



## **Design Therapeutics Reports Initial Results from Phase 1 Multiple-Ascending Dose Study of DT-216 for the Treatment of Friedrich Ataxia**

August 14, 2023

*DT-216 Resulted in a Significant Increase in FXN mRNA Levels in Skeletal Muscle of FA Patients*

*Treatment Generally Well-Tolerated; Injection Site Reactions Attributable to Current Formulation Composition*

*Design Plans to Proceed with an Improved DT-216 Formulation and Initiate a Multiple Dose Phase 1 Clinical Study in the Second Half of 2024*

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

CARLSBAD, Calif., Aug. 14, 2023 (GLOBE NEWSWIRE) -- Design Therapeutics, Inc. (Nasdaq: DSGN), a clinical-stage biotechnology company developing treatments for serious degenerative genetic diseases, today reported initial results from the company's Phase 1 multiple-ascending dose (MAD) clinical trial of DT-216 in patients with Friedrich ataxia (FA). As of a data cutoff date of August 7, 2023, results showed that DT-216 was generally well-tolerated and achieved a statistically significant and dose-related increase in frataxin (FXN) mRNA levels in skeletal muscle biopsies.

FA is a multisystem degenerative disease caused by a GAA nucleotide repeat expansion in the FXN gene that impairs transcription and reduces FXN mRNA. Low FXN expression 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.

"I'm encouraged by the data from the Phase 1 MAD trial of DT-216, which is the first to show a drug candidate increasing transcription of endogenous FXN mRNA in an affected tissue in FA," said Susan Perlman, M.D., Clinical Professor of Neurology and Director of Neurogenetics Clinical Trials at UCLA. "Given the lack of treatment options to address the root cause of this debilitating disease, DT-216 is a highly promising candidate, and I am eager to see its continued development."

### **Observational Biomarker Study in Friedreich Ataxia**

In parallel to the Phase 1 MAD study, Design conducted an observational study to evaluate FA biomarker assays in blood and skeletal muscle from individuals with FA, FA carriers and normal healthy volunteer controls for use in DT-216 interventional studies. The company developed procedures and methods to measure both FXN mRNA and FXN protein in muscle. Initial data from the observational study is based upon a data cutoff of August 7, 2023. The observational study enrolled a total of 56 participants. Skeletal muscle biopsies were obtained from study participants at two visits several days apart to measure FXN mRNA and protein levels and characterize inter- and intra-individual variability.

Study results showed that levels of endogenous FXN mRNA across individuals with FA, FA carriers and healthy individuals differed significantly. Additionally, levels in the interquartile range for FA patients did not overlap with FA carriers, which shows FXN mRNA levels between these two populations are distinct. Design believes these data support use of the muscle FXN mRNA assay as a sensitive indicator of clinical activity in FA, with the ability to discriminate clinically meaningful changes in endogenous FXN mRNA.

FXN protein measurements in skeletal muscle had substantial overlap between FA patients and carriers and showed high intra-individual variability. More than half of FA patients had 25% or more variation in FXN protein levels between visits, with intra-individual coefficient of variation of 69%. The variability of results observed with this current method substantially limited the utility of FXN protein measurements to assess DT-216 pharmacology.

### **DT-216 Phase 1 MAD Trial Design**

The Phase 1 MAD clinical trial is a randomized, double-blind, placebo-controlled study designed to evaluate multiple ascending 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 three weekly doses of DT-216 in FA patients. As an exploratory objective, the company also evaluated FXN expression including levels of FXN mRNA and protein in skeletal muscle biopsies obtained at pre-dose baseline and two and seven days after the third weekly dose.

Initial data from the Phase 1 MAD trial is based upon a data cutoff of August 7, 2023. The study is fully enrolled but currently ongoing, with blinded PK and pharmacodynamic (PD) data available in the full 100 and 200mg dose cohorts and 11 of 14 participants in the 300mg dose cohort. Safety data remain blinded.

The study enrolled 29 adult participants with genetically confirmed FA. Symptomatic FA patients were adequately distributed across dose cohorts. Study participants received three weekly intravenous injections across the 100mg, 200mg, and 300mg cohorts (N=4, 11, and 14, respectively) and were randomized to receive either DT-216 or matching placebo.

### **Blinded Safety**

DT-216 was generally well-tolerated after three intravenous doses of DT-216 or placebo:

- There were no treatment-related serious adverse events (SAEs) and no treatment-related discontinuations.
- All adverse events (AEs) were mild or moderate.
- There were five cases of injection site thrombophlebitis observed across all three cohorts; four were considered mild and

one was considered moderate.

- There were no new clinically significant safety observations.

### **Pharmacokinetics**

Plasma PK data were available in participants at 100mg, 200mg, and 300mg DT-216 doses. Plasma levels of DT-216 were approximately dose proportional. The average DT-216 concentration in muscle was approximately 8-10nM two days after the third weekly dose and approximately 1nM seven days after the third weekly dose in both the 200mg and 300mg cohorts. DT-216 muscle exposure in FA patients was lower than projected from animal studies but was sufficient to result in significant PD response in skeletal muscle.

### **DT-216 Pharmacodynamics**

To better understand the pharmacodynamics of DT-216 directly in tissues relevant for FA disease symptoms, the company developed procedures and methods to measure FXN expression in skeletal muscle. As of the data cutoff date, exploratory analyses of muscle FXN mRNA levels from the Phase 1 MAD study showed that:

- FA patients in the 300mg cohort had a 30% mean increase from baseline in FXN mRNA two days after the third weekly dose, which was significant compared to placebo ( $p < 0.05$ ), with a trend in increased FXN mRNA seven days post dose.
- The mean increase in FXN mRNA of the 300 mg cohort was above the 75<sup>th</sup> percentile of FA patients from the observational study
- There was a significant DT-216 dose-response trend ( $p < 0.05$ ) and tissue exposure-response relationship ( $p < 0.05$ ) with muscle FXN mRNA expression

Based on current methods and procedures, the treatment effect of DT-216 on FXN protein was inconclusive due to high intra-individual variability, consistent with what was seen in the observational study.

There was a transient increase of FXN mRNA in peripheral blood mononuclear cells (PBMCs) 24 hours after dose, which is consistent with and confirms the results from the Phase 1 single ascending dose study. As of this data cutoff, PBMC FXN protein results are not available.

### **DT-216 Program Next Steps**

The initial results from Design's Phase 1 multiple ascending dose trial underscore the promise of DT-216 as a potential disease-modifying treatment for FA.

The favorable systemic safety profile and FXN response support continued development of DT-216. However, the company has elected to complete dose escalation in this Phase 1 study at the 300mg cohort due to concern for potential worsening of injection site thrombophlebitis at higher doses with multiple administration. Design has shifted focus to developing DT-216 with an improved formulation to enable higher exposures and chronic intravenous administration for treatment of FA. Nonclinical studies showed that the injection site reactions were attributable to the excipients in the current DT-216 formulation, and that improving the formulation composition could enable higher doses and chronic administration. Design has since shown that an improved formulation had favorable injection site tolerability following multiple intravenous administrations and enabled dosing to increase tissue exposure.

The company is now conducting bridging nonclinical studies to resume clinical development and expects to begin a multiple-dose Phase 1 clinical trial to assess safety, pharmacokinetics and pharmacodynamics of an improved DT-216 formulation in the second half of 2024, with initial clinical data expected in the first half of 2025.

"Data from the Phase 1 program showed that the therapeutic hypothesis of DT-216 is playing out in FA patients —restoring endogenous transcription of FXN into therapeutically relevant levels," said João Siffert, M.D., president and chief executive officer of Design Therapeutics. "The totality of the data from our Phase 1 program supports the continued development of DT-216 for FA, and we believe leveraging an improved formulation will enable us to explore the full DT-216 therapeutic potential for treatment of people with FA, which is our ultimate goal. Our team will continue to work tirelessly such that clinical development with DT-216 can be resumed and we can report data from a multiple dose Phase 1 clinical trial in the first half of 2025. I am proud of the Design team for its incredible efforts, and we extend our sincerest gratitude to the patients and caregivers participating in our clinical trials."

### **Webcast and Conference Call Information**

Design will host a live webcast and conference call today at 4:30 pm ET to discuss these updates. The event is accessible through the "Events" section of the Investors page of [www.designtx.com](http://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. In addition to its lead GeneTAC™ small molecule, DT-216, in development for patients with Friedreich ataxia, the company is advancing programs in Fuchs endothelial corneal dystrophy and myotonic dystrophy type-1. Discovery efforts for multiple other serious degenerative disorders caused by nucleotide repeat expansions are also underway, including for fragile X syndrome, spinocerebellar ataxias, Huntington disease, spinobulbar muscular atrophy, and C9orf72-amyotrophic lateral sclerosis/frontotemporal dementia. For more information, please visit [designtx.com](http://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, nonclinical data and early-stage clinical data; the potential benefits of restoring FXN in FA patients; the side effect profile observed in nonclinical testing of improved formulations of DT-216 being indicative of the side effect profile that may be expected in clinical studies, and in general the ability to an improved formulation of DT-216 to prevent injection site thrombophlebitis or other limiting side effects; expectations for resuming clinical development in FA and announcing data therefrom and the timing thereof; the muscle FXN mRNA assay being a sensitive indicator of clinical activity in FA; Design's ability to meet its

stated milestones, near-term catalysts and advance the GeneTAC™ platform; the potential of Design's platform and approach; the potential of Design's GeneTAC™ small molecules to be a new class of therapies for patients suffering from devastating genetic diseases; 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," "aims," "plans to," "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 the acceptance of INDs by the FDA for the conduct of planned clinical trials of our product candidates and our proposed design of future clinical trials; risks associated with designing and implementing investigational drug product formulation improvements; 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 Design's planned clinical development of DT-216; the process of discovering and developing therapies that are safe and effective for use as human therapeutics and operating as a development stage company; the risk that undesirable side effects or other properties could cause Design or regulatory authorities to suspend or discontinue clinical trials which could delay or prevent Design's product candidates' development or regulatory approval; Design's ability to develop, initiate or complete nonclinical 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 nonclinical 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 nonclinical studies; Design's reliance on key third parties, including contract manufacturers and contract research organizations; 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 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 March 31, 2023, as filed with the SEC on May 9, 2023, and under the "Risk Factors" heading of Design's Quarterly Report on Form 10-Q for the quarter ended June 30, 2023, being filed with the SEC later today. 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.

**Investor Contact:**

Chelcie Lister  
THRUST Strategic Communications  
[chelcie@thrustsc.com](mailto:chelcie@thrustsc.com)

**Media Contact:**

Amanda Sellers  
Verge Scientific Communications  
[asellers@vergescientific.com](mailto:asellers@vergescientific.com)