# 4D Molecular Therapeutics Reports Interim Results from the 4D-310 Phase 1/2 Clinical Trial in Patients with Fabry Disease and Provides Clinical Data Update from the 4D-110 Phase 1/2 Clinical Trial in Patients with Choroideremia

October 25, 2021

*- First-ever clinical activity data reported on 4D-310 Fabry disease product candidate utilizing the proprietary C102 targeted and evolved vector invented through Therapeutic Vector Evolution*

*- AGA enzyme activity was within, or significantly above, the normal range in all three patients (up to 25-fold mean normal AGA activity)*

*- 4D-310 had a manageable safety profile and no dose-limiting toxicities*

*- 4D-110 was generally well-tolerated, with initial evidence of clinical activity observed*

*- 4DMT to host conference call and webcast on Monday, October 25, 2021 at 2:00 p.m PDT*

EMERYVILLE, Calif., Oct. 25, 2021 (GLOBE NEWSWIRE) -- 4D Molecular Therapeutics (Nasdaq: FDMT), a clinical-stage gene therapy company harnessing the power of directed evolution for targeted gene therapies, announced interim clinical data from the Phase 1/2 clinical trial of intravenous 4D-310 in patients with Fabry disease. The company also provided a clinical data update from the on-going Phase 1/2 clinical trial of 4D-110 in patients with choroideremia.

“Today we announced the first ever clinical data reported with an intravenous product invented from our Therapeutic Vector Evolution platform at 4DMT. These interim data demonstrate clinical proof-of-concept for tolerability and clinical activity,” said David Kirn, M.D., Co-founder and Chief Executive Officer of 4DMT. “These data support our belief that 4D-310 is well-tolerated, and has the potential to deliver patient benefit after a single intravenous injection. Importantly, the post-treatment AGA enzyme activity in patients’ blood was within, or significantly above, the normal range despite the presence of pre-existing anti-AGA antibodies, which are a result of prior ERT in these patients. To our knowledge, these initial clinical data are the first demonstration of durable serum AGA activity within the normal and above normal range following gene therapy in a difficult to treat classic Fabry disease patient population.”

“We designed 4D-310 for a unique dual mechanism of action, enabling the potential treatment of target tissues such as heart, blood vessel walls and kidney through cross-correction from high and stable serum AGA activity, as well as through direct transduction and AGA expression in target cells,” said Dr. Raphael Schiffmann, M.D., Senior Vice President & Clinical Therapeutic Area Head, Lysosomal Storage Diseases and Cardiology. “This dual MOA opens the potential to effectively treat the broadest possible range of Fabry patient populations. Given the encouraging initial clinical activity and tolerability profile of 4D-310, we plan to continue enrolling a broad patient population, including both anti-AGA antibody positive and negative patients, as well as classic and late-onset patients.”

“Fabry disease is a severe lysosomal storage disease with high unmet medical need despite ERT with an invasive biweekly infusion regimen,” said Dr. Jerry Vockley, M.D., PhD, 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 trial. “These interim clinical data suggest that 4D-310 is well-tolerated and has the potential to effectively treat a broad range of patients with Fabry disease.”

**4D-310 for Fabry Disease 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 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. The data cutoff date was October 12, 2021.

As of the data cut-off date, three patients with Fabry disease were enrolled, with post-treatment follow-up ranging from six weeks to six months. These patients were enrolled in the 1E13 vg/kg cohort, the lower of two planned dose escalation cohorts: 1E13 vg/kg and 3E13 vg/kg. Prior to dose-escalation, the trial is designed to allow enrollment of an additional 6 patients in the 1E13 vg/kg dose cohort. An oral corticosteroid prophylaxis taper was administered over 10 weeks post-dosing.

***Key Baseline Characteristics***

- All three patients currently enrolled are patients with classic Fabry disease, defined as having AGA activity <5% of mean normal in peripheral blood white cells and having one or more clinical characteristics such as acroparesthesia, hypohidrosis, angiokeratoma or cornea verticillata.
- Consistent with the classic Fabry disease phenotype, all three patients had serum AGA activity below mean normal at baseline, ranging from 0 – 0.42 nmol/hr/mL (population normal range: 4.44 – 27.42 nmol/hr/mL; population mean normal 9.9 nmol/hr/mL).
- All three patients had prior experience on enzyme replacement therapy (ERT). Patients 1 & 3 were enrolled while receiving ERT (ON-ERT). Patient 2 had prior experience with ERT but was not receiving ERT (OFF-ERT) for ~13 months prior to dosing. Consistent with prior ERT use, each patient had positive baseline anti-AGA antibody titers:
    - Patient 1: Baseline anti-AGA antibody titer 1:947
    - Patient 2: Baseline anti-AGA antibody titer 1:99,900
    - Patient 3: Baseline anti-AGA antibody titer 1:13,900

***4D-310 Preliminary Clinical Activity Summary***

- 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 titer positivity in all patients.
- Lyso-Gb3 substrate concentrations in serum decreased significantly in Patient 2, who enrolled in the trial OFF-ERT and therefore with an

elevated lyso-Gb3 level.
- Lyso-Gb3 substrate concentrations in serum remained low and stable in Patients 1 and 3 following discontinuation of ERT.

    - **Patients 1 & 3:**
        - Baseline: Both patients were receiving ERT and at baseline had low-lyso-Gb3 and positive pre-treatment anti-AGA antibody titers (1:947 – 13,900, respectively).
        - AGA Enzyme Activity: Both patients demonstrated an increase in serum AGA enzyme activity significantly above the normal range at all timepoints through last follow-up. Mean post-treatment serum AGA enzyme activity in patients 1 & 3 were well above the normal range at 2,506% (25-fold) and 2,114% (21-fold) mean normal (248.1 and 209.3 nmol/hr/mL, respectively).
        - Lyso-Gb3: Patient 1 serum lyso-Gb3 remained low and stable through week 26 and after ERT discontinuation at week 14. Patient 3 serum lyso-Gb3 remained low and stable through week 6 and following ERT discontinuation at week 2.

    - **Patient 2:**
        - Baseline: Patient 2 entered the trial OFF-ERT but had prior ERT treatment that was stopped ~13 months prior to dosing. As a result, Patient 2 had a high baseline lyso-Gb3 level (101 ng/mL). Patient 2 also had the highest pre-treatment anti-AGA antibody titer of all three patients treated and of all patients screened (1:99,900).
        - AGA Enzyme Activity: Patient 2 demonstrated a significant increase in serum AGA enzyme activity into the normal range. Mean serum AGA enzyme activity increased to 58% of mean normal (5.7 nmol/hr/mL).
        - Lyso-Gb3: Lyso-Gb3 decreased significantly (>50%) within the first four weeks and remained stable through week 12.

***4D-310 Interim Safety Data Summary***

- 4D-310 demonstrated a manageable safety profile in all three patients.
- No dose-limiting toxicities were observed.
- No serious adverse events were reported with Patient 1 and 3, and these patients did not have either atypical hemolytic uremic syndrome (aHUS) or liver toxicity, which are the 2 primary class-related toxicities associated with systemically administered AAV.
- Patient 2 developed transient, self-limited aHUS within approximately one week following treatment and was admitted to the hospital for observation and hydration and was discharged after four days. As a result of hospitalization, this event was classified as a serious adverse event (SAE).
    - The patient received no complement inhibitors; kidney function recovered without further intervention
    - Laboratory parameters improved daily throughout this observation period, and no lasting clinical sequelae resulted.
    - Transient and asymptomatic grade 1 (mild) transaminitis (AST/ALT) was also observed in this patient at a separate and single protocol-defined timepoint.
- No other SAEs were reported.

**4D-110 for Choroideremia Clinical Data Update Summary**

4D-110 is currently being studied in an ongoing Phase 1/2 dose escalation clinical trial in patients with choroideremia. To date, six patients with clinically advanced choroideremia have been enrolled. A standard 3+3 dose escalation design was used. Patients were enrolled in one of two dose cohorts: 3E11 vg/eye (cohort 1; n=3) and 1E12 vg/eye (cohort 2; n=3).

To date, at the 3E11 vg/eye dose (Cohort 1), 4D-110 was well-tolerated with no dose-limiting toxicities or serious adverse events. Initial signals of clinical activity were observed at this dose, through anatomical measurements of the retinal pigment epithelium (RPE) by fundus autofluorescence area and photoreceptors by ellipsoid zone area. We expect to continue enrolling at the 3E11 vg/eye dose level.

At the 1E12 vg/eye dose, pigment dispersion (iris transillumination) was observed in three patients in the 1E12 vg/eye cohort ~7 to 9 months following treatment. Two cases were asymptomatic and one patient reported mild glare. In each case the investigator described this as an SAE but no hospitalization or medical intervention was initiated. We believe this pigment dispersion finding is consistent with REP1 transgene overexpression in iris pigment epithelial cells (IPE); no association with inflammation was evident.

**Conference Call and Webcast Information**

4DMT will host a live conference call and webcast, Monday, October 25, 2021, at 2:00 p.m. PDT. Listeners can access the live webcast by visiting the 4DMT “Investor” section of the 4DMT website at www.4dmoleculartherapeutics.com.

To access the live call by phone, dial (833) 540-1164 (domestic) or (929) 517-0354 (international). The conference ID is 8517848. The recorded webcast will be available for at least two weeks following the call.

**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 in three therapeutic areas: ophthalmology, cardiology, 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. 4DMT is currently advancing five product candidates in clinical development: 4D-310 for Fabry disease, 4D-125 for XLRP, 4D-150 for wet AMD, 4D-710 for cystic fibrosis and 4D-110 for choroideremia. 4D Molecular Therapeutics™, 4DMT™, Therapeutic Vector Evolution™, and the 4DMT logo are trademarks of 4DM.

4D-310, 4D-125 and 4D-110 are our product candidates 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-125, or 4D-110 for the therapeutic use for which they are being studied.

**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, 4D-110's potential as a therapeutic product, and the dose level for future patients to enroll in 4D-110's Phase 1/2 dose-expansion trial. 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 August 12, 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.

**Contacts:**

**Media:**

Carolyne Zimmermann
Chief Business Officer
czimmermann@4dmt.com

**Investors:**

Mike Zanoni
VP, Investor Relations
mzanoni@4dmt.com