Category

Best Startup

Product/Solution Name

Design Therapeutics

Date of Approval

N/A

Indications

In clinical studies for Friedreich ataxia; future study in other rare diseases

Therapeutic Categories

small molecule, genomic medicines, rare diseases

Background information and need for solution/product

DT-216 is a clinical-stage GeneTAC™ (Gene Targeted Chimera) small molecule genomic medicine designed to address the underlying cause of Friedreich ataxia (FA), a monogenic, autosomal recessive, progressive disease with limited treatments options.

FA is caused by guanine-adenine-adenine (GAA) triplet repeat expansions in the first intron of the frataxin (FXN) gene, impairing transcription and reducing FXN mRNA. Reduced FXN transcription results in mitochondrial and cellular dysfunction. This multi-system disease impacts the heart, muscles, and nervous system causing ataxia, cardiomyopathy, severe physical disability, and early wheelchair dependence.

The estimated prevalence of FA is one in 40,000–50,000 people, affecting more than 5,000 individuals in the U.S. and more than 20,000 in Europe. Clinical onset typically occurs around puberty and affected individuals face reduced life expectancy. Despite our genetic understanding of the disease, there remain no approved disease modifying therapies.
The recent completion of mapping repeat sequences in the human genome in 2022 has made this category of diseases an area ripe for therapeutic opportunity. Design Therapeutics' approach of using a small molecule to modulate expression represents the forefront of a new field of genomic medicine. As a class, small molecules are much better understood, allowing for easier pharmacokinetic (PK)/pharmacodynamic (PD) and safety response prediction in humans based on preclinical data. Our expertise in medicinal chemistry allows us to develop GeneTAC molecules with favorable safety profiles, biodistribution, and the biological activity desired. With a more predictable translational path to the clinic, we can achieve an upregulation in the FXN gene without cutting, editing, or inserting genes.

Because the GAA mutation resides within an intron of the gene, the repeat portion will naturally be edited out when the gene is successfully transcribed. DT-216 is designed to overcome the transcriptional block caused by the GAA repeat expansion, allowing for increased transcription and production of normal natural FXN protein from a patient's own genome.

History of the development of the solution/product

Design Therapeutics was founded based on pioneering work by Dr. Aseem Ansari with funding from FARA, the Friedreich's Ataxia Research Alliance. GeneTAC, or Gene Targeted Chimera molecules, are heterobifunctional small molecules designed with two components connected by a linker. One end of the molecule targets DNA-and recognizes the repeat expansion to localize the GeneTAC to the mutant gene. The other end of the molecule engages and modulates the transcriptional machinery. GeneTAC molecules can be designed to target specific genetic sequences unique to a disease and then appropriately modulate gene expression up or down.

In the case of DT-216, the DNA targeting portion of the molecule recognizes the GAA repeat expansion and localizes DT-216 to the mutant FXN gene. The ligand, or engager portion of the molecule, is connected by a linker and recruits the transcriptional elongation complex to restore the normal transcription of the natural FXN gene thereby addressing the single root cause of FA.

Design's team of scientific researchers and senior advisors comprise the world's most celebrated experts on DNA-binding small molecules, and their collective knowledge fuels the company's innovative capabilities. We maintain deep IP and global expertise in medicinal chemistry and structure-activity relationships necessary to tailor-create these gene-targeting small molecules.

In March 2022, we initiated a Phase 1 clinical trial to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of FXN levels from single ascending doses of DT-216 in adult patients with FA.

In December 2022, we reported initial results from the single-ascending dose (SAD) portion of the Phase 1 trial. The results showed that DT-216 was generally well-tolerated and able to overcome the FXN transcription impairment that causes FA, with a greater than two-fold increase in FXN mRNA in the cohort with the highest response. Data from the ongoing multiple-ascending dose (MAD) Phase 1 trial are expected to be reported in the third quarter of 2023, with the anticipated Phase 2 clinical trial on track to begin in late 2023.

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

DT-216 is designed to address the underlying cause of FA by recruiting an endogenous transcriptional elongation complex to unblock the transcriptional machinery from the expanded GAA sequence and restore production of functional, natural FXN protein from a patient's own genome.

GeneTAC molecules are a novel class of genomic medicine based on small molecule chemistry that provide a range of advantages. Using small molecule therapies for genomic medicine is an overlooked, and powerful, innovation for the treatment of genetic diseases.

· These small molecules can target the root cause of genetic disease using a cell's natural machinery without modifying or cutting the genome.
· The effects of GeneTACs are reversible because there is no genome modification, and the molecules have reduced safety risks and progress to the clinic much faster.
· As small molecules, GeneTACs distribute widely to all tissues and pass through the blood-brain barrier to reach central nervous tissues to address the multi-organ symptoms of FA including heart, brain, muscle and pancreas.
· In preclinical studies (NHP and patient cells), DT-216 is expected to restore the natural production of

FXN protein in the key tissues affected, including the heart, muscle, and nervous system.
• Small molecule medicines are more cost-effective to manufacture.
Recent clinical results from our Phase 1 study of DT-216 show that our GeneTAC approach can dial up target FXN expression in FA patients after a single dose, demonstrating the promise of the platform. Our versatile platform allows us to tailor-create small molecule therapeutics for correcting nucleotide repeat expansion disorders.

Please provide appropriate references (ie Pubmed links)

1. https://pubmed.ncbi.nlm.nih.gov/29192133/
2. https://clinicaltrials.gov/ct2/show/NCT05285540
3. FARA: Design Therapeutics Informational Webinar https://www.youtube.com /watch?v=uSdWGp3cK4k