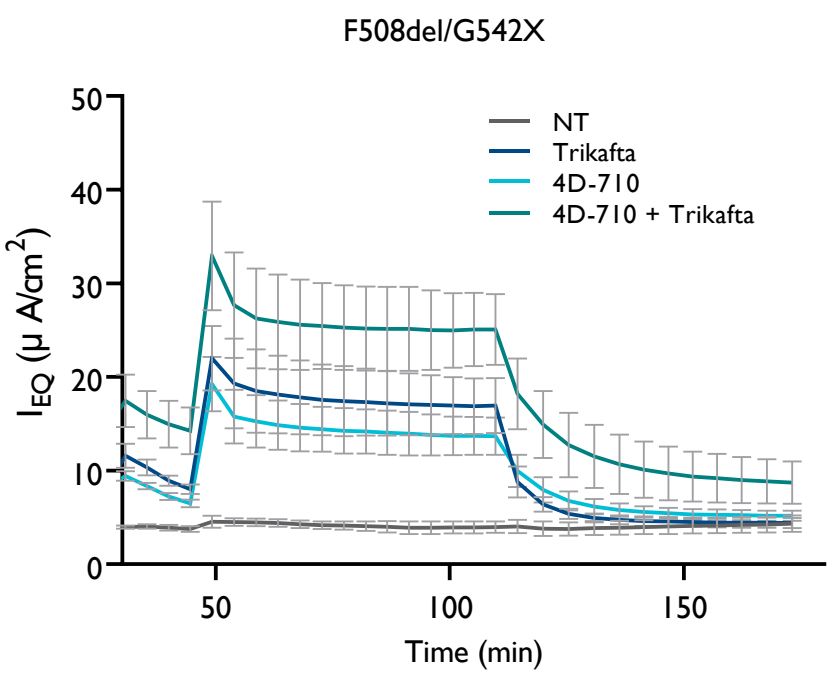
1. Fischer AC et al., *Mol Ther* 2003; 8:918-26 2. Beck SE et al. *J Virol* 1999; 73:9446-55 3. Tang Y et al., *Mol Ther Methods Clin Dev* 2020;19:186-200; Tang Y. et al., *Mol Ther Methods Clin Dev* 2023;29:70-80 4. Moss RB et al., *Chest* 2004;125:509-21; Moss RB et al., *Hum Gene Ther* 2007;18:726-32.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

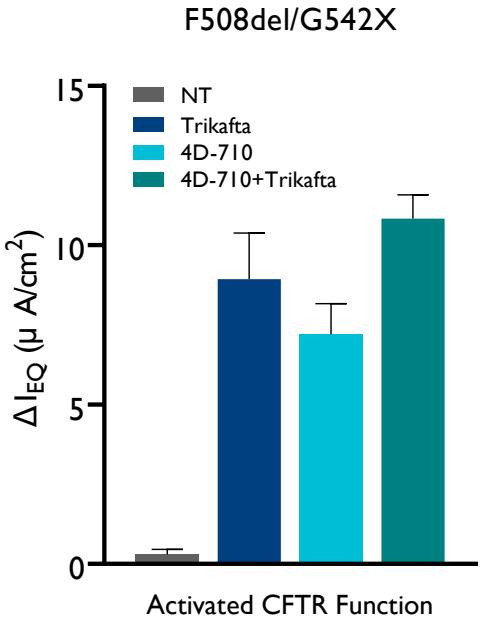
Strong Rationale for 4D-710 + Trikafta Combination

Rationale

- **Unmet need remains**
  - Trikafta Ph 3 results suggest population with minimal benefit, 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: Discuss development path with FDA in Q4 2023

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.