



4D Molecular Therapeutics Announces Updates on Clinical Pipeline and Additional Preclinical Programs

January 9, 2023

- *Expands Large Market Ophthalmology Portfolio Following Positive Clinical Data in wet Age-Related Macular Degeneration to Include Diabetic Macular Edema Clinical Program and Geographic Atrophy Preclinical Program*
- *Expands Large Market Pulmonology Portfolio Following Positive Clinical Data in Cystic Fibrosis to Include Alpha-1 Antitrypsin Deficiency Preclinical Program*
- *Reports Program Updates and Interim Clinical Data from Phase 1/2 Fabry Disease Cardiomyopathy Trials; Full Clinical Data to be Reported at WORLDSymposium in February 2023*
- *Cash Guidance Unchanged and Sufficient to Fund Operations into H1 2025*

EMERYVILLE, Calif., Jan. 09, 2023 (GLOBE NEWSWIRE) -- 4D Molecular Therapeutics, Inc. (Nasdaq: FDMT), a clinical-stage biotherapeutics company harnessing the power of directed evolution for targeted genetic medicines, announced product pipeline portfolio updates and preclinical product candidate additions for its large market ophthalmology and pulmonology programs, as well as clinical data and program updates for its 4D-310 Fabry disease program.

"These updates highlight 4DMT's diversified and growing product pipeline that is driven by our underlying directed evolution vector platform and our robust product design and development engine for genetic medicines," said David Kirm, M.D., Co-founder and Chief Executive Officer of 4DMT. "Given the promising early clinical trial data with 4D-150 in wet AMD and 4D-710 in cystic fibrosis lung disease that we announced in Q4 2022, plus cardiac endpoint clinical trial data reported today with 4D-310, we believe the broad potential of our platform is evident. We are pleased to announce the strategic decision to expand our large market indication portfolios in ophthalmology and pulmonology using vectors that have already been used in product candidates dosed in humans."

Ophthalmology Product Candidate Portfolio

4D-150 for the Intravitreal Treatment of Patients with Wet Age-Related Macular Degeneration (wet AMD) and Patients with Diabetic Macular Edema (DME)

Filed IND Application for Phase 2 SPECTRA Clinical Trial with Intravitreal 4D-150 in Patients with DME:

4DMT filed an Investigational New Drug (IND) Application for 4D-150 in patients with DME in December 2022, following pre-IND correspondence and alignment with the FDA. The Phase 2 SPECTRA clinical trial design consists of a Dose Confirmation stage followed by a masked Dose Expansion stage in which patients will be randomized to receive a single intravitreal injection at one of two dose levels of 4D-150 or aflibercept in a 1:1:1 ratio (n=54 patients). The doses to be evaluated in DME are expected to be similar to those used in the 4D-150 wet AMD clinical trial. We expect to initiate enrollment in the third quarter of 2023.

Initiated Randomized Phase 2 of PRISM Clinical Trial of Intravitreal 4D-150 in Patients with Wet AMD:

The Phase 2 stage of the Phase 1/2 PRISM clinical trial of 4D-150 in patients with wet AMD consists of three treatment groups. Patients will be randomized in masked fashion to receive a single intravitreal injection at one of two dose levels of 4D-150 (3E10 and 1E10 vg/eye) or aflibercept in a 2:2:1 ratio (n=50 patients). This Phase 2 stage of the trial was initiated in January 2023.

Expanded Portfolio with Preclinical Product Candidate 4D-175 for Geographic Atrophy (GA):

Geographic atrophy is a highly prevalent disease with significant unmet medical need. It is estimated that there are over one million individuals with GA in the United States according to published data. There are no disease modifying therapies approved for GA to date.

Preclinical development was initiated for a new product candidate designed for single dose intravitreal treatment of patients with GA; the product candidate will utilize 4DMT's proprietary R100 intravitreal vector currently used in the wet AMD and DME programs, and a transgene payload that addresses a complement pathway target (undisclosed). We anticipate that development and manufacturing activities will benefit from prior clinical experience and GMP manufacturing of three other R100-based ophthalmology product candidates that have been dosed in ophthalmology patients with wet AMD, X-Linked Retinitis Pigmentosa (XLRP) and choroideremia.

Arshad M Khanani, M.D., M.A., FASRS, Managing Partner and Director of Clinical Research at Sierra Eye Associates, Clinical Associate Professor at University of Nevada, Reno, and a Principal Investigator in the 4D-150 PRISM clinical trial for wet AMD added, "Based on the encouraging safety and tolerability observed to date with intravitreal 4D-150, as well as clinically significant reduction in annualized anti-VEGF injection rate following a single in-office injection in patients with wet AMD, it's exciting to evaluate the potential of 4D-150 in patients with diabetic macular edema, who also require frequent anti-VEGF injections and have a high treatment burden. Utilizing the novel intravitreal R100 vector and a dual transgene payload, 4D-150 is the first retinal genetic medicine that is designed to inhibit all four VEGF-related molecules that drive angiogenesis. In addition, I'm excited by the potential of 4D-175, the new preclinical product candidate utilizing the same R100 vector. Geographic atrophy affects a large number of people every year, and the unmet medical need of these patients remains high."

Program Updates on Rare Disease Product Candidates 4D-125 for XLRP and 4D-110 for Choroideremia:

Enrollment on the Phase 1/2 clinical trials for 4D-125 and 4D-110 was completed in the fourth quarter of 2022: 14 patients have been treated with 4D-125, and 13 with 4D-110. The safety and tolerability profiles for both product candidates remain unchanged from prior data releases. We will continue to follow these patients for 24 months to assess the magnitude and durability of key imaging endpoint changes in evaluable patients. We anticipate providing program and clinical data updates in 2024.

Pulmonology Product Portfolio

4D-710 for the Aerosol Treatment of Patients with Cystic Fibrosis (CF) Lung Disease

Treated First Patient in High Dose Cohort on Phase 1/2 Clinical Trial with Aerosol Delivered 4D-710 in Patients with Cystic Fibrosis Lung Disease that is Not Amenable to Treatment with CFTR Modulator Therapy:

Following three patients dosed in cohort 1 (1E15 vg), the first patient in the high dose cohort (2E15 vg) was treated in December 2022 and no 4D-710 related adverse events were reported through Day 28.

Expanded Portfolio with Initiation of Preclinical Research and Development of 4D-710 in Combination with CFTR Modulators:

Preclinical research was initiated with the combination of 4D-710 with CFTR modulator therapy to support development of 4D-710 in the approximately 85% of CF patients amenable to CFTR modulator therapy.

Expanded Portfolio with Addition of Preclinical Product Candidate 4D-725 for Alpha-1 Antitrypsin Deficiency:

Alpha-1 Antitrypsin Deficiency is a prevalent disease, affecting approximately 200,000 individuals in the United States and Europe according to the NIH. The significant unmet medical need remains despite approved therapies.

Preclinical development was initiated for a new product candidate designed for single dose aerosol treatment of patients with alpha-1 antitrypsin lung disease; this product candidate utilizes 4DMT's proprietary A101 aerosol vector currently used in the CF program and expresses a genetically-validated transgene. We anticipate that development and manufacturing activities will benefit from prior clinical experience and GMP manufacturing of the A101-based 4D-710 product candidate that has been dosed in CF patients.

"We are excited by the demonstration of widespread CFTR Δ R transgene expression in the airways of the first three Phase 1/2 study participants with CF lung disease, previously reported at NACFC, as well as the initial favorable safety results," said Richard B. Moss, MD, Emeritus Professor of Pediatrics (Pulmonary Medicine), Stanford University School of Medicine, and an advisor to the 4D-710 program. "These data are an important milestone in the development of treatments for CF lung disease in patients unable to use CFTR modulators, and they support examining the combination of 4D-710 with CFTR modulators in the broader population of people with CF. In addition, they raise the possibility that the A101 vector can be the backbone of treatments for other lung diseases such as alpha-1 antitrypsin deficiency."

4D-310 for Fabry Disease Cardiomyopathy

Interim 4D-310 INGLAXA Phase 1/2 Clinical Trials Data in Patients with Fabry Disease:

Two clinical trials, one in the U.S. and one in Taiwan and Australia (Asia-Pacific) are evaluating a single intravenous administration of 4D-310 in patients with classic or late-onset Fabry disease. Six patients have been treated at a dose of 1E13 vg/kg with a corticosteroid immunomodulation regimen. There were 3 instances of atypical hemolytic uremic syndrome (aHUS) across the 2 studies; these were the only treatment-related serious or \geq Grade 3 adverse events reported. The aHUS process resolved within approximately 2-4 weeks in all three patients. One episode of aHUS qualified as a grade 4 dose-limiting toxicity and required temporary hemodialysis in a 69-year-old man with underlying kidney dysfunction; the other two patients did not receive dialysis. No other clinically significant toxicities were reported, including no infusion-related reactions, and no clinically significant cardiac or liver toxicities (three patients had transient asymptomatic Grade 1 transaminase increases). Detailed safety data will be presented at the *WORLDSSymposium* on February 25, 2023.

Cardiac Functional, Imaging, and Biopsy Data Promising in Patients Based on Evaluable Data to Date:

Cardiac clinical endpoint assessments (functional and imaging) were performed over time, and the Asia-Pacific trial also included a single early post-treatment cardiac biopsy evaluation. Cardiac clinical endpoint data (MRI, echocardiography, cardiopulmonary exercise testing [CPET] and QOL assessment) from evaluations at baseline and 12 months after treatment were assessed. In addition, where available, patient results were compared with historical data from patients who received enzyme replacement therapy over 12 months. Three patients are evaluable for 12 month cardiac data (all on U.S. trial) as of the data cut-off date of December 5, 2022 (see Table below). All three patients demonstrated improvement in multiple cardiac endpoints.

One patient underwent cardiac biopsy at week 6 (n=1 in Asia-Pacific trial). All sample sections were positive for 4D-310 delivery by qPCR and widespread transgene expression was demonstrated at both the RNA level by RT-qPCR and ISH and protein levels by IHC.

Cardiac Clinical Endpoint Methods and Results

- Cardiopulmonary Exercise Testing to assess exercise function by peak VO₂ (FDA-recommended primary endpoint): Improvement in two of three patients
- KCCQ QOL to assess cardiomyopathy-associated quality-of-life (FDA-recommended primary endpoint): Improvement in two of two patients abnormal at baseline; third patient remained stable at 100% through 12 months
- Echocardiography to assess left ventricular function by global longitudinal strain: Improvement in three of three patients (FDA-recommended supportive clinical trial endpoint)
- Cardiac MRI to assess substrate in heart: Improvement in two of two patients (one pending)

4D-310 Cardiac clinical endpoints results summary (data cut-off date of December 5, 2022):

Pts (U.S. Trial)	Native T1 (CMR) (ms)	GLS (Echo)	Peak VO ₂ (CPET) (mL/kg/min)	Cardiac QoL (KCCQ-23)
------------------	----------------------	------------	---	-----------------------

	Baseline	Week 52	Baseline	Week 52	Baseline	Week 52	Baseline	Week 52 (Overall Summary Score)	Week 52 (Clinical Summary Score)
1	Abnormal	Improved (+30.6)	Borderline	Improved (-2.5%)	Abnormal	Improved (+2.0)	Normal	Stable 100%	Stable 100%
2	Abnormal	Improved (+9.1)	Normal	Improved (-1.1%)	Abnormal	Improved (+7.0)	Abnormal	Improved (+11.7)	Improved (+5.7)
3	Abnormal	<i>Pending</i>	Borderline	Improved (-3.3%)	Abnormal	-2.2	Abnormal	Improved (+7.3)	Improved (+10.4)
ERT natural history		Worsened (-4.0) ¹		Worsened (+1.1%) ¹		Worsened (-1.8) ²		n.a.	n.a.

- Minimal detectable difference (MDD): native T1 (29 ms); GLS (1.5%); Borderline: GLS range of -16 to -18%
- Minimal clinically important difference (MCID): peak VO2 (1.5 mL/kg/min); KCCQ (summary scores 5 points)
- References: 1. Nordin et al. *Circ Cardiovasc Imaging* 2019:e009430; 2. Lobo, *Internal Medicine Journal* 2008;38:407

Oral presentation and full clinical trial data release planned for *WORLD Symposium* on February 25, 2023.

Alignment with FDA on Pivotal Clinical Trial Primary Endpoints for 4D-310 for Fabry Disease Cardiomyopathy:

4DMT proposed, and FDA communicated alignment with, use of the following endpoints in a potential pivotal trial:

- Primary endpoint: Change from baseline at 12 and 24 months in cardiopulmonary exercise testing (peak VO2).
- Primary endpoint: Kansas City Cardiomyopathy Questionnaire (KCCQ; quality of life).
- Supportive endpoint: Left ventricular function as assessed by global longitudinal strain on echocardiography.

Next Steps for 4D-310 Clinical Development:

As of January 2023, no additional patients will be enrolled on the current Fabry disease clinical trials. The program will be evaluated in the second half of 2023 after 12-month clinical data are obtained on all six of the currently enrolled patients, including on-going safety and cardiac endpoints for a potential pivotal trial as recommended by the FDA: peak VO2 (CPET), Quality-of-life (KCCQ) and left ventricular function by global longitudinal strain (echocardiography). 4DMT does not plan to utilize the current corticosteroid regimen with 4D-310 in any future studies it decides to initiate. In parallel with patient followup, 4DMT will evaluate its preferred approach of utilizing the rituximab-sirolimus immune inhibition regimen with 4D-310; the rituximab and sirolimus combination is an established clinical regimen to prevent AAV-associated aHUS. 4DMT anticipates that any future clinical development of 4D-310 would be with rituximab-sirolimus under new clinical protocol(s) and an amended or new INDs.

Eric Adler, M.D., Professor of Medicine and Section Head for Heart Failure, University of California at San Diego, and a Principal Investigator on the 4D-310 INGLAXA Phase 1/2 clinical trial, added, "4D-310 holds promise as a potential first-in-class treatment for Fabry disease-associated cardiomyopathy, the leading cause of death in this patient population, as demonstrated by the cardiac clinical data announced today. Utilizing a novel vector invented at 4DMT with the goal of achieving increased delivery and transduction within the heart in humans, 4D-310 is designed to enable transgene expression and disease correction directly within cardiomyocytes. We look forward to working with the 4D team to design and evaluate potential treatment regimens based on rituximab and sirolimus which in our clinical experience is effective at preventing aHUS following intravenous AAV."

About 4D-150 and wet AMD and DME

4D-150 is comprised of our targeted and evolved intravitreal vector, R100, and a payload that expresses both aflibercept and a VEGF-C RNAi. R100 was invented at 4DMT through our proprietary Therapeutic Vector Evolution platform; we created this platform utilizing principles of directed evolution, a Nobel Prize-winning technology. This dual transgene payload inhibits 4 angiogenic factors: VEGF A, B, C and PlGF. 4D-150 is designed for a single low dose intravitreal delivery.

Wet AMD is a highly prevalent disease with estimated incidence rate of 200,000 new patients per year in the United States, according to published data. Wet AMD is a type of macular degeneration where abnormal blood vessels (choroidal neovascularization or CNV) grow into the macula, the central area of the retina. As a consequence, CNV causes swelling and edema of the retina, bleeding and scarring, and causes visual distortion and reduced acuity. The proliferation and leakage of abnormal blood vessels is stimulated by VEGF. This process distorts and can potentially destroy central vision and may progress to blindness without treatment.

DME is a highly prevalent disease with significant unmet medical need. It is estimated that there are approximately one million individuals with DME in the United States according to published data. DME is characterized by swelling in the macula (central retina) due to leakage from blood vessels. This can lead to blurred vision. DME is typically treated with intravitreal anti-VEGF agents administered approximately every 4-12 weeks.

About 4D-710 and Cystic Fibrosis

4D-710 is comprised of our targeted and evolved vector, A101, and a codon-optimized CFTR Δ R transgene. A101 was invented at 4DMT through our proprietary Therapeutic Vector Evolution platform; we created this platform utilizing principles of directed evolution, a Nobel Prize-winning technology. 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, as a single agent and/or 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 70,000 people worldwide are living with cystic fibrosis, with approximately 1,000 new cases of cystic fibrosis diagnosed in the United States each year. Cystic fibrosis is a multisystem disorder affecting the lungs, digestive system and reproductive tract. 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 4D-310 and Fabry Disease

4D-310 utilizes the targeted and evolved C102 vector to deliver a functional copy of the *GLA* gene and was designed for a unique mechanism of action, specifically to directly correct the AGA enzyme function within cardiomyocytes (heart muscle cells) after a single IV administration. C102 was invented at 4DMT through our proprietary Therapeutic Vector Evolution platform; we created this platform utilizing principles of directed evolution, a Nobel Prize-winning technology. The product is designed to generate both high local production of AGA directly within critically affected organs, including heart, blood vessels and kidney, as well as the potential for sustained blood levels of AGA for systemic cross-correction. This product design has the potential to address the cardiomyopathy in these patients that is the leading cause of death, as well as other significant unmet medical needs in patients with Fabry disease.

Affecting more than 50,000 people in the United States and European Union, Fabry disease is a genetic disorder of the *GLA* gene that results in the body's inability to produce an enzyme called alpha-galactosidase or AGA, causing the accumulation of the substrate globotriaosylceramide (Gb3) in critical organs, including the heart, kidney and blood vessels. Such substrate accumulation can lead to life-threatening hypertrophic cardiomyopathy, heart failure, arrhythmias, various degrees of kidney dysfunction and cerebrovascular stroke. Fabry disease progression results in increased morbidity, mortality and cost of care. Significant unmet medical needs remain for these patients despite enzyme replacement therapy (ERT), the current standard of care. ERT requires biweekly intravenous dosing which markedly decreases patients' quality of life. In addition, while benefit has been demonstrated in the kidney, ERT has not been shown to clearly benefit the heart. Cardiovascular disease remains the leading cause of death and disability in Fabry disease patients.

About 4DMT

4DMT is a clinical-stage biotherapeutics company harnessing the power of directed evolution for targeted genetic medicines. 4DMT seeks to unlock the full potential of genetic medicines using its proprietary vector invention platform, Therapeutic Vector Evolution, which combines the power of the Nobel Prize-winning technology directed evolution. We invented synthetic vector libraries with approximately one billion synthetic AAV capsid-derived sequences to invent targeted and evolved vectors for use in our products. All of our vectors are proprietary to 4DMT and were invented at 4DMT, including the vectors utilized in our clinical-stage and preclinical pipeline products: R100, A101 and C102. The company is initially focused on five clinical-stage products in three therapeutic areas for both rare and large market diseases: ophthalmology, pulmonology and cardiology (Fabry disease cardiomyopathy). The 4DMT targeted 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. The five 4DMT product candidates in clinical development are as follows: 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 as follows: 4D-175 for geographic atrophy and 4D-725 for alpha-1 antitrypsin deficiency.

4D-150, 4D-310, 4D-710, 4D-125 and 4D-110 are in clinical trials 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 4D-150, 4D-310, 4D-710, 4D-125, and 4D-110 for the therapeutic use for which they are being studied. 4D Molecular Therapeutics™, 4DMT™, Therapeutic Vector Evolution™, and the 4DMT logo are trademarks of 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, as well as the plans and related timing for the clinical development of 4D-150, 4D-310, 4D-710, 4D-125 and 4D-110. 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
Evoke Canale
Katherine.Smith@evokegroup.com

Investors:

August Moretti
Chief Financial Officer
amoretti@4dmt.com

Irina Koffler
LifeSci Advisors
ikoffler@lifesciadvisors.com
917-734-7387