4D Molecular Therapeutics Presents Interim Data from 4D-310 INGLAXA Phase 1/2 Clinical Trials & Development Plans for Fabry Disease Cardiomyopathy at WORLDSymposium™

February 22, 2023

- *All three patients with 12 months of follow-up demonstrated improvement in multiple FDA-recommended cardiac endpoints at relatively low dose of 1E13 vg/kg*
- *Cardiac biopsy demonstrated selective and widespread transgene expression within ~50% of cardiomyocytes*
- *Engaging with FDA to lift clinical hold and resume enrollment with updated exclusion criteria and highly effective rituximab/sirolimus immunosuppressive regimen to reduce risk of atypical hemolytic uremic syndrome ("aHUS")*
- *Otherwise, generally well-tolerated with no liver, heart, or dorsal root ganglia ("DRG") toxicity observed*
- *Company to host live webcast today at 4:30 p.m. EST*

EMERYVILLE, Calif., Feb. 22, 2023 (GLOBE NEWSWIRE) -- 4D Molecular Therapeutics (Nasdaq: FDMT, '4DMT'), a clinical-stage biotherapeutics company harnessing the power of directed evolution for targeted genetic medicines, today announced updated interim safety and efficacy data from the two 4D-310 INGLAXA Phase 1/2 clinical trials for Fabry disease cardiomyopathy. All three patients with 12 months of follow-up demonstrated improvement on cardiac contractility, exercise capacity and quality of life endpoints. Treatment was generally well tolerated, with transient acute aHUS being the only significant adverse event. Following a detailed investigation into the etiology of aHUS, 4DMT is engaging with the FDA to resume enrollment based on updated exclusion criteria and the highly effective rituximab/sirolimus immunosuppressive regimen. Data will also be presented at the WORLD*Symposium* ™ 2023 in Orlando, Florida on February 25th, 2023.

"As demonstrated by the positive cardiac outcomes and biopsy biomarker data, these clinical proof-of-concept results with 4D-310 mark another important milestone for 4DMT," said David Kirn, M.D., Co-founder and Chief Executive Officer of 4DMT. "This is our third proprietary vector that has been validated in clinical trials across three different therapeutic areas, which further validates our Therapeutic Vector Evolution platform. We are developing 4D-310 for the treatment of Fabry disease cardiomyopathy, which is the primary cause of death and not addressed by current therapies. In addition, our focus on patient safety led us to voluntarily pause enrollment on our two INGLAXA trials in January 2023 after observing an aHUS dose-limiting toxicity, and FDA subsequently put the program on clinical hold. Following an in-depth investigation in collaboration with world experts in immunology and AAV gene therapy to understand and mitigate aHUS, we are confident that the rituximab and sirolimus immunosuppressive regimen and updated exclusion criteria will mitigate safety risks and potentially further improve patient benefit."

INGLAXA Phase 1/2 Clinical Trials Design

- Dose-escalation and dose-expansion trial assessing a single intravenous infusion of 4D-310 in a broad and diverse Fabry disease patient population
- Treated patients in three geographies: INGLAXA-1 (U.S.) and INGLAXA-2 (Taiwan and Australia)
- Enrolled six patients, each treated with 1E13 vg/kg of 4D-310 and a prophylactic corticosteroid immunosuppressive regimen
- Assessed FDA-recommended pivotal trial cardiac endpoints in three patients who completed 12 months of follow-up (cut-off date of December 5, 2022) including:
  - Left ventricular contractility – Change from baseline at 12 months in global longitudinal strain on echocardiography (GLS on ECHO)
  - Exercise capacity – Change from baseline at 12 months in cardiopulmonary exercise testing (peak VO_2 by CPET)
  - Quality of life status – Change from baseline at 12 months in Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Cardiac biopsy available from one patient in the INGLAXA-2 trial

Cardiac Outcomes

- **Cardiac contractility (GLS) assessed on ECHO:** meaningful improvement in 3 of 3 patients (GLS worsened on ERT natural history study)
- **Exercise capacity (peak VO_2) assessed by CPET:** meaningful improvement in 2 of 3 patients (worsened on ERT natural history study)
- **Cardiac quality of life (physical limitations, symptoms) assessed with KCCQ:** clinically meaningful improvement in 2 of 2 patients, and the third remained stable at 100% (no possibility for improvement from baseline)
- **Cardiac biopsy:** healthy tissue, no inflammation, and widespread transgene expression in ~50% of cardiomyocytes; transgene expression was highly selective for cardiomyocytes: ~4.4 genomes/cardiomyocyte (qPCR) and ~16.2 RNA transcripts/cardiomyocyte (RT-qPCR)

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

Pts (U.S. Trial)	GLS (Echo)		Peak VO_2 (CPET) (mL/kg/min)		Cardiac QoL (KCCQ)		
	Baseline	Week 52	Baseline	Week 52	Baseline	Week 52 (Overall Summary Score)	Week 52 (Clinical Summary Score)
1	Borderline	**Improved (-2.5%)**	Abnormal	**Improved (+2.0)**	Normal	**Stable 100%**	**Stable 100%**
2	Normal	**Improved (-1.1%)**	Abnormal	**Improved (+7.0)**	Abnormal	**Improved (+11.7)**	**Improved (+5.7)**

3	Borderline	**Improved (-3.3%)**	Abnormal	-2.2	Abnormal	**Improved (+7.3)**	**Improved (+10.4)**
ERT natural history		Worsened (+1.1%)[1]		Worsened (-1.8)[2]		n.a.	n.a.

- 1. Minimal detectable difference (MDD): GLS (1.5%); Borderline: GLS range of -16 to -18%
- 2. 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, *Intern Med J* 2008;38:407

Safety and Tolerability

- Treatment was generally well-tolerated except as noted below – no liver, heart, or DRG toxicity observed
- Transient acute aHUS (n=3): ~Day 3-7 onset; resolution started within ~1-4 days
  - Known class effect of IV administered AAV due to rapid anti-AAV capsid IgM antibody rise, capsid binding and complement pathway activation
  - Investigation of single grade 4 DLT aHUS patient indicated that complement pathway activation, which drives aHUS, was present before 4D-310 dosing.
- Investigation of IV administered AAV associated aHUS and development of mitigation strategies were conducted in close collaboration with world experts in immunology and gene therapy including Paul J. Utz, M.D., Professor of Medicine, Immunology and Rheumatology Stanford University; Dimitris Mastellos, PhD, National Center for Research, Greece; and Barry Byrne, MD, PhD, University of Florida.

Next Steps for Development of 4D-310

- Align with FDA on plan to remove clinical hold and resume enrollment following protocol amendment including the following:
  - Implement highly effective rituximab/sirolimus immunosuppressive regimen
  - Exclude patients with pre-dosing complement activation
- Continue current protocol follow-up for all six patients enrolled to date, including cardiac efficacy assessments supportive of regulatory approval: peak VO_2 (CPET), quality of life (KCCQ), and left ventricular function (GLS on ECHO)
- Phase 3 CMC plans, assays & trial design aligned with FDA
- Provide program update in the second half of 2023

Webcast Information:

4D Molecular Therapeutics will host a conference call today, Wednesday February 22, 2023 at 4:30 p.m. EST. to discuss clinical data and development plans. Dr. Paul J. Utz will join today's webcast to discuss immunology related to intravenous AAV therapy.

Title:	4D-310 INGLAXA Phase 1/2 Clinical Data Webcast and Q&A
Date/Time:	Wednesday, February 22, 2023, 4:30 p.m. EST
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 at https://ir.4dmoleculartherapeutics.com/events.

About 4D-310 and Fabry Disease Cardiomyopathy

4D-310 utilizes the targeted and customized C102 vector to efficiently 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 low dose 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 systemic tissue cross-correction. This product design has the potential to treat and potentially reverse the cardiomyopathy in Fabry patients which 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 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 invention platform, Therapeutic Vector Evolution, which combines the power of the Nobel Prize-winning technology, directed evolution, with approximately one billion synthetic AAV capsid-derived sequences to invent targeted and evolved vectors for use in our product candidates. All of our vectors are proprietary to 4DMT and were invented at 4DMT, including the vectors utilized in our clinical-stage and preclinical pipeline product candidates: R100, A101, and C102. The Company is initially focused on five clinical-stage product candidates 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. 4DMT is currently advancing five product candidates in clinical development: 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 4D preclinical product candidates in development are: 4D-175 for geographic atrophy and 4D-725 for alpha-1 antitrypsin deficiency.

4D-150, 4D-710, 4D-310, 4D-125, and 4D-110 are our product candidates in clinical development 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-150, 4D-710, 4D-310, 4D-125, or 4D-110 for the therapeutic uses for which they are being studied.

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-310, including the implications of interim clinical data from 4D-310's Phase 1/2 clinical trial. 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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