4DMT Presents Positive Interim Data from Phase 1/2 AEROW Clinical Trial of Aerosolized 4D-710 for Cystic Fibrosis at 2023 NACFC

November 1, 2023

- *Aerosolized 4D-710 was generally well tolerated with no inflammation in any lung biopsy across Cohorts 1 and 2 (1E15 & 2E15 vg; n=7) with up to 17 months follow-up*
- *Promising, reproducible, CFTR expression significantly above normal levels across all participants and all lung tissue samples collected (n=34), substantially exceeding target profile*
- *Durable clinical activity demonstrated by improvements in quality of life by CFQ-R-RD and pulmonary function by ppFEV$_1$ through 12 months in Cohort 1*
- *FDA feedback on 4D-710 development path as monotherapy and in combination with approved CF modulator therapies expected in Q1 2024*
- *Company to host webcast today, Wednesday, November 1, 2023 at 4:30 p.m. ET*

EMERYVILLE, Calif., Nov. 01, 2023 (GLOBE NEWSWIRE) -- 4D Molecular Therapeutics (Nasdaq: FDMT, 4DMT, or the Company), a genetic medicines company with three novel, highly targeted next generation AAV vectors currently in human clinical studies, today announced interim data from the Phase 1/2 AEROW clinical trial evaluating aerosolized 4D-710 for treatment of cystic fibrosis lung disease. Results will also be presented at the 2023 North American Cystic Fibrosis Conference (NACFC) in both plenary and symposium sessions on November 2-3.

“We are pleased with the safety and tolerability of 4D-710 in participants in the AEROW study to date. Participants with cystic fibrosis in this clinical trial do not have the option of treatment with currently available disease modifying therapies and therefore have high unmet need,” said Jennifer L. Taylor-Cousar, M.D., MSCS, Professor, Departments of Medicine and Pediatrics, and Co-Director, Adult Cystic Fibrosis Program, Director, Cystic Fibrosis Foundation Therapeutics Development Center, National Jewish Health and lead Principal Investigator in the AEROW clinical trial, “By delivering copies of the *CFTR*Δ*R* transgene to the lung epithelium with a novel aerosolized AAV and achieving high levels of CFTR protein expression in airway cells, 4D-710 has the potential to provide durable benefit in these individuals and potentially all individuals affected by CF.”

“4D-710, our next generation aerosolized A101 vector, has the potential to address the limitations of prior aerosol gene therapies. Initial results from the AEROW study showed that 4D-710 resulted in CFTR expression in lung airways that significantly exceeded our target profile. Safety and pulmonary function measures reinforce a promising emerging tolerability and clinical activity profile,” said David Kirn, M.D., Co-founder and Chief Executive Officer of 4DMT. “We are also excited to welcome Dr. Alan Cohen as our Pulmonology Therapeutic Area Head. Alan brings more than 30 years of broad pulmonology expertise including in cystic fibrosis, alpha-1 antitrypsin deficiency, idiopathic pulmonary fibrosis, plus biotherapeutics and gene editing development, highlighting our commitment to pulmonology. Under Alan’s leadership, we expect to continue advancing the clinical development of 4D-710 for CF lung disease and 4D-725 for alpha-1 antitrypsin deficiency lung disease and future lung programs.”

“The high *CFTR* expression levels and durable clinical activity of 4D-710 as demonstrated by improvements in quality of life and stability in ppFEV$_1$ through 12 months in Cohort 1 have never been achieved with any gene delivery in CF, making a dose reduction feasible,” said Alan Cohen, M.D., SVP, Therapeutic Area Head of Pulmonology of 4DMT. “I’m excited to work closely with the CF Foundation, CF community, and regulatory agencies to advance the development of 4D-710, a potentially transformative medicine for people with CF. Given the efficiency we have observed in CF lungs, one of the most difficult organs for gene delivery vectors, I am also energized by the potential of A101 to deliver genetic payloads to treat multiple large-market pulmonology diseases including alpha-1 antitrypsin deficiency lung disease.”

Data below is from Cohort 1 (1E15 vg, n=3) and Cohort 2 (2E15 vg, n=4) of the ongoing Phase 1/2 AEROW trial.

Safety: Generally Well-Tolerated

- Acute safety (during and up to 4 h post dosing): Generally well tolerated, no clinically significant adverse events (AEs); no decrease in ppFEV$_1$ (percent predicted forced expiratory volume in 1 second) or bronchospasm reported
- Post-dosing safety (follow-up in 7 participants through 4-17 months); best available as of October 2023:
  - Generally well-tolerated
  - No inflammation observed in biopsies collected to date in all 7 participants
  - No related AEs in 6 of 7 patients at any timepoint
  - Single SAE (participant 3 of 4 dosed in Cohort 2; pneumonitis not otherwise specified): Serious due to hospitalization (<72 hours). High-resolution computed tomography (hospital radiologist reading) reported differential diagnosis as “atypical infection, cryptogenic organizing pneumonia.” Following discharge, lung lavage bacterial cultures confirmed *Inquilinus limosus* infection. Participant was treated with oral steroids and outpatient IV antibiotics, and AE subsequently resolved. AE consistent with bacterial pneumonia (*Inquilinus limosus*). Principal Investigator reported as possibly related to 4D-710

Lung Tissue Biomarkers: Expression Significantly Exceeded Target Profile in All Patients

- Robust and reproducible 4D-710-mediated CFTR protein (by immunohistochemistry, IHC) and RNA (by *in situ* hybridization, ISH) expression observed in airway epithelium 4-8 weeks following aerosol delivery in all 7 participants across all 34 airway biopsy and brushing samples collected

- CFTR protein detected in ~98% and ~99% of airway epithelial cells in samples from Cohort 1 and 2 participants, respectively versus ~44% of cells in normal control lung samples
- Mean CFTR protein expression levels by immunohistochemistry observed in Cohorts 1 and 2 participants were ~450% of levels in normal control lung samples, and ~1,000% of levels in control lung samples from individuals with CF
- All major airway cell types expressed CFTR protein and *CFTR∆R* RNA, including long-lived basal cells and secretory (Goblet) cells
- *In situ* hybridization (ISH) for RNA confirmed widespread, reproducible *CFTR∆R* transgene expression in all lung samples evaluated in all participants; positive signal observed in 40% and 53% of airway epithelial cells in samples from Cohort 1 and 2 participants, respectively. More cells were positive by IHC than by ISH

Biomarker	Lung Biopsy Measure*	**Control (Normal Lung)** (n=10 biopsy samples)	**Control (CF Lung)** (n=35 biopsy samples)	**Cohort 1** (1E15 vg, n=5 biopsy samples)	**Cohort 2** (2E15 vg, n=8 biopsy samples)
CFTR Protein Expression (by IHC)	*Mean (range) % of airway cells (+)*	44% (17-73%)	18% (1-62%)	**98%** (93-100%	**>99%**** (99-100%)
	Mean (Range) Intensity (H-Score)	47 (17-75)	19 (1-68)	**205** (133-253)	**225**** (143-280)

* ISH and IHC scoring performed with machine learning-assisted image analysis software (Visiopharm), with review and confirmation by independent certified M.D. pathologist masked to lung tissue source

** CFTR expression observed in Cohort 2 was not statistically significantly increased compared to Cohort 1

Cohort 1 Clinical Activity: Durable Through 12 Months and Beyond

- Clinical activity assessments collected through 12 months (amendment planned to collect additional follow-up data after 12 months):

	Participant with moderate lung impairment by $ppFEV_1$ (n=1)	**Participants with mild/no lung impairment by $ppFEV_1$ (n=2)**
Lung Function ($ppFEV_1$) Absolute ∆ from baseline over 12 months	**+1% to +10% improvement**	**Stable (±2%)**
Quality of Life (CFQ-R-RD*) ∆ from baseline over 12 months	Mean increase of **8.4 to 11.1** points over 12 month period consistently above MCID (MCID=±4); all 3 participants consistently improved beyond MCID	

* Cystic Fibrosis Questionnaire-Revised respiratory domain symptom score
MCID, minimal clinically important difference

- In all 3 participants, no pulmonary exacerbations were reported beyond 3 months through up to 17 months of follow-up
- Cohort 2 clinical activity pending following additional follow-up (consistent with Cohort 1 clinical activity reporting timeline)

Next Steps for 4D-710 Clinical Development

- Cohort 1 dose level (1E15 vg) selected to continue into Phase 2
- Dose ranging continues (5E14 – 2E15 vg) with lung biopsy CFTR expression profile significantly above normal controls, demonstrating the feasibility of effective treatment at lower doses; first participant dosed in lower dose Cohort 3 (5E14 vg)
- Additional functional measures added to AEROW study following strong proof-of-concept for above normal CFTR expression in airways: high-resolution computed tomography (HRCT), lung clearance index (LCI), mucociliary clearance index (MCI), number & severity of bacterial pulmonary exacerbations
- FDA feedback on development plan for monotherapy & approved CF modulator combination regimens expected to be shared in Q1 2024
- Next interim Phase 1 data update expected mid-2024

Increased Financial Commitment from Cystic Fibrosis Foundation (The CF Foundation) Brings Total Historical Commitment to Over $20 Million

- 4DMT has been supported by the CF Foundation since 2016, including a 2017 research agreement (“CF Foundation Agreement”) to discover and develop optimized next generation AAV vectors for use in genetic medicines targeting lung airway cells in people with CF
- In August 2023 the Company executed an amendment to the CF Foundation Agreement increasing the funding commitment under that agreement by $2.8 million to a total of $6.3 million, which covers anticipated spend for further development of our aerosolized lung epithelium gene delivery vectors

- In 2020 and 2021, the CF Foundation invested $14 million in 4DMT equity to support the development of 4D-710

Webcast Details:

Title:	4D-710 Phase 1/2 AEROW Interim Clinical Data and Program Update Webcast and Q&A
Date/Time:	Wednesday, November 1, 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 the following link: https://ir.4dmoleculartherapeutics.com/events.

About 4D-710 and Cystic Fibrosis Lung Disease

4D-710 is comprised of our targeted and evolved next generation vector, A101, and a codon-optimized CFTRΔR transgene. 4D-710 has the potential to treat a broad range of people 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 for the approximately 15% of people whose disease is not amenable to existing CFTR modulator medicines (based on variant-eligibility and/or drug intolerance) targeting the CFTR protein. In people 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 population, as a single agent and/or in combination with CFTR modulator small molecule medicines.

Cystic fibrosis is an inherited, progressive disease caused by mutations in the CFTR gene. It affects the lungs, pancreas, and other organs. According to the CF Foundation, nearly 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 in people with cystic fibrosis. 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. People 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 genetic medicines company with three novel, highly targeted next generation AAV vectors currently in human clinical studies targeting multiple large market diseases in ophthalmology and pulmonology, plus other therapeutic areas. 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 4DMT 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.

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 of 4DMT’s product candidates, as well as the plans, announcements and related timing for the clinical development of and regulatory interactions regarding 4D-710 and 4D-725. 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 Quarterly Report on Form 10-Q 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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