Design Therapeutics Reports Positive Data from Single-Ascending Dose Trial of DT-216 for the Treatment of Friedreich Ataxia and Portfolio Progress

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DT-216 was Generally Well-Tolerated and Resulted in a More than Doubling of Frataxin mRNA in Patients with Friedreich Ataxia

Second GeneTAC™ Development Candidate, DT-168, Selected for the Treatment of Fuchs Endothelial Corneal Dystrophy Administered as an Eye Drop; IND Expected in 2023

Advancing Myotonic Dystrophy Type-1 GeneTAC™ Lead Molecules; IND Expected in 2024

Conference Call to be Held Today at 4:30pm ET

CARLSBAD, Calif., Dec. 07, 2022 (GLOBE NEWSWIRE) -- Design Therapeutics, Inc. (Nasdaq: DSGN), a clinical-stage biotechnology company developing treatments for serious degenerative genetic diseases, today reported progress across its portfolio of novel GeneTAC™ small molecules. Today's updates include initial results on DT-216 from the company's single-ascending dose (SAD) Phase 1 clinical trial in patients with Friedreich ataxia (FA). The results show that DT-216 was generally well-tolerated and able to overcome the frataxin (FXN) transcription impairment that causes FA, with a greater than two-fold increase in FXN mRNA in the cohort with the highest response. These data support the continued advancement of DT-216 in the ongoing multiple-ascending dose (MAD) Phase 1 trial and the anticipated Phase 2 clinical trial in FA patients, which is on track to begin in 2023.

FA is a multisystem degenerative disease caused by a GAA nucleotide repeat expansion in the FXN gene that impairs transcription and reduces FXN mRNA. Reduced FXN transcription results in mitochondrial and cellular dysfunction and leads to all FA disease manifestations. DT-216 is a GeneTAC™ small molecule designed to specifically target the GAA repeat expansion mutation, unblock the transcriptional machinery, and restore the production of functional, natural FXN mRNA.

"It is very encouraging to see single doses of DT-216 overcome the RNA transcription block of the FXN gene that causes FA," said Susan Perlman, M.D., Professor of Neurology and Head of Neurogenetics Clinical Trials at UCLA. "These Phase 1 data underscore the potential for modifying the course of FA and improving the quality and length of life for those diagnosed with the condition. DT-216 is one of the most promising candidates for future treatment options for FA patients and I look forward to its continued development."

"We started Design to address the known monogenic causes of a range of inherited degenerative diseases and in just a few short years, are able to report clinical data that support our founding hypothesis," said Pratik Shah, Ph.D., executive chair of Design Therapeutics. "GeneTAC™ molecules are thoughtfully designed to dial up or down the expression of specific genes, addressing the root cause of disease without the need for irreversible genetic modification. In FA, where deficiency of FXN causes its clinical manifestations, we believe that FXN restoration by DT-216 can have a meaningful clinical impact. The data from our SAD trial demonstrate proof-of-concept with DT-216 and highlight its safety profile and ability to increase FXN mRNA – the first step to increasing FXN protein and restoring mitochondrial function."

DT-216 Phase 1 SAD Trial Design

The Phase 1 SAD clinical trial is a randomized, double-blind, placebo-controlled study designed to evaluate single doses of DT-216 administered intravenously in adult patients with FA.
The primary and secondary study objectives were to evaluate safety and tolerability, and pharmacokinetics (PK) of DT-216 in FA patients. Change in FXN mRNA and protein expression relative to baseline, measured in a circulating subset of white blood cells, known as peripheral blood mononuclear cells (PBMCs), were included as exploratory pharmacodynamic (PD) assessments.

Thirty-nine FA patients (mean age 32 years, 49% female) were dosed across six dose cohorts (5-10 patients per cohort) ranging from 25 mg to 600 mg and were randomized to receive either DT-216 (N=26) or placebo (N=13). All patients were homozygous for a GAA repeat expansion (mean=580, SD=203).

The study protocol was prospectively designed for DT-216 to be administered either as a single dose bolus or as a single dose split-administration on the same day. Patients in Cohorts 1-4 were dosed with a single bolus dose of DT-216 at increasing levels from 25 mg to 200 mg. Patients in Cohort 5 (400 mg) received either a single dose bolus or single dose split administration of DT-216, and all patients in Cohort 6 (600 mg) received a single dose split administration of DT-216. Safety assessments were conducted for 30 days post dosing.

Safety Results

Safety data are available by treatment assignment for Cohorts 1-5 (N=33). Cohort 6 (600 mg; N=6) treatment assignment remains blinded pending completion of the 30-day safety assessment, per study protocol.

DT-216 was generally well-tolerated throughout the Phase 1 SAD trial. Findings from Cohorts 1-5 were:

- No treatment-related serious adverse events (SAEs) reported
- 16 (73%) patients on DT-216 and eight (73%) patients on placebo reported at least one treatment-emergent adverse event

- Most adverse events (AEs) were mild and transient; there were no severe AEs
- No clinically significant changes in vital signs, physical exams, electrocardiogram, and clinical safety laboratories (including liver function tests and serum creatinine)
- Three patients had a localized superficial vein thrombosis at the injection site; of which two were mild and one was moderate; and all three were self-limited

The blinded safety profile of Cohort 6 is consistent with the prior cohorts.

Pharmacokinetic and Pharmacodynamic Results

PK data were available for 32 patients (Cohorts 1-3, 5 and 6). PD data were available for 33 patients; data from Cohort 4 (200 mg) were excluded from this analysis due to third-party issues with sample handling. Plasma levels of DT-216 increased in an approximately dose-proportional manner, with peak concentrations within minutes, followed by a decrease in plasma levels within several hours.

Treatment with a single dose of DT-216 resulted in a 2.24-fold increase in FXN mRNA, at 24 hours post-dose compared with pre-treatment baseline, in the cohort with the highest response ($p < 0.01$ DT-216 [N=3] vs. pooled placebo [N=11]). Treatment with a single dose of DT-216 in all cohorts 100 mg and above resulted in a statistically significant increase in FXN mRNA at 24 hours post dose. Individual patient responses to single doses of DT-216 ranging from 100-600 mg resulted in an increase in FXN mRNA at 24 hours ranging from 1.24 to 2.62-fold. A relationship between plasma exposure and treatment effect was observed in PBMCs.

As expected with short-term plasma exposure, there was no observed increase in FXN protein from baseline in PBMCs from patients treated with a single dose of DT-216 or placebo. *Ex vivo* DT-216 treatment for 60 hours of PBMCs isolated pre-treatment from patients enrolled in this trial elicited a doubling of FXN protein levels, confirming that, with sufficient duration of exposure to DT-216, an increase in FXN mRNA naturally translated to an increase in FXN protein.

Design is evaluating DT-216 in an ongoing MAD Phase 1 clinical trial designed to evaluate the safety, tolerability, PK, and PD effects of three weekly doses of DT-216 in adult patients with FA. The first MAD cohort of 100 mg has begun dosing. Design plans to dose at least three cohorts and report data from the MAD trial in mid-2023.

Pipeline Updates

Fuchs endothelial corneal dystrophy (FECD)

Design nominated its second GeneTAC™ development candidate, DT-168, an eye drop for the treatment of FECD, a genetic eye disease caused by a CTG repeat expansion. FECD is characterized by progressive degeneration of the corneal endothelium and subsequent loss of vision that affects millions of people. The company plans to submit an Investigational New Drug application (IND) for DT-168 in the second half of 2023.

Myotonic dystrophy type-1 (DM1)

Design has continued to advance its preclinical characterization of several lead DM1 GeneTAC™ molecules and now expects to submit an IND in 2024. Design's DM1 GeneTAC™ molecules are designed to prevent the formation of the CUG hairpin structures that trap splicing proteins and produce pathogenic nuclear foci. There is currently no cure for this debilitating and deadly neuromuscular disease.

"The clinical proof-of-concept of DT-216 in FA underscores the enormous opportunity of our small molecule GeneTAC™ platform to expand the therapeutic landscape for people suffering with serious monogenic diseases," said João Siffert, M.D., president and chief executive officer of Design Therapeutics. "Not only do these data support the continued advancement of our FA program, but they demonstrate our expertise in designing novel GeneTAC™ molecules and provide strong support for our entire portfolio of potential first-in-class GeneTAC™ programs, including in FECD and DM1. With one program in the clinic, an anticipated second clinical-stage program in 2023, and plans for a steady cadence of new GeneTAC™ candidates and clinical trials, we are well-positioned to deliver on our goals. I am proud of the Design team for its incredible efforts and extend our sincerest gratitude to the patients and caregivers participating in our clinical trials. We are also thankful to the Friedreich Ataxia Research Alliance for their steadfast support on behalf of the FA community."

Webcast and Conference Call Information
Design will host a live webcast and conference call today at 4:30 p.m. EST to discuss these updates. The event is accessible through the "Events" section of the Investors page of www.designtx.com. A replay of the webcast will be archived on the Design website for 30 days.

Dial-in information for conference participants may be obtained by registering for the event here.

About Design Therapeutics
Design Therapeutics is a clinical-stage biotechnology company developing a new class of therapies based on its platform of GeneTAC™ gene targeted chimera small molecules. The company's GeneTAC™ molecules are designed to either dial up or dial down the expression of a specific disease-causing gene to address the underlying cause of disease. Design's lead program is focused on the treatment of Friedreich ataxia, followed by programs in Fuchs endothelial corneal dystrophy and myotonic dystrophy type-1 and discovery efforts for multiple other serious degenerative disorders caused by nucleotide repeat expansions. For more information, please visit designtx.com.

Forward-Looking Statements
Statements in this press release that are not purely historical in nature are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to projections from early-stage programs, preclinical data and early-stage clinical data; the therapeutic potential of DT-216; expectations for reporting data and the timing thereof; the potential benefits of restoring FXN in FA patients; the expected initiation of Design's Phase 2 clinical trial for DT-216 in patients with FA and the timing thereof; DT-216's potential to be a promising candidate for future treatment of FA patients; Design's anticipated timeline to submit an IND and begin clinical development of DT-168 for the treatment of FECD; Design's FECD GeneTAC™ program and its potential therapeutic benefits and advantages; Design's anticipated timeline to begin clinical development of its GeneTAC™ program for the treatment of DM1; Designs ability to deliver on our short- and long-term goals; Design's ability to design and tailor GeneTAC™ molecules from our novel platform to address diverse monogenic diseases; anticipated steady cadence of new

GeneTAC™ candidates and clinical trials; and the capabilities and potential advantages of Design's pipeline of GeneTAC™ molecules. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Words such as "believes," "designed to," "anticipates," "planned," "expects," "estimate," "intends," "will," "potential" and similar expressions are intended to identify forward-looking statements. These forward-looking statements are based upon Design's current expectations and involve assumptions that may never materialize or may prove to be incorrect. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of various risks and uncertainties, which include, without limitation, risks associated with conducting a clinical trial and patient enrollment, which is affected by many factors, and any difficulties or delays encountered with such clinical trial or patient enrollment may delay or otherwise adversely affect such clinical trial; the process of discovering and developing therapies that are safe and effective for use as human therapeutics and operating as a development stage company; Design's ability to develop, initiate or complete preclinical studies and clinical trials for its product candidates; the risk that promising early research or clinical trials do not demonstrate safety and/or efficacy in later preclinical studies or clinical trials; changes in Design's plans to develop its product candidates; uncertainties associated with performing clinical trials, regulatory filings and applications; risks associated with reliance on third parties to successfully conduct clinical trials and preclinical studies; Design's ability to raise any additional funding it will need to continue to pursue its business and product development plans; regulatory developments in the United States and foreign countries; Design's reliance on key third parties, including contract manufacturers and contract research organizations; Design's ability to obtain and maintain intellectual property protection for its product candidates; Design's ability to recruit and retain key scientific or management personnel; competition in the industry in which Design operates, which may result in others discovering, developing or commercializing competitive products before or more successfully than Design; and market conditions. For a more detailed discussion of these and other factors, please refer to Design's filings with the Securities and Exchange Commission ("SEC"), including under the "Risk Factors" heading of Design's Quarterly Report on Form 10-Q for the quarter ended September 30, 2022, as filed with the SEC on November 3, 2022. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. All forward-looking statements are qualified in their entirety by this cautionary statement and Design undertakes no obligation to revise or update this press release to reflect events or circumstances after the date hereof, except as required by law.

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