



4DMT Presents Positive Interim Data from Phase 1/2 AEROW Clinical Trial of Aerosolized 4D-710 for Modulator-Ineligible/-Intolerant Cystic Fibrosis at 47th European Cystic Fibrosis Conference

June 6, 2024

- Clinically meaningful improvements in ppFEV₁ at 12 months observed in 2 of 3 participants with mild to moderate baseline lung function impairment (ppFEV₁ 50-80%) and >6 months follow up
- Aerosolized 4D-710 was well tolerated at doses up to 1E15 vg (n=6)
- Dose-dependent and widespread 4D-710-mediated CFTR transgene RNA and protein expression observed in all lung biopsies from all participants evaluated to date
- Pre-existing AAV immunity cross-reactive with A101 did not affect transgene expression, biological activity or safety
- 1E15 vg dose cleared for evaluation in Phase 2 Dose Expansion stage; enrollment expected to begin in H2 2024 and next interim data update expected in mid-2025
- Company to host live webcast today at 8:00 a.m. ET with Dr. Jennifer L. Taylor-Cousar, lead Principal Investigator in the AEROW clinical trial

EMERYVILLE, Calif., June 06, 2024 (GLOBE NEWSWIRE) -- 4D Molecular Therapeutics (Nasdaq: FDMT, 4DMT or the Company), a leading clinical-stage genetic medicines company focused on unlocking the full potential of genetic medicines to treat large market diseases, today announced positive interim clinical data from the 4D-710 Phase 1/2 AEROW clinical trial for the treatment of cystic fibrosis (CF) lung disease. Interim data from the study will be presented by Jennifer L. Taylor-Cousar, M.D., MSCS, in an oral presentation titled, "CFTR transgene expression in airway epithelial cells following aerosolized administration of the AAV-based gene therapy 4D-710 to adults with cystic fibrosis lung disease," at the 47th European Cystic Fibrosis Conference held in Glasgow, UK on Thursday, June 6 at 5:00 p.m. BST.

"We are pleased with the widespread CFTR transgene and protein expression in airway cells from all participants at all doses in the AEROW clinical trial," said 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 and lead Principal Investigator in the AEROW clinical trial. "The consistent widespread 4D-710-mediated CFTR expression and initial clinical activity in Phase 1 are encouraging and suggest that 4D-710 has the potential to be the first treatment option for those living with cystic fibrosis who do not currently benefit from available disease-modifying therapies."

"The clinical data to date from the AEROW clinical trial continues to strongly support the advancement of 4D-710 to the next stage of development for CF lung disease," said Alan H. Cohen, M.D., SVP, Therapeutic Area Head of Pulmonology of 4DMT. "Based on the emerging favorable safety and clinical activity profile, we look forward to beginning our Phase 2 Dose Expansion stage in participants with mild to moderate lung function impairment, to confirm the clinical activity of the 1E15 vg dose."

"The interim data we shared today from the AEROW clinical trial continues to showcase the breadth and depth of our platform, product engine and pipeline," said David Kirn, M.D., Co-Founder and Chief Executive Officer of 4DMT. "4D-710 is well positioned as the lead program in our pulmonology portfolio as we move into mid to late-stage development. These clinical results also support continued use of our next-generation A101 pulmonary vector for large-market lung diseases such as alpha-1 antitrypsin deficiency lung disease, for which we are developing 4D-725, an aerosolized genetic medicine currently in IND-enabling preclinical studies."

AEROW Clinical Trial Phase 1 Dose Exploration Stage Background & Summary

- 10 participants with CF lung disease who are ineligible for or intolerant of CFTR modulator therapy have been enrolled in the Phase 1 Dose Exploration stage across four dose cohorts:
 - 2E15 vg Cohort: n=4
 - 1E15 vg Cohort: n=3
 - 5E14 vg Cohort: n=2
 - 2.5E14 vg Cohort: n=1
- Participants enrolled in the Phase 1 Dose Exploration stage had a broad range of baseline ppFEV₁ impairment ranging from 56% to 100%
- Participants received a single aerosolized dose of 4D-710 administered via an AeroEclipse II breath-actuated nebulizer
- All results below are based on best available data as of May 24, 2024

Interim Safety Data

- High Dose – 2E15 vg (n=4):
 - Complete resolution of previously reported serious adverse event (SAE) (pneumonitis not otherwise specified); ppFEV₁ in this participant improved by 6% from baseline to month 12 (last timepoint assessed)
 - Lung biopsy results:

- No evidence of inflammation or toxicity from histological analysis of tissue samples
- Widespread expression of CFTR protein compared to normal (non-CF) lung samples and no increase vs. 1E15 vg dose
- Evidence of consistent CFTR protein expression in all major airway epithelial cell types, as well as in interstitial tissue cells; interstitial CFTR expression was not detected in normal lung control samples
- Based on all available data for 2E15 and 1E15 vg dose level participants, 1E15 vg was selected as the highest dose for Dose Expansion; 2E15 vg dose will not be further evaluated
- Lower Doses – 2.5E14 to 1E15 vg (n=6):
 - 4D-710 was well tolerated, with no 4D-710–related adverse events after administration, no dose-limiting toxicities, and no SAEs

Interim CFTR Biomarker Data

- Biomarker analyses demonstrated robust, consistent and widespread *CFTR*DR transgene mRNA and CFTR protein expression throughout all lung biopsy samples from all participants at all four dose levels
 - Dose-dependent *CFTR*ΔR transgene RNA expression, with the mean % of airway epithelial cells testing positive ranging from 14% to 53%
 - Robust, widespread and above-normal CFTR protein expression at all doses
 - Protein levels in lung tissue from 4D-710–treated participants 2–4 fold higher than in normal (non-CF) samples, and ~8-12 fold higher than in CF lung samples
 - Protein expression observed in multiple airway epithelial cell types, including basal cells
- Pre-existing AAV immunity that cross-reacted with A101 did not affect transgene expression, biological activity or safety; transgene expression levels, clinical activity and safety were similar regardless of pre-existing immunity

Interim Clinical Activity Data

- All participants in 2E15 vg and 1E15 vg Cohorts had at least 12 months of follow up (maximum duration of ppFEV₁ assessments per original protocol) and had generally stable or improved in ppFEV₁ at 12 months
 - Two of three participants with baseline mild to moderate lung function impairment (ppFEV₁ 40-80%) showed clinically meaningful improvement in ppFEV₁ at 12 months:
 - 2E15 vg Cohort: +6%
 - 1E15 vg Cohort: +5%
- Quality of Life (CFQ-R-R) scores in 1E15 vg Cohort showed durable and clinically meaningful mean improvement throughout 12 months

Next Steps and Upcoming Expected Milestones for 4D-710

- Advancing to AEROW Phase 2 Dose Expansion stage (n= up to 9), enrollment to begin in H2 2024
 - 1E15 vg dose level cleared for enrollment
 - Inclusion of 5E14 vg dose pending enrollment and follow-up of third participant in Phase 1
- Amendment to AEROW protocol submitted to the Cystic Fibrosis Foundation-supported Therapeutics Development Network to open a new cohort to evaluate 4D-710 in participants on CFTR modulators with persistent moderate to severe CF lung disease; enrollment expected to begin in H2 2024
- Interim data update from AEROW clinical trial is expected in mid-2025
- Following supportive Phase 2 data, Phase 3 initiation is expected in H2 2025

Corporate Webcast Details:

Title: 4D-710 Phase 1/2 AEROW Interim Clinical Data & Program Update
 Date/Time: Thursday, June 6, 2024 at 8:00 a.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: <https://ir.4dmoleculartherapeutics.com/events>.

The presentation from the 47th European Cystic Fibrosis Conference will also be available on the 4DMT website: <https://4dmoleculartherapeutics.com/pipeline/#posters-and-publications>.

About Cystic Fibrosis Lung Disease

Cystic fibrosis (CF) is an inherited progressive disease caused by variants in the *CFTR* gene. It affects the lungs, pancreas and other organs. According to the Cystic Fibrosis Foundation, nearly 40,000 people in the United States and more than 105,000 people worldwide are living with CF, with approximately 1,000 new cases of CF diagnosed in the United States each year. Lung disease is the leading cause of morbidity and mortality in people with CF. CF 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 CF require lifelong treatment with multiple daily medications. The complications of the disease result in progressive loss of lung function, increasing need for IV antibiotics and hospitalizations, and ultimately leading to end-stage respiratory failure.

About 4D-710

4D-710 combines our targeted and evolved next generation AAV vector, A101, with a codon-optimized *CFTR* Δ R transgene. 4D-710 has the potential to treat a broad range of people with CF, independent of the specific *CFTR* mutation, and is designed for aerosol delivery to achieve targeted *CFTR* expression within lung airway epithelial cells. 4D-710 is being developed for approximately 35% of people with CF initially. The AEROW Phase 1/2 clinical trial focuses initially on the ~15% of people with CF whose disease is not amenable to existing *CFTR* modulator medicines (based on variant-eligibility and/or drug intolerance). In people with *CFTR* variants that are amenable to modulator medicines, the improvement in lung function is variable and often incomplete. We therefore expect to develop 4D-710 for use in this broader "on modulator" population. 4D-710 has received the Rare Pediatric Disease Designation and Orphan Drug Designation from the U.S. Food and Drug Administration (FDA).

About 4DMT

4DMT is a leading clinical-stage genetic medicines company focused on unlocking the full potential of genetic medicines to treat large-market diseases in ophthalmology and pulmonology. 4DMT's proprietary invention platform, Therapeutic Vector Evolution, 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 wholly owned and partnered product candidates. Our product design, development, and manufacturing engine help us efficiently create and advance our diverse product pipeline with the goal of revolutionizing medicine with potential curative therapies for millions of patients. Currently, 4DMT is advancing five clinical-stage and two preclinical product candidates, each tailored to address rare and large market diseases in ophthalmology, pulmonology and cardiology. In addition, 4DMT is also advancing programs in CNS through a gene editing partnership. 4D Molecular Therapeutics™, 4DMT®, 4D®, Therapeutic Vector Evolution™, and the 4DMT logo are trademarks of 4DMT.

All of our product candidates are in clinical or preclinical development and have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA) or any other regulatory authority. No representation is made as to the safety or effectiveness of our product candidates for the therapeutic uses for which they are being studied.

Learn more at www.4DMT.com and follow us on [LinkedIn](https://www.linkedin.com/company/4DMT).

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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