



4DMT Presents Positive Interim Data from Aerosolized 4D-710 Phase 1/2 AEROW Clinical Trial in Patients with Cystic Fibrosis at the ECFS 46th Annual Meeting

June 7, 2023

- *Reported data from cohort 1 (n=3, 1E15 vg dose) of cystic fibrosis modulator treatment ineligible/intolerant participants with 9-12 months follow-up*
- *Quality of life outcomes measured by Cystic Fibrosis Questionnaire-Revised respiratory symptom score (CFQ-R-R) meaningfully improved for all three participants*
- *Percent predicted forced expiratory volume in one second (ppFEV₁) meaningfully improved in participant with moderate ppFEV₁ impairment at baseline; ppFEV₁ maintained stable in participants with normal or mild impairment at baseline*
- *Bronchoscopy sample results demonstrated widespread and consistent expression of the cystic fibrosis transmembrane conductance regulator (CFTR) transgene protein in 92-99% of lung airway cells, at levels significantly above normal control lung tissues*
- *Dose selection and initiation of Phase 2 Dose Expansion stage expected in H2 2023; additional interim data including for cohort 2 participants (2E15 vg dose) expected at the North American Cystic Fibrosis Conference in November 2023*
- *Company to host live webcast today at 4:30 p.m. ET with cystic fibrosis specialist Dr. Jennifer L. Taylor-Cousar*

4D-710 Clinical Activity & Biomarker Summary for Cohort 1 (n=3)

Participant	Baseline		Change from Baseline		ISH (CFTR/LR RNA)	Lung Biomarkers (4D-710 LSC / RML)					
	ppFEV ₁ (ppFEV ₁)	QoL by CFQ-R-R	ppFEV ₁ (%)	QoL by CFQ-R-R max (%)		CFTR Protein Expression (By IHC)			Expression Intensity (By IHC)		
						%+ cells	4D-710 Control (CF)	4D-710 Control (CF)	4D-710 Control (CF)	4D-710 Control (CF)	4D-710 Control (CF)
1	83 (Mild)	72	0 (Mo 0)	+11 (Mo 12)	41% / 47%	99.8% / 99.8%	201 / 258	201 / 258	201 / 258	201 / 258	201 / 258
2	69 (Moderate)	61	-7 (Mo 9)	+25 (Mo 9)	38% / 38%	92.4% / 92.4%	41.5 / 22	22	130	44.3	23.6
3	80 (Normal)	83	3 (Mo 6)	+6 (Mo 6)	38% / 38%	99.8% / 99.8%	213 / 227	213 / 227	213 / 227	213 / 227	213 / 227

Phase 1 Dose Exploration Cohort 1 Interim Clinical Activity Data: Table 1

EMERYVILLE, Calif., June 07, 2023 (GLOBE NEWSWIRE) -- 4D Molecular Therapeutics (Nasdaq: FDMT, 4DMT, or the Company), a clinical-stage biotherapeutics company harnessing the power of directed evolution for targeted genetic medicines, today announced positive interim clinical data from the 4D-710 Phase 1/2 AEROW clinical trial for the treatment of cystic fibrosis lung disease. 4D-710 is comprised of our targeted and evolved vector, A101, and a codon-optimized CFTR Δ R transgene and is designed for aerosol delivery to achieve CFTR expression within lung airway epithelial cells. In this clinical update, participants ineligible for (n=2) or intolerant of (n=1) existing CFTR modulators were dosed with 4D-710 in cohort 1 (dose 1E15 vg) and showed meaningful improvement in cystic fibrosis-related quality of life measured by CFQ-R-R and improved or stabilized ppFEV₁. Interim data from the study will be presented in an oral presentation titled, "AAV mediated gene therapy for cystic fibrosis: Interim results from a Phase 1/2 clinical trial," at the European Cystic Fibrosis Society (ECFS) 46th Annual Meeting held in Vienna, Austria on Thursday, June 8 at 5:00 p.m. CET (11:00 a.m. ET).

"This evidence of tolerability, high level CFTR protein expression and early clinical activity in three participants is promising for the ongoing development of this aerosolized product candidate for cystic fibrosis lung disease," said Jennifer L. Taylor-Cousar, MD, MSCS, Professor, Departments of Medicine and Pediatrics, and Co-Director, Adult Cystic Fibrosis Program, Director, Cystic Fibrosis Foundation Therapeutics Development Center, National Jewish Health, "I'm highly encouraged that the robust and consistent transduction observed is translating into improvements in quality of life and stabilization or improvement in the pulmonary function in these individuals with cystic fibrosis who otherwise do not have disease modifying therapy available to them. Historical data suggests that on average these measures would have declined without treatment in this population."

"The widespread CFTR transgene expression demonstrated in all lung samples from participants in cohort one is a critical first step for the development of 4D-710, especially given the signals of clinical activity in this CF population with the highest unmet medical need," said David Kim, MD, Co-founder and Chief Executive Officer of 4DMT. "We believe that 4D-710 represents a potentially transformative new treatment for people with CF. These interim results also demonstrate the potential of our proprietary aerosolized A101 vector for other lung diseases such as alpha-1 antitrypsin deficiency lung disease and other highly prevalent lung diseases."

Phase 1/2 AEROW Clinical Trial for Patients with Cystic Fibrosis: Design and Baseline Characteristics

- Phase 1 Dose Exploration stage (n=6-12; two dose cohorts of 3-6 participants each at 1E15 vg and 2E15 vg) followed by a Phase 2 Dose Expansion stage (n=up to 12 at the selected dose) in people with CF lung disease who are ineligible for or intolerant of CFTR modulator therapy
- Participants enrolled in cohort 1 of the Phase 1 Dose Exploration stage were ineligible for CFTR modulator therapy (n=2) or had discontinued due to adverse events (n=1)
- Participants received a single aerosolized dose of 4D-710 administered via AeroEclipse II breath-actuated nebulizer
- All data below are as of the data cutoff date of April 12, 2023

Phase 1 Dose Exploration Cohort 1 Interim Safety Data

- The aerosol delivery procedure for 4D-710 was well tolerated. One patient experienced mild dry throat and fatigue during aerosol delivery
- Following aerosol administration, 4D-710 was well tolerated in all 3 participants (9-12 months follow up) with no 4D-710 related adverse events, dose-limiting toxicities or serious adverse events

Phase 1 Dose Exploration Cohort 1 CFTR Biomarker Data

- Biomarker analyses demonstrated widespread and consistent CFTR expression throughout all lung biopsy samples:
 - As previously reported, 100% (3/3) participants were positive for CFTR Δ R DNA and RNA in the lung. 100% (11/11) of the lung samples were positive for CFTR Δ R RNA and DNA
 - CFTR protein expression was observed by immunohistochemistry (IHC) in 92 to 99% of airway epithelial cells, including in all major epithelial cell types, including basal cells, goblet cells and ciliated columnar cells. The percentage of cells that were positive by CFTR IHC were significantly higher than in both normal lung control samples (n=10; P=0.004) and CF lung-derived samples (n=7; P=0.0009) using machine learning-assisted image analysis
 - CFTR expression intensity was higher than in both normal lung control samples (n=10; P=0.0005) and CF lung-derived samples (n=7; P=0.0004) using machine learning-assisted image analysis. Expression was confirmed at the apical membrane

Phase 1 Dose Exploration Cohort 1 Interim Clinical Activity Data

- Background on historical cystic fibrosis patient outcomes for clinical measures:
 - Spirometry (ppFEV₁): Mean annual decline for CFTR modulator-untreated Δ F508 (most common CFTR variant) individuals is approximately **-2.3pp¹**
 - Quality of Life (CFQ-R-R): Mean change for untreated patients at 48 weeks is approximately **-4 points²**

1. Konstan et al. *Lancet Respir Med* 2017
2. Ramsey et al. *N Engl J Med* 2011

4D-710 Clinical Activity & Biomarker Summary for Cohort 1 (n=3)											
Participant	Baseline		Change from Baseline		Lung Biomarkers (4D-710: LSC / RML)						
	ppFEV ₁ (Impairment)	QoL by CFQ-R-R	ppFEV ₁ (f/u)	QoL by CFQ-R-R max (f/u)	ISH (CFTR Δ R RNA)	CFTR Protein Expression (by IHC)					
					% (+) cells	% (+) cells			Expression Intensity (H-score)		
						4D-710 (Mean)	Control (Norm)	Control (CF)	4D-710 (Mean)	Control (Norm)	Control (CF)
1	83 (Mild)	72	0 (Mo 12)	+11 (Mo 12)	41% / 47%	99.8% / 99.9%	41.5	23	201 / 205	44.3	23.6
2	69 (Moderate)	61	+7 (Mo 9)	+22 (Mo 9)	NA / 36%	NA / 92.4%			NA / 133		
3	95 (Normal)	83	-2 (Mo 6*)	+6 (Mo 6*)	36% / 38%	99.5% / 99.6%			253 / 227		

LSC: Left secondary carina

RML: Right middle lobe carina

*Respiratory-related adverse event within 21 days of Month 9 assessment

Upcoming Expected Milestones for 4D-710

- 4D-710 in the CFTR modulator ineligible/intolerant population:
 - Phase 1 Dose Exploration stage (Cohort 1 & 2) interim data expected to be presented at the North American Cystic Fibrosis Conference in November 2023
 - Dose selection for and initiation of Phase 2 Dose Expansion stage expected in H2 2023
 - FDA discussion on pivotal endpoints expected in Q4 2023
- 4D-710 in combination with CFTR modulators:
 - Development plan update expected in Q4 2023

Webcast Details:

The Company will host a webcast today, Wednesday, June 7, 2023 at 4:30 p.m. Eastern Time to discuss clinical data and development plans. Dr. Jennifer L. Taylor-Cousar will also join the webcast.

Title: 4D-710 Phase 1/2 AEROW Interim Clinical Data Webcast and Q&A

Date/Time: Wednesday, June 7, 2023 at 4:30 p.m. ET

Registration: [Link](#)

An archived copy of the webcast will be available for up to one year by visiting the "Investors & Media" section of the 4DMT website at <https://ir.4dmoleculartherapeutics.com/events>.

About 4D-710 and Cystic Fibrosis Lung Disease

4D-710 is comprised of our targeted and evolved vector, A101, and a codon-optimized CFTR Δ R transgene. 4D-710 has the potential to treat a broad range of patients with cystic fibrosis, independent of the specific CFTR mutation, and is designed for aerosol delivery to achieve CFTR expression within lung airway epithelial cells. 4D-710 is being initially developed in the approximately 15% of patients whose disease is not amenable to existing CFTR modulator medicines targeting the CFTR protein. In patients with CFTR mutations whose disease is amenable to modulator medicines, the improvement in lung function is incomplete and is variable. We therefore expect to potentially develop 4D-710 in this broader patient population in combination with CFTR modulator small molecule medicines.

Cystic fibrosis is a major inherited disease caused by mutations in the CFTR gene. According to the CF Foundation, approximately 40,000 people in the United States and more than 105,000 people worldwide are living with cystic fibrosis, with approximately 1,000 new cases of cystic fibrosis diagnosed in the United States each year. Lung disease is the leading cause of morbidity and mortality. Cystic fibrosis causes impaired lung function, inflammation and bronchiectasis and is commonly associated with persistent lung infections and repeated exacerbations due to the inability to clear thickened mucus from the lungs. Patients with cystic fibrosis require lifelong treatment with multiple daily medications. The complications of the disease result in progressive loss of lung function and hospitalizations, and ultimately lead to end-stage respiratory failure.

About 4DMT

4DMT is a clinical-stage biotherapeutics company harnessing the power of directed evolution for genetic medicines targeting large market diseases. 4DMT seeks to unlock the full potential of genetic medicines using its proprietary invention platform, Therapeutic Vector Evolution, which combines the power of the Nobel Prize-winning technology, directed evolution, with approximately one billion synthetic AAV capsid-derived sequences to invent customized and evolved vectors for use in our product candidates. All of our vectors are proprietary to 4DMT and were invented at 4DMT, including the vectors utilized in our clinical-stage and preclinical pipeline product candidates: R100, A101, and C102. The Company is initially focused on five clinical-stage product candidates in three therapeutic areas for both rare and large market diseases: ophthalmology, pulmonology, and cardiology. The

4DMT customized and evolved vectors were invented with the goal of being delivered at relatively low doses through clinically routine, well-tolerated, and minimally invasive routes of administration, transducing diseased cells in target tissues efficiently, having reduced immunogenicity and, where relevant, having resistance to pre-existing antibodies. 4DMT is currently advancing five product candidates in clinical development: 4D-150 for wet AMD and DME, 4D-710 for cystic fibrosis lung disease, 4D-310 for Fabry disease cardiomyopathy, 4D-125 for XLRP, and 4D-110 for choroideremia. The 4D preclinical product candidates in development are: 4D-175 for geographic atrophy and 4D-725 for AATLD.

4D-150, 4D-710, 4D-310, 4D-125, and 4D-110 are our product candidates in clinical development and have not yet been approved for marketing by the US FDA or any other regulatory authority. No representation is made as to the safety or effectiveness of 4D-150, 4D-710, 4D-310, 4D-125, or 4D-110 for the therapeutic uses for which they are being studied.

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Forward Looking Statements:

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements regarding the therapeutic potential, and clinical benefits, as well as the plans and related timing for the clinical development of 4D-710. The words "may," "might," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" and similar words or expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including risks and uncertainties that are described in greater detail in the section entitled "Risk Factors" in 4D Molecular Therapeutics' most recent Annual Report on Form 10-K, as well as any subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent 4D Molecular Therapeutics' views only as of today and should not be relied upon as representing its views as of any subsequent date. 4D Molecular Therapeutics explicitly disclaims any obligation to update any forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward looking statements.

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A table accompanying this announcement is available at: <https://www.globenewswire.com/NewsRoom/AttachmentNg/1e0c28bc-4e67-4141-a2b0-3c3e1cf595c3>