P-029

Tividenofusp Alfa Treatment in a Male Sibling Pair with Non-Neuronopathic Mucopolysaccharidosis Type II

Irene J Chang,[1] Jacqueline Madden,[1] Annie Sako,[1] Jill Dwyer,[1] Daniel Fertek,[2] Adam Scheller,[2] Sharon O'Byrne,[2] Imanol Zubizarreta Arambarri,[2] Peter Chin,[2] Paul Harmatz[1]

[1]UCSF Benioff Children's Hospital, Oakland, CA, USA; [2]Denali Therapeutics Inc., South San Francisco, CA, USA

Introduction

- Tividenofusp alfa is a drug designed to cross the blood–brain barrier and treat both CNS and somatic manifestations of MPS II (Hunter syndrome)[1]
- We present data for a male sibling pair enrolled in the ongoing open-label Phase 1/2 study of tividenofusp alfa (NCT04251026), including standard-of-care follow-up data beyond the study protocol

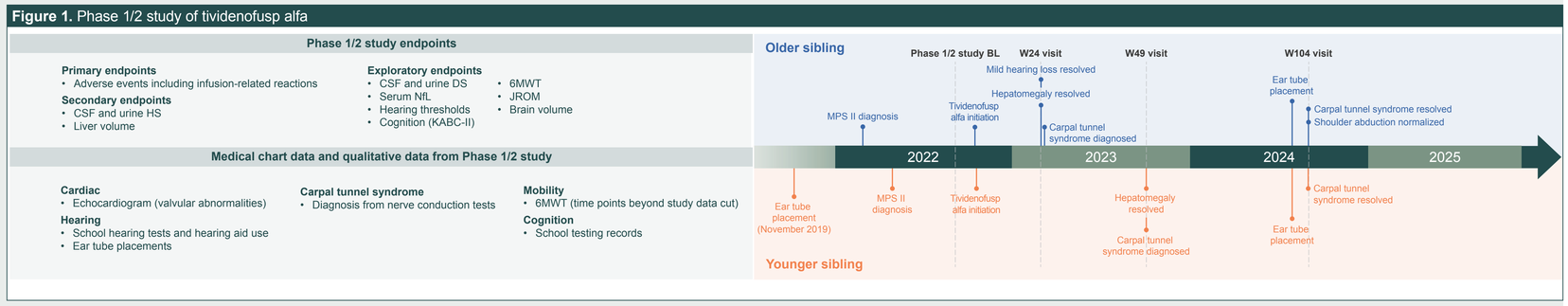
Conclusions

- Tividenofusp alfa treatment substantially reduced and normalized MPS II disease biomarkers and improved somatic manifestations in siblings with non-neuronopathic MPS II
- For cognition, KABC-II findings aligned with parent-reported academic and functional observations, supporting the interpretation of meaningful gains in cognitive abilities and processing
- Given the open-label nature of the study, the results presented here should be interpreted with caution. COMPASS, a Phase 2/3, multicenter, double-blind, randomized efficacy and safety study of tividenofusp alfa versus idursulfase in MPS II is ongoing (NCT05371613)

Phase 1/2 study participation

- Informed consent was obtained for male siblings with non-neuronopathic MPS II enrolled in the Phase 1/2 study of tividenofusp alfa (**Figure S1**)
  - In this study, 47 male participants with MPS II were enrolled into five cohorts (A–E) that differed in inclusion criteria for characteristics such as participant age and MPS II phenotype
  - Both siblings were enrolled in cohort D for individuals with preexisting hepatomegaly and initiated tividenofusp alfa 15 mg/kg weekly intravenously in September 2022
  - The younger sibling missed W24 assessments owing to illness not related to the study drug
- In addition to trial participation, the brothers were followed up as part of standard of care, and data beyond the study protocol are also presented in this poster (**Figure 1**)

Figure 1. Phase 1/2 study of tividenofusp alfa



Results

Medical history and Phase 1/2 study baseline

- Before enrollment in the Phase 1/2 study, the older brother initially presented with constipation and an abdominal X-ray revealed an enlarged liver. Orange peel rash was noted and subsequent genetic testing revealed a hemizygous missense variant in the *IDS* gene (**Table 1**)

Table 1. Phase 1/2 study baseline demographics and clinical characteristics

	Older sibling	Younger sibling
Age at diagnosis	6Y0M	3Y10M
Age at tividenofusp alfa initiation	6Y8M	4Y3M
Race and ethnicity	White, not Hispanic or Latino	White, not Hispanic or Latino
Genetic variant	c.1583A>T; p.(Asp528Val)	c.1583A>T; p.(Asp528Val)
Iduronate-2-sulfatase activity	< 1.5 nmol/h/mL	< 1.5 nmol/h/mL
Any prior therapy for MPS II	No	No
Composite cognitive DQ[a]	130.19	102.77
ADA and Nab status	Negative	Negative
Height	120.4 cm	108.7 cm
Weight	22.4 kg	19.8 kg
Physical exam	Orange peel rash on shoulders, mild coarse facial features, mild enlarged tongue, and very mild clawed hands (all clinically nonsignificant)	Very mild clawed hands (clinically nonsignificant)

[a]DQ was calculated as developmental age divided by chronologic age multiplied by 100; a score of 100 indicates age-expected development.

Biomarker assessments from Phase 1/2 study

HS and DS

- In both siblings, levels of CSF HS and DS, and urine HS and DS at study baseline were above the ULN. All levels normalized by W49 to within the range for children without MPS II and substantial reductions were maintained through W104
- For the older sibling (**Figure 2**):
  - CSF and urine HS were below the ULN at W24 and W21, respectively; CSF and urine DS were below the ULN at W49
  - At W24, CSF HS and DS had decreased from baseline by 80.5% and 65.2%, respectively; urine HS and DS had decreased by 95.8% and 97.6%, respectively
  - At W104, CSF HS and DS had decreased from baseline by 83.3% and 75.1%, respectively; urine HS and DS had decreased by 96.6% and 99.3%, respectively
- For the younger sibling (**Figure 2**):
  - W24 data are not available because the visit was missed. Urine HS and DS were below the ULN at W13; CSF HS and DS were below the ULN at W49
  - At W104, CSF HS and DS decreased from baseline by 82.0% and 87.8%, respectively; urine HS and DS decreased by 92.3% and 96.7%, respectively

Serum NfL

- Serum NfL, a marker of neuronal damage, was below the ULN at baseline and remained as such throughout the study for both siblings

Somatic manifestations

Liver

- Both siblings had hepatomegaly at the start of the Phase 1/2 trial, which normalized by W24 in the older sibling and W49 in the younger sibling (**Figure 1**)

Heart

- Echocardiogram results from medical records showed that neither sibling had any clear valvular abnormalities at baseline or throughout the study period

Hearing

- Pooled pure tone average data for both siblings from the Phase 1/2 trial are shown in **Figure 3**
- Medical records for the older sibling noted that mild hearing loss was diagnosed after failing school hearing tests. He received hearing aids, which he used for approximately 8 months
  - He stopped using hearing aids after the W24 study visit, when his mild hearing loss was considered resolved
- Both siblings' medical records noted that they received ear tube placements owing to recurrent ear infections and chronic middle ear effusion (older sibling, July 2024; younger sibling, November 2019 and July 2024)

Carpal tunnel syndrome

- Per medical records, mild carpal tunnel syndrome was diagnosed on the older sibling's right side (nerve conduction test, February 2023) and bilaterally in the younger sibling (nerve conduction test, August 2023). Follow-up testing in August 2024 showed their carpal tunnel syndrome to be resolved

Figure 2. Change from Phase 1/2 study BL in CSF HS and DS, and urine HS and DS

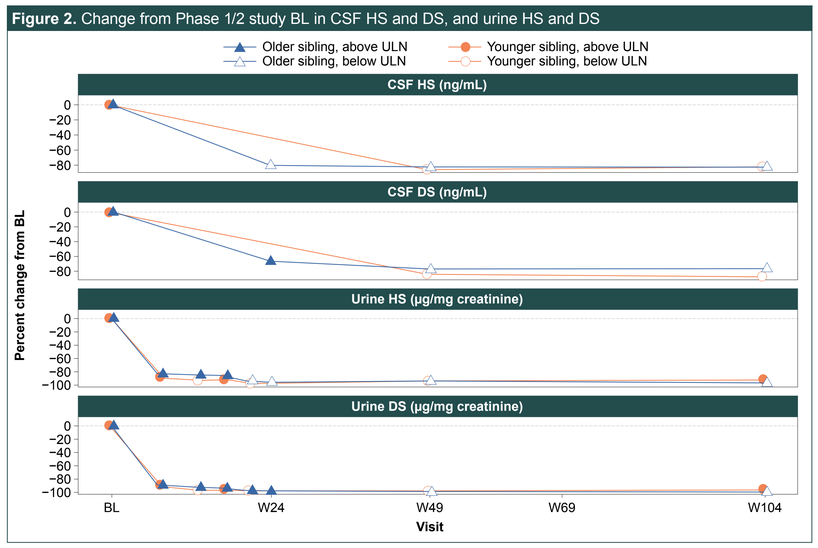
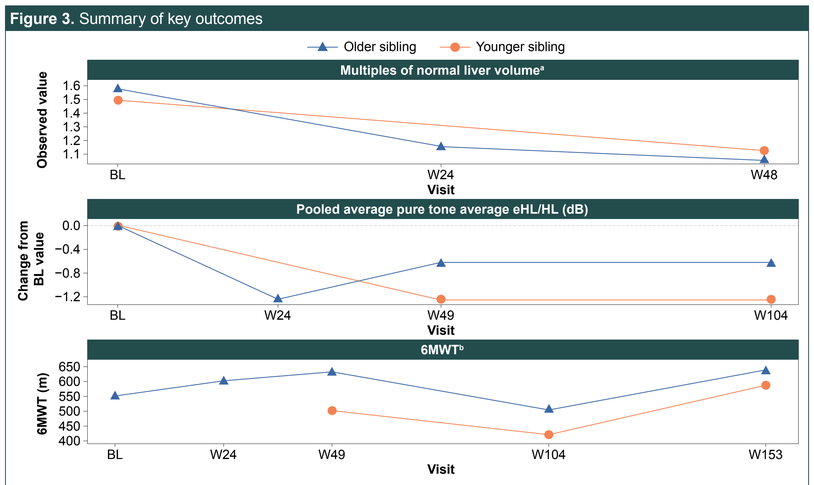


Figure 3. Summary of key outcomes



[a]Assessed by MRI. [b]The younger sibling was too young at BL to undertake the 6MWT. The W104 test was undertaken after lumbar puncture procedure; W153 data for 6MWT are provided from patient medical records because they occurred after the interim Phase 1/2 study data cutoff (October 2024).

Table 2. KABC-II analyses

	Subtest	Screening raw score (age 6Y7M)	W129 raw score (age 9Y1M)	Screening scaled score (age 6Y7M)[a]	W129 scaled score (age 9Y1M)[a]	Screening scaled score based on age 5Y norms[b]	W129 scaled score based on age 5Y norms[b]
Older sibling	**Conceptual thinking**	21	25	12	NA	15	17
	Face recognition	15	13	NA	NA	13	11
	Expressive vocabulary	29	35	14	16	16	19
	Triangles	25	36	15	17	17	19
	Pattern reasoning	NA	42	NA	15	NA	19
	Hand movements	10	14	12	12	15	19
	NVI[c]	–	–	122[d]	143[d]	141[d]	158
	Subtest	**Screening raw score (age 4Y3M)**	**W129 raw score (age 6Y9M)**	**Screening scaled score (age 4Y3M)[a]**	**W129 scaled score (age 6Y9M)[a]**	**Screening scaled score based on age 5Y norms[b]**	**W129 scaled score based on age 5Y norms[b]**
Younger sibling	**Conceptual thinking**	10	22	10	13	8	15
	Face recognition	11	16	10	NA	9	13
	Expressive vocabulary	20	31	11	15	10	18
	Triangles	11	26	10	16	8	18
	Pattern reasoning	NA	13	NA	11	NA	16
	Hand movements	5	11	10	12	9	16
	NVI[c]	–	–	102	122[d]	89[d]	146

[a]Based on age-appropriate norms, mean = 10, SD = 3. [b]Based on age 5Y norm set, mean = 10, SD = 3. [c]NVI normative population mean = 100, SD = 15. [d]Prorated per manual guidance.

Joint movement

- In the Phase 1/2 study W24 interview, their parents noted improvements in both children's wrists as they both wanted to play video games now and before they did not because their wrists hurt
- The older sibling had impaired shoulder abduction at Phase 1/2 study baseline (right side, 146°; left side, 156°), which normalized at W104 (both 180°)
- In study interviews, the parents noted the older sibling's continually improved performance on the monkey bars. Before initiating treatment, he could not hang on at all; at W24 he was able to do two bars, and at W49 he was able to do the full monkey bars
- The younger sibling had normal shoulder abduction at study baseline, which remained stable through W104

Mobility and endurance

- The Phase 1/2 study care team noted gains in strength and mobility in both siblings, which enabled them to carry their own backpacks while hiking on family trips
  - At Phase 1/2 study baseline, the older sibling reached 552 m on the 6MWT (the younger sibling was too young at baseline to undertake the 6MWT) (**Figure 3**)
  - At their most recent 6MWT (August 2025; medical records), the older sibling and younger sibling reached 639 m and 589 m, respectively
  - These distances are within the typical ranges expected for boys of their respective ages[2]

Growth

- Both siblings followed typical height and weight trajectories expected for their ages, with the most recent height measurements for the older sibling and younger sibling around the 50th and 90th percentiles, respectively

Scan the QR code for participant videos and photos

CNS manifestations

Cognition

- Select KABC-II subtest scores increased for both siblings from screening to W129 (**Table 2**)
- At screening, estimated NVI scores were 122 (older sibling; above average) and 102 (younger sibling; average)
- By W129, both siblings demonstrated notable KABC-II gains
  - Older sibling: NVI score increased from 122 at screening to 143 at W129
  - Younger sibling: NVI score increased from 102 at screening to 122 at W129
- At W129, processing and cognitive abilities were in the above average to upper extreme ranges for their ages
- Standard score gains indicate cognitive development exceeding age-matched KABC-II NU norms
- Using age-constant norms, the younger sibling showed a faster rate of growth
  - Older sibling: age-constant score increased from 141 to 158
  - Younger sibling: age-constant score increased from 89 to 146
- KABC-II improvements were consistent with parent-reported academic and functional gains, supporting clinically meaningful cognitive change

Brain

- Both siblings had unchanged prominent perivascular spaces in the periventricular white matter throughout the Phase 1/2 study based on brain MRI

Safety

- Both siblings experienced mild-to-moderate infusion-related reaction TEAEs, which were managed with standard medications and reduced over time. Both maintained long-term dosing of tividenofusp alfa 15 mg/kg
- The younger sibling experienced two mild anemia-related TEAEs

ABBREVIATIONS

6MWT, 6-minute walk test; ADA, antidrug antibody; BL, baseline; CNS, central nervous system; CSF, cerebrospinal fluid; dB, decibels; DQ, developmental quotient; DS, dermatan sulfate; eHL, estimated hearing level: HL, hearing level; HS, heparan sulfate; *IDS*, gene encoding iduronate-2-sulfatase; JROM, joint range of motion; KABC-II, Kaufman Assessment Battery for Children, Second Edition; M, months; MPS II, mucopolysaccharidosis type II; MRI, magnetic resonance imaging; NA, not administered; Nab, neutralizing antibody; NfL, neurofilament light chain; NU, normative update; NVI, nonverbal index; SD, standard deviation; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; W, week; Y, years.

REFERENCES

1. Muenzer J *et al. N Engl J Med* 2026;394:39–50.
2. Cacau LAP *et al. Braz J Cardiovasc Surg* 2016;31:381–8.

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DISCLOSURES

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