Safety and pharmacokinetics of single ascending doses of TAK-594/DNL593, a brain-penetrant progranulin replacement, in healthy volunteers: Interim results from Part A of a Phase 1/2 clinical trial

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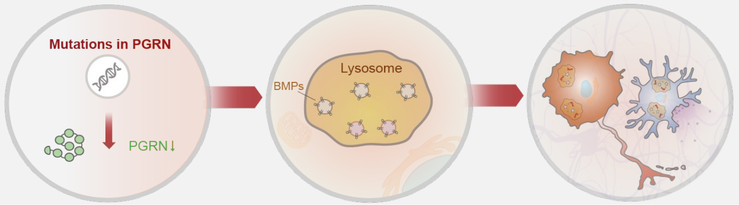
TAK-594/DNL593 is an investigational drug and has not been approved by any Health Authority

Background

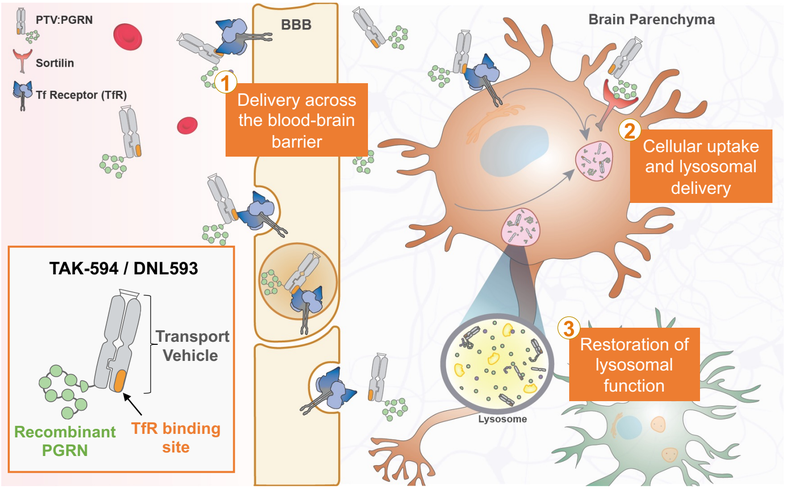
- In FTD caused by *GRN* mutations (FTD-GRN), chronic lysosomal dysfunction due to cellular progranulin (PGRN) deficiency leads to microglial dysfunction, inflammation, and neuron death.
- TAK-594/DNL593 is an investigational, peripherally administered PGRN replacement therapy that is designed to cross the blood-brain barrier (BBB) and restore cellular PGRN.
- Chronic treatment with TAK-594/DNL593 in *Grn* deficient mice corrected biomarkers of lysosomal function, inflammation, and neurodegeneration.

Disease Pathogenesis in FTD-GRN

GENETICS	PATHWAY	PATHOLOGY
Mutations in *GRN* lead to decreased PGRN levels	PGRN deficiency causes lysosomal dysfunction	Lysosomal dysfunction leads to inflammation and neurodegeneration

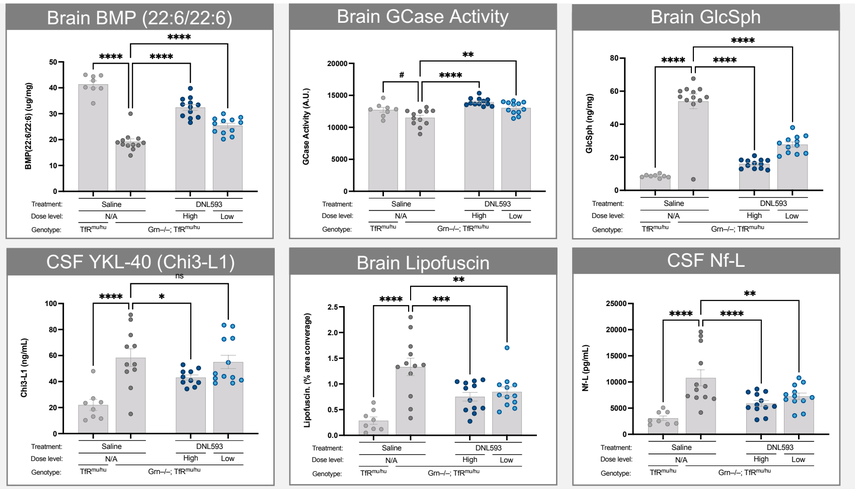


Proposed Mechanism of Action of TAK-594 / DNL593



Correction of Disease Biomarkers in Preclinical Models

12mo *Grn* KO; $TfR^{mu/hu}$ KI mice treated x6mo with **Low** or **High** dose TAK-594/DNL593



Phase 1/2 Study Design

Part A: Single Ascending Dose in Healthy Participants → **Part B: 6-month Double-Blind** in Participants with FTD-GRN (**2:1** randomization, drug to placebo) → **Part C: 18-month Open-Label Extenstion** in Participants Who Complete Part B

A5: 30x
A4: 20x
A3: 10x
A2: 3.3x
A1: 1x

Key Eligibility
- Pathogenic *GRN* mutation (no-cost genotyping available)
- FTD-related symptoms or diagnoses
- CDR® plus NACC-FTLD global score ≥ 0.5

Endpoints
- Safety and tolerability
- Pharmacokinetics
- Pharmacodynamic biomarkers including markers of lysosomal function, inflammation, and neurodegeneration in blood and CSF
- MRI including volumetric and diffusion tensor imaging
- Functional and cognitive assessments (CDR® plus NACC FTLD, FTD Rating Scale, neuropsychological and digital language assessments)

Single Dose Safety Results in Healthy Participants

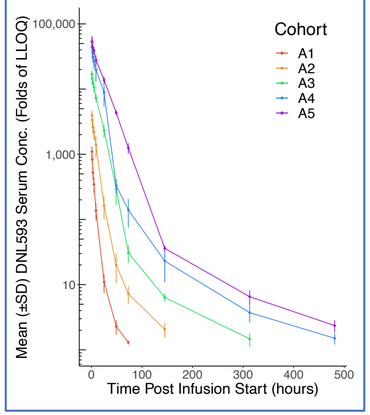
	Placebo (N = 12)	ALL DNL593 (N = 26)	Cohort A1 1x (N = 5)	Cohort A2 3.3x (N = 5)	Cohort A3 10x (N = 6)	Cohort A4 20x (N = 5)	Cohort A5 30x (N = 5)
≥ 1 TEAE	6 (50.0%)	14 (53.8%)	4 (80.0%)	2 (40.0%)	4 (66.7%)	1 (20.0%)	3 (60.0%)
≥ 1 TEAE reported in ≥ 2 participants in Placebo or Total DNL593							
Post LP syndrome	2 (16.7%)	6 (23.1%)	-	2 (40.0%)	1 (16.7%)	1 (20.0%)	2 (40.0%)
Back pain	1 (8.3%)	1 (3.8%)	-	-	-	-	1 (20.0%)
Musculoskeletal chest pain[a]	-	2 (7.7%)	-	-	1 (16.7%)	-	1 (20.0%)
Headache	1 (8.3%)	1 (3.8%)	1 (20.0%)	-	-	-	-

[a] Related to incidental physical trauma

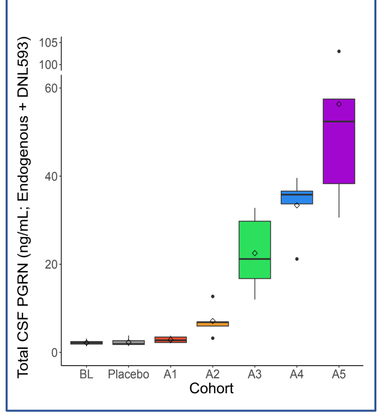
- 1 severe and serious adverse event (AE) of ureterolithiasis, assessed as not related to study intervention, was observed in a participant in Cohort A3.
- The remaining AEs were mild or moderate.
- There were no clear dose-related trends in the frequency or severity of treatment-emergent AEs (TEAEs).
- No infusion-related reactions were observed.
- No clinically significant abnormalities were found in vital signs, physical/neurological examination, ECG, or safety laboratory tests.

Single Dose Serum PK and CSF PGRN in Healthy Participants

SERUM PK



CSF PGRN (24HR)



- TAK-594/DNL593 serum and CSF concentrations increased dose dependently following single IV doses of TAK-594/DNL593.
- Variability in C_{max} and AUC_{inf} was low (≤30%) across the dose range.

Summary

- Study DNLI-H-0001 is a Phase 1/2 study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of TAK-594/DNL593.
  - Part A was a single-center, first-in-human, randomized, placebo-controlled, double-blind, single ascending dose study of TAK-594/DNL593 in healthy participants.
  - Single IV doses of TAK-594/DNL593 were generally safe and well tolerated.
  - The relationship between dose and systemic exposures following single IV doses was predictable, with low variability, across the dose range.
  - CSF PGRN increased dose-dependently, consistent with brain delivery of TAK-594/DNL593.
- Part B is a currently enrolling, multicenter, 6-month, randomized, placebo-controlled, double-blind, multiple dose study in participants with FTD-GRN, followed by Part C, an 18-month open-label extension.

For more information about Study DNLI-H-0001, visit ClinicalTrials.gov (ID: NCT05262023) or EudraCT (ID: 2021-005733-16).