Poster number: P-272

Phase 3 Study Design: Evaluation of Efficacy and Safety of DNL126 in Mucopolysaccharidosis IIIA

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**At the time the work was performed*

Summary

- Zafinofusp alfa is an ERT designed to bind to TfR to cross the BBB, with potential to be a novel, disease-modifying treatment for patients with MPS IIIA
- Planning is underway for this Phase 3, global, multicenter, open-label study to evaluate the efficacy and safety of zafinofusp alfa across a broad age range of participants with MPS IIIA

Introduction

- MPS IIIA is caused by a genetic deficiency of the lysosomal enzyme SGSH, resulting in substrate accumulation, lysosomal dysfunction, and neurodegeneration[1,2] (**Figure 1**)
- MPS IIIA is primarily characterized by severe neurocognitive deterioration during childhood leading to premature death[1–4]
- MPS IIIA remains an area of high unmet medical need, with no approved therapies due in part to the BBB, which is a major obstacle to brain delivery of enzymes[1,2]
- Zafinofusp alfa (DNL126; Enzyme TransportVehicle™:SGSH) is an investigational intravenous ERT designed to use the TfR to cross the BBB and deliver SGSH to the brain, as well as facilitate distribution of SGSH to peripheral tissues (**Figure 2**)
- Preliminary Phase 1/2 clinical data in pediatric participants with MPS IIIA demonstrated that safety was generally consistent with that of established ERTs for other lysosomal diseases, and that weekly zafinofusp alfa dosing resulted in substantial reductions in CSF and peripheral biomarkers at Week 49, with some participants achieving normalization (see Poster P-294)
- Here, we describe DNLI-I-0002, a Phase 3, global, multicenter, open-label study of zafinofusp alfa in participants with MPS IIIA and a severe (rapidly progressing) phenotype

Figure 1. MPS IIIA pathogenesis, biomarkers, and clinical manifestations

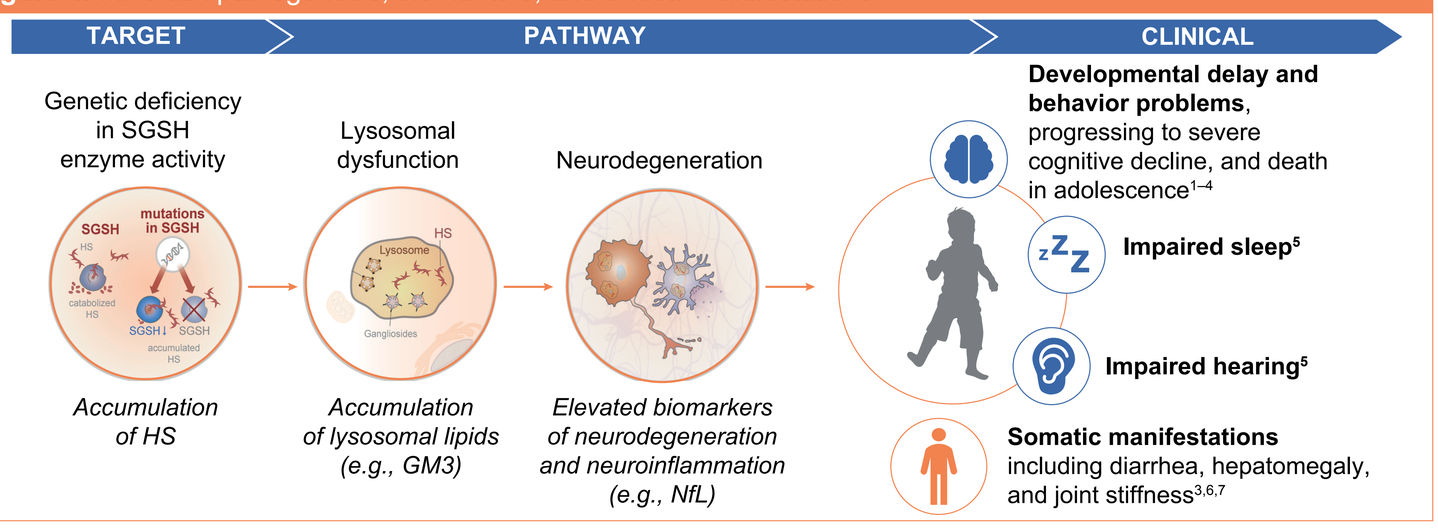
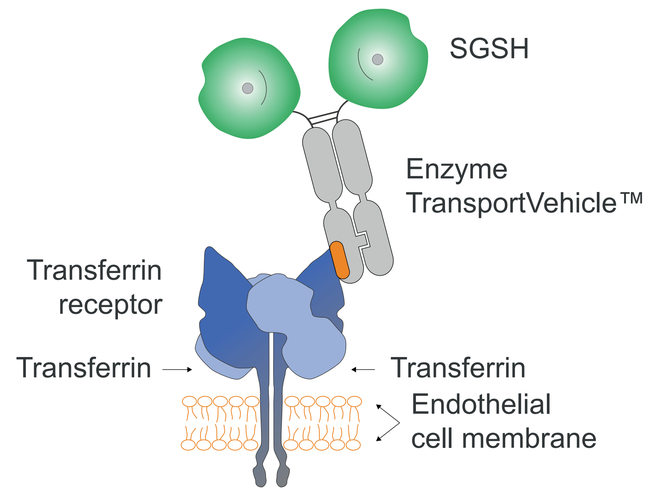


Figure 2. Structure of zafinofusp alfa (ETV:SGSH)



Study Overview

Study design

- DNLI-I-0002 will comprise two parts (Parts A and B) that will be conducted in parallel (**Figure 3**)
  - In Part A, participants aged < 28 months will receive open-label zafinofusp alfa from Week 1 through the 72-months-of-age visit (target enrollment, n = 13)
  - In Part B, participants aged ≥ 28 months will be randomized 1:1 to receive either zafinofusp alfa or no treatment for 24 weeks followed by a 25-week open-label extension period through Week 49 and a long-term extension period through Week 97, with all participants receiving zafinofusp alfa during the extension periods (target enrollment, n = 14)
  - Enrollment in Part B will initially be limited to siblings of participants in Part A
- The study will be conducted across multiple sites and will allow international relocation from select countries

Dosing regimen

- Zafinofusp alfa will be administered as a weekly intravenous infusion
- A dose-escalation regimen from low to middle to high doses will be used over approximately 12 weeks
- Prophylactic immunomodulatory therapy will be administered concurrently with zafinofusp alfa

Inclusion and exclusion criteria

- Key eligibility criteria are summarized in **Table 1**; additional criteria will be assessed by investigators

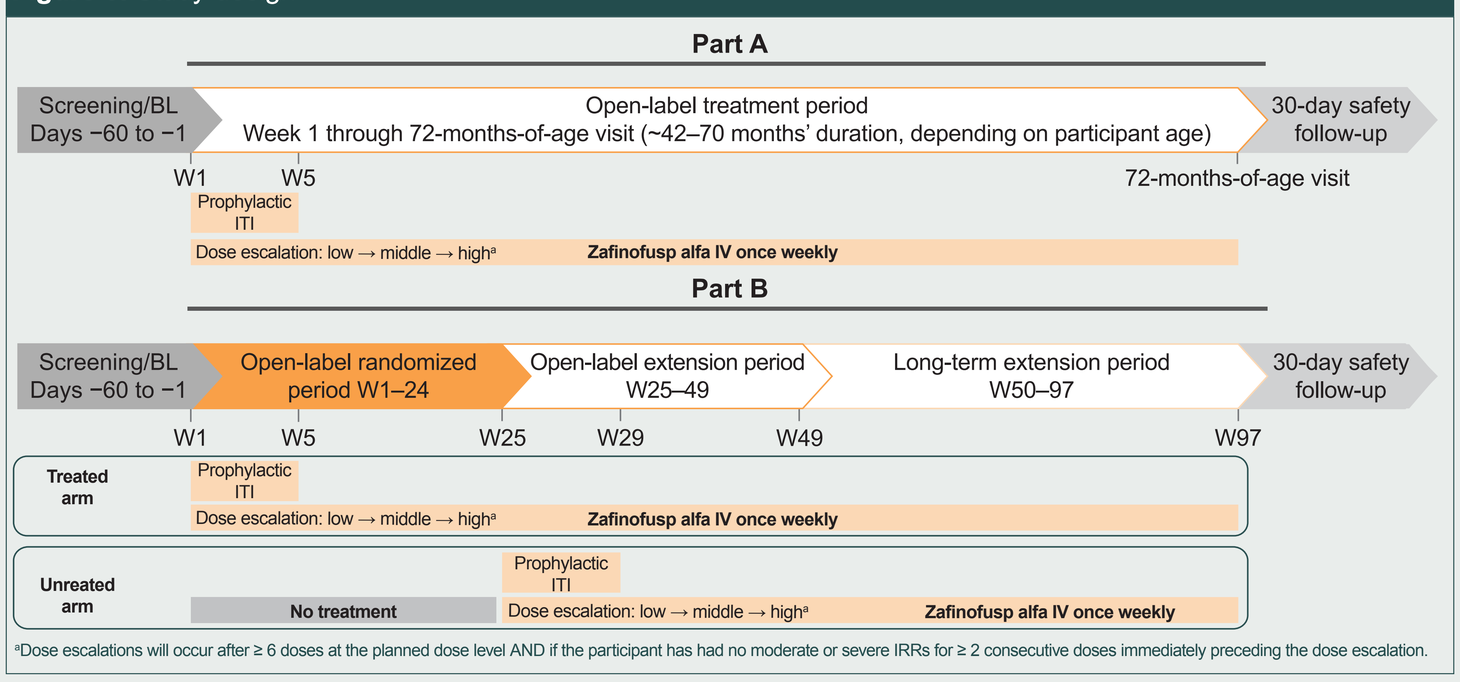
Study outcomes

- The primary objective is to evaluate the efficacy of zafinofusp alfa on cognitive function in younger participants, assessed by the BSID-III
- In Part B, additional efficacy and safety analyses will compare endpoints between older participants receiving zafinofusp alfa and the untreated group up to Week 25
- Study endpoints are presented in **Table 2**

Table 1. Key inclusion and exclusion criteria

Key inclusion criteria
Confirmed diagnosis of MPS IIIA
Severe (rapidly progressing) phenotype
Received standard vaccination schedule for the country of origin
Additional criteria for **Part A only** • < 28 months of age at screening • BSID-III cognitive composite score ≥ 80
Additional criteria for **Part B only** • ≥ 28 months of age at screening • ≥ 3 of the following at screening, in the opinion of the investigator: – hearing impairment – hepatomegaly (assessed by physical examination or prior imaging) – impaired physical performance – sleep disturbance – diarrhea
Enrollment in Part B will initially be limited to eligible siblings of participants in Part A, until Part A enrollment is complete
Key exclusion criteria
Homozygous or compound heterozygous SGSH p.S298P variant or other variant associated with an attenuated phenotype, or a sibling with the same SGSH genotype who has an attenuated phenotype
Other pathogenic/likely pathogenic variant (excluding SGSH variants) known to cause developmental delay or CNS disorders
History of HSCT, gene therapy, or any CNS-targeted MPS IIIA ERT or participated in any other investigational drug trial or taken any other investigational drug within 30 days of screening
Unable to walk or unable to take majority of nutrition orally
Additional criteria for **Part B only** • Have used (or intend to use) genistein or anakinra within 30 days of screening

Figure 3. Study design



[a]Dose escalations will occur after ≥ 6 doses at the planned dose level AND if the participant has had no moderate or severe IRRs for ≥ 2 consecutive doses immediately preceding the dose escalation.

Table 2. Primary, secondary, and safety endpoints

Endpoint	
Primary	Proportion of participants with a BSID-III cognitive raw score of ≥ 69 points at 54 months of age (Part A only)
	Proportion of participants with a BSID-III cognitive raw score of ≥ 69 points at 72 months of age (Part A only)
Secondary	Change from baseline in CSF HS concentration at Week 49 (Part A only)
	Change from baseline in CSF HS concentration at Week 25 (Part B only)
	Change from baseline in serum NfL concentration at Week 73 (Part A only)
	Response across the following domains at Week 25 (Part B only) • Hearing • Liver volume • Endurance • Sleep • Stooling
Safety	Incidence, severity, and seriousness of AEs
	Changes from baseline in safety laboratory values, vital sign measurements, ECG results, and physical and neurological examinations

ABBREVIATIONS

AE, adverse event; BBB, blood–brain barrier; BL, baseline; BSID-III, Bayley Scales of Infant and Toddler Development, Third edition; CNS, central nervous system; CSF, cerebrospinal fluid; ECG, electrocardiogram; ERT, enzyme replacement therapy; ETV, Enzyme TransportVehicle™; GM3, ganglioside; HS, heparan sulfate; HSCT, hematopoietic stem cell transplantation; IRR, infusion-related reaction; ITI, immune tolerance induction; IV, intravenously; MPS IIIA, mucopolysaccharidosis IIIA; NfL, neurofilament light chain; SGSH, N-sulfoglucosamine sulfohydrolase; TfR, transferrin receptor; TV, TransportVehicle™; W, Week.

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DISCLOSURES

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