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# A Phase 1, Multicenter, Open-Label Study Design to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of DNL952 in Adult Participants with Late-Onset Pompe Disease

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## Introduction

- In Pompe disease, GAA deficiency causes glycogen accumulation in muscle, resulting in progressive motor deterioration and respiratory weakness despite available ERTs
- In addition, there is growing evidence that glycogen buildup in the nervous system causes severe neurological deficits (including seizures and encephalopathy) in IOPD,[1–3] and may contribute to weakness in LOPD[4–6]
- Therefore, innovative new approaches are needed that enhance ERT delivery to muscles and to the nervous system

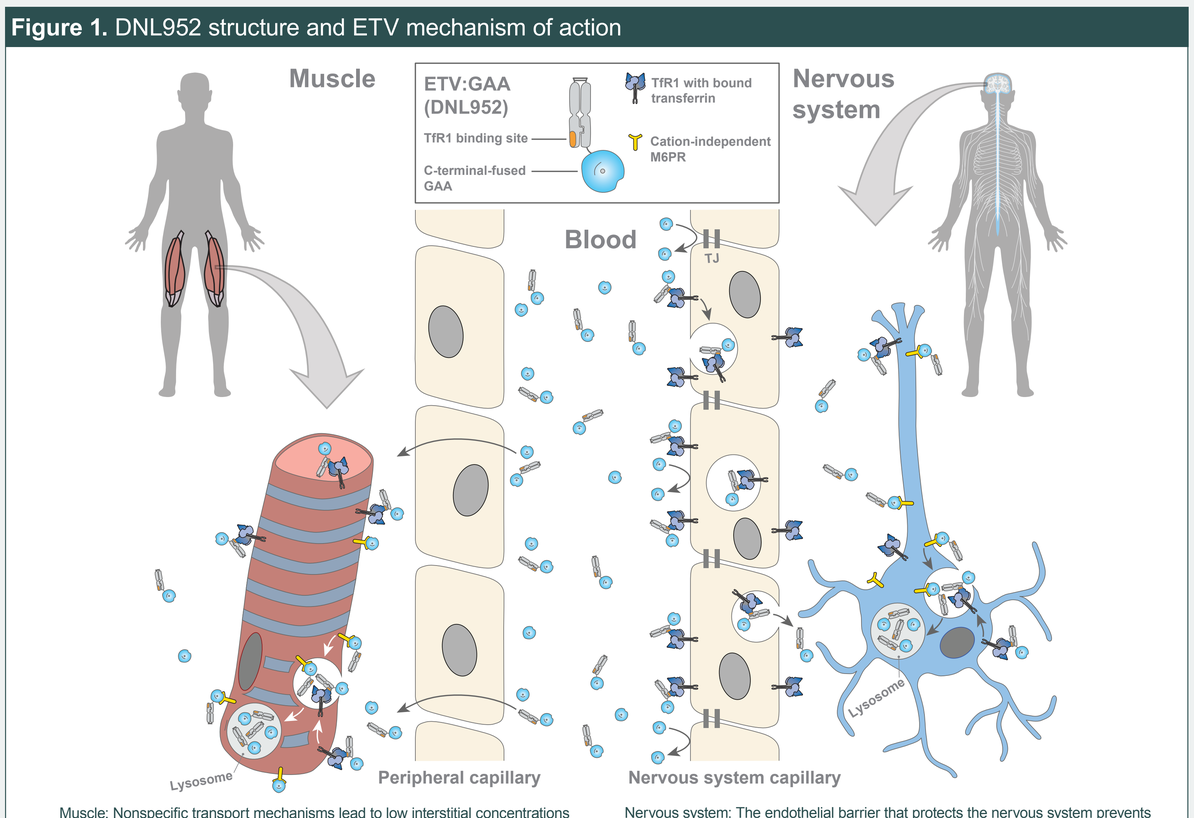
## Conclusions

- DNL952 is an investigational, next-generation ERT for Pompe disease that leverages the TfR to improve enzyme delivery to muscles and to the nervous system
- Study DNLI-J-0001 is the first in-human study of DNL952
- Safety, PK, and PD data obtained in this study will support identification of a well-tolerated and potentially effective dose for future studies in Pompe disease
- For more information, please visit ClinicalTrials.gov (NCT07354724)

## Background on DNL952

- DNL952 is a novel, investigational ERT for Pompe disease that has been designed to enhance GAA delivery to muscles and to the nervous system
- DNL952 (ETV:GAA) consists of recombinant GAA fused to an ETV – with an Fc region engineered to bind the TfR – which improves GAA distribution to TfR-expressing tissues (such as muscles and the nervous system) via receptor-mediated cellular uptake and transcytosis (**Figure 1**)
- The PD effects of DNL952 were evaluated in *Gaa* KO;TfR$^{mu/hu}$ KI mice, a Pompe disease model that is GAA-deficient and also expresses a chimeric TfR. This TfR binds the ETV with similar affinity to the human TfR while preserving the function and expression of the murine TfR, thereby enabling the evaluation of TfR-mediated pharmacology. *Gaa* KO;TfR$^{mu/hu}$ KI mice received five IV doses administered EOW of either vehicle, DNL952 at various dose levels, or avalglucosidase alfa 20 mg/kg
- Vehicle-treated *Gaa* KO;TfR$^{mu/hu}$ KI mice developed glycogen accumulation in quadriceps muscle and in brain tissue. In addition, staining for the lysosomal marker LAMP2 and autophagosomal marker P62 revealed marked lysosomal vacuolization and autophagic buildup in the quadriceps, consistent with impaired lysosomal function and autophagic flux, pathologic hallmarks of Pompe disease that are also observed in muscle biopsies from human patients[7–9]
- DNL952 treatment significantly reduced glycogen to near-normal levels in both quadriceps muscle and brain tissue across various dose levels. DNL952 demonstrated greater efficacy than avalglucosidase alfa in correcting glycogen accumulation in both of these tissues (**Figure 2**)
- Treatment with DNL952 at low, medium, and high doses resulted in dose-dependent reduction of lysosomal volume and autophagic burden that was greater than that achieved with avalglucosidase alfa (**Figure 3**)
- The differentiated mechanism of action of DNL952 and data from nonclinical studies support its potential as a next-generation therapy for Pompe disease (see Poster 290 [Priya R *et al.*] for additional nonclinical data)

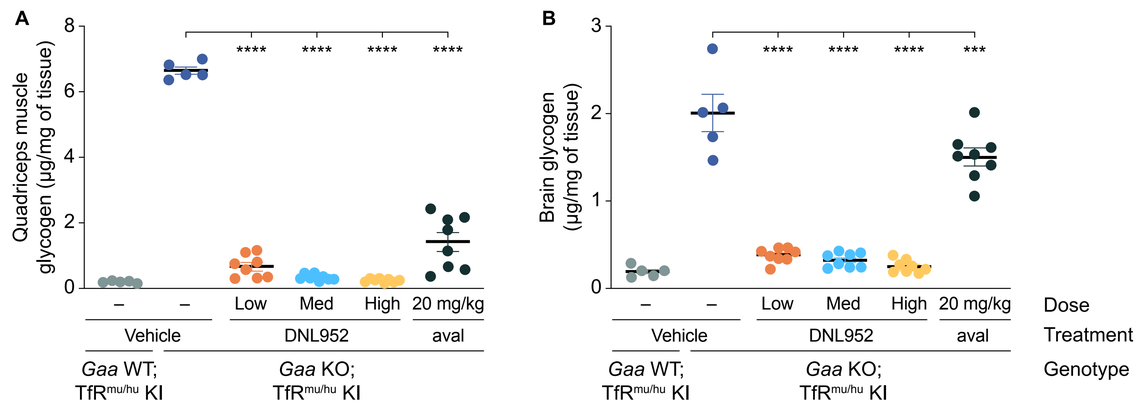
**Figure 1.** DNL952 structure and ETV mechanism of action




Muscle: Nonspecific transport mechanisms lead to low interstitial concentrations of GAA ERTs. The ability of DNL952 to engage the TfR, in addition to the M6PR, enables improved cellular uptake and lysosomal delivery

Nervous system: The endothelial barrier that protects the nervous system prevents efficient delivery of GAA. TfR engagement by DNL952 enables receptor-mediated transcytosis across the endothelium as well as cellular uptake and lysosomal delivery

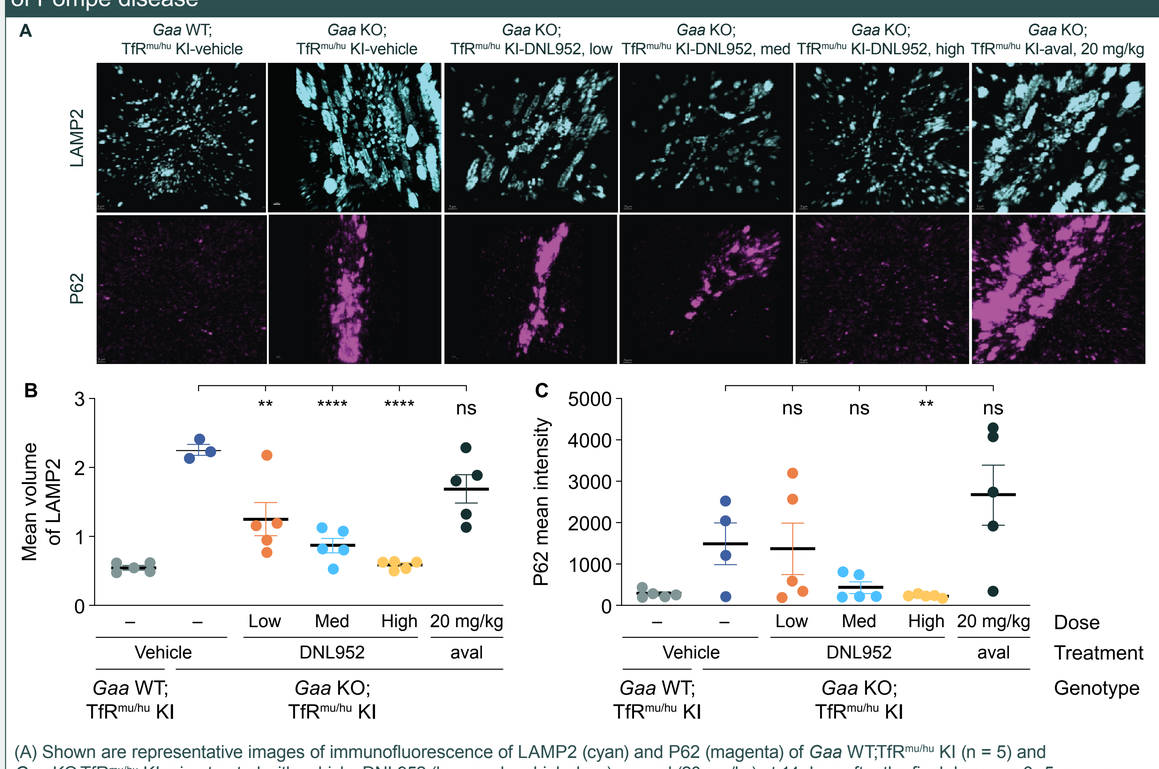
**Figure 2.** DNL952 improved glycogen correction in a mouse model of Pompe disease




*Gaa* KO;TfR$^{mu/hu}$ KI animals (n = 8 per group) received five IV dosings of DNL952 (low, med, or high dose) or aval (20 mg/kg) administered EOW. Vehicle-treated *Gaa* WT;TfR$^{mu/hu}$ KI (n = 5) and *Gaa* KO;TfR$^{mu/hu}$ KI (n = 5) mice served as the nondisease and disease comparator groups, respectively. Levels were assessed using an LC-MS/MS–based method. Data are presented as mean ± SEM

$^{***}P < 0.001$; $^{****}P < 0.0001$

**Figure 3.** DNL952 improved correction of markers of lysosomal and autophagic dysfunction in a mouse model of Pompe disease




(A) Shown are representative images of immunofluorescence of LAMP2 (cyan) and P62 (magenta) of *Gaa* WT;TfR$^{mu/hu}$ KI (n = 5) and *Gaa* KO;TfR$^{mu/hu}$ KI mice treated with vehicle, DNL952 (low, med, or high dose), or aval (20 mg/kg) at 14 days after the final dose; n = 3–5 per group. Scale bar = 2 mm. (B,C) Data are mean ± SEM of quantified (B) LAMP2 and (C) P62 signal. $^{**}P < 0.01$; $^{****}P < 0.0001$

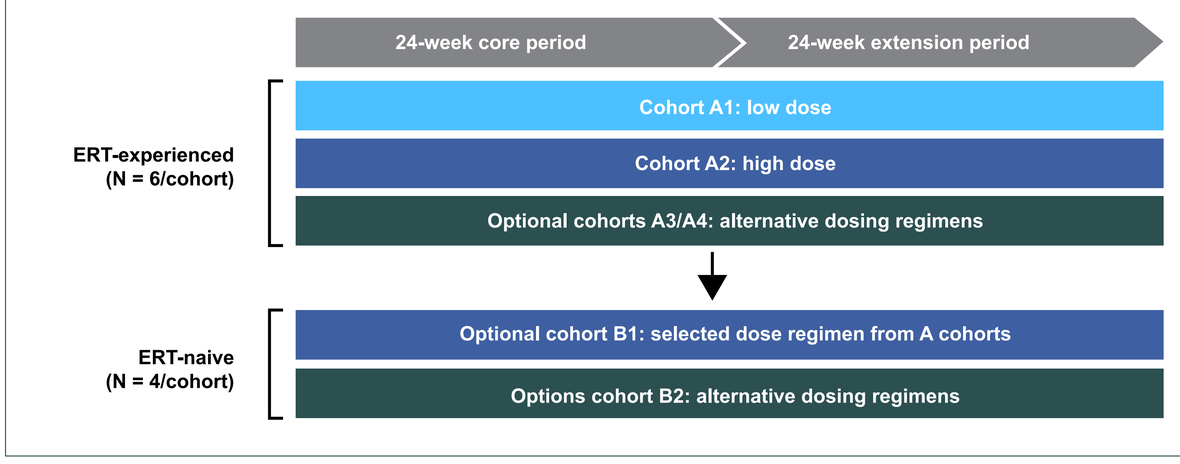
## Study Design

- Study DNLI-J-0001 is a Phase 1, multicenter, open-label study to evaluate the safety, tolerability, PK, and PD of DNL952 in adult participants with LOPD (**Table 1**; **Figure 4**)

**Table 1.** Overview of the Phase 1 study design

| | | Study overview |
|---|---|---|
| **Key eligibility** | All cohorts | • Age ≥ 18 and ≤ 75 years<br>• Confirmed diagnosis of LOPD<br>• Upright FVC ≥ 30% of predicted normal value<br>• Able to ambulate ≥ 40 m (use of assistive devices is acceptable) |
| | A cohorts: ERT-experienced | • Have received avalglucosidase alfa or cipaglucosidase alfa at a dose of 20 mg/kg every 2 weeks for at least 12 months |
| | Optional B cohorts: ERT-naive | • Have not received any ERT for at least 12 months and have received no more than four total doses at any time |
| **Sample size** | | • Up to 32 participants |
| **Key endpoints** | Primary | • Safety and tolerability |
| | Secondary | • PK<br>• Immunogenicity |
| | Exploratory | • PD: urine Glc4, serum CK, and exploratory biomarkers<br>• Efficacy: motor and respiratory strength and function and patient-reported outcomes |

**Figure 4.** Phase 1 study schema




- Two planned dose-exploration cohorts will enroll ERT-experienced participants
- Additional optional cohorts may be included to explore alternative doses or dosing frequencies, or to evaluate DNL952 in ERT-naive participants

**ABBREVIATIONS**

aval, avalglucosidase alfa; CK, creatine kinase; EOW, every other week; ERT, enzyme replacement therapy; ETV, Enzyme TransportVehicle™; Fc, fragment crystallizable; FVC, forced vital capacity; GAA, acid α-glucosidase; *Gaa*, mouse acid α-glucosidase gene; Glc4, glucose tetrasaccharide; IOPD, infantile-onset Pompe disease; IV, intravenous; KI, knock-in; KO, knockout; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LAMP2, lysosomal-associated membrane protein 2; LOPD, late-onset Pompe disease; M6PR, mannose-6-phosphate receptor; med, medium; ns, not significant; PD, pharmacodynamics; PK, pharmacokinetics; SEM, standard error of the mean; TfR, transferrin receptor; TfR$^{mu/hu}$, a chimeric mouse–human transferrin receptor; TJ, tight junction; WT, wild type.

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**DISCLOSURES**

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**ACB**, **IVC**, **MG**, **SH-R**, **SD**, and **DJ** are employees of Denali Therapeutics Inc., which has filed patent applications related to the subject matter. **MDT** and **CH** were employees of Denali Therapeutics Inc. at the time the study was designed.

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