4D Molecular Therapeutics Presents Interim Results from the Ongoing 4D-125 Phase 1/2 Clinical Trial in Patients with Advanced X-linked Retinitis Pigmentosa at the ASRS Annual Meeting

October 10, 2021

- *4D-125 was well tolerated in all patients treated to-date (n=8), with no dose-limiting toxicities, no serious adverse events and no chronic inflammation*
- *Clinical activity observed through anatomical measurements of reduced photoreceptor loss in treated vs untreated control eyes on ellipsoid zone area endpoints*
- *Clinical activity observed through functional improvements in treated vs untreated control eyes on two microperimetry endpoints: (1) mean retinal sensitivity and (2) number of loci with ≥7 dB improvement*
- *4DMT plans to continue enrollment at the 1E12 vg/eye in the dose expansion cohort, including in less advanced patients*
- *4DMT to host conference call and webcast on Monday, October 11, 2021 at 8:00 a.m EDT*

EMERYVILLE, Calif., Oct. 10, 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 safety and clinical activity data from the Phase 1/2 clinical trial of intravitreal 4D-125 in patients with advanced X-linked retinitis pigmentosa (XLRP). The interim data were presented today in a late-breaking presentation at the American Society of Retina Specialists (ASRS) 39th Annual Meeting.

“These are the first clinical data reported with a product invented from our Therapeutic Vector Evolution platform at 4DMT, and these interim data demonstrate clinical proof-of-concept for safety, tolerability and clinical activity,” said David Kirn, M.D., Co-founder and Chief Executive Officer of 4DMT. “These data support our belief that 4D-125 is well tolerated, and has the potential to both slow the progressive loss of photoreceptors in patients with XLRP after a single intravitreal injection and to improve visual function. We believe these results validate the potential of our platform, and of the R100 vector, which is also deployed in 4DMT targeted product candidates designed to treat a variety of large market diseases. Consistent with our prior guidance, we expect our first R100-based large-market product candidate, 4D-150 for wet AMD, to enter clinical development before year-end.”

“Given the encouraging data we have seen with our intravitreal gene therapy, we plan to continue enrolling patients at the top dose level of 1E12 vg/eye in the dose expansion cohort, including treatment of patients with less advanced disease who are evaluable for both anatomical and functional endpoints,” said Dr. Robert Kim, M.D., Senior Vice President & Clinical Therapeutic Area Head, Ophthalmology. “We designed 4D-125 to be administered via intravitreal administration, which targets the entire surface of the retina and thereby enables the potential to treat broader patient populations, including early stage patients, more effectively than is feasible with subretinal approaches. In the case of XLRP, we believe that early stage patient populations may have the potential to benefit from our gene therapy even more than advanced patients given our goal of preserving photoreceptors. We plan to explore development paths that include treating both early stage and advanced patient populations.”

“XLRP is a slowly progressing inherited retinal dystrophy that leads to vision loss and ultimately blindness,” said Dr. Cagri Besirli, M.D., Ph.D., University of Michigan, Kellogg Eye Center and a principal investigator on the 4D-125 Phase 1/2 clinical trial. “There are currently no treatment options available to these XLRP patients. 4DMT’s gene therapy is a promising approach because, unlike other gene therapy approaches, it is delivered via intravitreal injection, a routine clinical route of administration that targets the entire surface of the retina. These interim clinical data suggest that 4D-125 is well-tolerated and has the potential to both slow the loss of the photoreceptor ellipsoid zone area and enhance retinal sensitivity.”

4D-125 Interim Clinical Data Summary

The data described are from the first-in-human, on-going Phase 1/2 dose escalation and dose expansion clinical trial assessing intravitreal 4D-125, 4DMT’s targeted and evolved R100-based product candidate for XLRP. As of the data cutoff date (September 1, 2021), eight patients with clinically advanced XLRP due to RPGR gene mutation had been enrolled. A standard 3+3 dose escalation design was used, followed by a dose expansion cohort. Patients were enrolled in one of three dose cohorts: dose-escalation cohort 1 (3E11 vg/eye; n=3), dose-escalation cohort 2 (1E12 vg/eye n=3) and the dose expansion cohort (1E12vg/eye; n=2 to date). Patients enrolled in the dose escalation cohorts of the first-in-human clinical trial had clinically-advanced XLRP, with patients having limited or no measurable remaining photoreceptor area or retinal sensitivity. As of the data cutoff date, two dose escalation patients (n=1 at 3E11 vg/eye; n=1 at 1E12 vg/eye) were evaluable for clinical activity defined as having both measurable ellipsoid-zone area (EZ Area) by spectral domain optical coherence tomography (SD-OCT) and retinal sensitivity by microperimetry in both the treated and untreated control eye with at least six months follow-up; dose expansion cohort patients (n=2) had not yet reached six months follow-up but are expected to be evaluable with sufficient follow up. On-going enrollment in the dose expansion cohort is expected to enroll patients with less advanced disease than those enrolled in dose escalation, and who we expect to be evaluable for clinical activity based on central reading center confirmation at screening.

Interim Safety Data Summary

- 4D-125 was well-tolerated in all eight XLRP patients, including in five patients at the top dose level of 1E12 vg/eye.
- No dose-limiting toxicities or serious adverse events were observed.
- No chronic inflammation was observed.
- Transient, grade 1+ anterior chamber and/or vitreous cells were observed in two of the eight patients at a single protocol-defined assessment timepoint (SUN[1] & NEI[2] grading scales)
  - One patient had grade 1+ vitreous and anterior chamber cells
  - One additional patient had grade 1+ vitreous chamber cells

Interim Clinical Activity Summary

- In the two dose escalation patients who were evaluable for clinical activity in both the treated and untreated control eyes, interim data from both patients demonstrated anatomical retina preservation as measured by EZ Area progression, a measurement of intact photoreceptors, in the treated eye as compared to the untreated control eye in the same patient. In addition, interim data from both patients demonstrated functional improvements as measured by increases in the mean retinal sensitivity in the treated eye, and a greater number of loci gaining ≥ 7 dB sensitivity in the treated eye, as compared to the untreated control eye in the same patient.

    - **Patient 3 (3E11 vg/eye cohort – 9 months follow-up)**: Decreases from baseline EZ Area were -12.4% in the treated eye compared to -16.2% in the untreated control eye (~23% lower relative progression rate). An increase in mean retinal sensitivity was demonstrated, with an increase of +1.65 dB in the treated eye from baseline compared to +0.25 dB in the untreated control eye. The number of loci gaining greater than ≥ 7 dB sensitivity were six in the treated eye compared to one in the untreated control eye.

    - **Patient 5 (1E12 vg/eye cohort – 6 months follow-up):** Decreases from baseline EZ Area were -20.2% in the treated eye compared to -28.7% in the untreated control eye (~30% lower relative progression rate). An increase in mean retinal sensitivity was demonstrated, with an increase of +0.90 dB in the treated eye from baseline compared to +0.10* dB in the untreated control eye. The number of loci gaining greater than ≥ 7 dB sensitivity were three in the treated eye compared to zero in the untreated control eye.

    **note: microperimetry data for this patient's untreated eye were evaluable at 4 months but not available at month 6 due to an inability to fixate with the untreated control eye at that visit.*

1. *Standardization of Uveitis Nomenclature Grading Scheme - SUN Working Group 2005 (Jabs et al., 2005)*
2. *National Eye Institute Grading System for Vitreous Cells - (Mahendradas, Khanna, Kawali, & Shetty, 2014)*

Conference Call and Webcast Information

4DMT will host a live conference call and webcast tomorrow, Monday, October 11, 2021, at 8:00 a.m. EDT. 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 1234677. 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. 4DMT 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 conducting three clinical trials: 4D-125 is in a Phase 1/2 clinical trial for XLRP patients, 4D-110 is in a Phase 1 clinical trial for choroideremia patients and 4D-310 is in a Phase 1/2 clinical trial for Fabry disease patients.

Cautionary Note Regarding 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 plans and timelines for the clinical development of 4D-310, 4D-125, 4D-110, 4D-150 and 4D-710, including the therapeutic potential and clinical benefits thereof; whether 4D-125 has the potential to slow the progressive loss of photoreceptors in patients with XLRP after a single intravitreal injection and to also improve visual function; the timing of 4D-150 entering clinical development; and 4DMT's clinical development plans for 4D-125 . 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, without limitation, risks associated with: the impact of COVID-19 on countries or regions in which we have operations or do business, as well as on the timing and anticipated results of our clinical trials, strategy and future operations; the delay of any current or planned clinical trials for the development of 4D Molecular Therapeutics' drug candidates, the risk that the results of our clinical trials may not be predictive of future results in connection with future clinical trials; 4D Molecular Therapeutics' ability to successfully demonstrate the safety and efficacy of its drug candidates; the timing and outcome of our planned interactions with regulatory authorities; and obtaining, maintaining and protecting our intellectual property. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in 4D Molecular Therapeutics' most recent Quarterly Report on Form 10-Q filed on August 12, 2021, 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.

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.

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