4DMT Acquires Complement Pathway Inhibitor Payload for 4D-175 Product Candidate for Geographic Atrophy

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- *4DMT acquires all world-wide rights to short-form human complement factor H (sCFH) from Aevitas Therapeutics, Inc.; technology invented at University of Pennsylvania*
- *Announces sCFH as payload for 4D-175 lead product candidate for geographic atrophy (GA); sCFH extensively characterized in 3 genetic mouse models and in non-human primates (NHP)*
- *CFH variants with reduced complement inhibitory function are a well-validated genetic risk factor for GA secondary to age-related macular degeneration (AMD), with approximately 75% of AMD patients carrying a high-risk variant of CFH; utilizing a precision medicine approach, this population represents a potential target population for 4D-175*
- *Continues expansion of the proprietary R100 retinotropic vector-based large-market ophthalmology portfolio beyond 4D-150 for wet AMD and diabetic macular edema (DME)*

EMERYVILLE, Calif., April 24, 2023 (GLOBE NEWSWIRE) -- 4D Molecular Therapeutics (Nasdaq: FDMT, “4DMT”), a clinical-stage biotherapeutics company harnessing the power of directed evolution for genetic medicines targeting large-market diseases, today announced that it acquired the rights and know-how for short-form human complement factor H (sCFH) from Aevitas Therapeutics, Inc. The transgene encoding sCFH, a shortened and optimized form of a natural inhibitor of the inflammatory complement pathway invented at the University of Pennsylvania, will be combined with 4DMT’s proprietary retinotropic R100 vector to engineer the product candidate 4D-175 for treatment of GA secondary to AMD.

Geographic atrophy is a highly prevalent disease with a significant unmet medical need. According to published estimates, there are over one million individuals with GA in the U.S. alone as of 2022. The first treatment for GA, complement inhibitor pegcetacoplan injection, was approved in the U.S. in February 2023 and is administered by intravitreal (IVT) injection once every 25 to 60 days. Similar treatment regimens with anti-VEGF agents for neovascular (wet) AMD have proven difficult to maintain. Challenges in adhering to monthly or every-other-month treatment for wet AMD can lead to suboptimal clinical outcomes, suggesting the same may be encountered in the treatment of GA. Thus, a treatment that achieves consistent expression of a therapeutic could lead to more optimal clinical outcomes. 4D-175 is designed to achieve continuous expression of sCFH in the retina from a single injection in order to inhibit the inflammatory complement pathway in patients with GA without requiring repeated injections.

Complement Factor H (CFH) is a master regulator of the complement system, functioning as a natural inhibitor of the alternative complement pathway. Dysregulation of the complement system can lead to autoimmune and inflammatory diseases, including GA. Mutations in the gene encoding CFH are among the strongest genetic risk factors for AMD including GA, with approximately 75% of patients carrying a high-risk variant of CFH with reduced complement inhibitory function, leading to complement pathway hyperactivity.

sCFH is an engineered and optimized version of CFH that can fit into AAV vectors with robust expression and full functionality confirmed in human cells in vitro, and in multiple preclinical animal models and species *in vivo*. The construct was co-invented by Wenchao Song, Ph.D., Professor of Pharmacology at the Perelman School of Medicine at the University of Pennsylvania. Dr. Song has extensive experience researching complement-mediated inflammatory, autoimmune, and thrombotic vasculopathy disorders. Restoring CFH function using sCFH protein could restore normal complement regulation and reduce retinal injury that manifests as progressive GA. Preclinical proof-of-concept for this approach using 1) human sCFH delivered systemically using an adeno associated virus (AAV) in a mouse model of atypical hemolytic uremic syndrome (aHUS) and 2) a mouse version of sCFH delivered using an AAV in mouse models of C3 glomerulopathy and aHUS each demonstrated recovery from complement dysregulation, reduced organ damage, and improved survival.

“The potential of delivering sCFH with a clinically-validated retinotropic AAV vector in R100 for complement-mediated ophthalmologic diseases is an exciting step in advancing meaningful therapies toward the clinic,” said Dr. Song. “I look forward to working with the 4DMT team to continue the development of sCFH to potentially treat GA and other diseases.”

“We are pleased to add an innovative and differentiated preclinical GA product candidate into our large market ophthalmology portfolio, which leverages our clinically-validated R100 retinotropic vector,” said David Kirn, M.D., Co-founder and Chief Executive Officer of 4DMT. “This represents continued value generation from our robust product design and development engine to leverage the vector modularity of our platform in the ophthalmology therapeutic area.”

“Providing patients with a low-dose, safe and tolerable long-duration treatment option with the potential to preserve vision in patients with GA would be a tremendous breakthrough,” said Robert Kim, M.D., Chief Medical Officer of 4DMT. “We are working relentlessly to leverage our existing clinical, nonclinical, and CMC experience with the R100 vector in three different patient populations to rapidly bring this important product candidate to the clinic.”

About 4DMT

4DMT is a clinical-stage biotherapeutics company harnessing the power of directed evolution for genetic medicines targeting large market diseases. 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 customized 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 customized 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 AATLD.

4D-150, 4D-710, 4D-310, 4D-125, and 4D-110 are 4DMT's 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.

The laboratory of Dr. Song at the University of Pennsylvania has received sponsored research funding from Aevitas Therapeutics. Penn and Dr. Song have either received, or may receive in the future, financial consideration related to the licensing of certain Penn intellectual property to 4DMT. Dr. Song holds an equity stake in Aevitas, is a scientific founder of Aevitas and is a member of their Scientific Advisory Board.

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 development plans and related timing for the clinical development of 4D-175. 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 Annual Report on Form 10-K, 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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