4DMT Announces Update on Regulatory Interactions and Development Path for 4D-710 for Treatment of Cystic Fibrosis

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- *Conducted initial pivotal study interactions with the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA); Company has clear registration path for 4D-710 for treatment of cystic fibrosis (CF) lung disease in people with CF (pwCF) who are ineligible for or cannot tolerate approved CF modulator therapies*
- *AEROW clinical trial Phase 2 Expansion Cohort dose selection and initiation expected in Q2 2024, with pivotal trial initiation anticipated in H2 2025*
- *Initial GMP-ready suspension manufacturing process completed in-house at 500 liter scale; technology transfer initiation to commercial CDMO anticipated H1 2025*
- *Phase 1/2 AEROW clinical trial interim clinical data expected at the European Cystic Fibrosis Conference June 5-8, 2024, including safety, lung biomarker and clinical activity data on all nine patients dosed across four dose level cohorts*

EMERYVILLE, Calif., March 28, 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 an update on its regulatory interactions and development path for 4D-710, an aerosolized genetic medicine for the treatment of CF lung disease.

Given high-level cystic fibrosis transmembrane conductance regulator (CFTR) transgene expression in all lung airway biopsies disclosed to date (significantly above normal lung CFTR levels), dose exploration continues with the evaluation of lower doses in the 4D-710 Phase 1/2 AEROW clinical trial in pwCF dosed at 5E14 vg (Cohort 3; n=1) and 2.5E14 vg (Cohort 4; n=1); nine pwCF total have been dosed to date (dose range 2.5E14 to 2E15 vg). Phase 2 Expansion Cohort dose selection is expected in Q2 2024 based on all clinical and lung biopsy data; the Company anticipates enrolling a total of six to nine pwCF in the Phase 2 Expansion Cohort. The Company submitted an AEROW trial amendment to the Cystic Fibrosis Therapeutics Development Network (TDN) as follows: 1) to enroll pwCF with lower baseline percent predicted forced expiratory volume in 1 second ($ppFEV_1$) (50-90%) to assess $ppFEV_1$ response to 4D-710, and 2) to add a second lung biopsy procedure at a longer-term timepoint (12 months or later) to study long term durability of 4D-710 CFTR transgene expression and optimal timing for redosing. The Company plans to share the following at the 47th European Cystic Fibrosis Conference (ECFS) held on June 5-8, 2024 in Glasgow, United Kingdom: 1) interim AEROW clinical and lung biomarker data on all nine pwCF dosed to date, 2) update on AEROW trial amendment status, and 3) development plan update for pwCF who are on modulators.

In addition, the Company recently had discussions with the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), regarding the registrational path for 4D-710 for treatment of CF lung disease in pwCF who are ineligible for or cannot tolerate approved CF modulator therapies. With regards to a full product approval in this patient population, the Company anticipates a Phase 3 randomized, controlled pivotal study enrolling approximately 60-80 pwCF with low baseline $ppFEV_1$ (planned to be approximately 40-80%). Phase 3 clinical endpoints include changes after 4D-710 treatment in $ppFEV_1$, quality-of-life (Cystic Fibrosis Questionnaire Revised Respiratory Domain, CFQ-R-RD) and frequency of pulmonary exacerbations. 4DMT is preparing for initiation of a Phase 3 clinical trial in H2 2025.

Given the high unmet need in this CF population, an accelerated approval path may be feasible. The Company intends to have discussions with the FDA and EMA on an accelerated approval pathway, in parallel with Phase 3 planning, following additional AEROW clinical and lung biomarker data in pwCF with low baseline $ppFEV_1$. 4D-710 is the first genetic medicine product candidate to demonstrate widespread and high-level CFTR expression (both RNA and protein) in the airways of pwCF; the Company will continue to evaluate the correlation between clinical endpoints and biomarker endpoints in participants with low baseline $ppFEV_1$ in anticipation of further interactions on an accelerated approval pathway.

In addition, the Company has completed in-house process development of a suspension GMP-ready manufacturing process for 4D-710 at 500 liter scale for the pivotal study and potential commercialization. This process, in combination with investigating lower doses, enables potentially lower cost of goods. The Company anticipates initiation of technology transfer to a commercial contract development and manufacturing organization (CDMO) in H1 2025.

“We are encouraged by our productive interactions with the FDA and EMA on pivotal development plans for 4D-710, which we believe has the potential to be a transformative therapy for people with the highest unmet medical need for CF lung disease,” said David Kirn, M.D., Co-founder and Chief Executive Officer of 4DMT. “We are committed to advancing 4D-710 into pivotal trial development efficiently, while maintaining our current focus on initiation and completion of two Phase 3 wet AMD studies with 4D-150. Our goal is to initiate Phase 3 development in H2 2025 with 4D-710 suspension GMP process clinical trial material. We look forward to sharing interim clinical data from the AEROW Phase 1/2 clinical trial at the ECFS conference in June 2024.”

About Cystic Fibrosis Lung Disease and 4D-710

Cystic fibrosis (CF) is an inherited, progressive disease caused by mutations in the CFTR gene. It affects the lungs, pancreas, and other organs. According to the Cystic Fibrosis Foundation, close to 40,000 people in the United States and an estimated 105,000 people people have been diagnosed with CF across 94 countries, 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, ultimately leading to end-stage respiratory failure.
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 CF, 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 10-15% 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, and in some people with CF 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. 4D-710 has received the Rare Pediatric Disease Designation and Orphan Drug Designation from the 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 helps 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™, Therapeutic Vector Evolution™, and the 4DMT logo are trademarks of 4DM

All of our product candidates are in clinical or preclinical development and have not yet been approved for marketing by the 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.

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 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 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.

Contacts:

Media:

Katherine Smith
Inizio Evoke Comms
Katherine.Smith@inizioevoke.com

Investors:

Julian Pei
Head of Investor Relations and Corporate Finance
Investor.Relations@4DMT.com