



4D-710 for Cystic Fibrosis: Phase I Interim Data

December 17, 2025

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Today's Speakers



David Kirn, M.D.

Co-founder and Chief Executive Officer



**Jennifer L. Taylor-Cousar,
M.D., MSCS**

*Professor, Departments of Medicine and Pediatrics, and Co-Director, Adult Cystic Fibrosis Program, Director, Cystic Fibrosis Therapeutics Development Center, National Jewish Health
Lead Principal Investigator in the AEROW clinical trial*



**Felix Ratjen,
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Professor of Pediatrics at the University of Toronto, Program Head and Senior Scientist in the Translational Medicine research program at SickKids Research Institute, and Co-Head of the Cystic Fibrosis Center at SickKids

Phase I Interim Data: Key Takeaways from Lower Dose Cohorts 3 & 4



4D-710

Durable, Redosable, Variant-Agnostic, Disease-Modifying Treatment Potential for People with CF Lung Disease with Remaining High Unmet Need

SAFETY DATA: Well Tolerated with 4 to 24 Months follow-up

LUNG FUNCTION: Clinically Meaningful Activity (FEV₁, LCI_{2.5})

QUALITY-OF-LIFE: Clinically Meaningful Activity (CFQ-R-R)

PHASE 2: Enrollment Underway at Cohort 4 dose level

DURABILITY: 4D-710-mediated CFTR transgene expression through at least 1 year

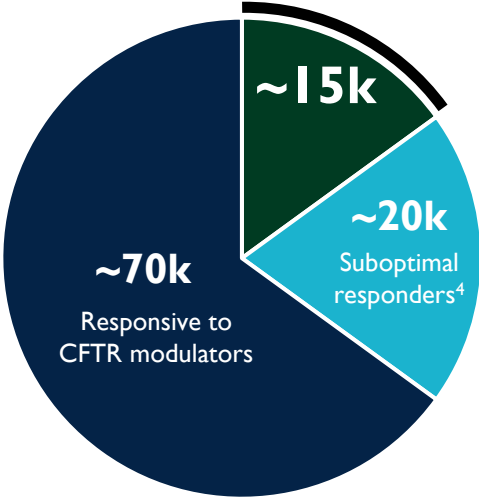
Cystic Fibrosis Lung Disease: High Unmet Need Despite Modulators

Lung Disease Burden



Burdensome Daily Supportive Care:
Airway clearance (~100 mins), inhaled antibiotics & bronchodilators

CF Epidemiology^{2,3}



Ineligible or Intolerant to CFTR modulators
AEROW
Initial study population evaluating 4D-710 as monotherapy

~105,000 People with CF in 94 Countries

CFTR Modulator Market Size

~\$11 Billion (2024)⁵

- **Persistent symptoms** with cough, shortness of breath, infections & reduced exercise tolerance
- Pulmonary exacerbations, often requiring **hospitalization and IV antibiotics**
- **Lung transplantation** as a last resort
- **Median survival** (pre-modulator era): ~40 years¹

1. Ramsey & Welsh. *Am J Respir Crit Care Med* 2017;195(9):1092–9. 2. Guo J et al. *Journal of Cystic Fibrosis* 2022; 21:456-62. 3. Cystic Fibrosis Foundation. 4. Based on assumptions derived from Middleton, 2019 and CFF registry analysis. 5. Vertex Pharmaceuticals FY 2024 financial results.

Conventional Gene Therapy Trials in CF Lung Failed Due to Lack of Effective Gene Delivery & Expression

- **Prior AAV Gene Therapy Study Design^{1,2}**

- AAV2-based CFTR gene therapy (tgAAVCF)
- Randomized Phase 2 trial (n=51)
- Repeat aerosol administration on days 1 & 30

- **Clinical Data Reports**

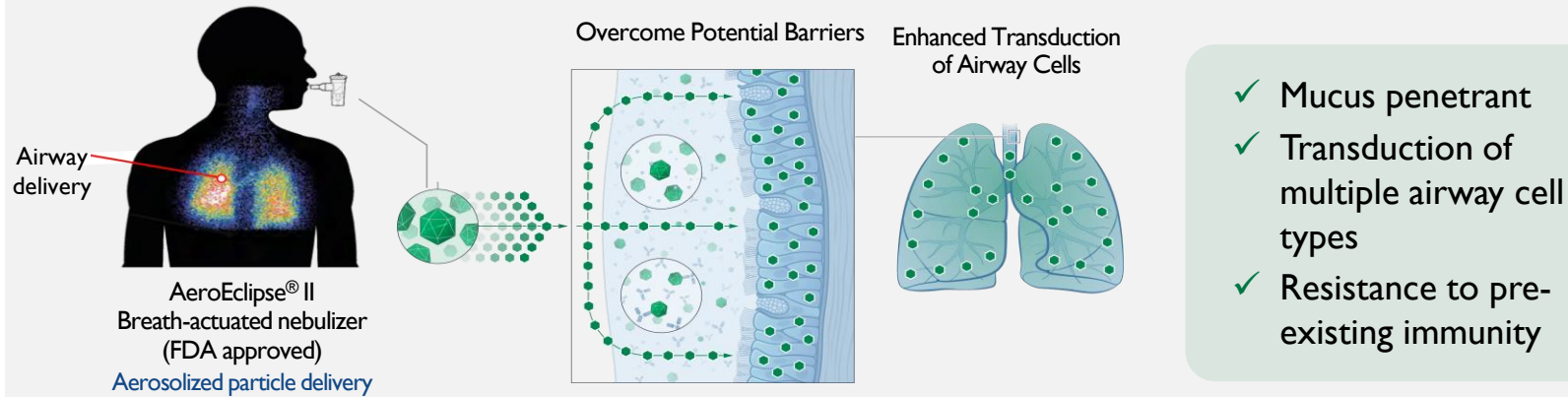
- Safe & well tolerated
- NO expression of CFTR transgene in lung
- NO clinical benefit

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.

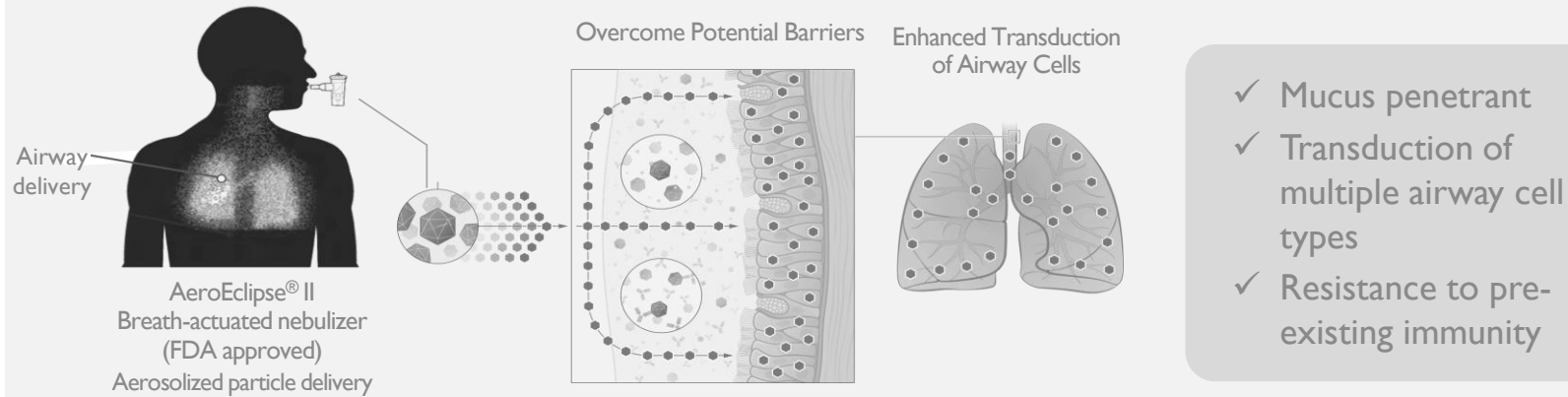
4D-710 Design: Aerosol Delivery of Novel A101 Vector Invented with Directed Evolution

Novel AAV Vector: A101

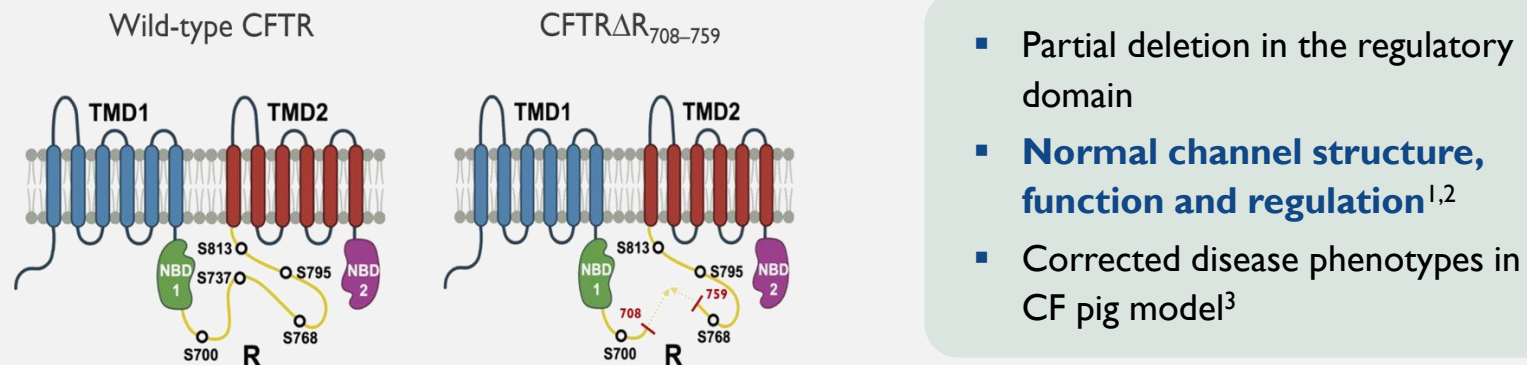


4D-710 Design: Highly Functional CFTR Transgene Payload

Novel AAV Vector: A101



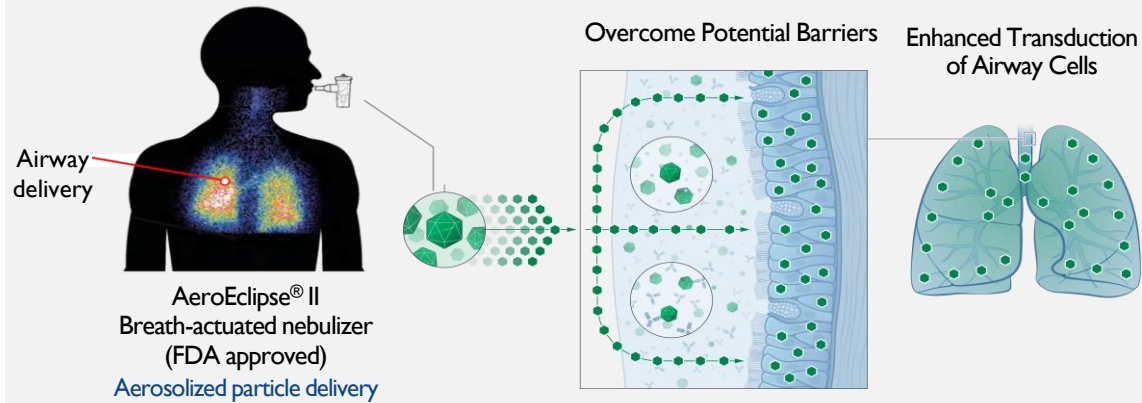
Payload: *CFTR* Δ R Transgene



1. Ostedgaard et al. *PNAS* 2002;99:3093-8; 2. Calton et al. *AJRCMB* 2025; 3. Steines et al. *JCI Insight* 2016.

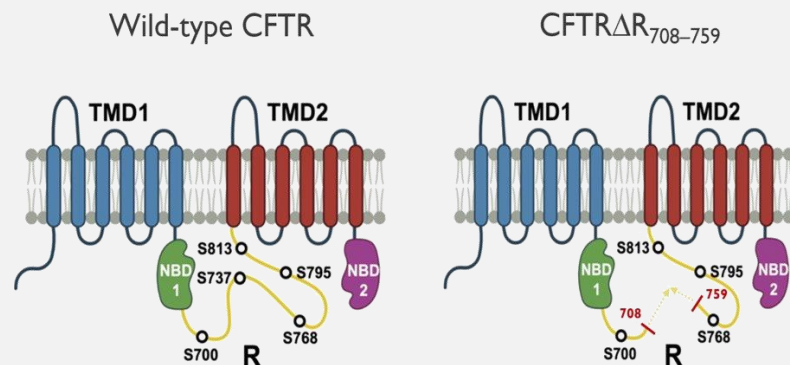
4D-710 Design: Durable, Redosable, Variant-agnostic Disease-modifying Therapy for CF Lung Disease

Novel AAV Vector: A101



- ✓ Mucus penetrant
- ✓ Transduction of multiple airway cell types
- ✓ Resistance to pre-existing immunity

Payload: *CFTR*ΔR Transgene



- Partial deletion in the regulatory domain
- **Normal channel structure, function and regulation**^{1,2}
- Corrected disease phenotypes in CF pig model³

4D-710



Therapeutic Objective:

Durable, redosable, variant-agnostic disease-modification via introduction of functional CFTR to lung airway cells

1. Ostedgaard et al. *PNAS* 2002;99:3093-8; 2. Calton et al. *AJRCMB* 2015; 3. Steines et al. *JCI Insight* 2016.

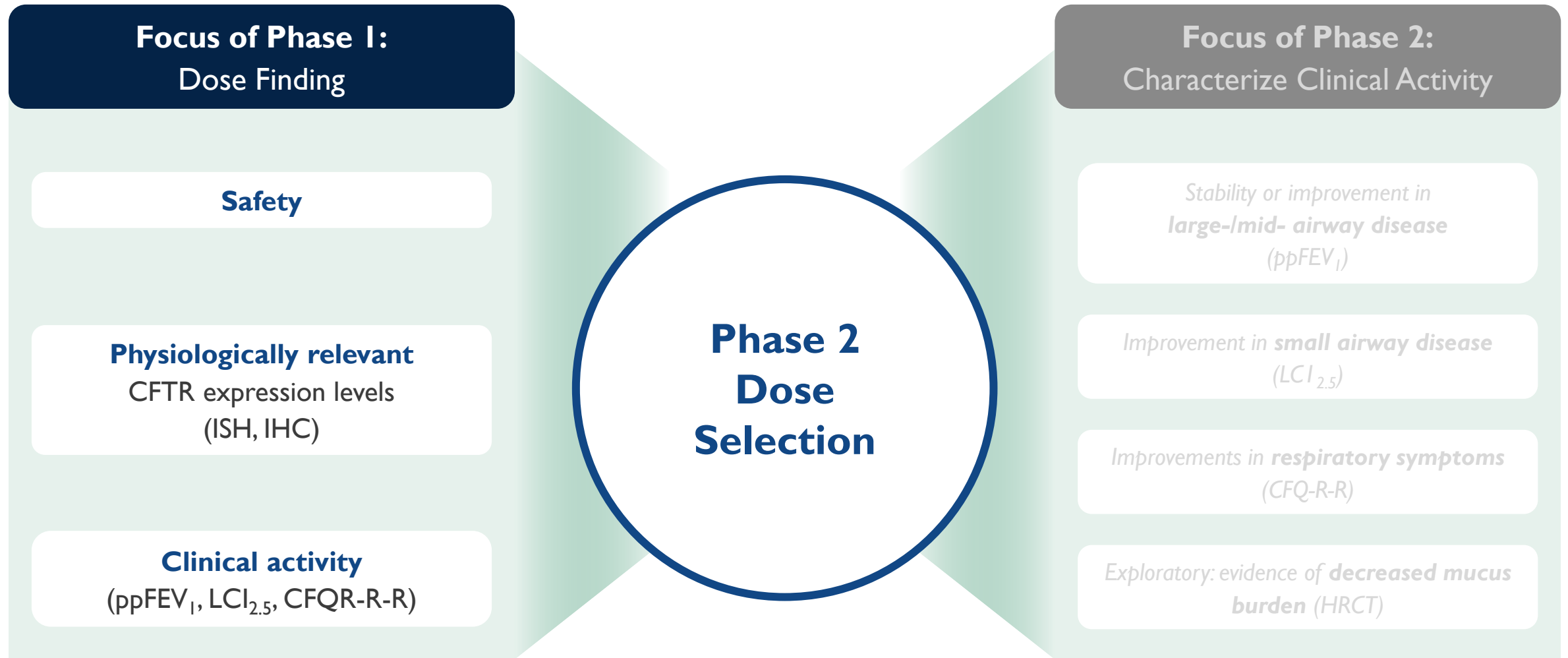


4D-710 Interim Phase I Data: Study Design, Baseline Characteristics, Safety

Jennifer L. Taylor-Cousar, M.D., MSCS,
National Jewish Health

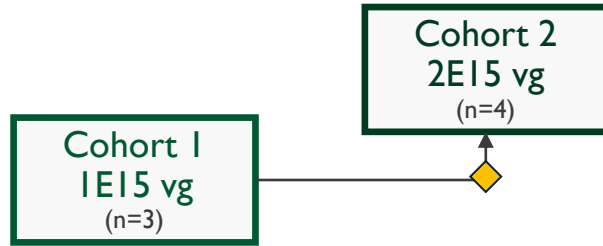
Data Cutoff: December 1, 2025

Phase I: Dose Selection Framework for Further Development of 4D-710



Initial Phase I Protocol: Designed to Characterize Safety & Expression to Inform Dose Selection

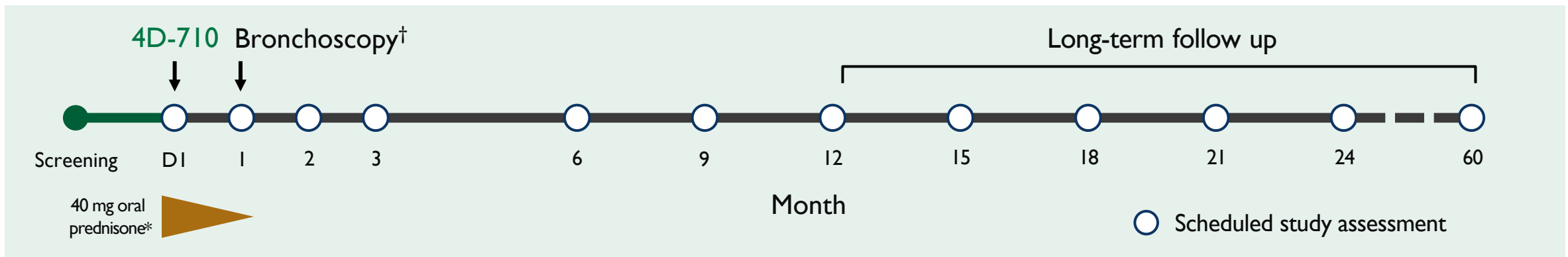
Phase I (Dose Ranging)



Key Endpoints:

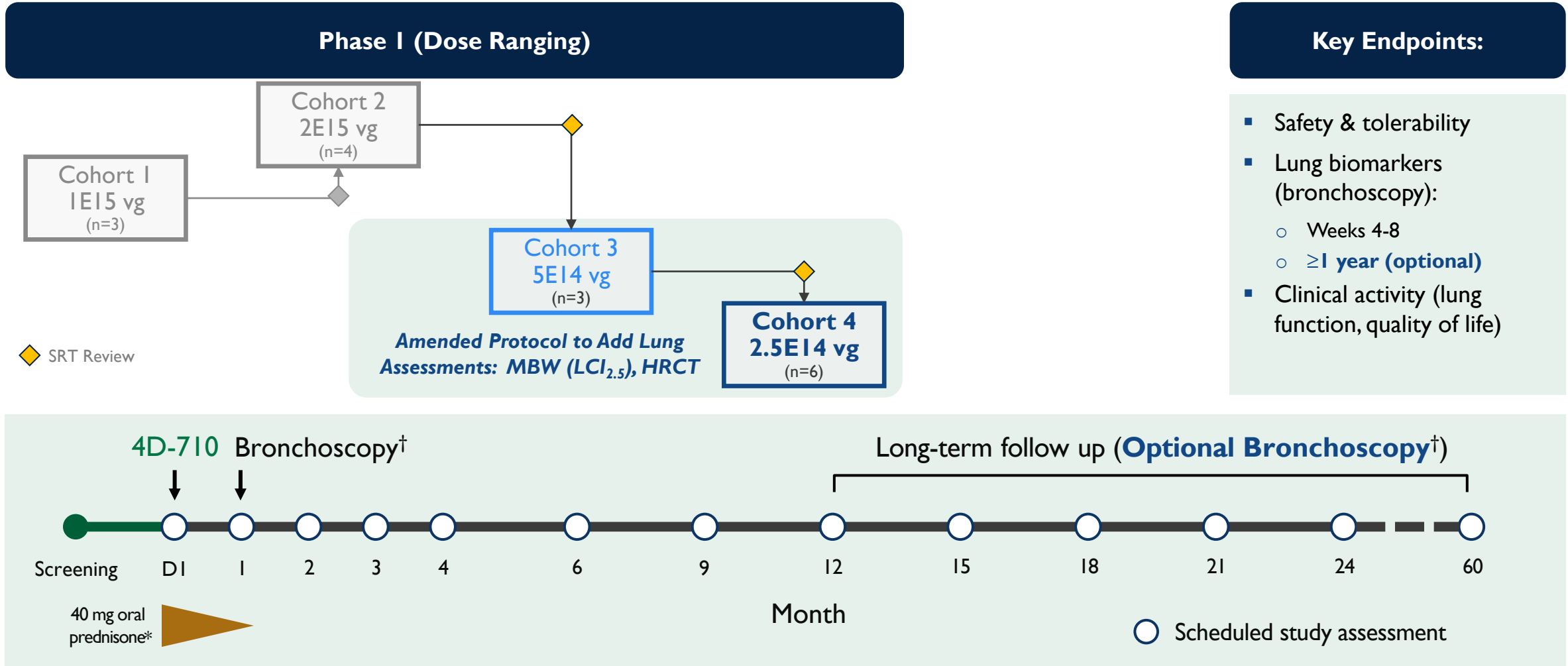
- Safety & tolerability
- Lung biomarkers (bronchoscopy):
 - Weeks 4-8
- Clinical activity (lung function, quality of life)

◆ SRT Review



*28-day taper. †Endobronchial biopsy (4D-710 transgene and protein expression). ppFEV₁, percent predicted forced expiratory volume in 1 second; SRT, Safety Review Team

Protocol Amendment: Endpoints Added for Pulmonary Clinical Activity Assessments, 2nd Biopsy to Assess Durability at 1 Yr & Beyond



*28-day taper. †Endobronchial biopsy (4D-710 transgene and protein expression). ppFEV₁, percent predicted forced expiratory volume in 1 second; SRT, Safety Review Team; MBW, Multiple Breath Washout; LCI_{2.5}, Lung Clearance Index at 2.5% of starting concentration; HRCT, High Resolution Computed Tomography.

AEROW Clinical Trial: Lower Dose Cohorts 3 & 4 (N=9)

Demographics & Baseline Characteristics

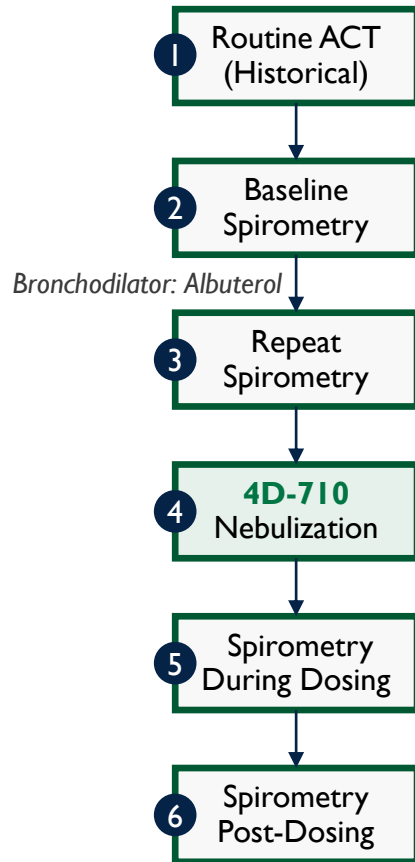
	Cohort 3: 5E14 vg			Cohort 4: 2.5E14 vg					
Participant Number	1	2	3	1	2	3	4	5	6
Age, y	42	40	34	26	54	37	56	33	37
Sex	Female	Female	Male	Male	Female	Female	Male	Male	Male
CFTR mod. status	Intolerant	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible
CFTR Variants	F508del/ R751L	4209TGTT>AA/ 3120+1G>A	Q220X/ Q493X	c.2184_2185insA/ c.2184_2185insA	1471delA/ 1717-1G>A	W1282X/ H1079P	3659delC/ 5T	S466X/ 1342-1delG	G542X/ W1282X
ppFEV ₁	100	77	62	58	89	50	90	76	63
LCI _{2.5} (Normal: <7)	N/A	14.7	18.2	14.3	13.2	N/A	N/A	15.8	13.0
CFQ-R-R score (0-100)	72	78	44	28	72	56	93	89	61

Impairment: **Mild/Normal**, **Moderate/Severe/Abnormal**.

CFTR, cystic fibrosis transmembrane conductance regulator; CFQ-R-R, Cystic Fibrosis Questionnaire–revised (respiratory domain); FEV₁, forced expiratory volume in 1 second.

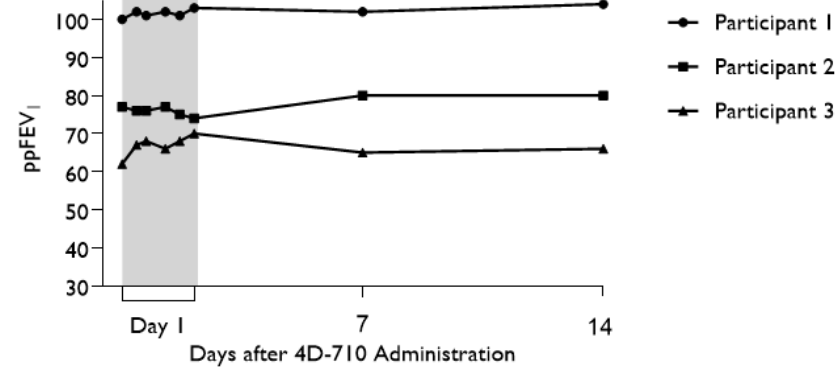
4D-710 Safety & Tolerability Day 1-14: Well-Tolerated in Lower Dose Cohorts with Transient & Generally Mild AEs Typical of Nebulized Therapies

Day 1 Dosing Activities



ppFEV₁

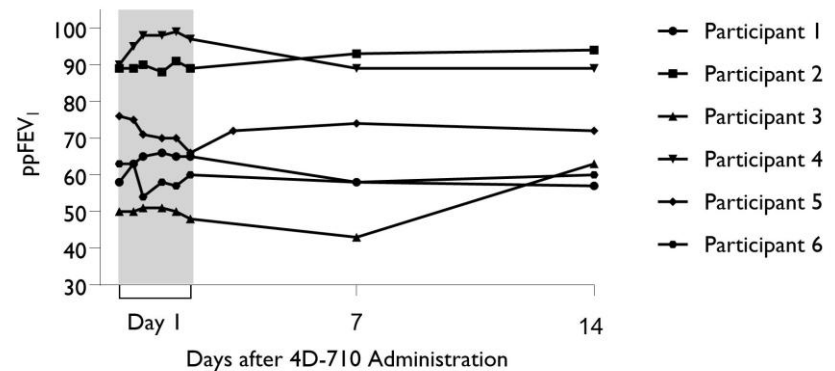
5E14 vg
Admin. Time
~90 Mins



4D-710-Related AE

- Participant 1: **throat irritation** after dosing (Grade 1, ~5 sec), increased **productive cough** (Grade 1, Day 4-13)

2.5E14 vg
Admin. Time
~45 Mins



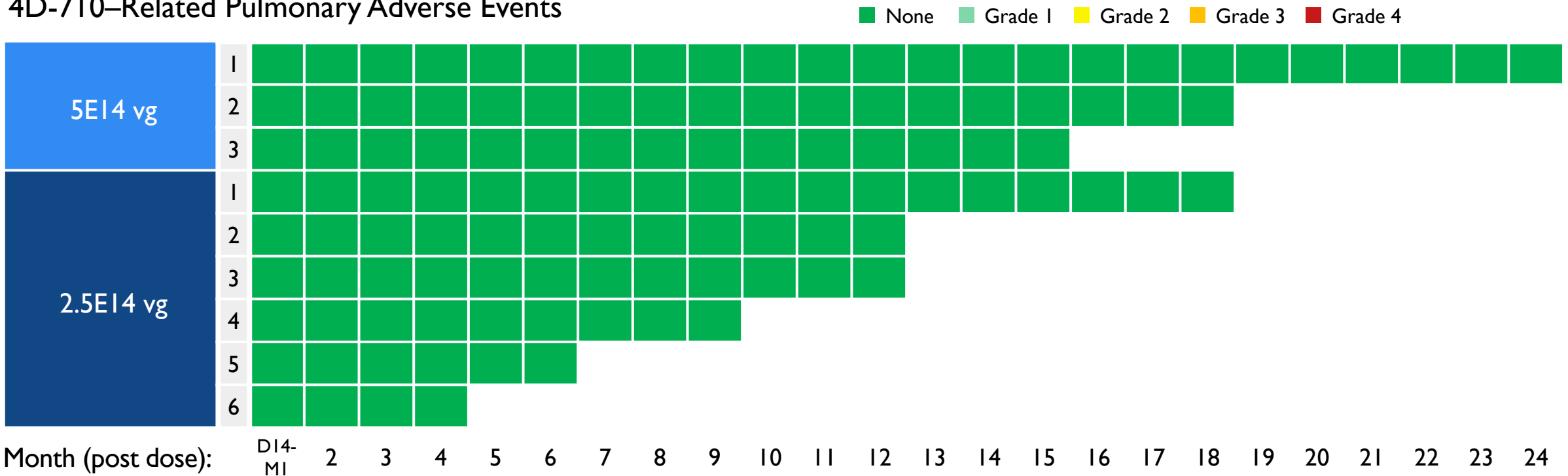
- Participant 5: increased **cough and lightheadedness** during dosing (Grade 1, resolved Day 1 without intervention), **chest tightness and decrease in FEV₁** (Grade 2, Day 1-8)

AE, Adverse Event; ACT, Airway Clearance Technique.

4D-710 Safety & Tolerability: Well-Tolerated in Lower Dose Cohorts

No Pulmonary 4D-710–related AEs After Day 14

4D-710–Related Pulmonary Adverse Events



- Higher dose cohorts (1E15 & 2E15 vg): NO new related AEs since last update (up to 3.5 years of follow up)
- Non-Pulmonary 4D-710–Related AEs:
 - 5E14 vg (Participant 3): 1) Mental Fogginess: Grade 2, started Day 24 and resolved Day 35; 2) Stuttering: Grade 2, started Day 25 and resolved Day 35
 - 2.5E14 vg (Participant 5): 1) Elevated AST & GGT: Grade 1, identified at IM visit (Day 36) and resolved by 2M visit (Day 57). Participant with history of elevated LFTs at baseline

AEs from 2E15 and 1E15 doses previously disclosed.



4D-710 Interim Phase I Data: Transgene Expression

Jennifer L. Taylor-Cousar, M.D., MSCS
National Jewish Health

Data Cutoff: December 1, 2025

Lung Biopsy Analysis Methods: Rationale & Endpoints

	CFTR/ΔR mRNA Expression: ISH	CFTR/ΔR Protein Expression: IHC
Strength	Highly Specific	Highly Sensitive Intracellular Localization
Readouts	% of airway cell (+)	% of airway cell (+) Intensity Localization Cell types
Evaluation Purpose	Quantitative for dose selection	Qualitative for mRNA translation confirmation & expression pattern

ISH, *in situ* hybridization, IHC, immunohistochemistry.

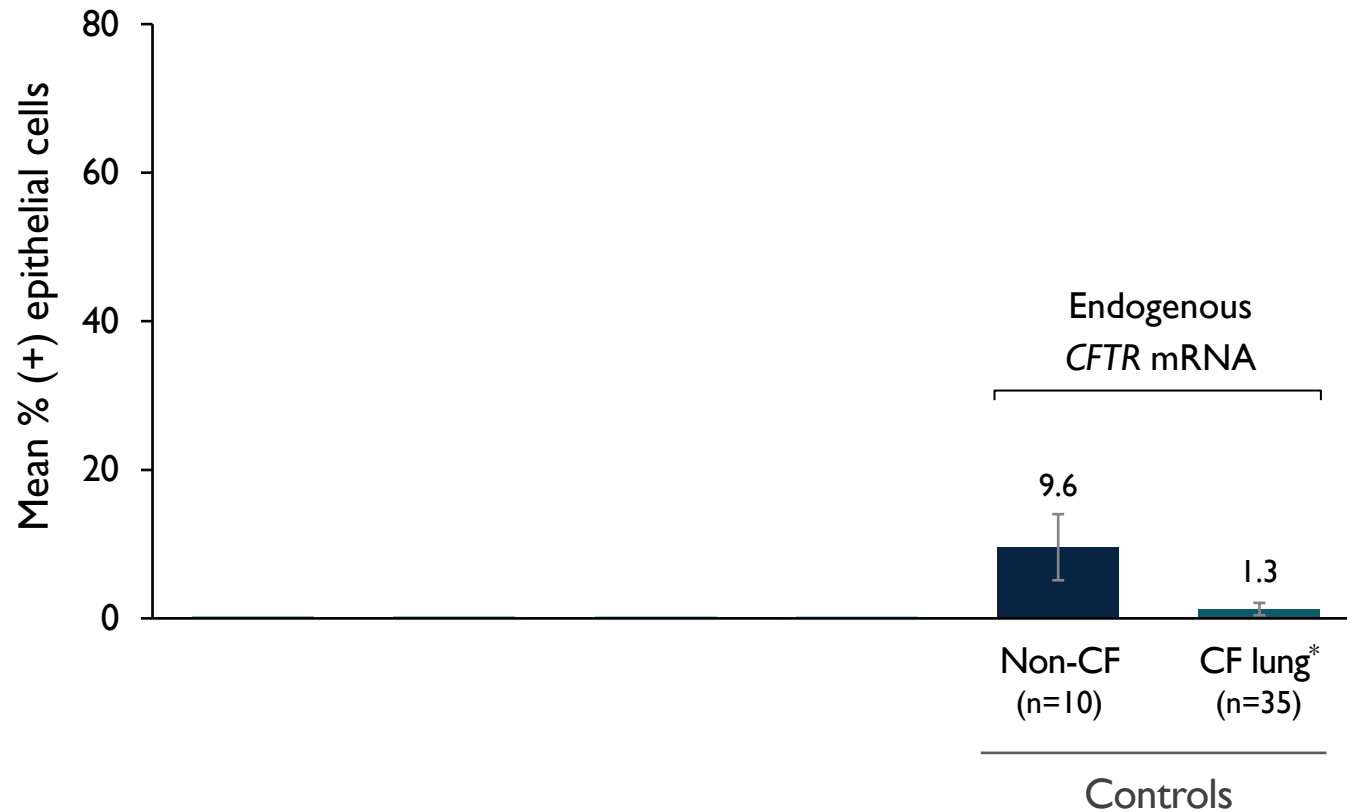
Target Expression Profile for 4D-710 CFTR: Phase 2 Dose Selection Transgene Expression Analyses from Biopsies & Brushings ~1 Month Post-Dose

Dose Selection Criteria:	Target Airway BIOPSY Profile	Target Airway BRUSHING Profile
CFTR Δ R RNA expression (ISH)	10-25% airway cells ^{1,2}	100% of samples positive
CFTR protein expression (IHC)		
Cell types transduced	Staining Pattern: Normal localization & levels	N/A
	Basal cells & secretory cells (\pm others) No significant expression in interstitial cells	Lower lobe epithelium
Pre-existing A101 immunity	No effect on expression	

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.

CFTR Transgene RNA Expression in Airway Biopsies (ISH): Non-CF Lung & Non-Treated CF Biopsy Controls

CFTR RNA (ISH): Airway Epithelial Cells



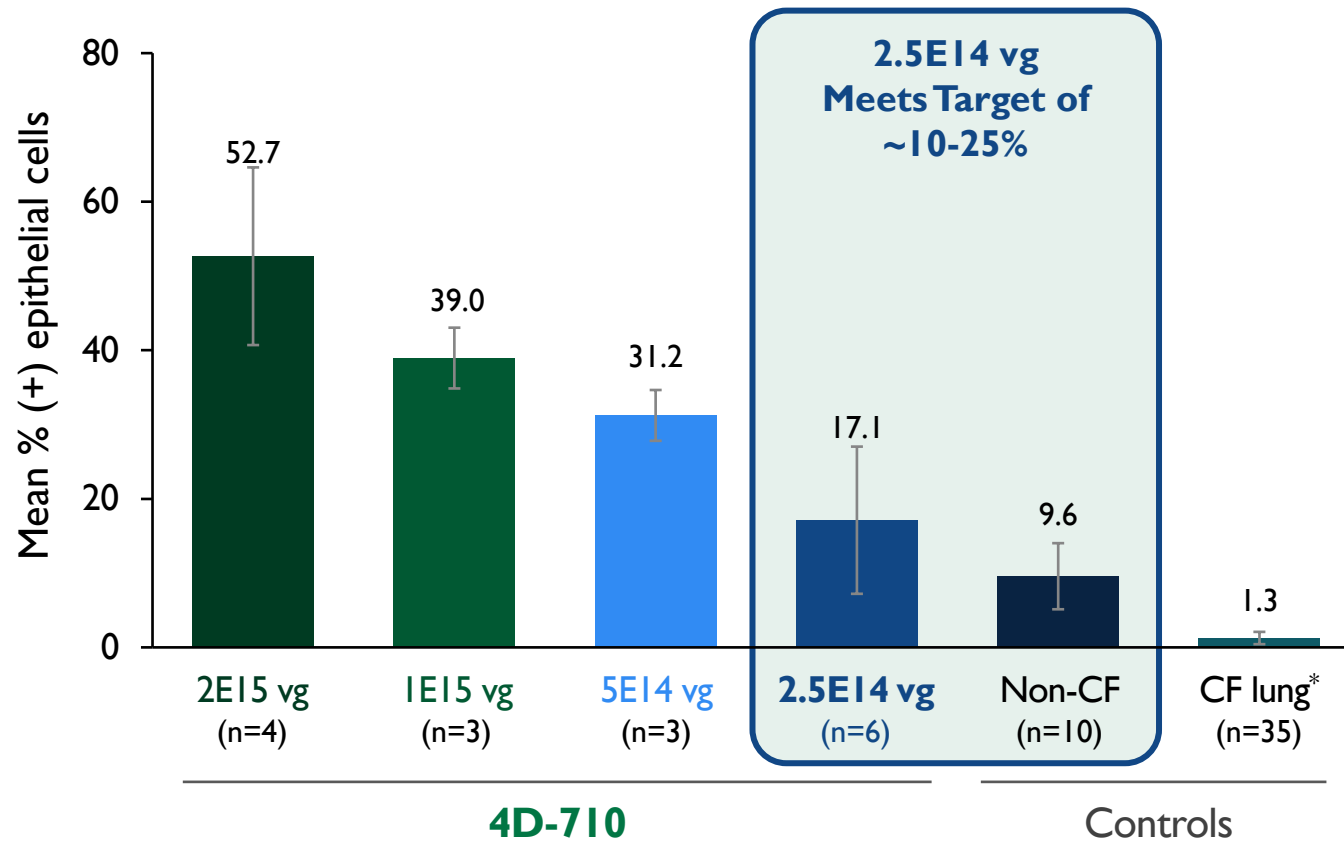
- Commercial non-CF samples positive for endogenous *CFTR* mRNA expression, used to identify target expression profile^{1,2}

Quantification by Visiopharm® AI machine Learning analysis.

*Attempts to genotype commercial CF samples yielded results for 13/35 samples; of these, a majority were $\Delta F508$ homozygous mutations. CFTR, cystic fibrosis transmembrane conductance regulator; ISH, *in situ* hybridization
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.

Dose-dependent *CFTR* Transgene RNA Expression Following 4D-710 Administration: Cohort 4 (2.5E14 vg) Meets Target Expression Profile

CFTR RNA (ISH): Airway Epithelial Cells



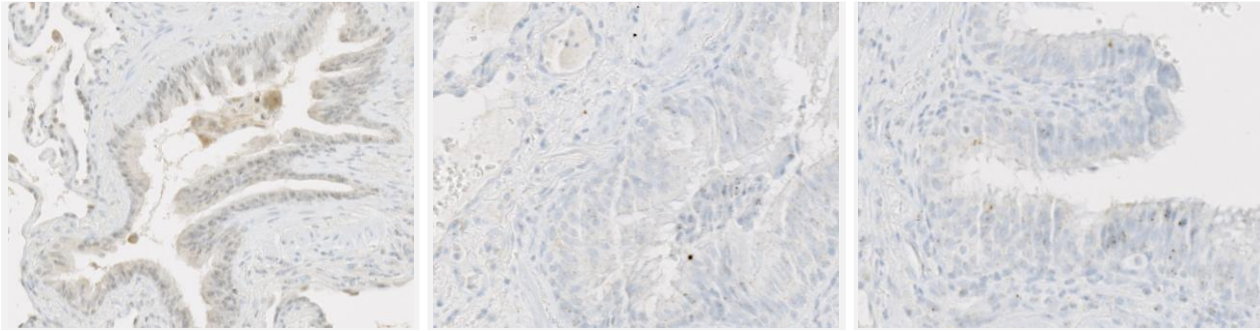
- Dose-dependent *CFTR* Δ R mRNA expression in airway cells
- **2.5E14 vg dose (Cohort 4) meets target expression profile^{1,2}**

4D-710 biopsies analyzed Day 28 – Day 56

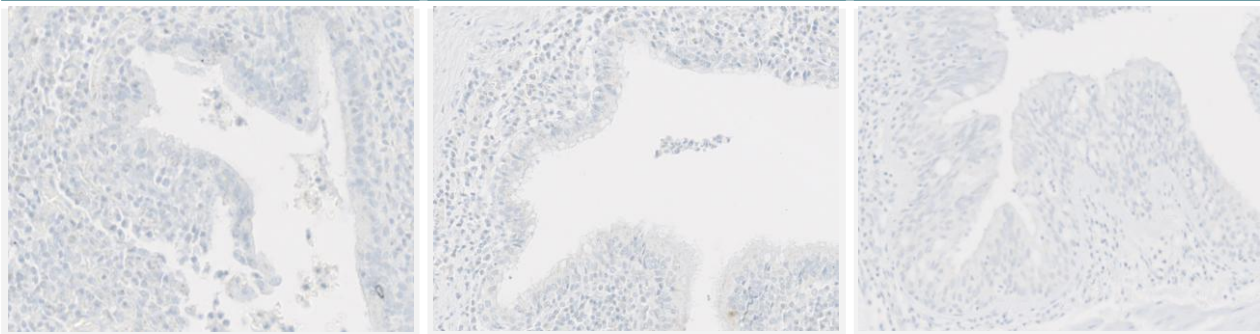
CFTR, cystic fibrosis transmembrane conductance regulator; ISH, *in situ* hybridization. Quantification by Visiopharm® AI machine Learning analysis. *Attempts to genotype commercial CF samples yielded results for 13/35 samples; of these, a majority were Δ F508 homozygous mutations. 1. Dannhoffer L et al. Am J Respir Cell Mol Biol 2009; 40:717–23. 2. Bell S et al. Lancet Res Med 2020; 8:65–124.

CFTR Transgene Protein Expression Pattern in Airway Biopsies (IHC): Non-CF Lung & Non-treated CF Biopsy Controls

Non-CF Lung Control



CF Lung Control

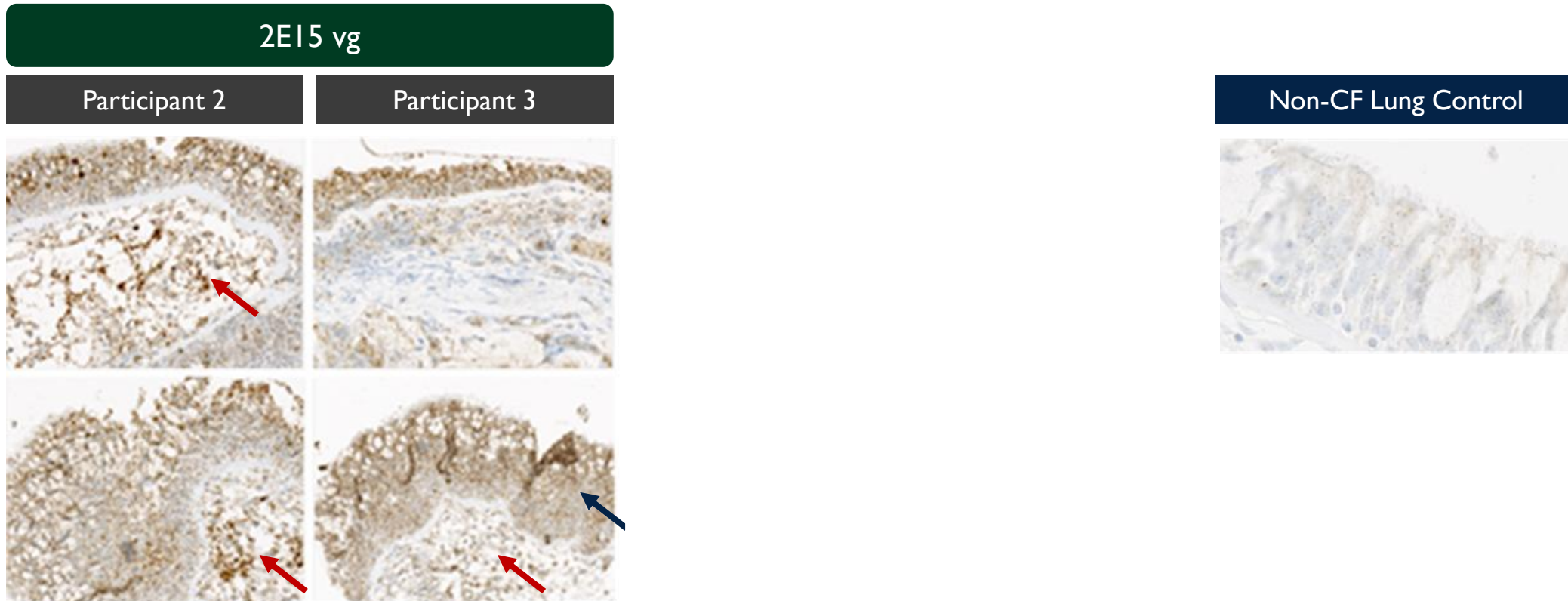


- Commercial non-CF tissues are used as benchmark for target tissue expression quantity & level^{1,2}
- CFTR overexpression may lead to protein mis-sorting to the basolateral membrane and reduced function³
- Abnormal levels of CFTR may be undesirable as it could contribute to altering ion balance⁴

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. 3. Farmen SL. et al. Am J Physiol Lung Cell Mol Physiol. 2005 Dec;289(6):L1123-30. 4. Laurence S Hanssens LS et al. Cells. 2021 Oct 22;10(11):2844.

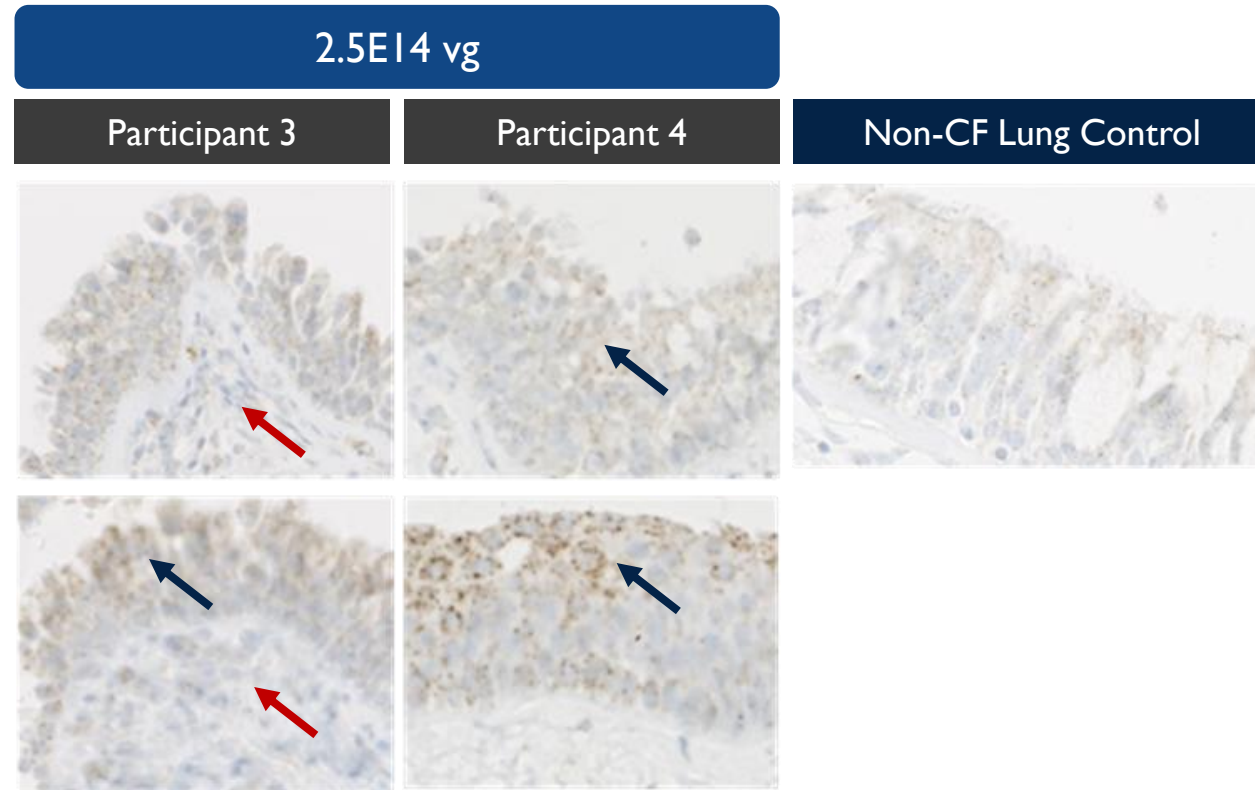
†Attempts to genotype commercial CF samples yielded results for 13/35 samples; of these, a majority were $\Delta F508$ homozygous mutations. IHC, immunohistochemistry.

CFTR Transgene Protein Expression Pattern in Airway Biopsies (IHC): Over-Expression Pattern at Highest Dose (Cohort 2)



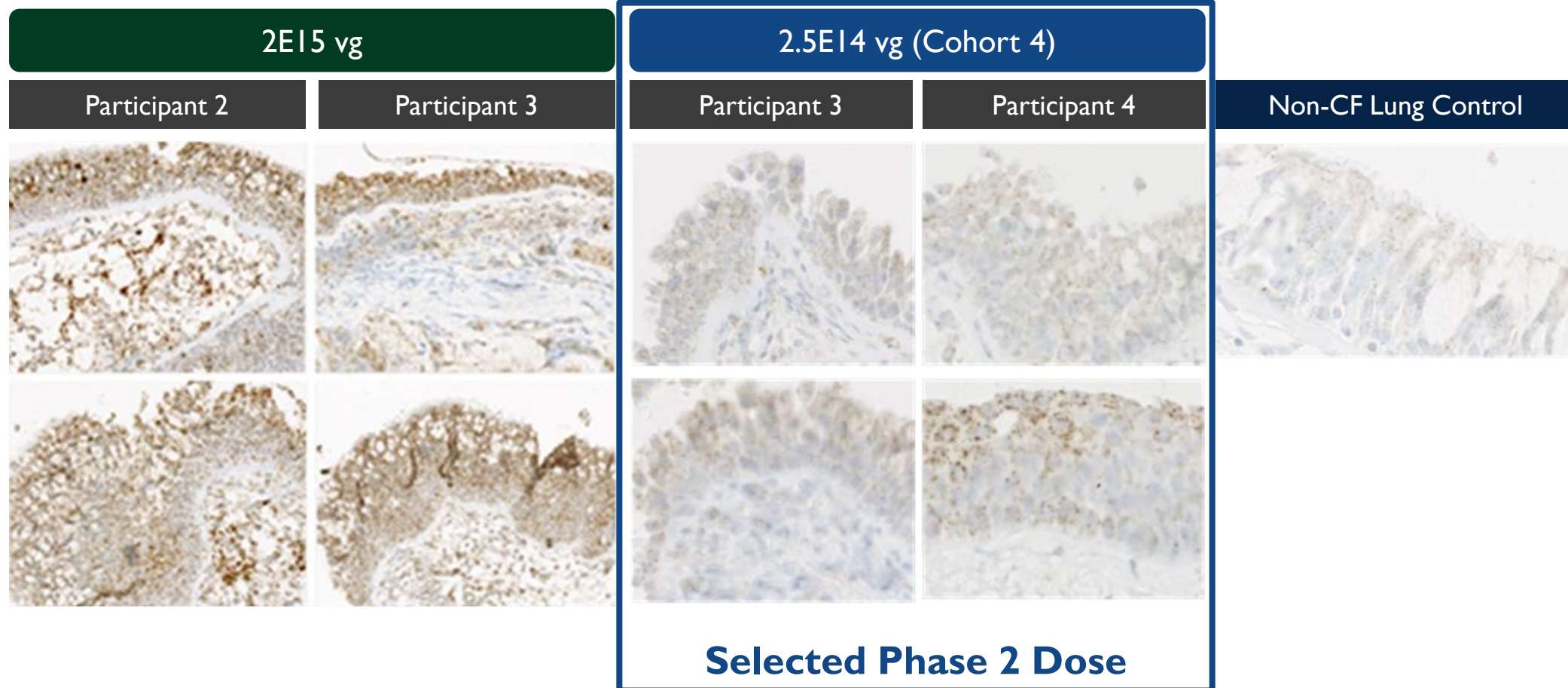
- CFTR protein IHC staining pattern improved at 2.5E14 dose:
 - **Abnormal** cellular **localization** pattern and protein **levels** in airway cells (**black** arrows)
 - High protein in **interstitial** areas of lung (**red** arrows)

CFTR Protein Expression Meets Target Expression Pattern in Airway & Interstitial Areas at 2.5E14 vg Dose (Cohort 4)



- CFTR protein IHC staining pattern improved at 2.5E14 dose:
 - **Normal** cellular localization pattern & protein levels in airway cells (**black** arrows)
 - **Minimal/no protein** in interstitial areas of lung (**red** arrows)

Dose-Related CFTR IHC Staining Patterns: 2.5E14 vg Dose Meets Target Protein Expression Pattern



Target Expression Profile Met at 2.5E14 vg Dose: Phase 2 Selection

	Dose Selection Criteria:	Target Profile	2E15 vg (n=4)	1E15 vg (n=3)	5E14 vg (n=3)	2.5E14 vg (n=6)
Upper Airway Biopsies	CFTR Δ R RNA expression (ISH)	10-25% cells ^{1,2}	✗ 53%	✗ 39%	✗ 31%	✓ 17%
	CFTR protein expression (IHC)	Positive	✓	✓	✓	✓
	Cell types transduced	Basal cells & secretory cells	✓	✓	✓	✓
		Minimal/no expression in interstitial cells	✗	✗	✓	✓
	Pre-existing A101 Immunity	No effect on expression	✓	✓	✓	✓
Lower Lobe Brushings	CFTR/ Δ R Expression (ISH/IHC)	100% of samples positive	✓	✓	✓	✓
						Selected Ph2 Dose

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.



4D-710 Interim Phase I Data: Clinical Activity

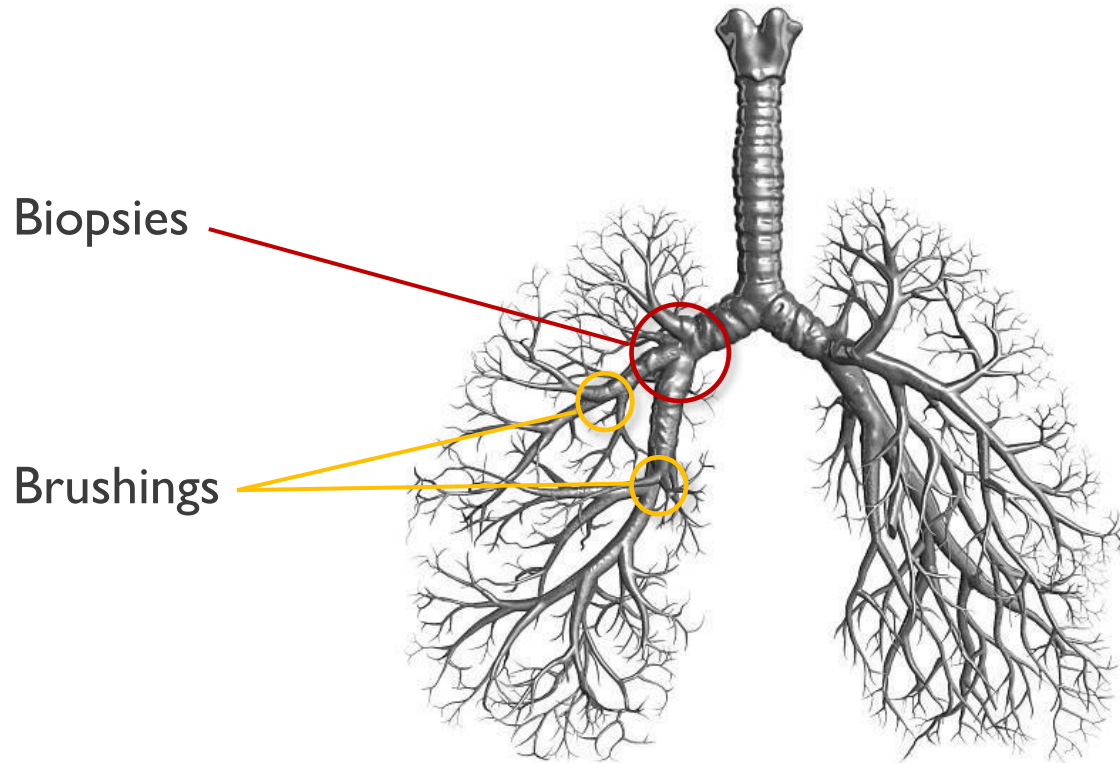
Jennifer L. Taylor-Cousar, M.D., MSCS
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University of Toronto, Program Head, SickKids Research Institute, and Co-
Head of the Cystic Fibrosis Center at SickKids

Data Cutoff: December 1, 2025

Integrated Biomarker & Clinical Endpoint Strategy to Demonstrate Mechanism of Action & Clinical Activity in AEROW Phase I Trial

Lung Tissue Biomarkers



Pulmonary Clinical Activity Endpoints

Larger Airways

- ppFEV₁

Small Airways

- Lung Clearance Index (LCI_{2.5})

New in Lower Dose Cohorts

Pulmonary Symptoms

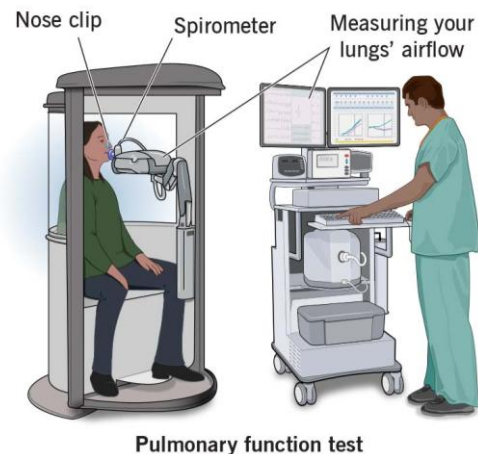
- CFQ-R-R

Structural/Functional Changes

- HRCT (analyses pending)

ppFEV₁, percent predicted forced expiratory volume in 1 second; LCI_{2.5}, Lung Clearance Index at 2.5% of starting concentration; CFQ-R-R, Cystic Fibrosis Questionnaire–revised respiratory domain; HRCT, High Resolution Computed Tomography.

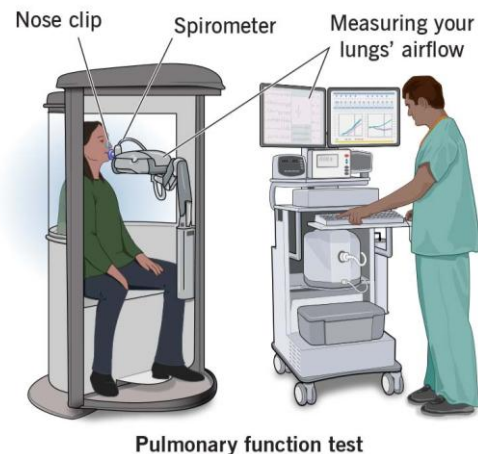
ppFEV₁ & LCI_{2.5}: Complementary Measures of Lung Function



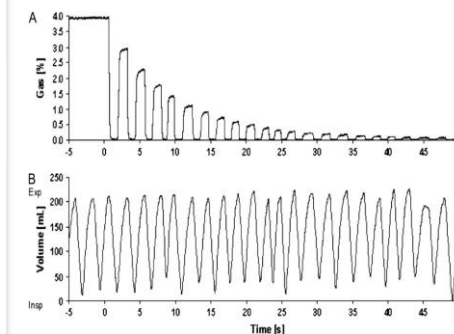
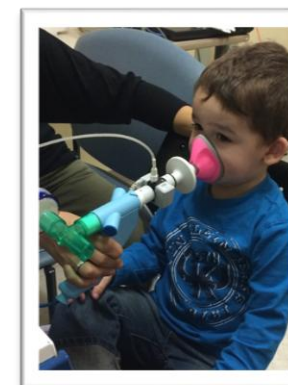
Cleveland Clinic ©2024

Measure / Endpoint	Spirometry: ppFEV ₁
Measures	Lung restriction/obstruction, marker of larger airway disease
Effort Dependent	Yes
Sensitivity to Early Disease	Low
Responsiveness to Intervention	Medium <i>may miss subtle improvement in early/mild disease</i>
Correlation to Clinical Outcomes (Survival, Exacerbations, QoL)	Yes
Regulatory Acceptance	Gold Standard in Adults

ppFEV₁ & LCI_{2.5}: Complementary Measures of Lung Function

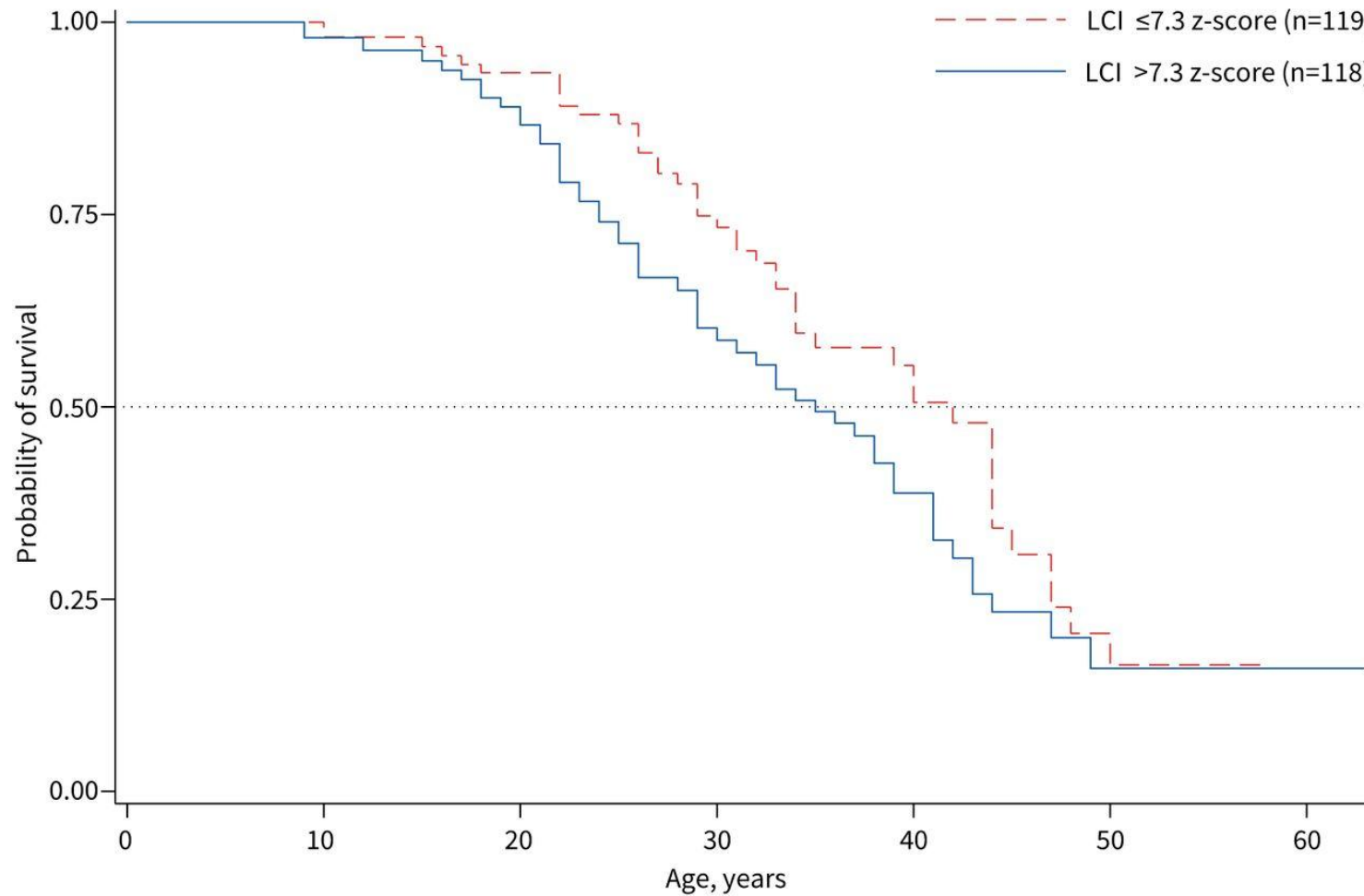


Cleveland Clinic ©2024



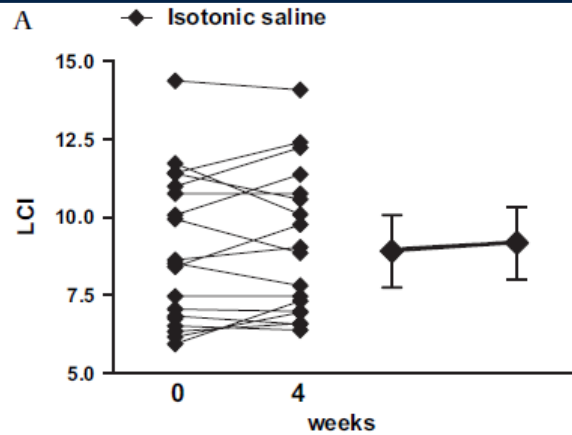
Measure / Endpoint	Spirometry: ppFEV ₁	Multiple Breath Washout: LCI _{2.5}
Measures	Lung restriction/obstruction, marker of larger airway disease	Ventilation inhomogeneity, marker of small airway disease
Effort Dependent	Yes	No
Sensitivity to Early Disease	Low	High
Responsiveness to Intervention	Medium <i>may miss subtle improvement in early/mild disease</i>	High
Correlation to Clinical Outcomes (Survival, Exacerbations, QoL)	Yes	Yes
Regulatory Acceptance	Gold Standard in Adults	EMA Primary in Pediatrics FDA Key Efficacy Endpoint in Pediatrics

LCI_{2.5} Score Severity Correlates Significantly with Survival (N=237)

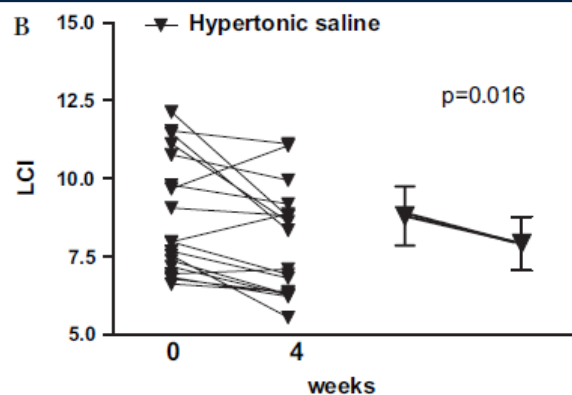


LCI_{2.5} Demonstrated Significantly Greater Sensitivity than ppFEV₁ for Treatment Effect: Required <19 Subjects vs ~350

Inactive Control



Modestly Active Treatment



Treatment effect size:
 1.16 ± 0.94
 $[0.27, 2.05]$
 $p=0.016$

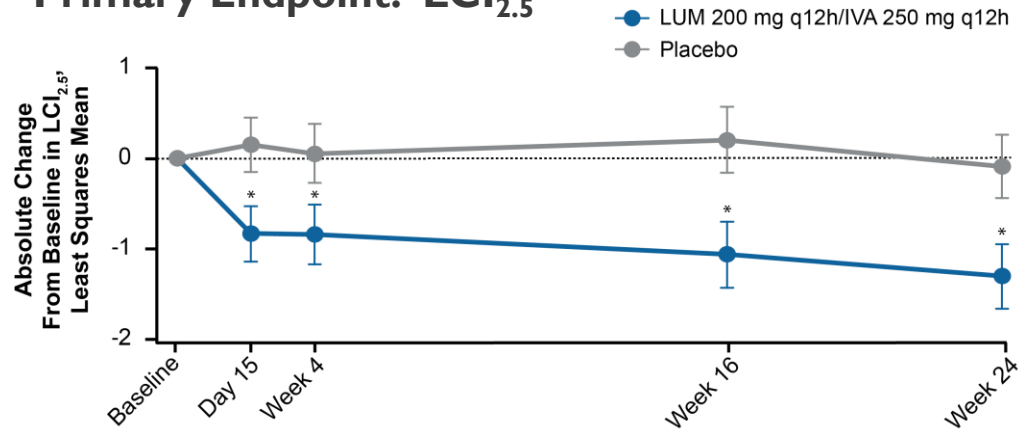
Outcome Analysis	HS vs. IS Treatment Effect*	Required Sample Size†
<i>Spirometry:</i>		
ppFEV ₁	1.8 ± 12.0	351
ppFEF ₂₅₋₇₅	5.3 ± 22.3	141
<i>CFQ-R Questionnaire:</i>		
Respiratory Domain	5.2 ± 14.2	61
<i>Multiple-Breath Washout</i>		
LCI _{2.5}	1.16 ± 0.94 (p=0.016)	≤19

LCI_{2.5} able to detect subtle treatment effects

Amin et al, *Thorax* 2010. *Absolute difference for isotonic saline vs hypertonic saline, Values are expressed as means ± SD. †Required number of patients for a crossover trial to achieve 80% power at a 5% significance level.

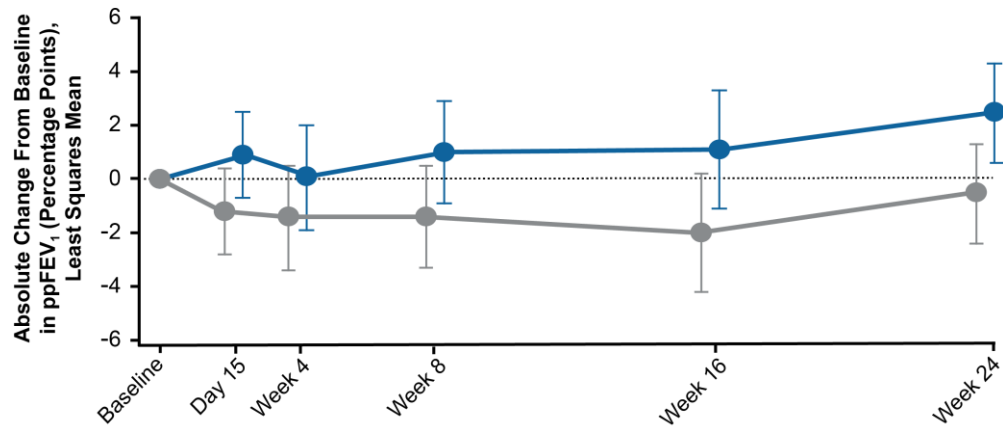
In Orkambi® Trial in Children, LCI_{2.5} Demonstrated Robust Treatment Response at Every Timepoint vs. Placebo in Contrast to ppFEV₁

Primary Endpoint: LCI_{2.5}



Endpoint	Placebo (n=101)	LUM/IVA (n=103)	Treatment Difference vs Placebo
Absolute change in LCI _{2.5} through week 24	0.08 (-0.18 to 0.34)	-1.01 (-1.27 to -0.75)	-1.09 (-1.43 to -0.75) P<0.0001

Secondary Endpoint: ppFEV₁



Endpoint	Placebo (n=101)	LUM/IVA (n=103)	Treatment Difference vs Placebo
Absolute change in ppFEV ₁ through week 24	-1.3 (-2.8 to 0.2)	1.1 (-0.4 to 2.6)	2.4 (0.4 to 4.4) P=0.0182

*Ratjen F et al, *Lancet Respir Med* 2017

P<0.0001 vs placebo; all values in table are least squares mean (95% confidence interval [CI]). LCI, lung clearance index; LUM/IVA, lumacaftor/ivacaftor.



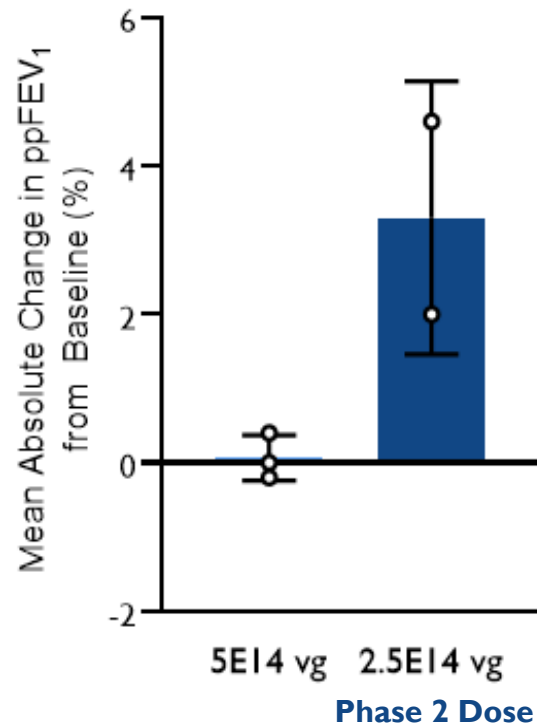
4D-710 Interim Phase I
Clinical Activity Data:
Lower Dose Cohorts

Jennifer L. Taylor-Cousar, M.D., MSCS
National Jewish Health

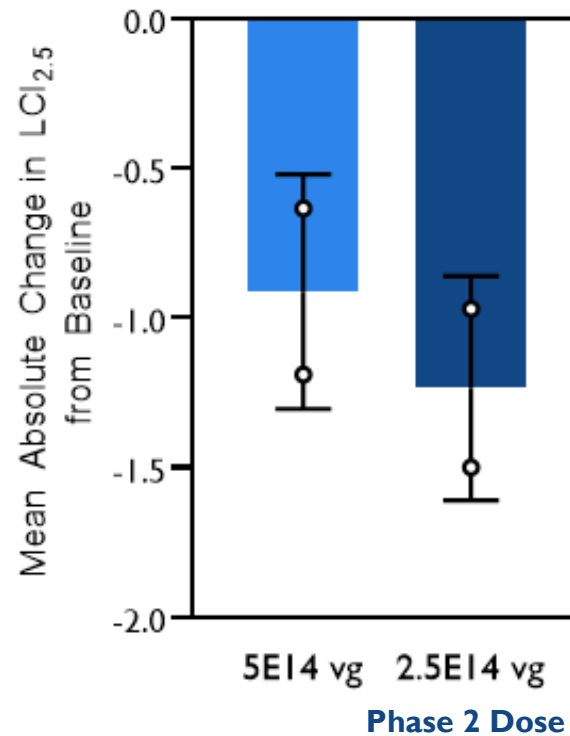
Data Cutoff: December 1, 2025

Pulmonary Clinical Activity: Mean Change in ppFEV₁, LCI_{2.5} & CFQ-R-R in Lower Dose Cohorts From Baseline Through 1 Year of Follow-up (Months 3 to 12*)

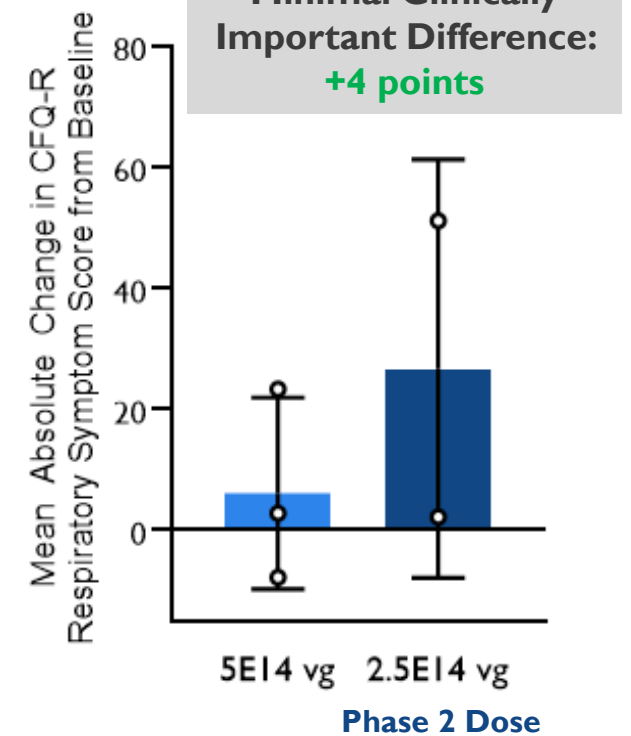
ppFEV₁



LCI_{2.5}



CFQ-R-R



*Post-Hoc analysis of evaluable data: Mean values for each participant calculated from 3M to 12M values, excluding non-evaluable time points with acute pulmonary AEs within 14 days of a study visit. If Month 12 visit was missed or non-evaluable then Month 15 timepoint was used. Note: Analysis for participants in cohort who had at least 12 months of follow-up. Excludes 2.5E14 vg Participant 3.



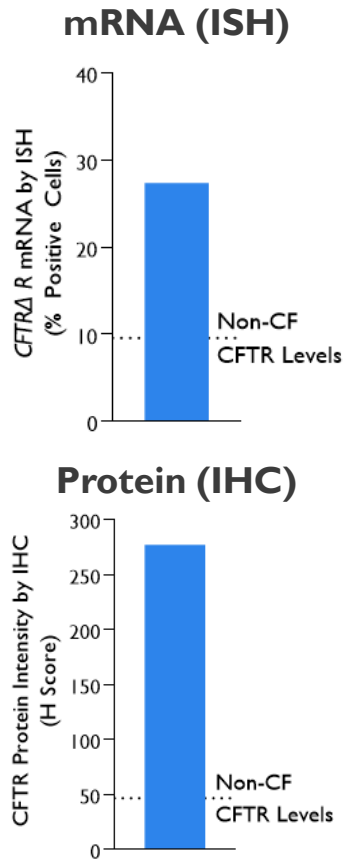
Participant-level Clinical Activity Data Following **5E14** vs **Dosing (Cohort 3)**

Jennifer L. Taylor-Cousar, M.D., MSCS
National Jewish Health

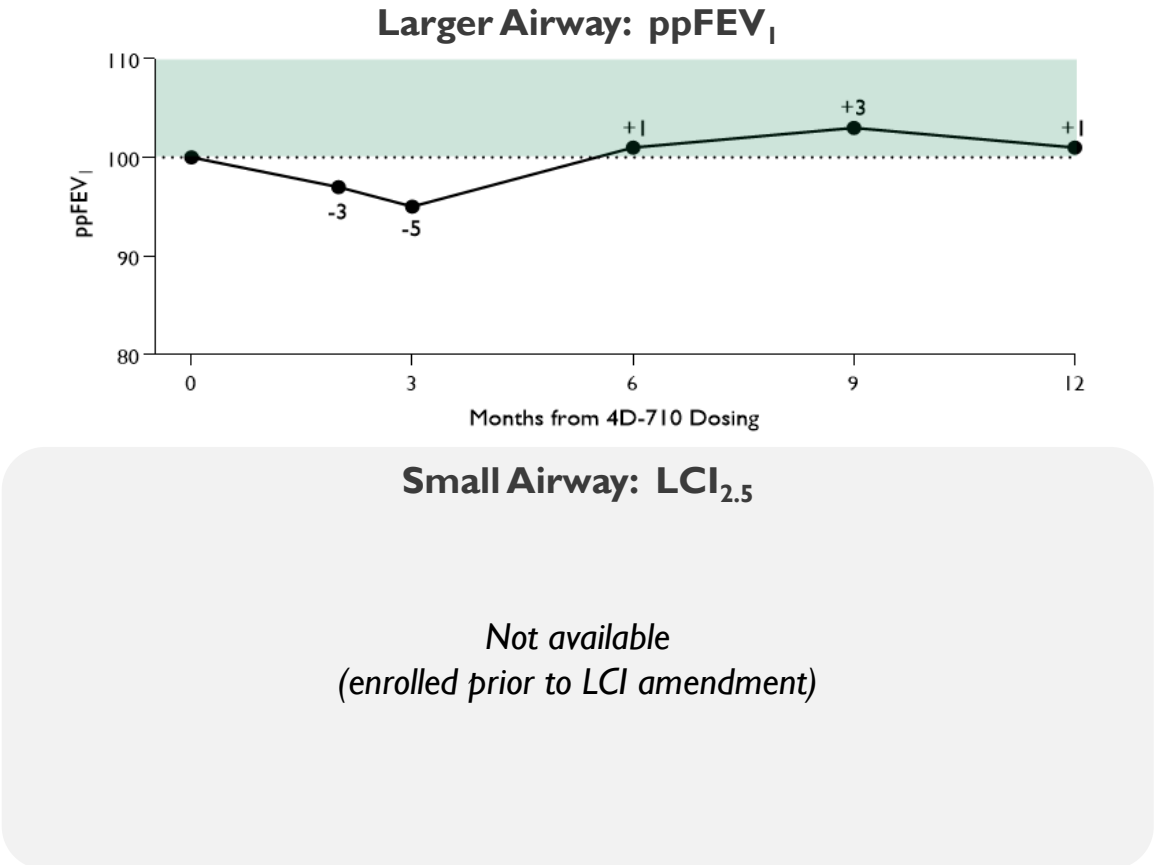
Data Cutoff: December 1, 2025

5E14 vg Participant 1: 42 y.o. Female with Normal Baseline Lung Function by ppFEV₁; LCI_{2.5} Not Available

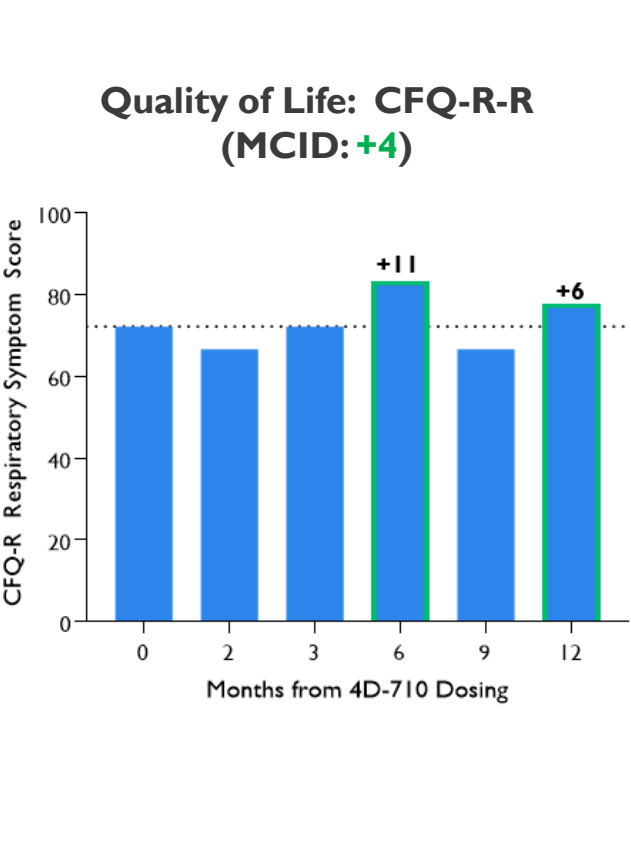
CFTR Δ R Expression



Lung Function



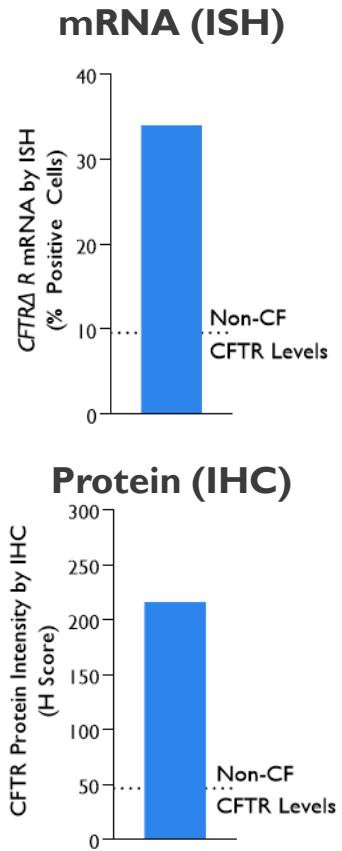
Pulmonary Symptoms



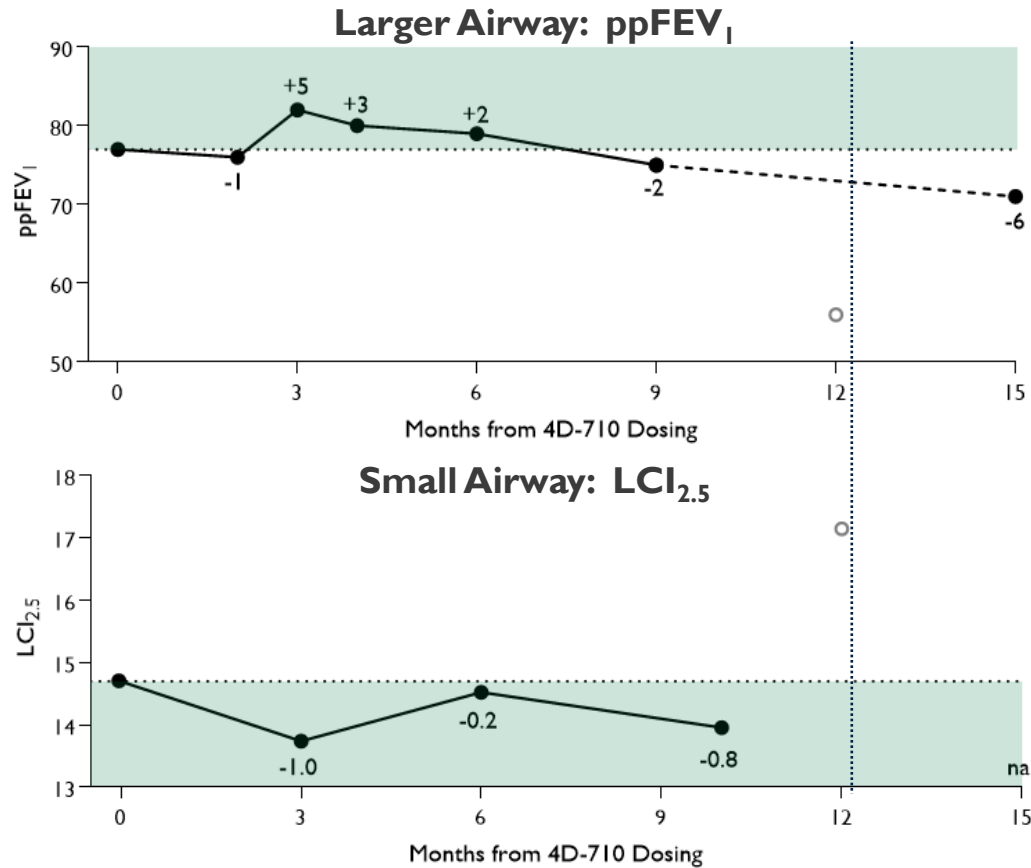
Numbers represent change from baseline values.

5E14 vg Participant 2: 40 y.o. Female with Moderate Lung Disease, Positive 4D-710 Response by Transgene Expression, $LCI_{2.5}$, ppFEV₁ & CFQ-R-R

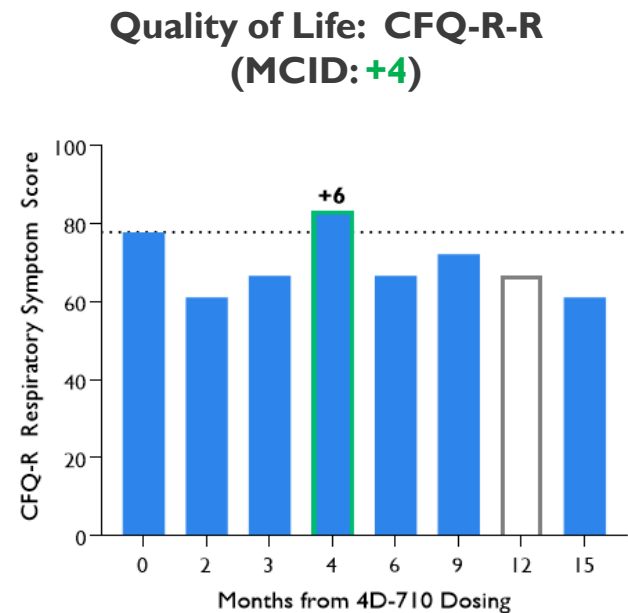
CFTR Δ R Expression



Lung Function



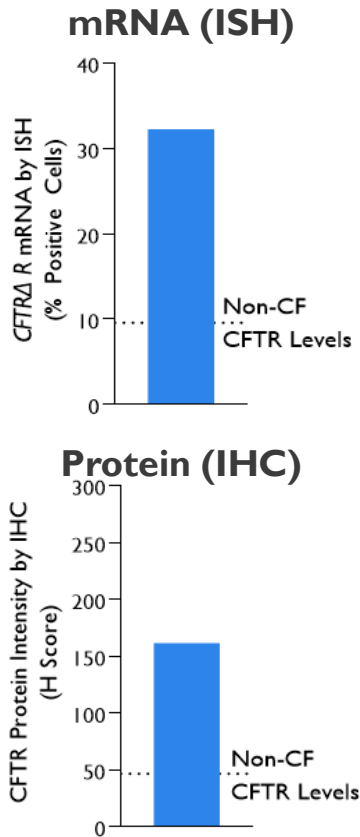
Pulmonary Symptoms



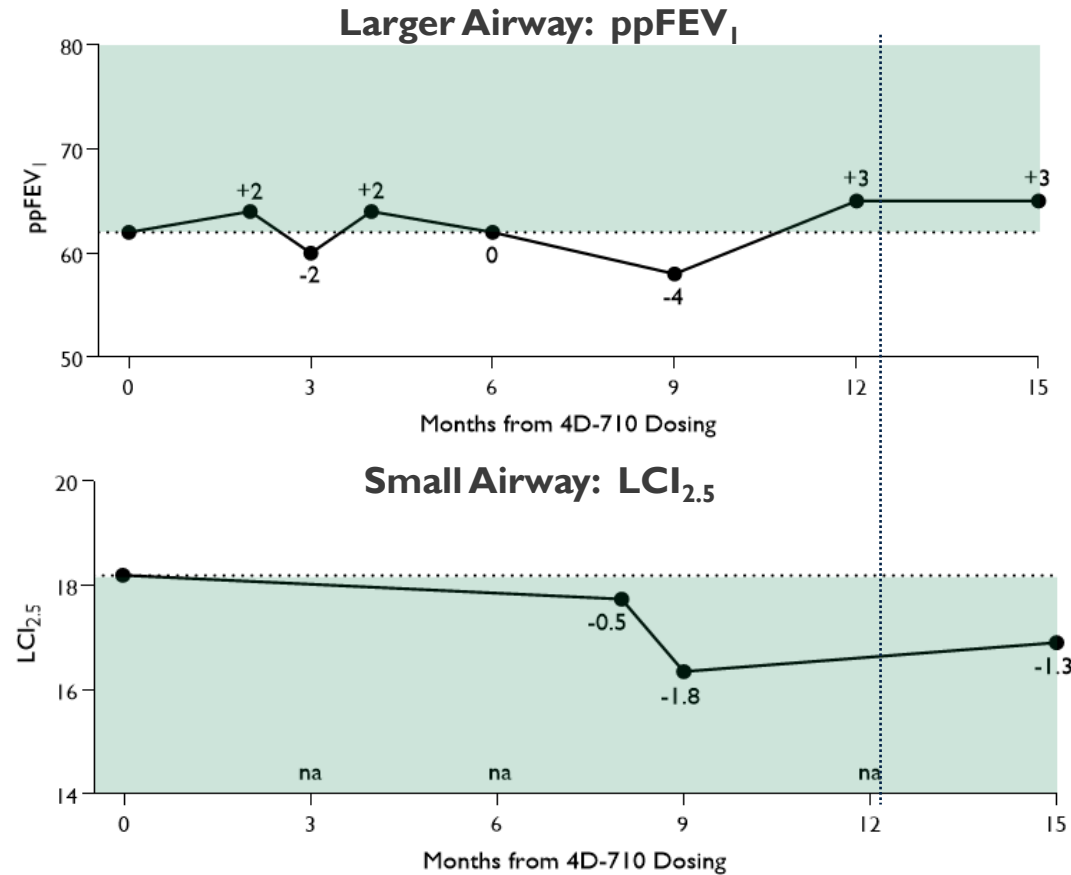
Numbers represent change from baseline values. $LCI_{2.5}$ performed at 10M unscheduled visit due to 9M MBW not passing QC. na = data not available due to participant not able to perform at 15M study visit. Open circles or columns represent study visits within 2 weeks of an acute pulmonary AE. 15M spirometry & CFQ-R-R shown due to acute pulmonary event associated with 12M visit.

5E14 vg Participant 3: 34 y.o. Male with Moderate Lung Disease, Positive 4D-710 Response by Transgene Expression, $LCI_{2.5}$, ppFEV₁ & CFQ-R-R

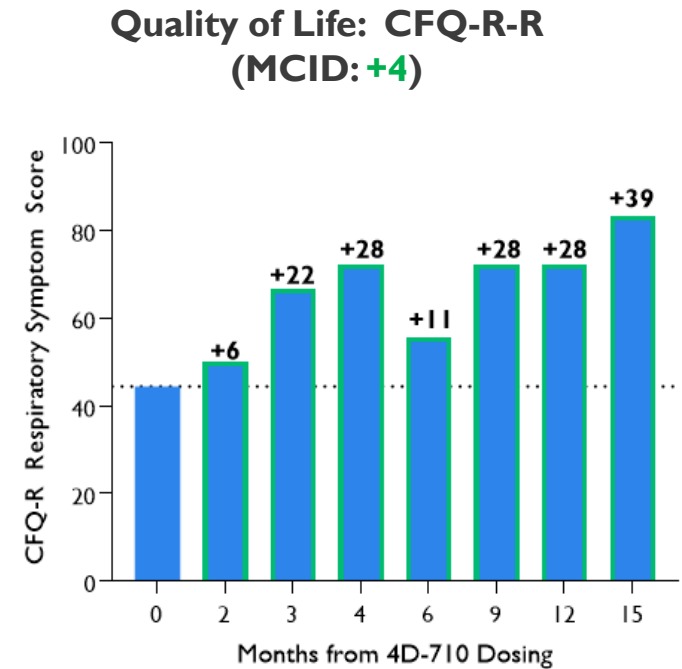
CFTR Δ R Expression



Lung Function



Pulmonary Symptoms



Numbers represent change from baseline values. na = data not available due to testing not passing central reading QC. 8M unscheduled visit performed for repeat MBW from 6M study visit not passing QC. 15M spirometry & CFQ-R-R shown due to for context with 15M $LCI_{2.5}$.



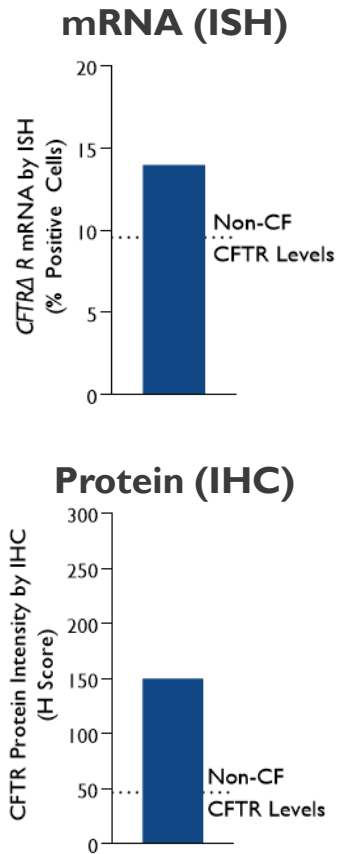
Participant Clinical Activity Data Following **2.5E14** vg Dosing (**Cohort 4, Phase 2 Dose**)

Jennifer L. Taylor-Cousar, M.D., MSCS
National Jewish Health

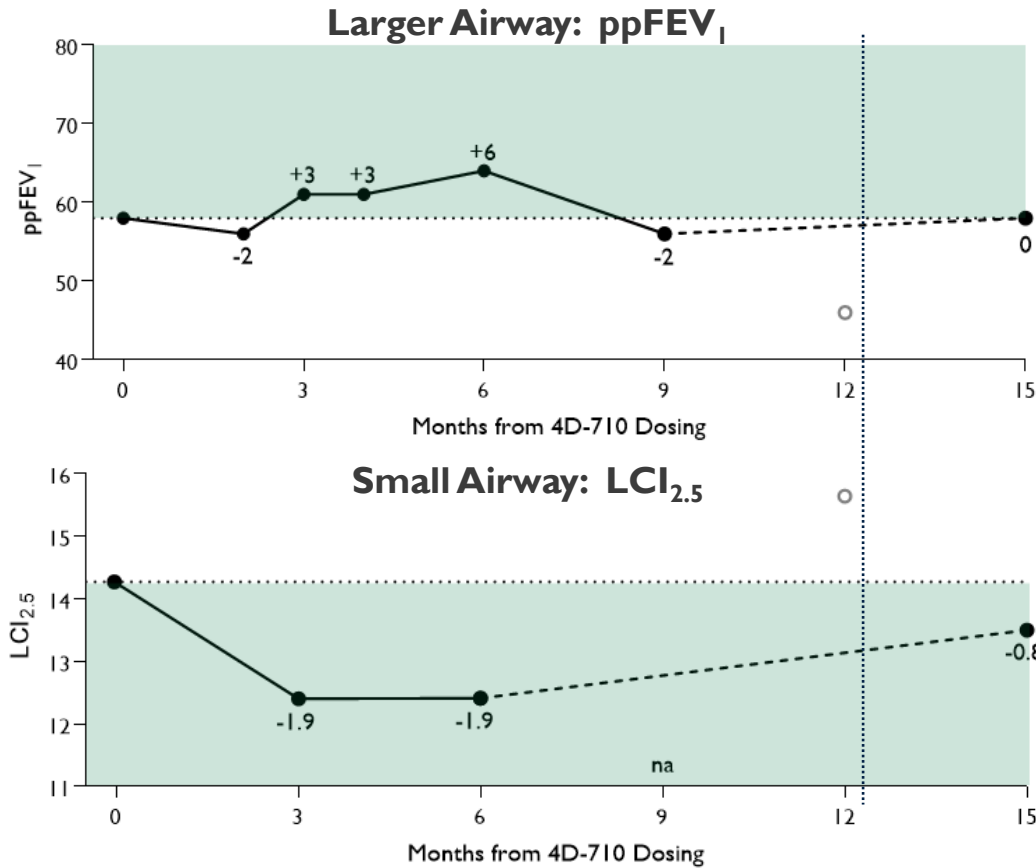
Data Cutoff: December 1, 2025

2.5E14 vg Participant I: 26 y.o. Male with Moderately Severe Lung Disease Positive 4D-710 Response by Transgene Expression, LCI_{2.5}, ppFEV₁ & CFQ-R-R

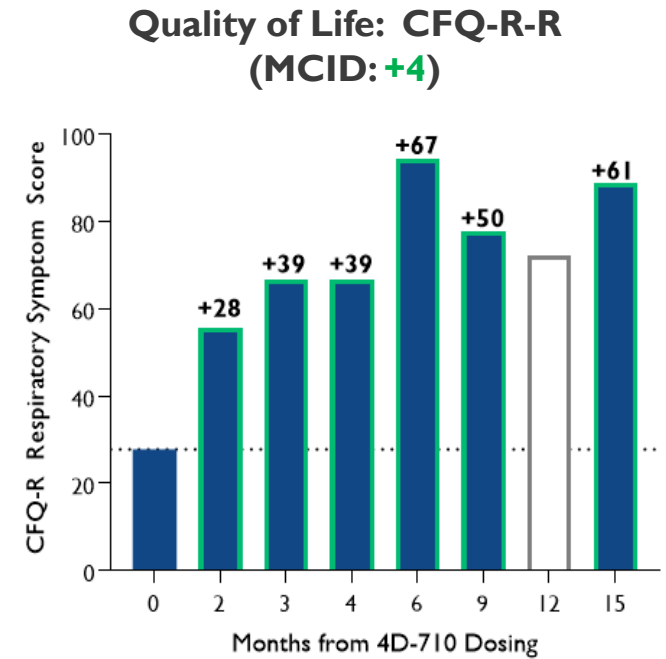
CFTR Δ R Expression



Lung Function



Pulmonary Symptoms

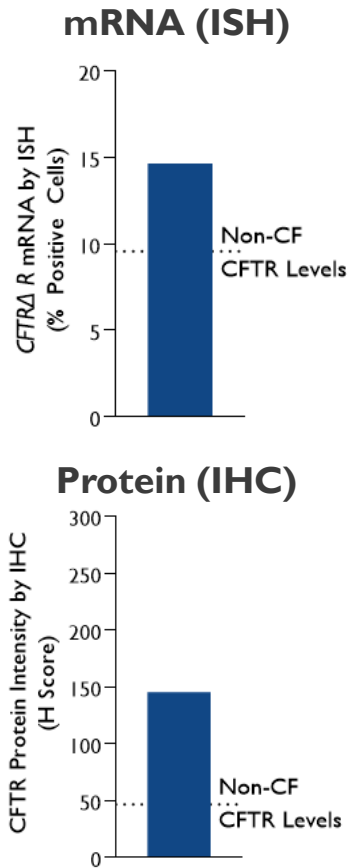


Numbers represent change from baseline values. na = data not available due to testing not passing central reading QC. Additional MBW performed at 15M due to acute pulmonary AE at 12M. 15M spirometry & CFQ-R-R shown due to acute pulmonary event associated with 12M visit. Open circles or columns represent study visits within 2 weeks of an acute pulmonary AE.

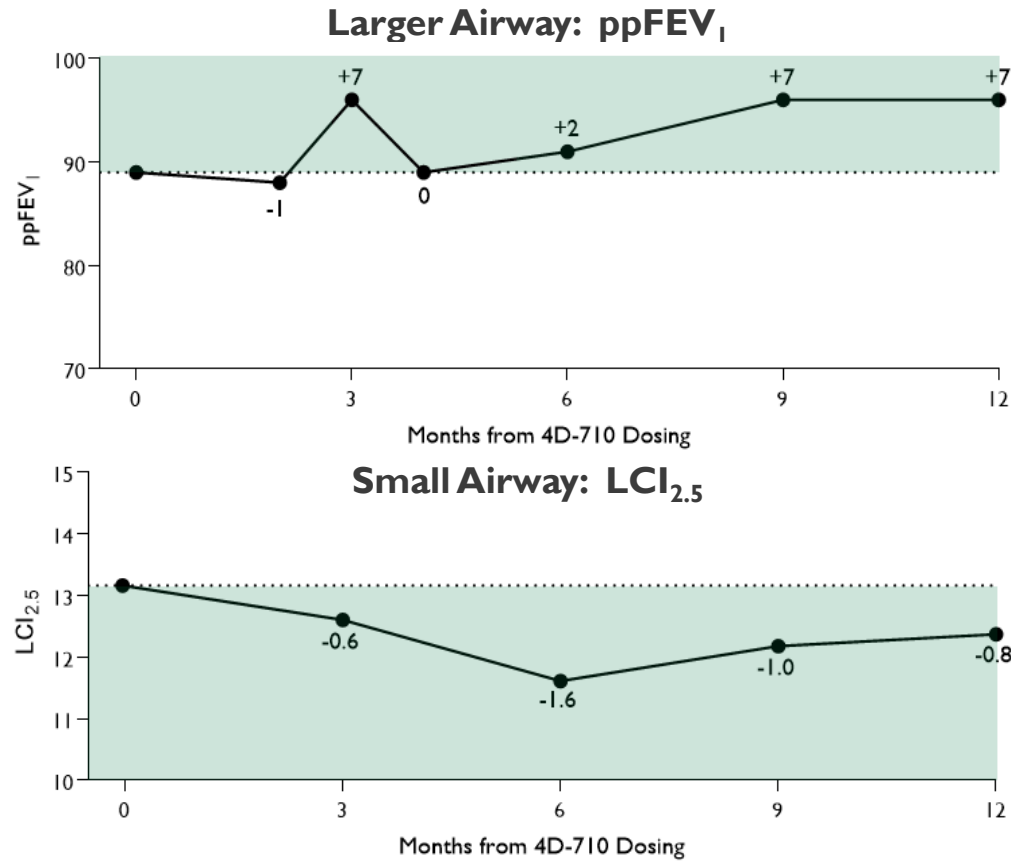
2.5E14 vg Participant 2: 54 y.o. Female with Mild Lung Disease

Positive 4D-710 Response by Transgene Expression, LCI_{2.5}, ppFEV₁ & CFQ-R-R

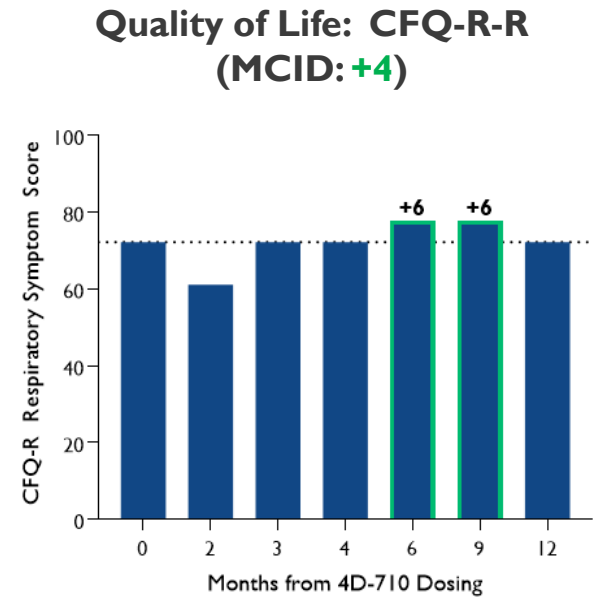
CFTR Δ R Expression



Lung Function



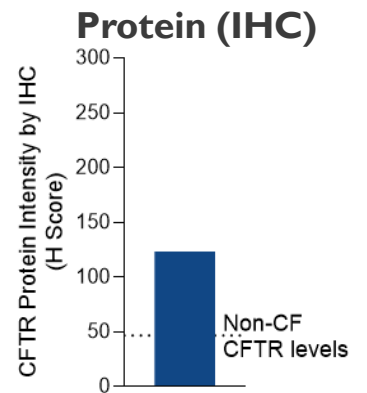
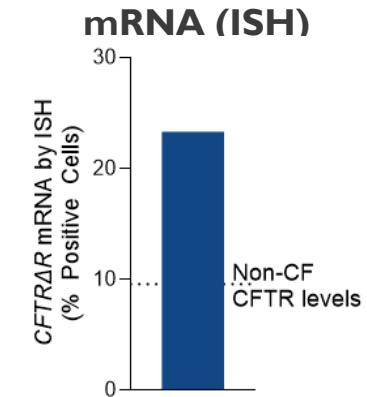
Pulmonary Symptoms



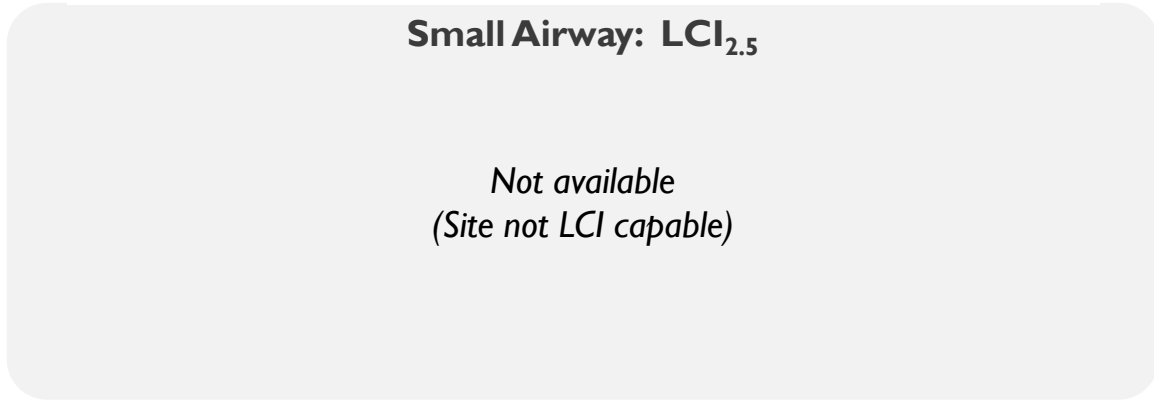
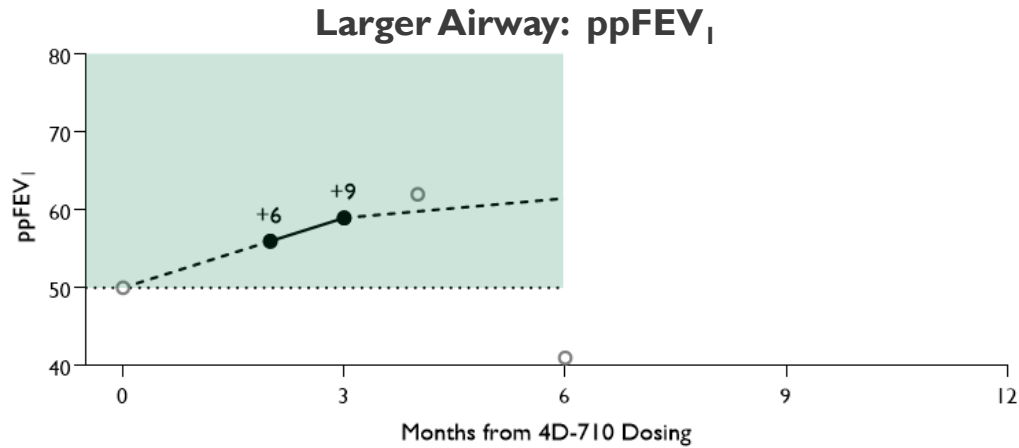
Numbers represent change from baseline values.

2.5E14 vg Participant 3: 37 y.o. Female with Moderately Severe Lung Disease, Positive 4D-710 Response by Transgene Expression

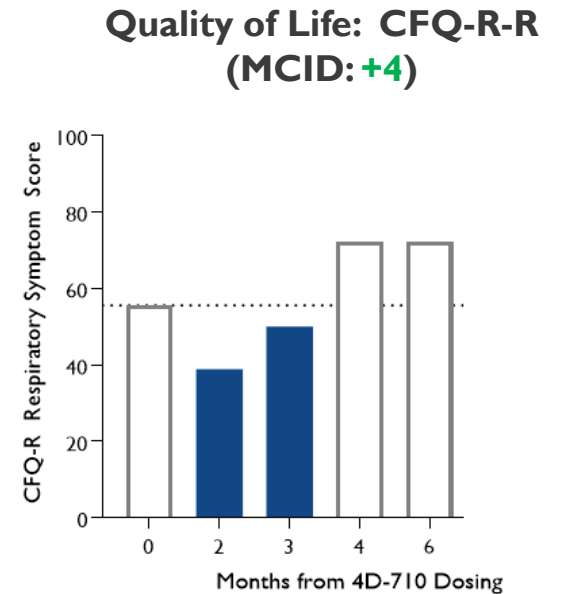
CFTR Δ R Expression



Lung Function



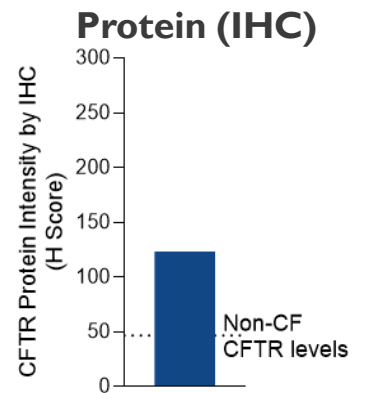
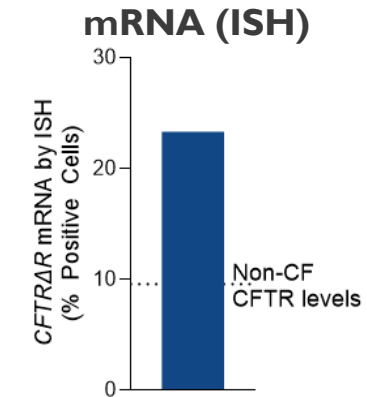
Pulmonary Symptoms



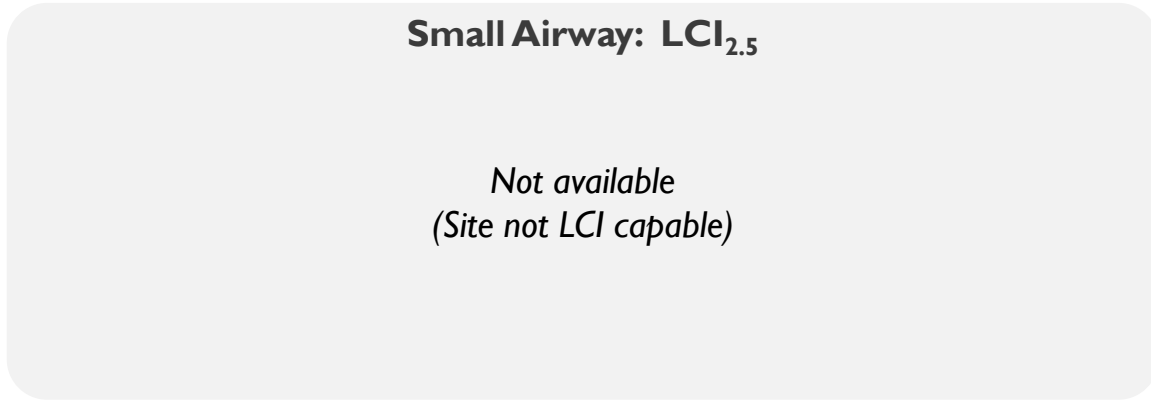
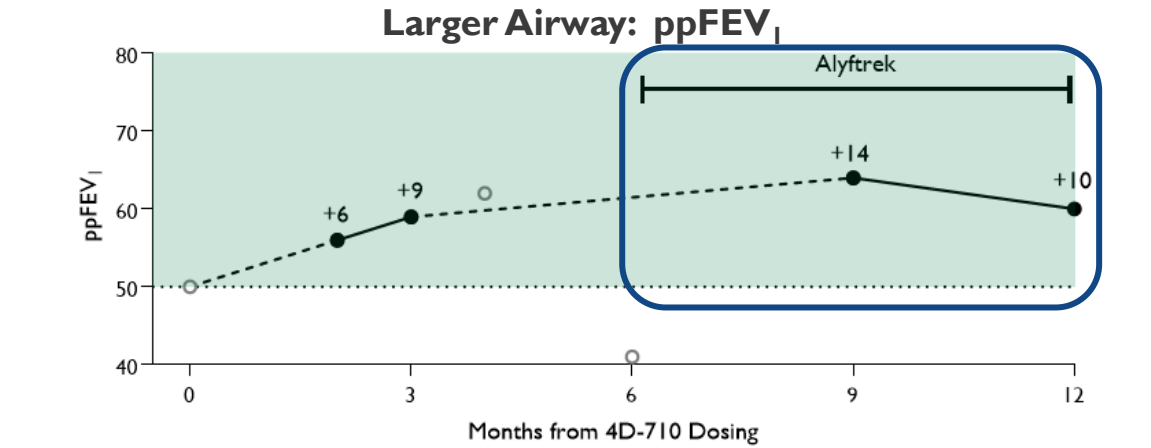
Numbers represent change from baseline values. na = data not available due to testing not passing central reading QC.
Open circles or columns represent study visits within 2 weeks of an acute pulmonary AE. Participant's baseline value is inappropriately low due to ongoing RSV infection.

2.5E14 vg Participant 3 Addition of Modulator at 8 Months: Positive 4D-710 + Modulator Safety (Clinical Activity Not Evaluable)

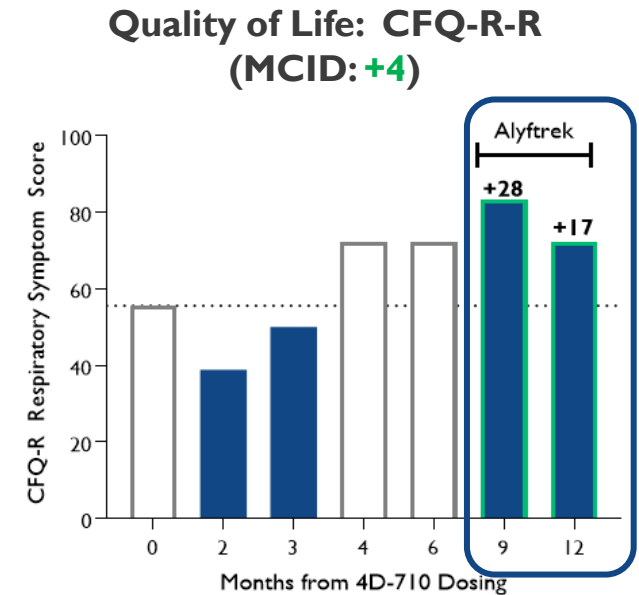
CFTR Δ R Expression



Lung Function



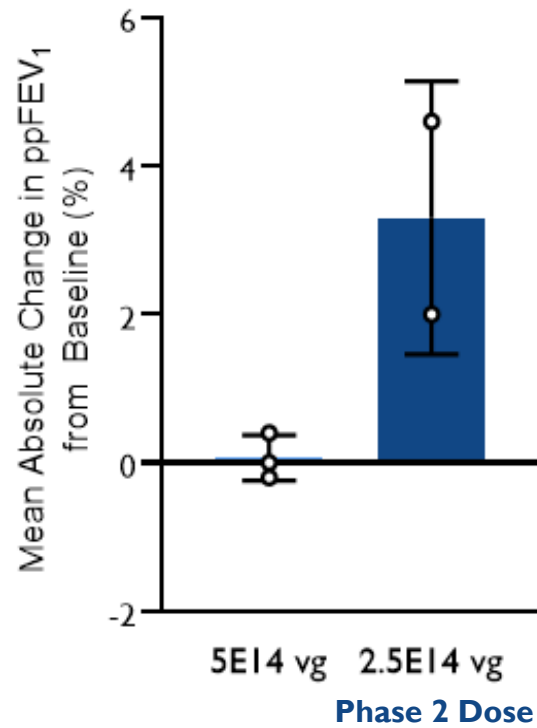
Pulmonary Symptoms



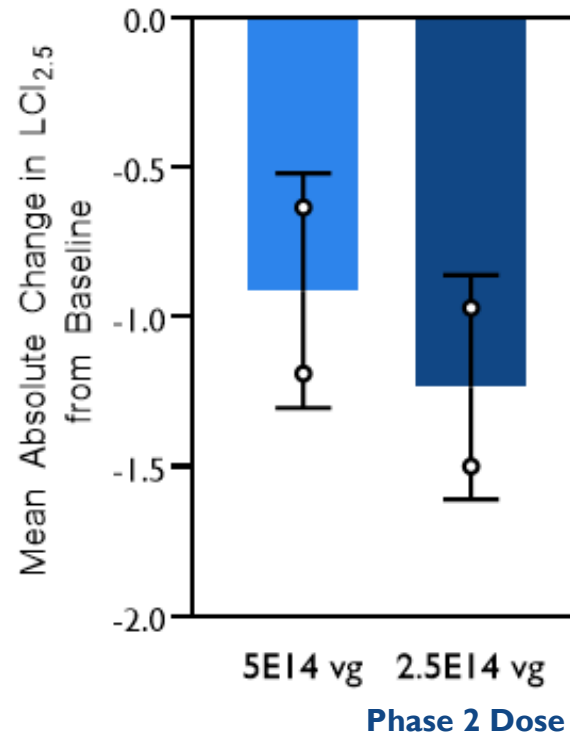
Numbers represent change from baseline values. na = data not available due to testing not passing central reading QC.
Open circles or columns represent study visits within 2 weeks of an acute pulmonary AE. Participant's baseline value is inappropriately low due to ongoing RSV infection.

Pulmonary Clinical Activity: Mean Change in ppFEV₁, LCI_{2.5} & CFQ-R-R in Lower Dose Cohorts From Baseline Through One Year of Follow-up (Months 3 to 12*)

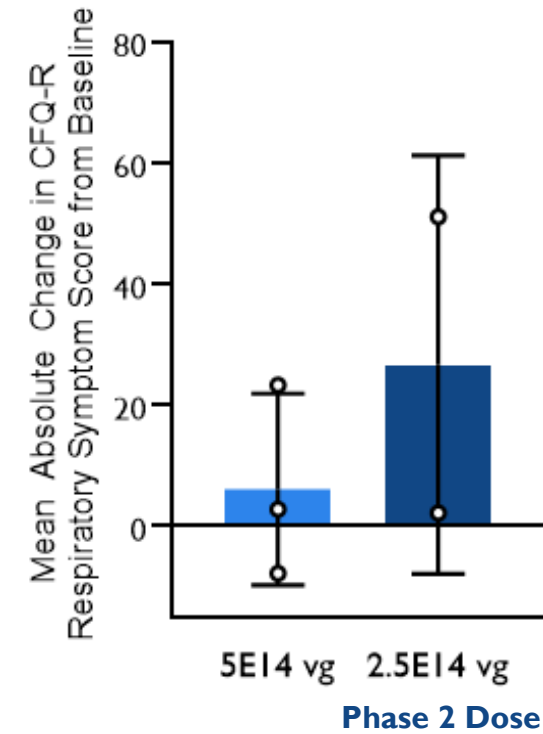
ppFEV₁



LCI_{2.5}



CFQ-R-R



*Post-Hoc analysis of evaluable data: Mean values for each participant calculated from 3M to 12M values, excluding non-evaluable time points with acute pulmonary AEs within 14 days of a study visit. If Month 12 visit was missed or non-evaluable then Month 15 timepoint was used. Note: Analysis for participants in cohort who had at least 12 months of follow-up. Excludes 2.5E14 vg Participant 3.

Dose Selection Framework for Further Development of 4D-710

Focus of Phase 1: Dose Finding

Safety ✓

Physiologically relevant
CFTR expression levels
(ISH, IHC) ✓

Clinical activity
(ppFEV₁, LCI_{2.5}, CFQR-R-R) ✓

**Phase 2
Dose:
2.5E14 vg**

Focus of Phase 2 (**Enrolling**): Characterize Clinical Activity

Stability or improvement in
large-/mid- airway disease
(ppFEV₁)

Improvement in **small airway disease**
(LCI_{2.5})

Improvements in **respiratory symptoms**
(CFQR-R-R)

Exploratory: evidence of **decreased mucus burden** (HRCT)



Transgene Expression Durability Data & Next Steps

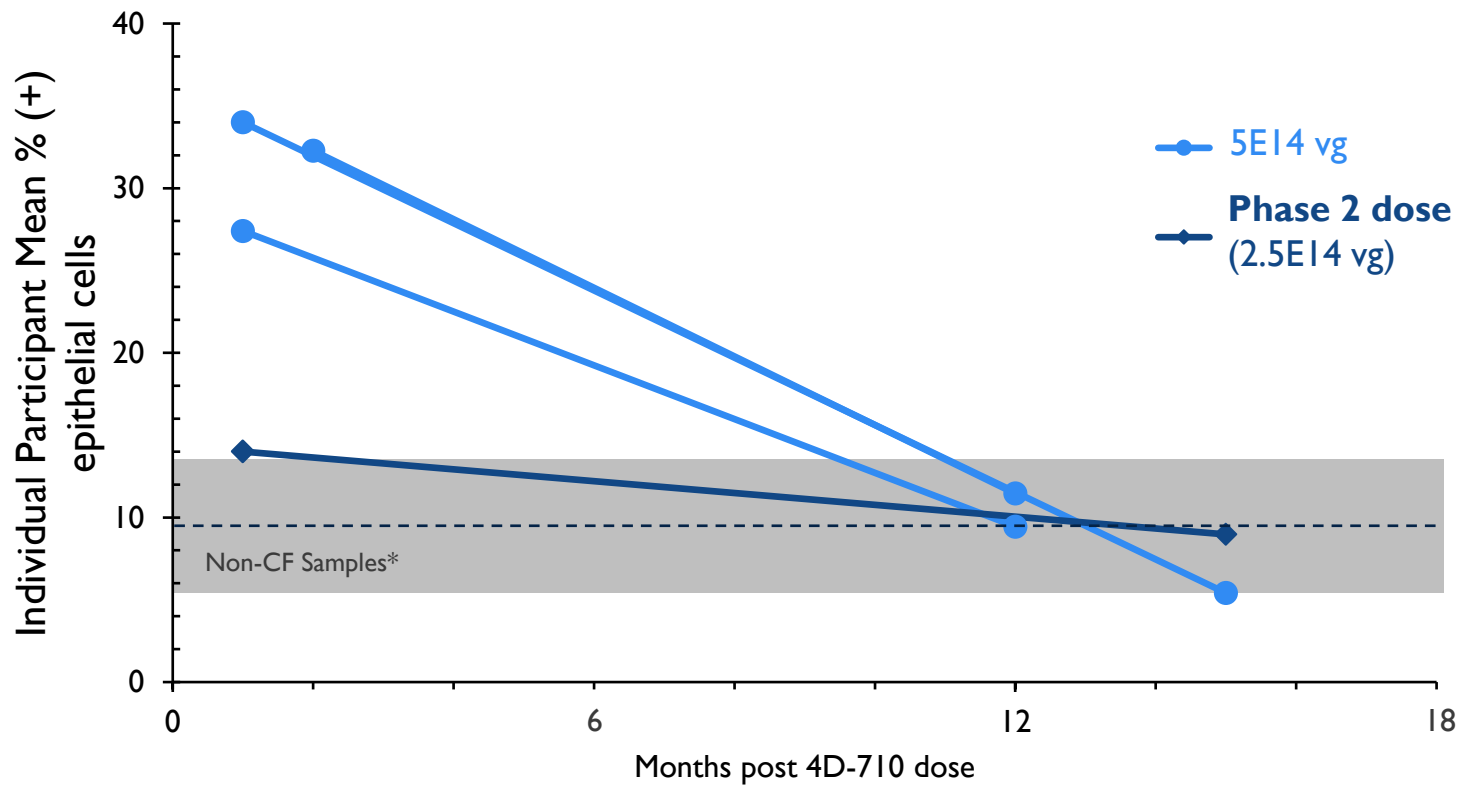
David Kirn, M.D.

Co-founder and Chief Executive Officer

Data Cutoff: December 1, 2025

Durability of 4D-710–mediated CFTR Expression in Airway Biopsies: Persistent within Target Therapeutic Range through Over 1 Year

Durability of 4D-710–Mediated *CFTR* Δ R Expression (ISH): Mean % of Airway Epithelial Cells (+) in Individual Patients with Optional Paired Biopsies



Population & Methods

Participants in 1E15, 5E14, and 2.5E14 vg dose cohorts elected to a bronchoscopy to collect paired lung biopsies at ≥ 1 -year post-4D-710 dosing. 5E14, 2.5E14 vg data shown here (*1E15 vg data in appendix*)

Key Findings

Durable expression with levels consistent with the non-CF % (+) epithelial cells and expression levels over 1 year

Next Steps

Collect additional paired biopsy data alongside clinical activity measures with focus on Phase 2 dose to inform redosing strategy

Quantification by Visiopharm® AI machine Learning analysis. *Mean (\pm SD) in non-CF samples = 9.6% (\pm 4%). CFTR, cystic fibrosis transmembrane conductance regulator; ISH, *in situ* hybridization

Advancing 4D-710 Together with CFF: 10 Year Collaboration & ~\$31M in Financial Support From CFF



Mechanism	Financials	Benefits
Research Grant (2016)	\$6.3M	<ul style="list-style-type: none"> JSC governance structure to coordinate strategic planning for 4D-710 development Senior development, biostats, and regulatory expertise Scientists & specialists <i>In vitro</i> assays Animal models World renowned research lab CF patient samples Patient registry including data from >32k people with CF
Equity Investment (2020-21)	\$14M	
Equity Investment (2025)	\$11.1M*	



*Trial Conduct
within TDN*

- Deep development experience conducting >150 clinical studies for CF
- Access to >80 accredited care centers with demonstrated expertise in clinical research

*\$7.5M upfront with \$3.6M at 4DMT's option after meeting certain milestones.

4D-710 Next Steps



4D-710

Durable, Redosable, Variant-Agnostic, Disease-Modifying Treatment Potential for People with CF Lung Disease with Remaining High Unmet Need

Expected Milestones:

- **HI 2026: Complete Phase 2 enrollment**
- **2026: Advance redosing strategy**
 - Collect additional paired biopsy data in 2.5E14 vg dose
 - Update redosing strategy based on emerging durability and clinical activity data
- **H2 2026: Program update**



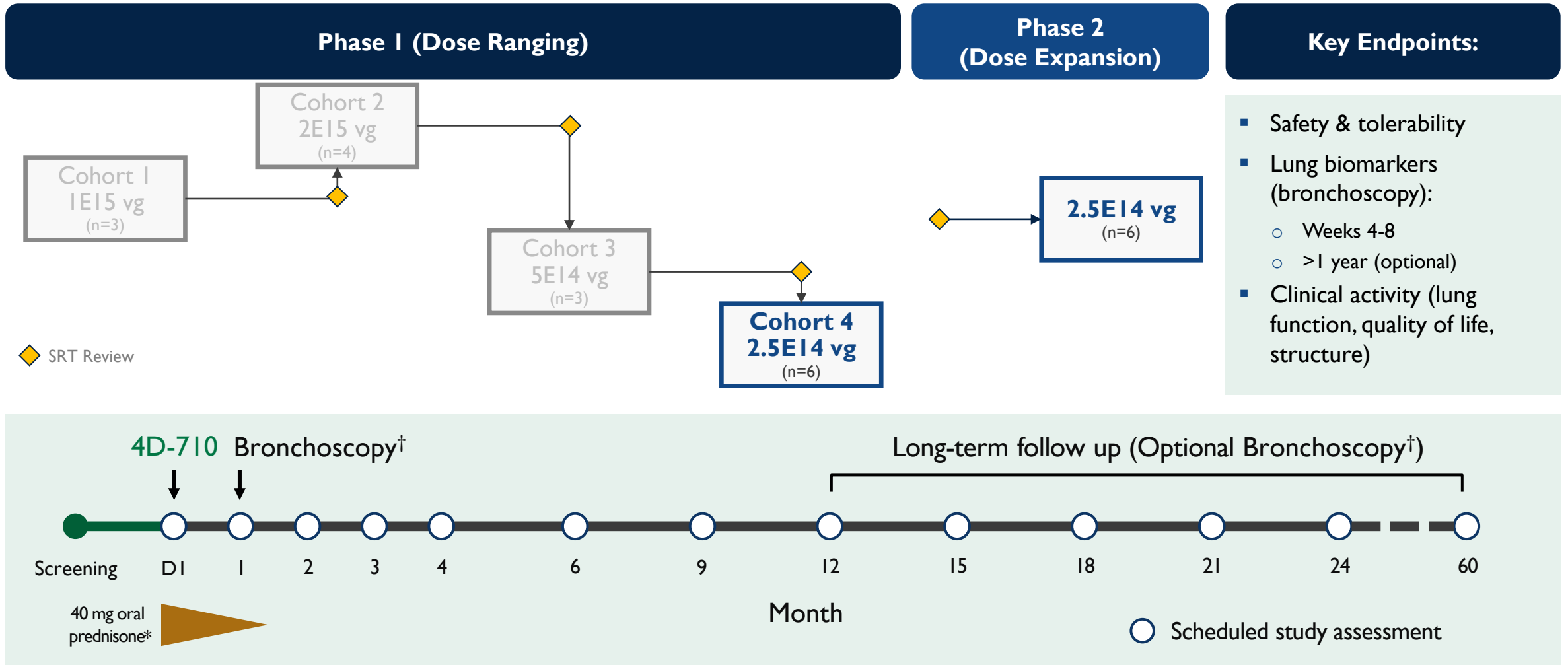
THANK YOU

5858 Horton Street, Suite 455 | Emeryville, California 94608

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

IR.4DMT.com | [LinkedIn](#)

Protocol Amended with Novel Lung Endpoints to Enhance Clinical Activity Assessments, Additional Biopsy to Assess Durability



*28-day taper. †Endobronchial biopsy (4D-710 transgene and protein expression). ppFEV₁, percent predicted forced expiratory volume in 1 second; SRT, Safety Review Team; MBW, Multiple Breath Washout; LCI_{2.5}, Lung Clearance Index at 2.5% of starting concentration; HRCT, High Resolution Computed Tomography.

4D-710 Phase 1/2 Clinical Trial: Dose Exploration

Demographics and Baseline Characteristics (Higher Doses, n=7)

	Cohort 1: 1E15 vg			Cohort 2: 2E15 vg			
Participant Number	1	2	3	1	2	3	4
Age, y	36	24	20	37	27	32	69
Sex	Male	Male	Female	Female	Male	Female	Female
CFTR modulator status	Intolerant	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible	Intolerant
CFTR Variants	<i>F508del/5T</i>	<i>c.1393-1G>A/7T/9T</i>	<i>621+1G>T/N1303K</i>	<i>1213delT/1154insTC</i>	<i>G542X/2823delCTCA</i>	<i>R1162X/R1162X</i>	<i>F508del/1336K</i>
Sweat chloride, mmol/L [†]	74	103	110	84	96	103	114
ppFEV ₁	83	69	95	90	56	80	86
CFQ-R-R score (0-100)	72	61	83	78	72	89	78

[†]Sweat chloride normal range ≤29 mmol/L, *Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation (2017)*. Ab, antibody; CFTR, cystic fibrosis transmembrane conductance regulator; CFQ-R-R, Cystic Fibrosis Questionnaire–revised (respiratory domain); FEV₁, forced expiratory volume in 1 second.

4D-710 Phase 1/2 Clinical Trial: Dose Exploration



Demographics and Baseline Characteristics (Lower Doses, n=9)

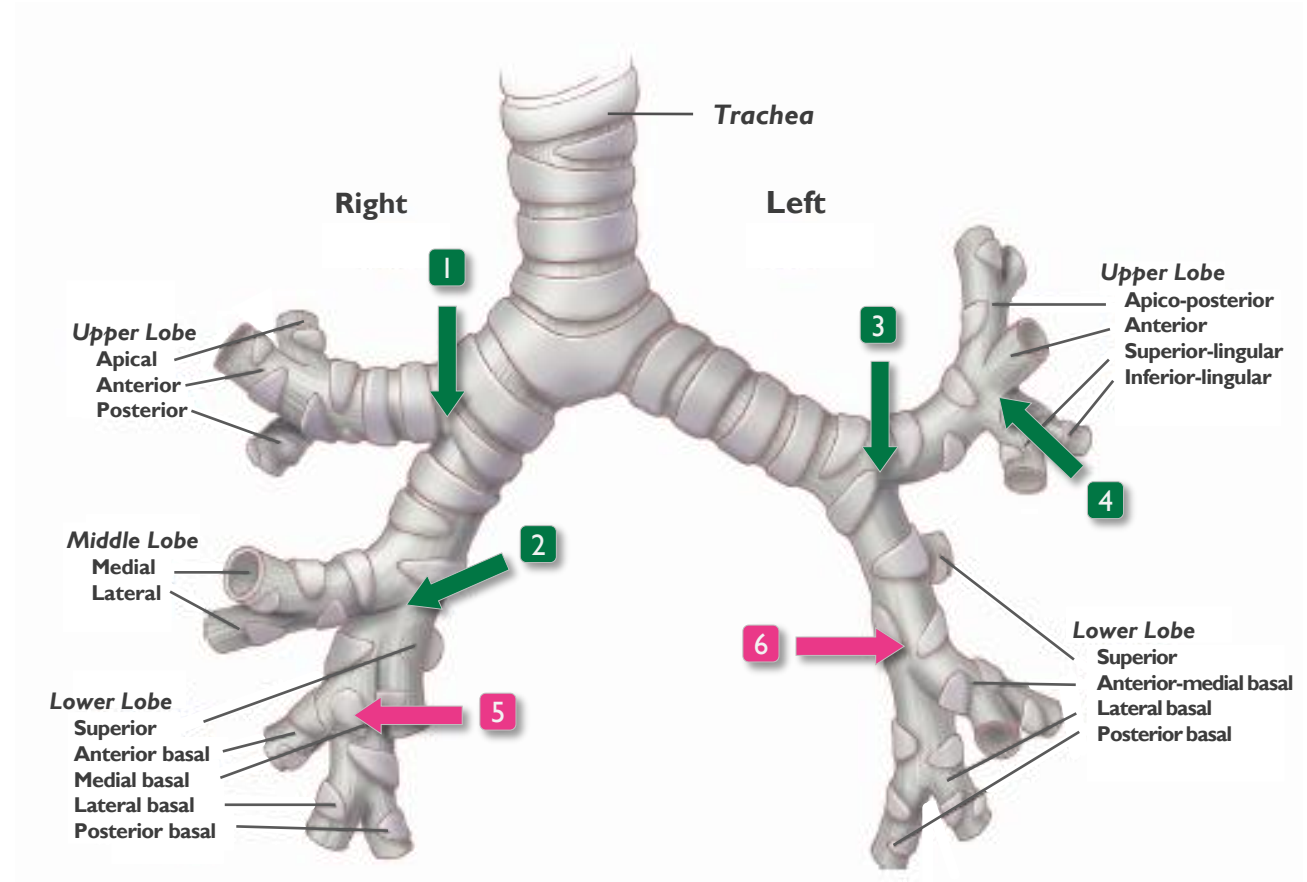
	Cohort 3: 5E14 vg			Cohort 4: 2.5E14 vg					
Participant Number	1	2	3	1	2	3	4	5	6
Age, y	42	39	34	25	54	36	56	32	37
Sex	Female	Female	Male	Male	Female	Female	Male	Male	Male
CFTR mod. status	Intolerant	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible
CFTR Variants	<i>F508del/</i> <i>R751L</i>	<i>4209TGTT>AA/</i> <i>3120+1G>A</i>	<i>Q220X/</i> <i>Q493X</i>	<i>c.2184_2185insA/</i> <i>c.2184_2185insA</i>	<i>1471delA/</i> <i>1717-1G>A</i>	<i>W1282X/</i> <i>H1079P</i>	<i>3659delC/</i> <i>5T</i>	<i>S466X/</i> <i>1342-1delG</i>	<i>G542X/</i> <i>W1282X</i>
Sweat chloride, mmol/L [†]	107	134	118	120	61	98	62	108	97
ppFEV ₁	100	77	62	58	89	50	90	76	63
LCI _{2.5} (Normal: <7)	N/A	14.7	18.2	14.3	13.2	N/A	N/A	16.9	13.0
CFQ-R-R score (0-100)	72	78	44	28	72	56	93	89	61

[†]Sweat chloride normal range ≤29 mmol/L, *Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation* (2017). Ab, antibody; CFTR, cystic fibrosis transmembrane conductance regulator; CFQ-R-R, Cystic Fibrosis Questionnaire–revised (respiratory domain); FEV₁, forced expiratory volume in 1 second.

Biopsies & Brushings Collected in Multiple Lung Lobes Bilaterally For Evaluation of DNA, RNA & Protein

Bronchoscopy: Week 4*

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



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

*Conducted at next visit if pulmonary exacerbation prevents bronchoscopy.

4DMT CFTR IHC Assay Development

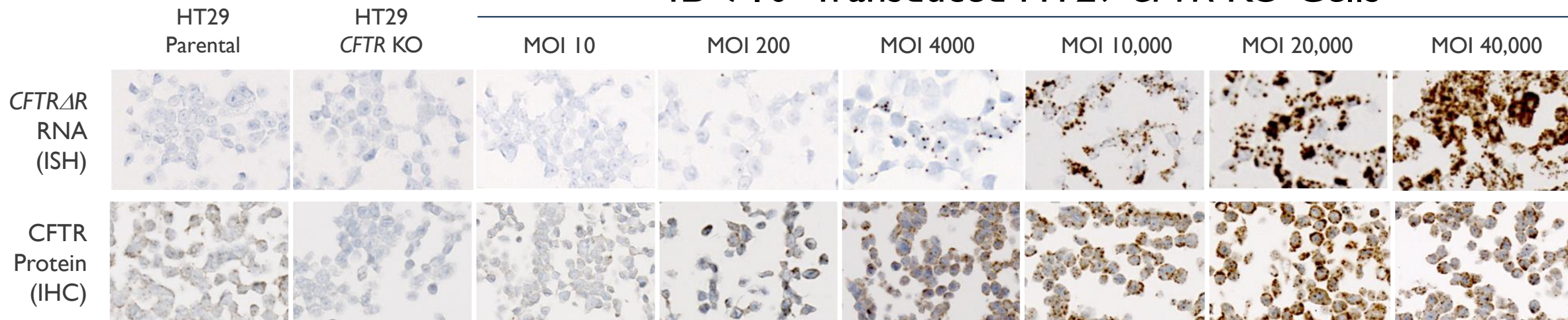
Validated by Extensive Control Testing to Ensure Specificity to CFTR Epitope

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

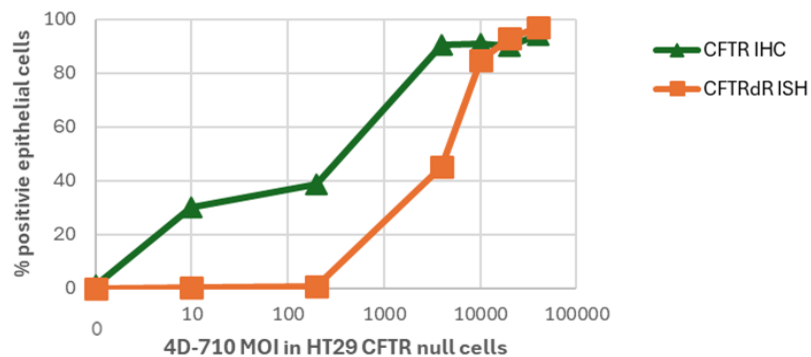
IHC & ISH Assay Specificity and Sensitivity

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

4D-710–Transduced HT29 *CFTR* KO Cells



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

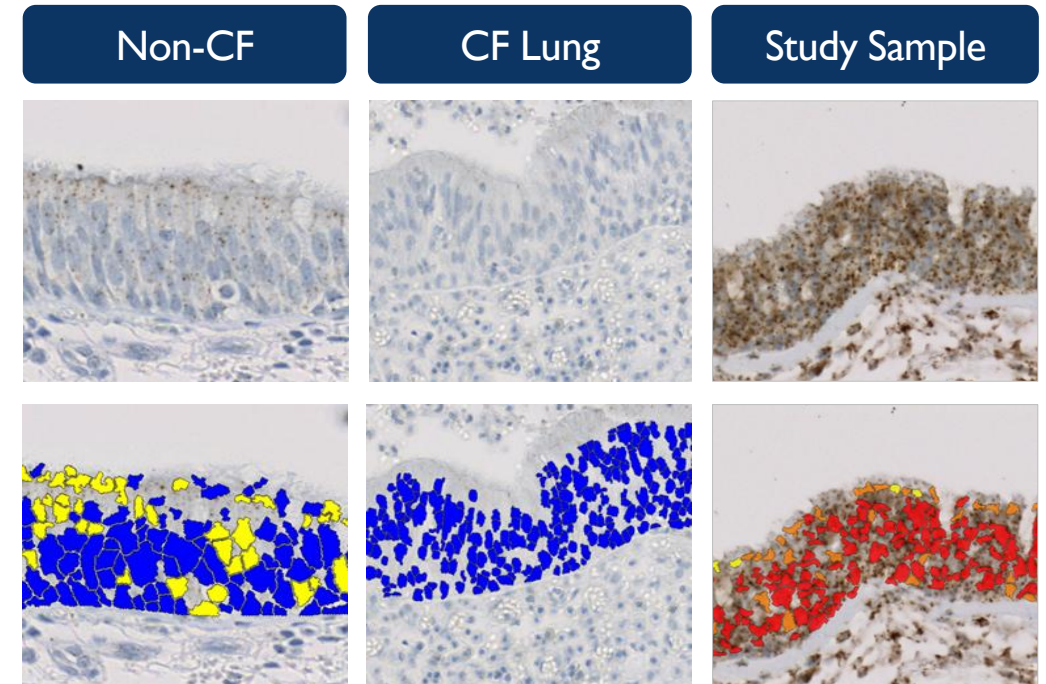


- IHC is more sensitive and has a different dynamic range compared to ISH

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

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

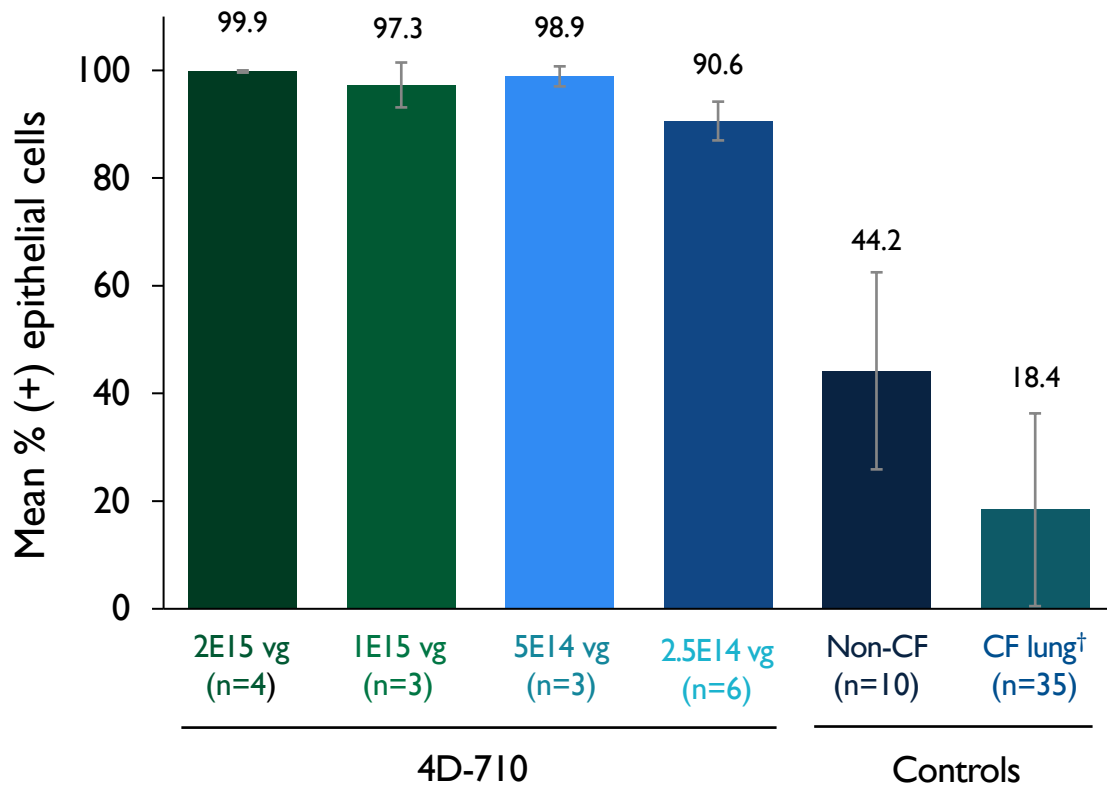


IHC staining intensity: ■ 0 ■ 1⁺ ■ 2⁺ ■ 3⁺

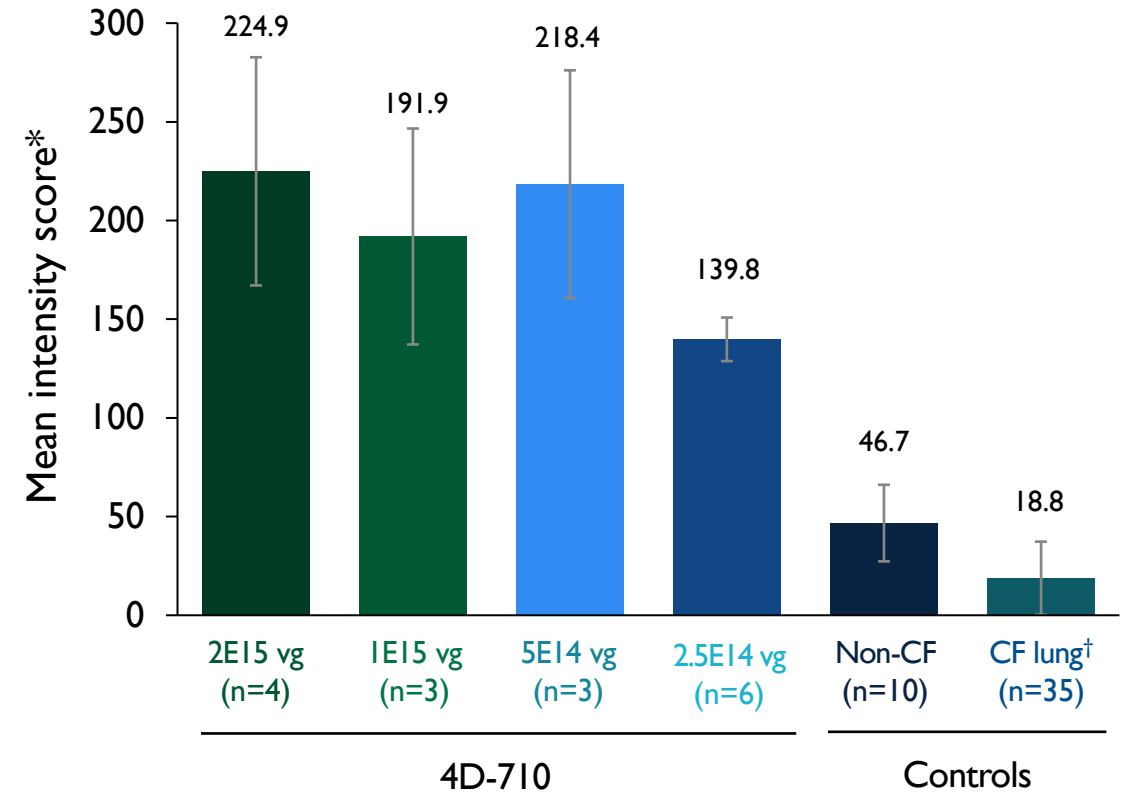
*Visiopharm® image analysis software. CFTR, cystic fibrosis transmembrane conductance regulator; IHC, immunohistochemistry.

4D-710–Mediated CFTR: Protein Expression Confirmed, Above Non-CF and CF Lung Controls

CFTR % (+) Epithelial Cells (IHC)



CFTR Staining Intensity (IHC)*

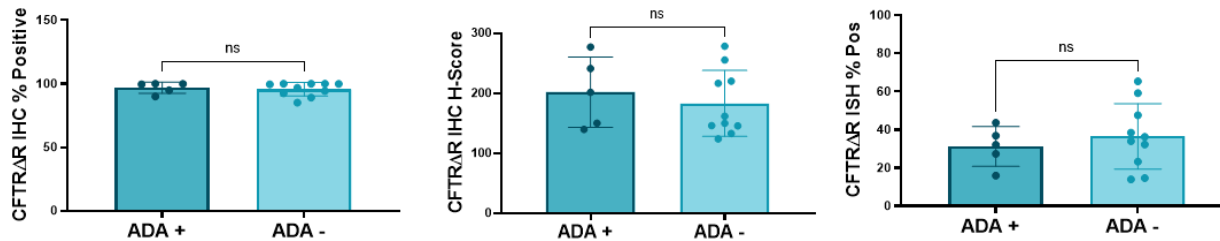


4D-710 biopsies analyzed Day 28 – Day 56

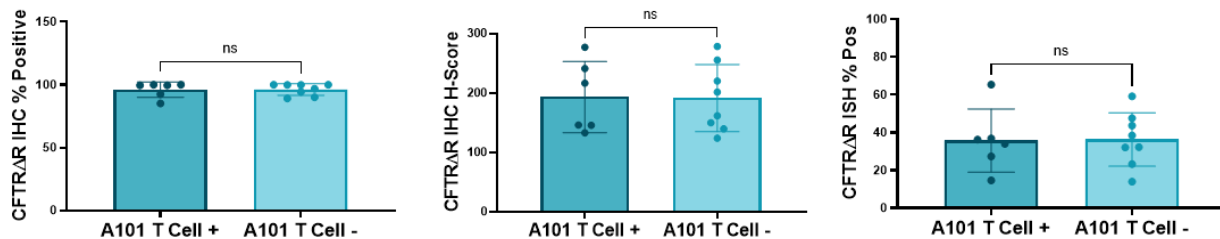
Quantification by Visiopharm® AI machine Learning analysis. *H-score. †Attempts to genotype commercial CF samples yielded results for 13/35 samples; of these, a majority were $\Delta F508$ homozygous mutations. IHC, immunohistochemistry.

Pre-existing A101 Immunity Did Not Affect *CFTR* ΔR RNA or *CFTR* Protein Expression

No Impact on *CFTR* Expression In Lung From Pre-Existing Capsid ADA*



No Impact on *CFTR* Expression In Lung From A101 Specific T Cells*



Pre-existing Anti-A101 Capsid Antibodies

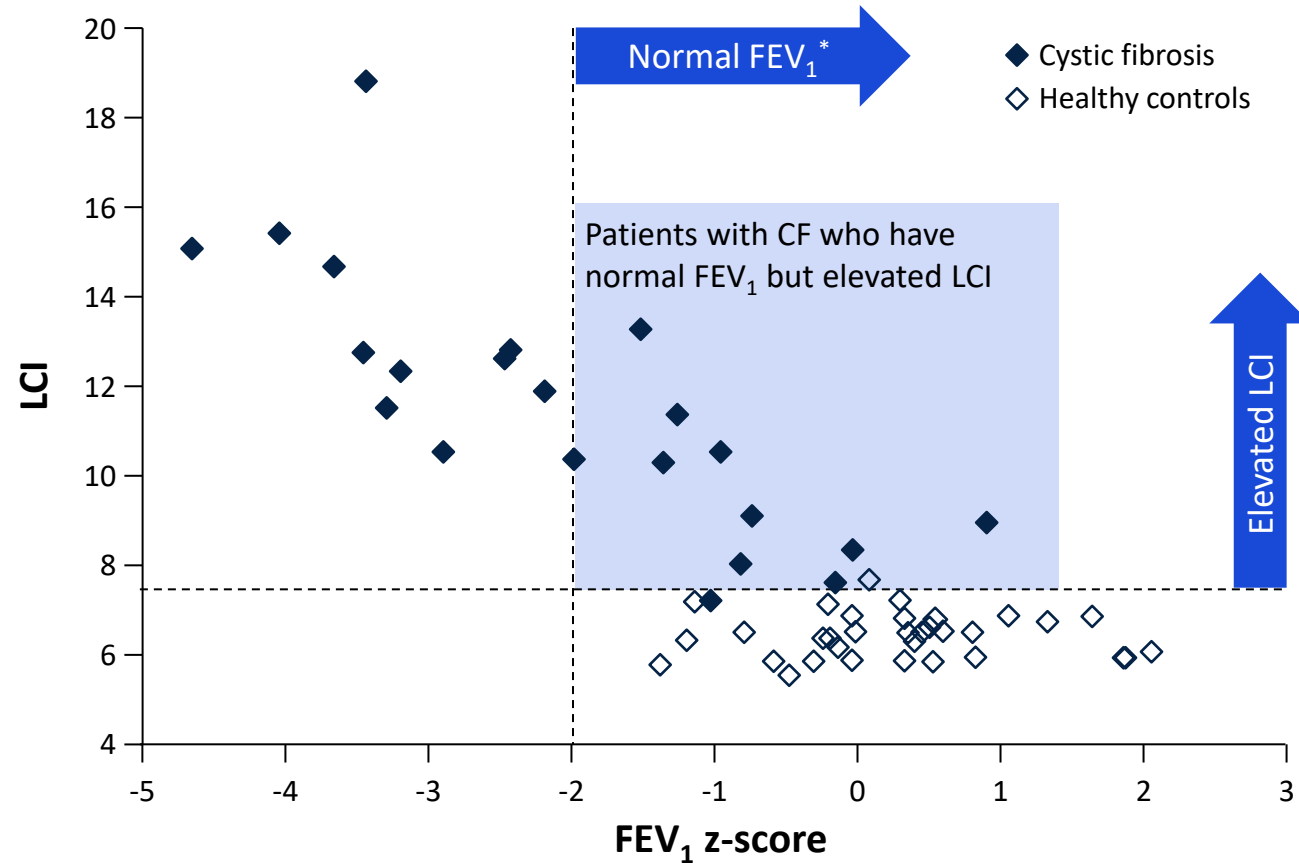
- 5/16 positive for pre-existing A101 capsid antibodies
- No significant difference in mRNA/protein expression** between participants with (n=5) and without (n=11) pre-existing A101 antibodies
- No observed effect of pre-existing antibodies on safety

Pre-existing A101-specific T cells

- 5/16 positive for pre-existing A101-specific T cells[†]
- No significant difference in mRNA/protein expression** between participants with (n=5) and without (n=11) pre-existing A101-specific T cells

*Data represented as group mean with error bars representing standard deviation

LCI Detects Early Airway Disease in Children Before Noticeable FEV₁ Decline



- 50% of children (age 6 to 16 years) with CF had a FEV₁ z-score within the normal range and LCI above the normal range

*FEV₁ results were converted into standard deviation scores (z-scores) using published reference data with a z-score of less than -1.96 being categorized as abnormal.
Aurora P et al. *Thorax*. 2004;59(12):1068-1073.

LCI_{2.5} Accepted by Regulatory Agency (Vertex Products)

In Pivotal Trial to Support Drug Approval

Product	Agency	Primary/Secondary Endpoint	Population	Approval
Orkambi	EMA	Primary in 1 trial	CF 6–11 y	Label extension to 6–11 y (efficacy and safety)
		Secondary in 3 trials	CF 2–5 y	Label extension to 2–5 y (safety)
	FDA	Secondary in 2 trials	CF 6–11 y	Label extension to 2–11 y (safety)
		Secondary in 1 trial	CF 2–5 y	
Symdeko (Symkevi)	EMA	Primary in 1 trial	CF 6–11 y	Label extension to 6–11 y (efficacy and safety)
Trikafta (Kaftrio)	EMA	Primary in 1 trial Secondary in 3 trials	CF 6–11 y	Label extension to 6–11 y (efficacy and safety)
		Secondary in 2 trials	CF 2–5 y	Label extension to 2–5 y (safety)
	FDA	Secondary in 1 trial	CF 6–11 y	Label extension to 2–11 y (safety)
		Secondary in 1 trial	CF 2–5 y	

Redosing Considerations: Biological Context and Data Support Feasibility of Repeat Dosing for Aerosolized 4D-710

Rationale

- Lung epithelium expected, repeat dosing expected to be required
- Historical data demonstrates feasibility:
 - **NHP¹**: Repeat dose **safe and well-tolerated**, transgene expression levels for repeat dose **similar to single dose**
 - **Rabbit² and ferret³**: **Similar** transgene expression results for repeat dose in the presence of **treatment emergent serum & anti-capsid NABs**
 - **Human⁴**: 70 patients with aerosol AAV.CFTR – 3 doses over 2 months was **well tolerated**

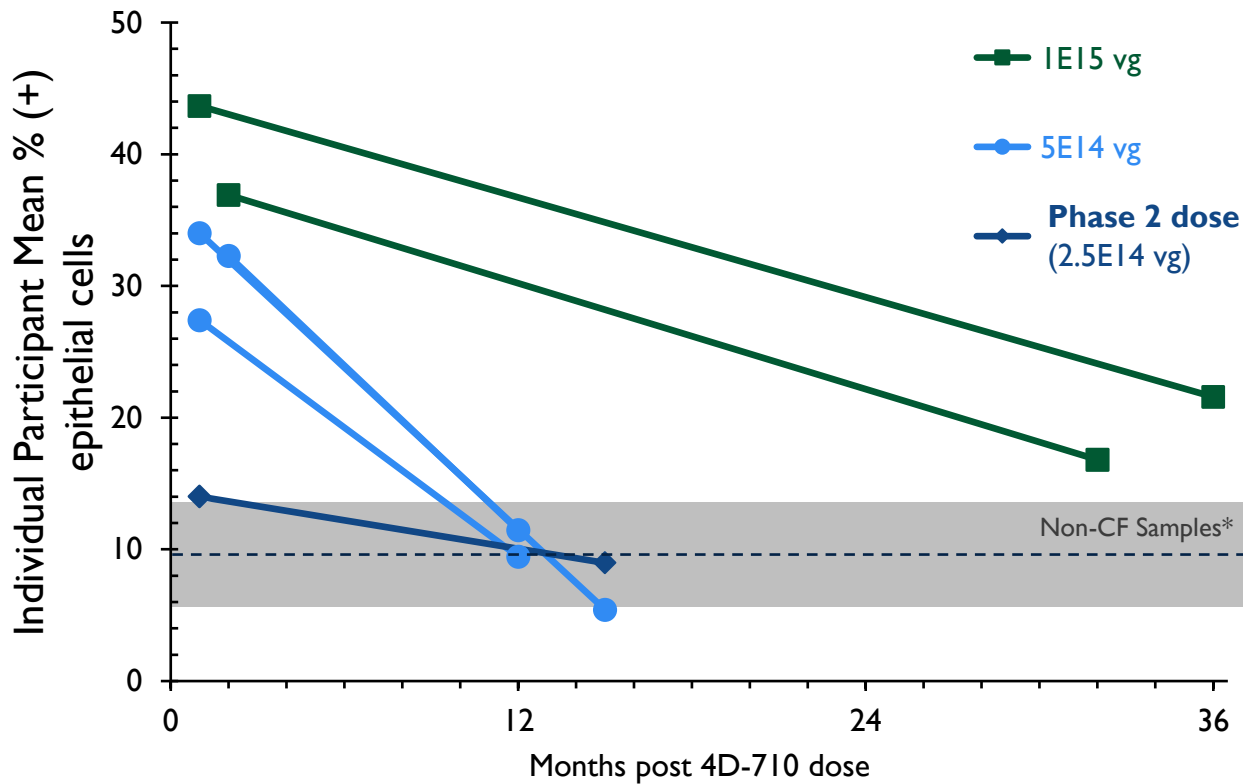
4DMT Results

- NHP pre-existing anti-A101 immunity (cross-reactivity): Safe & equivalent transduction vs immune (-) NHP
- 4D-710 AEROW pre-existing anti-A101 immunity: Safe & equivalent transduction vs immune (-) pwCF
- 4D-710 expression generally durable beyond 1-year at doses that approach target therapeutic range

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; ppFEV₁, percent predicted forced expiratory volume in 1 second.

First-time Durability in CF Lung with 4D-710–mediated CFTR Expression Persistent within Target Therapeutic Range through 1 to 3 Years

**Durability of 4D-710–Mediated *CFTR*Δ*R* Expression (ISH):
Mean % of Airway Epithelial Cells (+) in Individual Patients with Optional Paired Biopsies**



Population & Methods

Participants in the Phase I 1E15, 5E14, and 2.5E14 vg dose cohorts elected to an optional bronchoscopy to collect paired lung biopsies at ≥1-year post-4D-710 dosing

Key Findings

Durable expression with levels consistent with the non-CF % (+) epithelial cells and expression levels during follow up ranging from 1 to 3 years

Next Steps

Collect additional paired biopsy data alongside clinical activity measures with focus on Phase 2 dose to inform redosing strategy

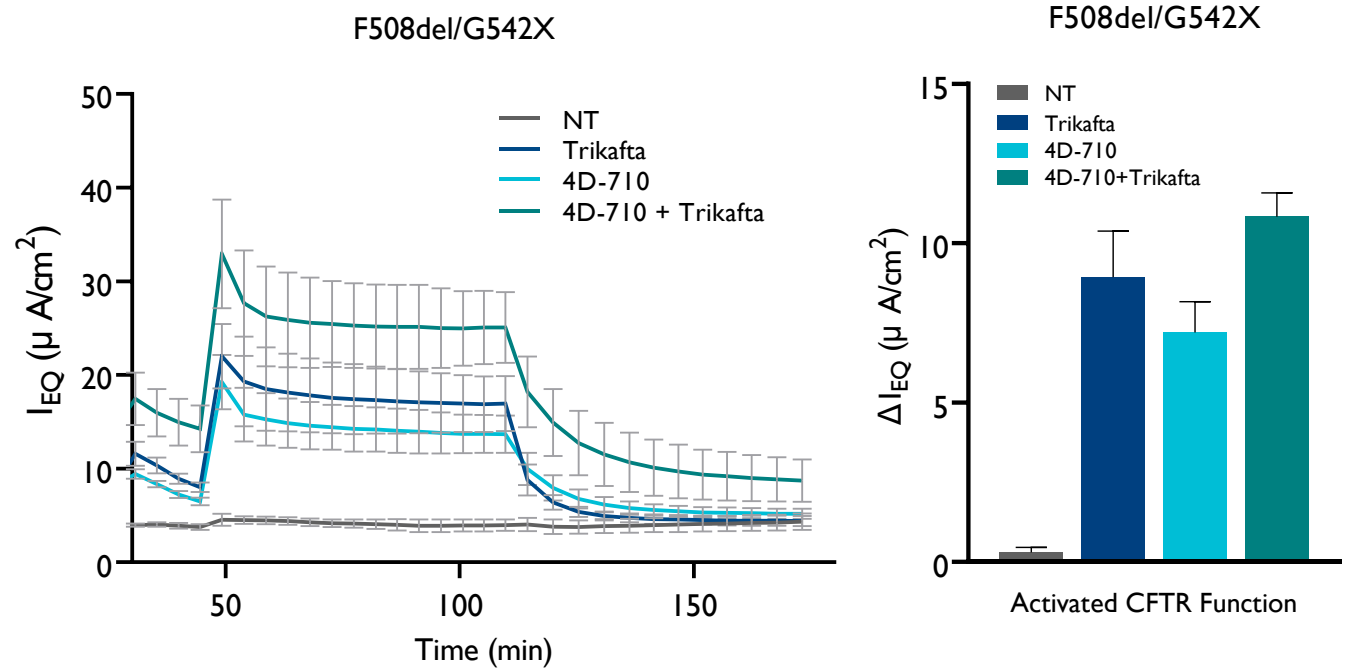
Quantification by Visiopharm® AI machine Learning analysis. *Mean (±SD) in non-CF samples = 9.6% (±4%). CFTR, cystic fibrosis transmembrane conductance regulator; ISH, *in situ* hybridization

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 CFTR Δ R function
 - Targeting different cell types & distribution

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



Next Steps: Plan combination cohort
pending additional monotherapy Phase 1/2 data

CFTR activity in CFhBE ALI airway epithelial cultures transduced with 4D-710 (1×10^6) 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, \pm SEM. F508del/F508del Donor ID#: KKCFFT006f; F508del/G542X Donor ID#: KKD017K. CFhBE, cystic fibrosis primary human bronchial epithelial cells; ALI, air-liquid interface; CFTR, cystic fibrosis transmembrane conductance regulator; NT, not treated.