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Saturday

Safety, pharmacokinetics, and pharmacodynamics of a brain penetrant PGRN (DNL593) in healthy volunteers and participants with frontotemporal dementia caused by GRN mutations: Ph1/2 Study Design

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State of the art: Heterozygous loss of function granulin (GRN) gene mutations cause progranulin protein (PGRN) haploinsufficiency and is a known cause of frontotemporal dementia (FTD-GRN). Patients with FTD-GRN have abnormal lysosomal, inflammatory and neurodegeneration biomarkers. DNL593 is a novel CNS-penetrant protein replacement therapy, consisting of a Fc fragment engineered to contain a human transferrin receptor binding domain fused to recombinant human PGRN. Increasing PGRN levels in the CNS via DNL593 may correct lysosomal dysfunction due to PGRN deficiency in FTD-GRN. NCT05262023 is a Phase 1/2 study that will determine the safety, pharmacokinetics, and pharmacodynamics of DNL593.

Methodology: This is a three part (A, B and C), multicenter, randomized, double-blind, placebo-controlled study. Part A is a single ascending dose study with healthy volunteers. Part B is a 24-week treatment period, enrolling adults aged 18-80 years with symptoms related to FTD and are heterozygous GRN mutation carriers. Participants will be randomized in a 2:1 ratio to receive DNL593 or placebo. Part C is an 18-month open label extension (OLE). The primary, secondary objectives of Parts A and B are safety and pharmacokinetics of DNL593. Exploratory objectives include assessment of pharmacodynamic biomarkers and clinical function. Part C will assess the long-term safety of DNL593 in participants with FTD-GRN.

Results: This study in North America, Europe, Latin America will include approximately 106 participants across all three parts.

Discussion: NCT05262023 is designed with a randomized, double-blind, placebo-controlled part to generate well-controlled safety and biomarker data, and an OLE to provide longer term safety understanding.

Conflicts of interest

Tsai RM, Lockwood S, Chiu C, Jarfanejad M, Gadkar K, Henne K, Bhalla A, Ho C and Troyer M are employees of Denali Therapeutics and have equity ownership/stock options with Denali Therapeutics.
Simen A, Shanbhag NM, Bednar M are employees of Takeda Pharmaceuticals and have equity ownership/stock options with Takeda Pharmaceuticals