Interim Analysis of Key Clinical Outcomes From a Phase 1/2 Study of Weekly Intravenous DNL310 (Brain-Penetrant Enzyme Replacement Therapy) in MPS II

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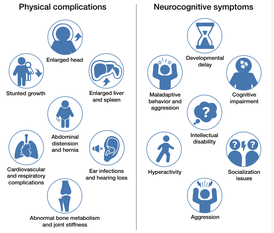
BACKGROUND

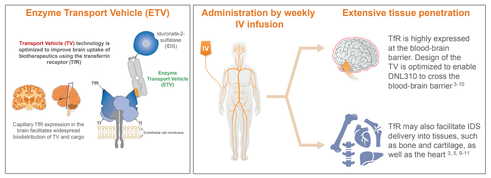
- Mucopolysaccharidosis type II (MPS II; Hunter Syndrome) is a rare inherited lysosomal storage disorder caused by iduronate-2-sulfatase (IDS) deficiency[1,2]
- A hallmark of the disease is accumulation of the glycosaminoglycans (GAGs): heparan and dermatan sulfate (HS and DS)[1,2]
- Multiple tissues and organs are affected, and two-thirds have a severe neuronopathic form (**Figure 1**)[1,2]
- Current standard of care is a weekly intravenous (IV) infusion of a recombinant form of IDS, which cannot cross the blood-brain barrier and has no clear effect on neurodevelopment[1,2]
- Brain delivery is a critical unmet need in the treatment of MPS II
- DNL310 (enzyme transport vehicle [ETV];IDS) is an investigational IDS fusion protein designed to treat both the brain and physical manifestations of MPS II (**Figure 2**)

Figure 1. Physical Complications and Neurocognitive Symptoms of MPS II (Hunter Syndrome)



MPS II, mucopolysaccharidosis type II.

Figure 2. DNL310 Is Engineered to Cross the Blood-Brain Barrier and Address the Treatment Challenge Associated With MPS II



OBJECTIVE

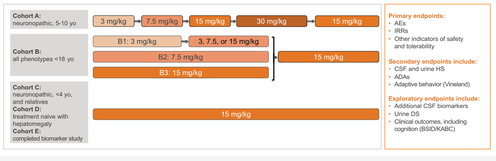
- To report interim safety and efficacy data for DNL310 treatment in participants with MPS II in the phase 1/2 study

METHODS

Ongoing DNL310 Phase 1/2 Study in Pediatric Participants With MPS II (NCT04251026)

- The DNL310 phase 1/2 trial is an open-label, 24-week study followed by an open-label extension (**Figure 3**)
- Approximately 45 participants ≤18 years of age with MPS II are enrolling into 5 cohorts (A-E); treatment-naive and -experienced participants are eligible
- Differences between the cohorts include age, phenotype, and dose levels
- Participants receiving IDS at baseline switch to DNL310 without a washout period

Figure 3. Overview of the Study Design of the DNL310 Phase 1/2 Study



ADA, anti-drug antibodies; AE, adverse event; BSID, Bayley Scales of Infant Development; CSF, cerebrospinal fluid; DS, dermatan sulfate; HS, heparan sulfate; IDS, iduronate-2-sulfatase; IRR, infusion-related reaction; KABC, Kaufman Assessment Battery for Children; yo, years old.

RESULTS

Participants

Table 1. Participant Populations From the DNL310 Phase 1/2 Study Interim Analysis[a]

	No. of Participants at Study Week[a]				
	1	24	49	73	104
Safety population: participants who received ≥1 dose of DNL310	28	26	20	17[b]	4
Clinical outcomes population: participants with expected data, from cohorts that have completed ≥49 weeks (ie, cohorts A and B)	23	22	20	17	4
Biomarker population: participants with available CSF or urine samples (CSF collection once per year after first year)[c]	27	25	20	0	4

CSF, cerebrospinal fluid. Clinical cutoff date (CCOD) of September 1, 2022.
[a] 3 participants discontinued; 1 each at weeks 20, 31, and 92. [b] One participant with 71 weeks of exposure data was included as this participant had their week 73 outcome assessment.
[c] At 104 weeks, 1 participant with data post CCOD was included.

Table 2. Baseline Demographics and Disease Characteristics of Participants in the DNL310 Phase 1/2 Study

	Cohorts A-E (safety population) n=28	Cohorts A and B (clinical outcomes population) n=23		Cohorts A-E (safety population) n=28	Cohorts A and B (clinical outcomes population) n=23
Neuronopathic, n (%)	27 (96)	22 (96)	**Race, n (%)**		
Non-neuronopathic, n (%)	1 (4)	1 (4)	Asian	3 (11)	3 (13)
Age, median (range), years	5 (2-12)	6 (2-12)	Black or African American	2 (7)	2 (9)
Pre-study enzyme replacement			White	15 (54)	12 (52)
Participants with pre-study IDS, n (%)	25 (89)	23 (100)	Race not reported, unknown, or other	8 (29)	6 (26)
Duration of IDS treatment, median (range), years	2.1 (0.4-11.2)	2.3 (0.4-11.2)	**Ethnicity, n (%)**		
Pre-study treatment naive, n (%)	3 (11)	0	Hispanic or Latino	5 (18)	5 (22)
Participants per age group, n (%)			Not Hispanic or Latino or not reported/unknown	23 (82)	18 (78)
2 to <4 years	8 (29)	5 (22)			
4 to <8 years	14 (50)	12 (52)			
≥8 years	6 (21)	6 (26)			

IDS, iduronate-2-sulfatase.

Interim Safety Overview

- Interim safety results from the phase 1/2 study were consistent with those previously reported for DNL310 and with standard-of-care enzyme replacement therapies (ERTs)[12,13]
- Independent Data Monitoring Committee recommended continuing study without modifications (October 2022; clinical cutoff date: July 12, 2022)
- Cumulative information, including previously reported:[12,13]

Treatment-emergent adverse events (TEAEs)

- All participants reported TEAEs, which were mostly mild or moderate
- There were no dose-related safety findings
- Infusion-related reactions (IRRs) were the most frequent TEAEs
- Adverse events of special interest (AESIs) were as follows:
  - 15 participants experienced moderate, and 1 participant experienced severe IRRs
  - 3 participants (all with mild baseline anemia or a history of anemia) had moderate anemia (1 resolved, 1 stable, and 1 resolving); dosing continued in all 3 cases
- One discontinuation related to TEAEs (including IRRs and other non-drug–related AEs) was observed in a participant with complex underlying disease; 2 other discontinuations occurred due to social reasons (family circumstances, relocation)

Serious adverse events (SAEs)

- SAEs were reported in 7 participants; of these, 2 had IRRs, and 5 participants had SAEs unrelated (per the investigators) to study drug or procedures (including constipation, upper respiratory tract infection, progressive cervical stenosis/thoracic syrinx, increased episodes of apnea, vomiting, and diarrhea)

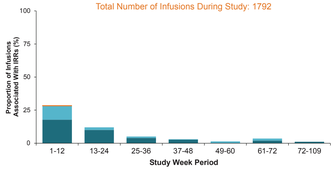
Safety laboratory measurements

- Prior to treatment, 11 participants had elevated total urine GAGS (colorimetric assay); all normalized after receiving DNL310
- There were no other notable abnormalities or trends in safety laboratory evaluations post initiation of DNL310 treatment

Infusion-Related Reactions

- Tolerance to DNL310 occurred with longer-term dosing (**Figure 4**)

Figure 4. IRRs

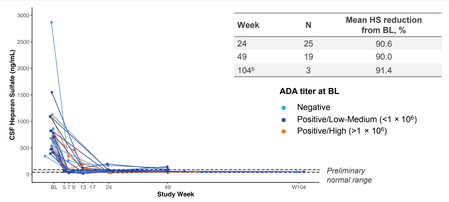


IRR, infusion-related reaction.

Biomarkers

- For assessment of urine HS and DS in the DNL310 phase 1/2 study, please refer to Bhalla et al, Poster 48
- The safety profile enabled achievement of healthy, normal levels of CSF HS, sustained over time, including in those with high pre-existing anti-drug antibody (ADA) titers (**Figure 5**)

Figure 5. CSF HS Biomarkers[a]



Week	N	Mean HS reduction from BL, %
24	25	90.6
49	19	90.0
104[b]	3	91.4

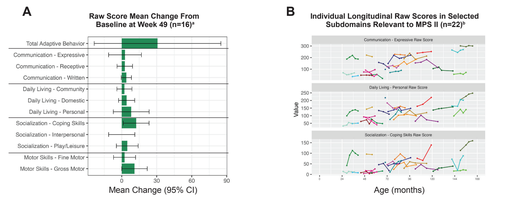
ADA titer at BL
- Negative
- Positive/Low-Medium (<1 × 10⁶)
- Positive/High (>1 × 10⁶)

ADA, anti-drug antibody; BL, baseline; CSF, cerebrospinal fluid; GAG, glycosaminoglycan; HS, heparan sulfate; W, week.
[a] Preliminary normal range (10th and 90th percentile) determined using 30 healthy adult CSF samples (age range, 18-81 years; median, 52 years). Total CSF GAG levels were similar in adults and children.[14] Normal range for CSF HS, 39.1-92.51 ng/mL. HS was measured as a sum of the disaccharides D0A0, D0A6, D0S0, D2S6. [b] Data for 1 week 104 time point was collected post clinical cutoff date.

Clinical Outcomes

- Over 49 weeks, mean Vineland Adaptive Behavior Scales-II (VABS-II) raw scores increased across subdomains, including those most relevant to MPS II families, reflecting adaptive behavior skill gain (**Figure 6**)

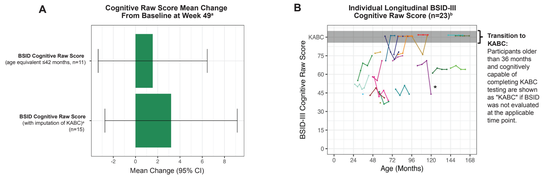
Figure 6. VABS-II Assessment



MPS II, mucopolysaccharidosis type II; VABS-II, Vineland Adaptive Behavior Scales II.
[a] Data from 4 participants either unavailable (n=1) or only VABS-3 collected (n=3) at week 49. The Total Adaptive Behavior raw score derives from all Communication, Daily Living, and Socialization subdomains except for Communication-Written, Daily Living-Domestic, and Daily Living-Community. [b] Data shown extend to 104 weeks post baseline.

- Over 49 weeks, mean Bayley Scales of Infant Development-III (BSID-III) cognitive raw scores increased and were larger in magnitude when accounting for participants cognitively capable of completing the Kaufman Assessment Battery for Children (**Figure 7**)

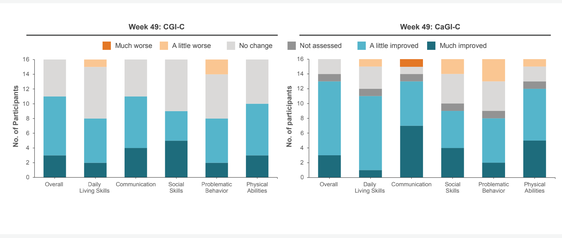
Figure 7. BSID-III Assessment



BSID-III; Bayley Scales of Infant Development-III; KABC, Kaufman Assessment Battery for Children.
[a] Imputed KABC scores used maximum BSID score of 91. Participants with imputed values at both baseline and week 49 (n=3) were not included in the mean change (would be uninformative); 2 participants expected to have data did not complete either cognitive assessment at Week 49. [b] Data shown extend to 104 weeks post-baseline. [c] Participant missed 44% of weekly infusions between last 2 time points.

- Most participants demonstrated stabilization or improvement across all domains in global impression scales; most had improvement in overall MPS II symptoms (**Figure 8**)

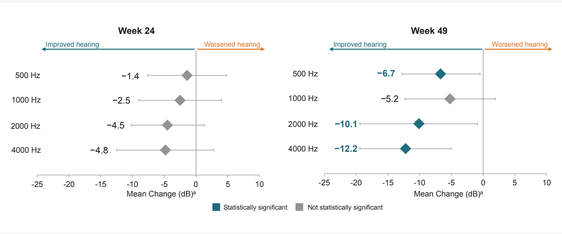
Figure 8. Clinician and Caregiver Global Impression Scales of Change[a]



CGI-C, Clinical Global Impression of Change; CaGI-C, Caregiver Global Impression of Change.
[a] CGI/CaGI-C version 3; graph does not include 4 participants assessed using version 2; a subset (n=12) was previously presented at SSIEM 2022.[15]

- Hearing, as assessed by Auditory Brainstem Response (ABR), improved after initiation of DNL310 (**Figure 9**)
- ABR thresholds improved across all frequencies; improvements tended to be greater at higher frequencies

Figure 9. Change in Estimated Hearing Loss (ABR Testing)



ABR, Auditory Brainstem Response; ERT, enzyme replacement therapy.
[a] Results are based on air conduction tests. Least squares mean (95% CI), adjusted for age at ERT initiation. n=18 to 23 participants (varies by frequency).

SUMMARY OF INTERIM RESULTS

Clinical Safety
- Interim safety profile was consistent with other ERTs
- IRRs accounted for the most frequent TEAEs and decreased in frequency and severity with continued dosing

Biomarkers
- Rapid normalization or near normalization of CSF HS was observed in all participants, sustained at week 49, and remained normal in the 3 participants tested at week 104
- Normalization of CSF HS was observed even in participants with high pre-existing ADA

Clinical Outcomes
- Interim clinical outcomes data, including VABS-II and BSID raw scores and global impression scales, suggest positive change with DNL310 treatment
- ABR data suggested that DNL310 treatment improves auditory function

CONCLUSIONS

- DNL310 is a novel investigational brain-penetrant ERT intended to treat both brain and physical manifestations of MPS II
- A potentially registrational Phase 2/3 study with sites in North America, South America, and Europe is enrolling (NCT05371613)

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