4D Molecular Therapeutics Announces Updated Interim Results from the 4D-310 Phase 1/2 Clinical Trial in Patients with Fabry Disease at the 18th Annual WORLDSymposium

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- *Following discontinuation of ERT, AGA activity was stable at 14-fold mean normal level through week 37 (Patient 1) and stable at 10-fold mean normal levels through week 20 (Patient 3)*
- *Preliminary clinical data suggest encouraging improvement in cardiac imaging endpoints, specifically native T1 for assessment of substrate content and GLS for assessment of left ventricular function*
- *Preliminary clinical data suggest encouraging improvements in the cardiac-related quality-of-life score (KCCQ) endpoint*

EMERYVILLE, Calif., Feb. 09, 2022 (GLOBE NEWSWIRE) -- 4D Molecular Therapeutics, Inc. (Nasdaq: FDMT), a clinical-stage gene therapy company harnessing the power of directed evolution for targeted gene therapies, announced updated interim clinical data from the ongoing Phase 1/2 clinical trial of 4D-310 in patients with Fabry disease at the 18th Annual WORLD*Symposium.*

“The dual mechanism-of-action design of 4D-310 opens the potential to treat target tissues through cross-correction from high and sustained blood AGA activity, as well as through direct transduction and AGA expression in target tissues such as the heart, kidney and blood vessels,” said Raphael Schiffmann, M.D., Senior Vice President & Therapeutic Area Head, Lysosomal Storage Diseases and Cardiology. “The evidence of AGA clinical activity and tolerability of 4D-310, as well as the initial encouraging effects on cardiac endpoints, strengthen our belief that 4D-310 represents a promising therapeutic approach for a broad range of patients with Fabry disease.”

“These clinical data suggest that 4D-310 is well-tolerated over time and has the potential to effectively treat a broad range of patients with Fabry disease,” said Jerry Vockley, M.D., Ph.D., Chief of Genetic and Genomic Medicine at the University of Pittsburgh School of Medicine and a principal investigator on the 4D-310 Phase 1/2 clinical trial. “These updated data highlight encouraging trends toward stability of high levels of blood AGA activity following discontinuation of ERT. In addition, the initial effects on cardiac endpoints suggest the design of 4D-310 has potential for benefit in the heart. ”

4D-310 for Fabry Disease Updated Interim Clinical Data Summary

The data described are from the ongoing Phase 1/2 dose-escalation and dose-expansion clinical trial assessing intravenous 4D-310, 4DMT’s targeted and evolved C102 vector-based product candidate designed for treatment of a broad Fabry disease patient population. The primary endpoint of the trial is safety and tolerability. Key secondary endpoints include change from baseline in serum AGA activity and serum lyso-Gb3 over time. Cardiac endpoints include cardiac MRI-based (cMRI) assessment of glycosphingolipid substrate accumulation using the septal native T1 signal, echocardiographic assessment of cardiac function by Global Longitudinal Strain (GLS), and heart-related quality of life assessed by the Kansas City Cardiomyopathy Questionnaire. The data cutoff date was January 13, 2022.

As of the data cutoff date, three patients with Fabry disease had post-treatment follow-up ranging from 13 weeks to 37 weeks. These patients were enrolled in the 1E13 vg/kg cohort. The trial is designed to allow enrollment of up to 6 patients in the 1E13 vg/kg dose cohort.

Updated Interim Clinical Activity and Safety Results

- Serum AGA overview: Following 4D-310 infusion, mean serum AGA enzyme activity was within, or significantly above, the normal range in all three patients, despite pre-treatment anti-AGA antibody positivity in all patients.
- Serum AGA activity over time in patients off of ERT: Updated serum AGA activity data show that following discontinuation of enzyme replacement therapy (ERT), AGA activity was stable at 14-fold mean normal at week 37 in Patient 1, and at 10-fold mean normal at week 20 in Patient 3.
    - Patients 1 and 3 demonstrated an increase in serum AGA enzyme activity significantly above the normal range at all timepoints through last follow-up. Post-treatment serum AGA enzyme activity was well above the normal range at 139.7 nmol/hr/mL (14-fold mean normal) at week 37 and 98.8 nmol/hr/mL (10-fold mean normal) at week 20 in Patient 1 & 3, respectively.
    - As previously reported, despite a high pre-treatment anti-AGA antibody titer, Patient 2 demonstrated a significant increase in serum AGA enzyme activity into the normal range. This patient entered the study off ERT and therefore had high lyso-Gb3 levels at baseline. Lyso-Gb3 decreased significantly (>50%) within the first four weeks following 4D-310 treatment. Patient 2 did not have additional serum AGA activity data as of the data cut off.
- Cardiac imaging and cardiac-related quality-of-life: Initial clinical data suggests encouraging effects on cardiac endpoints.
    - Patient 1 reached the initial 6-month cardiac MRI and echocardiogram endpoint assessments (6-month data for Patient 2 and 3 were not yet available as of data cutoff).
    - Patient 1 experienced encouraging improvement beyond the minimal detectable difference on the cMRI native T1 signal, which is consistent with glycosphingolipid substrate reduction. In addition, Patient 1 had encouraging improvement beyond the minimal detectable difference on cardiac function (left ventricular contractility) by GLS as assessed by echocardiography.
    - All three patients experienced increases in quality-of-life scores using the Kansas City Cardiomyopathy Questionnaire. Patient 2’s score increased beyond the minimal clinically important difference (last follow-up month 3). Patient 3’s score increased to the minimal clinically important difference (last follow-up month 3). Patient 1 had relatively mild symptoms at baseline, and had an increased score that was less than the minimal clinically important difference (last follow-up month 6).

- Safety and tolerability: 4D-310 continues to demonstrate a manageable safety profile. Of note, no cardiac toxicity has been reported as of the data cutoff. Cardiac safety was evaluated based on serial assessments of multiple blood biomarkers (including troponin T, CK-MB and Galectin-3), electrocardiograms and echocardiograms.

The presentation will be made available shortly after being presented on the 4DMT website at https://ir.4dmoleculartherapeutics.com/events.

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 dual mechanism of action after a single IV administration. The product is designed to generate both high sustained blood levels of AGA for systemic cross-correction of tissues, as well as for a complementary high local production of AGA directly within critically affected organs, including heart, blood vessels and kidney. This product design has the potential to address the significant unmet medical needs in patients with Fabry disease, and we believe either mechanism would represent a significant clinical advancement on its own, and together, these mechanisms could be synergistic.

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 company harnessing the power of directed evolution for targeted gene therapies. 4DMT seeks to unlock the full potential of gene therapy using its platform, Therapeutic Vector Evolution, which combines the power of directed evolution with approximately one billion synthetic capsid sequences to invent evolved vectors for use in targeted gene therapy products. The company is initially focused on five clinical-stage products in three therapeutic areas: ophthalmology, cardiology (including Fabry disease) and pulmonology. The 4DMT targeted and evolved vectors are invented with the goal of being delivered 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 : 4D-310 for Fabry disease, 4D-150 for wet AMD, 4D-125 for XLRP, 4D-110 for choroideremia and 4D-710 for cystic fibrosis.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (Securities Act), and Section 21E of the Securities Exchange Act of 1934, as amended. In some cases, you can identify forward-looking statements by terminology such as "aim," "anticipate," "assume," "believe," "contemplate," "continue," "could," "design," "due," "estimate," "expect," "goal," "intend," "may," "objective," "plan," "positioned," "potential," "predict," "seek," "should," "target," "will," "would" and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology. All statements other than statements of historical facts contained in this press release are forward-looking statements. These forward-looking statements include, but are not limited to, statements about 4D-310's potential as a therapeutic product, including its potential to effectively treat a broad range of patients with Fabry disease and its potential to benefit the heart. Forward-looking statements are not guarantees of future performance and are subject to risks and uncertainties that could cause actual results and events to differ materially from those anticipated, including, but not limited to, risks and uncertainties related to: the company's history of net operating losses and limited operating history; the company's ability to obtain necessary capital to fund its clinical programs; the risk and uncertainties inherent in the clinical drug development process; the early stages of clinical development of the company's product candidates and the limited regulatory and clinical experience to date for novel AAV gene therapy product candidates; the effects of COVID-19 or other public health crises on the company's clinical programs and business operations; the company's ability to obtain regulatory approval of and successfully commercialize its product candidates; any undesirable side effects or other properties of the company's product candidates; the company's reliance on third-party suppliers and other service providers; the outcomes of any current or future collaboration and license agreements; and the company's ability to adequately maintain intellectual property rights for its product candidates. These and other risks are described in greater detail under the section titled "Risk Factors" contained in the company's most recent Quarterly Report on Form 10-Q filed as of November 10, 2021, as well as any subsequent filings with the Securities and Exchange Commission . Any forward-looking statements that the company makes in this press release are made pursuant to the Private Securities Litigation Reform Act of 1995, as amended, and speak only as of the date of this press release. Except as required by law, the company undertakes no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise.

4D-310, 4D-150, 4D-125 and 4D-110 are in clinical trials 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-310, 4D-150, 4D-125 or 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 4DM.

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