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Preliminary Results from Phase 1/2, First-in-Human, Open-Label Study of DNL126 in Children with Mucopolysaccharidosis IIIA (MPS IIIA)

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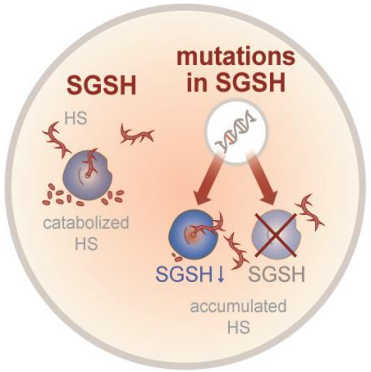
MPS IIIA Pathogenesis, Biomarkers, and Clinical Manifestations

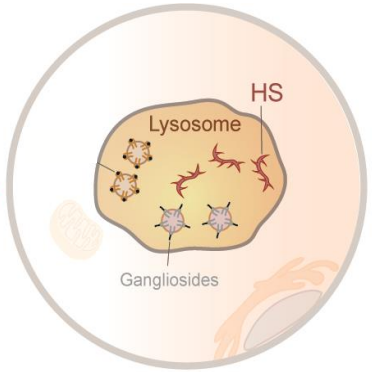
TARGET → **PATHWAY** → **CLINICAL**

Genetic deficiency in SGSH enzyme activity



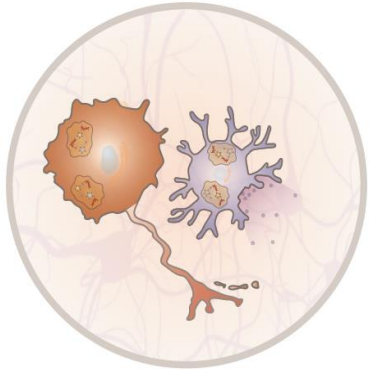
Accumulation of heparan sulfate

Lysosomal dysfunction

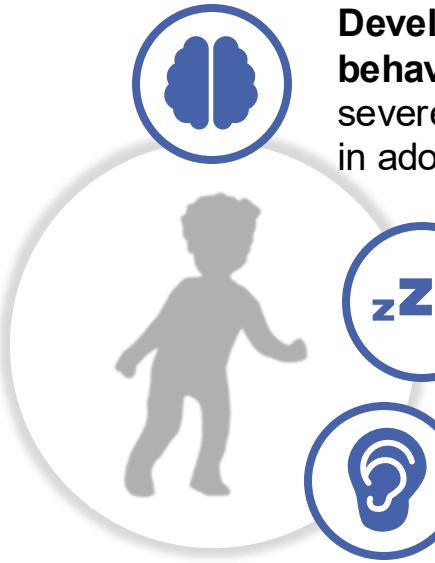


Accumulation of lysosomal lipids (e.g., GM3)

Neurodegeneration



Elevated biomarkers of neurodegeneration and neuroinflammation (e.g., NfL)



Developmental delay and behavior problems, progressing to severe cognitive decline, and death in adolescence[1–4]

Impaired sleep[5]

Impaired hearing[5]

Somatic manifestations including diarrhea, hepatomegaly, and joint stiffness[3,6,7]

Currently, there are no approved therapies for MPS IIIA, representing a high unmet medical need

GM3, ganglioside monosialic 3; HS, heparan sulfate; MPS IIIA, mucopolysaccharidosis type IIIA; NfL, neurofilament light chain; SGSH, sulfoglucosamine sulfohydrolase.

1. Lavery C *et al. Orphanet J Rare Dis* 2017;12:168; 2. Harmatz P *et al. Mol Genet Metab* 2022;136:249–59; 3. Shapiro EG *et al. Mol Genet Metab* 2017;122S:1–7; 4. Wijburg FA *et al. Acta Paediatr* 2013;102:462–70; 5. Buhrman D *et al. J Inherit Metab Dis* 2014;37:431–7; 6. Heon-Roberts R *et al. J Clin Med* 2020;9:344; 7. Muschol N *et al. Orphanet J Rare Dis* 2022;17:391.

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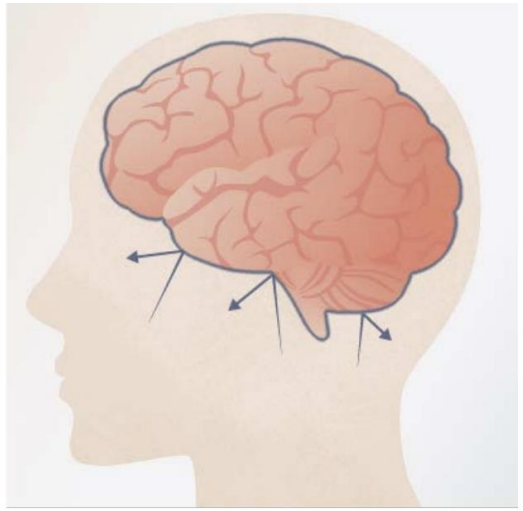
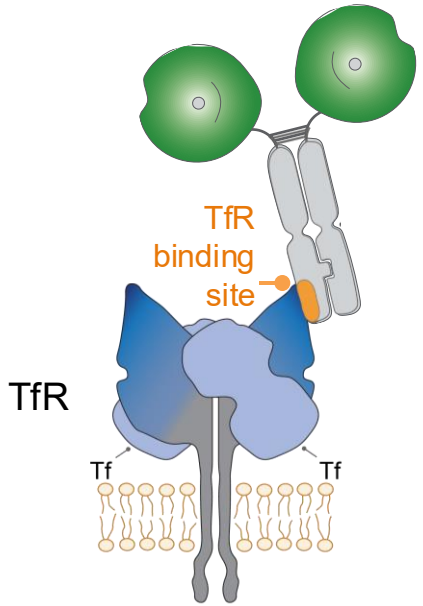
Our Approach to Enzyme Replacement Therapy

THE BBB CHALLENGE



- The BBB is a major obstacle for brain delivery of enzymes

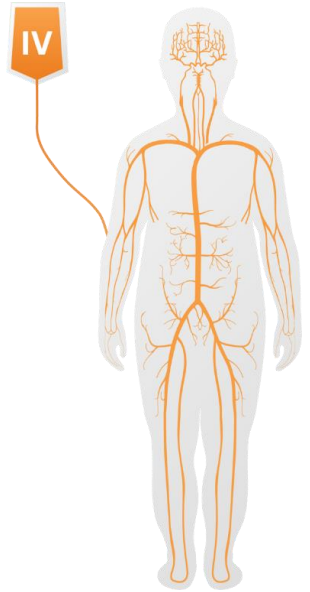
DNL126



DNL126 (ETV:SGSH)

- DNL126 is designed to use the TfR to cross the BBB and enhance delivery of biotherapeutics into the brain
- The TfR is the body's mechanism for iron transport from blood into brain and is highly expressed at the BBB

IV ADMINISTRATION AND BROAD BIODISTRIBUTION



- Design of DNL126 is optimized to enable it to cross the BBB and may also facilitate uptake into peripheral tissues

DNL126 is an investigational ERT for MPS IIIA engineered to be brain penetrant and administered by IV infusion

BBB, blood–brain barrier; ERT, enzyme replacement therapy; IV, intravenous; Tf, transferrin; TfR, transferrin receptor.

Jefferies WA *et al.* 1984; Qian ZM *et al.* 2002; Bakardjiev AI, 2021; Arguello A *et al.* 2021; Arguello A, Mahon CS *et al.* 2022; Ullman JC *et al.* 2020; Wang S *et al.* 2020; Gammella E *et al.* 2017; Carlevaro MF, *et al.* 1997.

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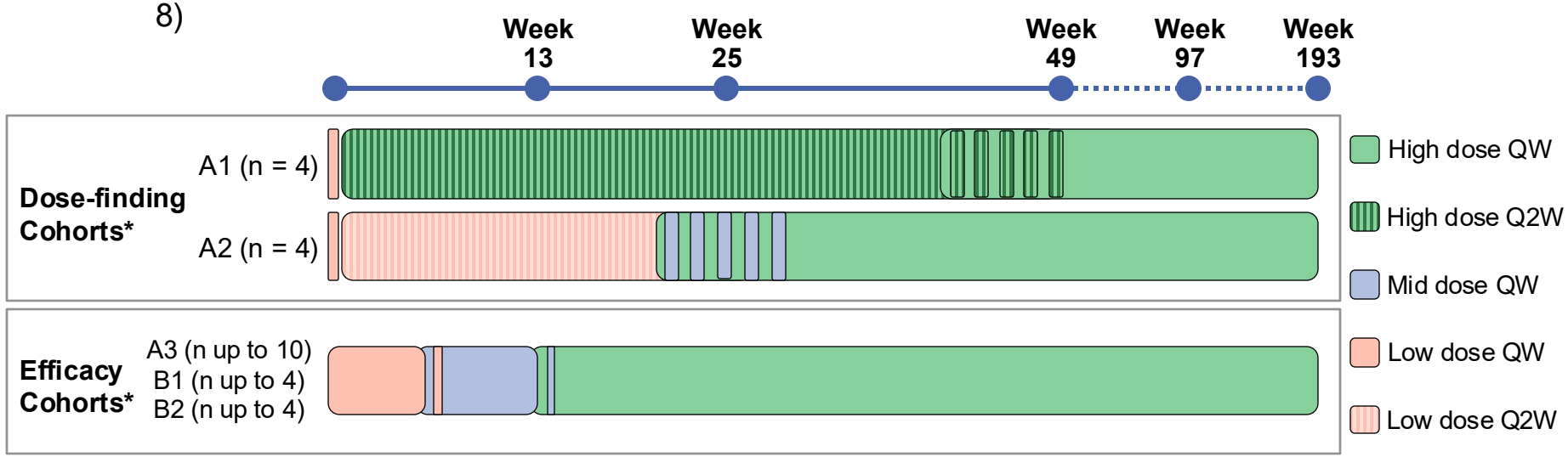
DNL126 Phase 1/2 Study in Pediatric Participants with MPS IIIA

- Study DNLI-I-0001 is a multicenter, open-label, 25-week study followed by an open-label extension period through 193 weeks (NCT06181136) in up to 26 pediatric participants with MPS IIIA in up to 5 cohorts
- Preliminary data through cut-off date of June 4, 2025
  - **Safety Outcomes:** Dose-finding and efficacy cohorts (n = 14)
  - **Efficacy Outcomes:** Dose-finding cohorts only; at Week 49, dose finding cohorts were receiving the high dose either QW or Q2W (n = 8)



Cohort A1–A3: children with severe and attenuated phenotypes aged ≥ 2 to < 18 years

Cohort B1: children < 28 months of age with a predicted severe phenotype

Cohort B2: siblings of children in Cohort B1

Primary Endpoint

- Percent change from baseline in CSF HS at W49 *(efficacy cohorts only)*

Secondary Endpoints

- Percent change from baseline in urine HS at W49
- Change from baseline in liver volume at W49
- Percent change from baseline in serum NfL at W73
- Participants with CSF HS in normal range at W49 *(efficacy cohorts only)*

Study enrollment (n = 20) completed in September 2025

*Intraparticipant dose escalation occurred at varying times.

CSF, cerebrospinal fluid; QW, once weekly; Q2W, once every 2 weeks; W, week.

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All Cohorts: Participant Demographics and Characteristics

	Dose-finding cohorts		Efficacy cohorts*		
	Cohort A1 (n = 4)	Cohort A2 (n = 4)	Cohort A3 (n = 4)	Cohort B1 (n = 2)	All cohorts (n = 14)
DNL126 treatment duration					
Completed up to Week 25	4 (100.0%)	4 (100.0%)	4 (100.0%)	1 (50.0%)	13 (92.9%)
Completed up to Week 49	4 (100.0%)	4 (100.0%)	0 (0.0%)	0 (0.0%)	8 (57.1%)
Age at screening (months)					
Median	47.0	57.5	51.5	27.0	49.0
Min – Max	36.0 – 55.0	51.0 – 78.0	33.0 – 87.0	27.0 – 27.0	27.0 – 87.0
Sex					
Female	2 (50%)	4 (100%)	3 (75%)	0	9 (64.3%)
Male	2 (50%)	0	1 (25%)	2 (100%)	5 (35.7%)
Race					
White	4 (100%)	4 (100%)	4 (100%)	2 (100%)	14 (100%)
Ethnicity					
Hispanic or Latino	0	1 (25%)	0	0	1 (7.1%)
p.S298P heterozygous	1 (25%)	1 (25%)	1 (25%)	0	3 (21.4%)

Study population includes a broad spectrum of pediatric ages and genotypes

*No participants were enrolled in Cohort B2.

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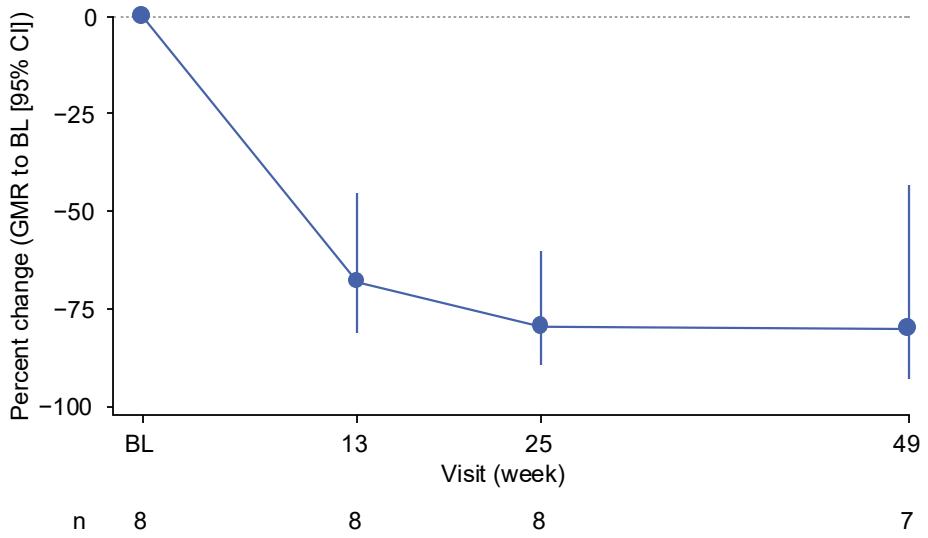
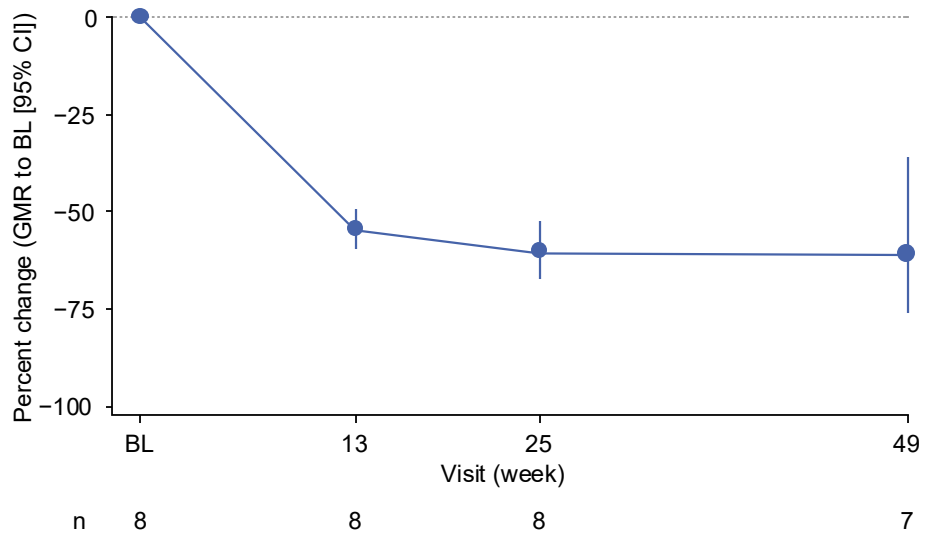
Preliminary Data Phase 1 Dose-finding Cohorts (A1 and A2)

CNS Biomarkers: CSF Heparan Sulfate and GM3

CSF HS



CSF GM3



In Cohorts A1 and A2 at Week 49:

Mean reduction of 80% in CSF HS with 3 of 7* participants within normal range**

Mean reduction of 61% in GM3 with 6 of 7* participants within normal range***

*n = 7 at Week 49 as one participant had lumbar puncture performed early at Week 37. **Age-based biomarker reference ranges were established based on CSF samples from 67 individuals without MPS IIIA (median [min, max] age: 8.88 [0.06, 25.3] years). ***Age-based biomarker reference ranges were established based on GM3 samples from 70 individuals without MPS IIIA (median [min, max] age: 8.77 [0.06, 25.3] years).

BL, baseline; CI, confidence interval; CNS, central nervous system; GMR, geometric mean ratio.

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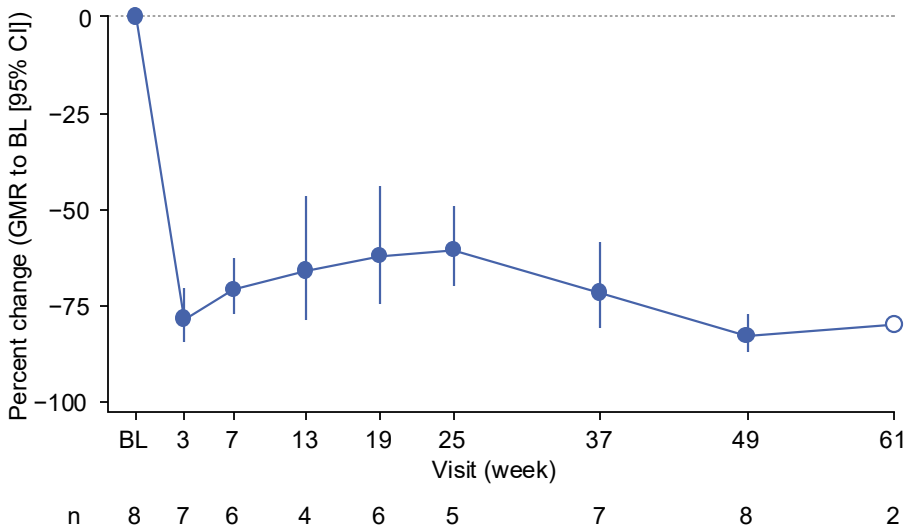
Preliminary Data Phase 1 Dose-finding Cohorts (A1 and A2)

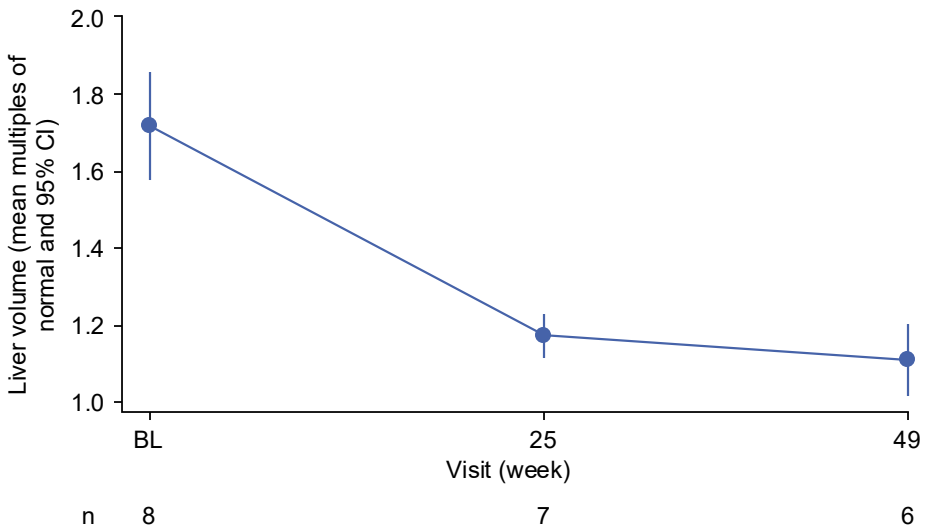
Peripheral Measures: Urine HS and Liver Volume

Urine HS



- Substantial reduction observed by Week 3
  - Variability in response beyond Week 3 due to intra participant differences in dose frequency and dose escalation

Liver volume



- Mean liver volumes 1.72 times normal at baseline
- At Week 49, mean reduction of 0.6 (SD: 0.14) in liver volume multiples of normal

In Cohorts A1 and A2 at Week 49:

Mean reduction of 83% in urine HS, 0 of 8 participants within normal range*

Mild hepatomegaly improved by Week 25; 6 of 6 participants within normal range**

Open circles represent timepoints with less than three samples. MRI, magnetic resonance imaging; SD, standard deviation.

* ULN ranges were determined as the 97.5th percentile using urine samples from 149 pediatric individuals without MPS IIIA (median [min, max] age: 4.93 [0.05, 17.2] years). **One participant had MRI performed outside of Week 49 analysis window, and one did not have data available at time of data cut. Values less than the upper bound of the 95% prediction interval for liver volume based on weight and height are defined as normal (Herden U *et al. Transpl Int* 2013;26:1217–24).

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All Cohorts: Safety Overview

- All participants (n = 14) experienced a TEAE assessed by the investigator as related to the study intervention
- The majority of participants experienced TEAEs with a maximum severity of Grade 1 or Grade 2
  - There were no Grade 4 or Grade 5 TEAEs
- Serious TEAEs were reported in 4 (28.6%) participants; none were considered treatment-related
- IRRs were common and reported in all participants
- There were no deaths or TEAEs that led to early discontinuation from the study intervention or the study

TEAEs reported in >30% of participants

Preferred term	All cohorts (n = 14) [n (%)]
Infusion-related reaction	14 (100)
Upper respiratory infection	9 (64.3)
Vomiting	9 (64.3)
Nasal congestion	7 (50.0)
Cough	6 (42.9)
Diarrhea	5 (35.7)
Ear infection	5 (35.7)
Fall	5 (35.7)
Gastroenteritis	5 (35.7)
Irritability	5 (35.7)

Preliminary data demonstrate that the safety profile of DNL126 in children with MPS IIIA was generally consistent with established enzyme replacement therapies

AESI, adverse event of special interest; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.

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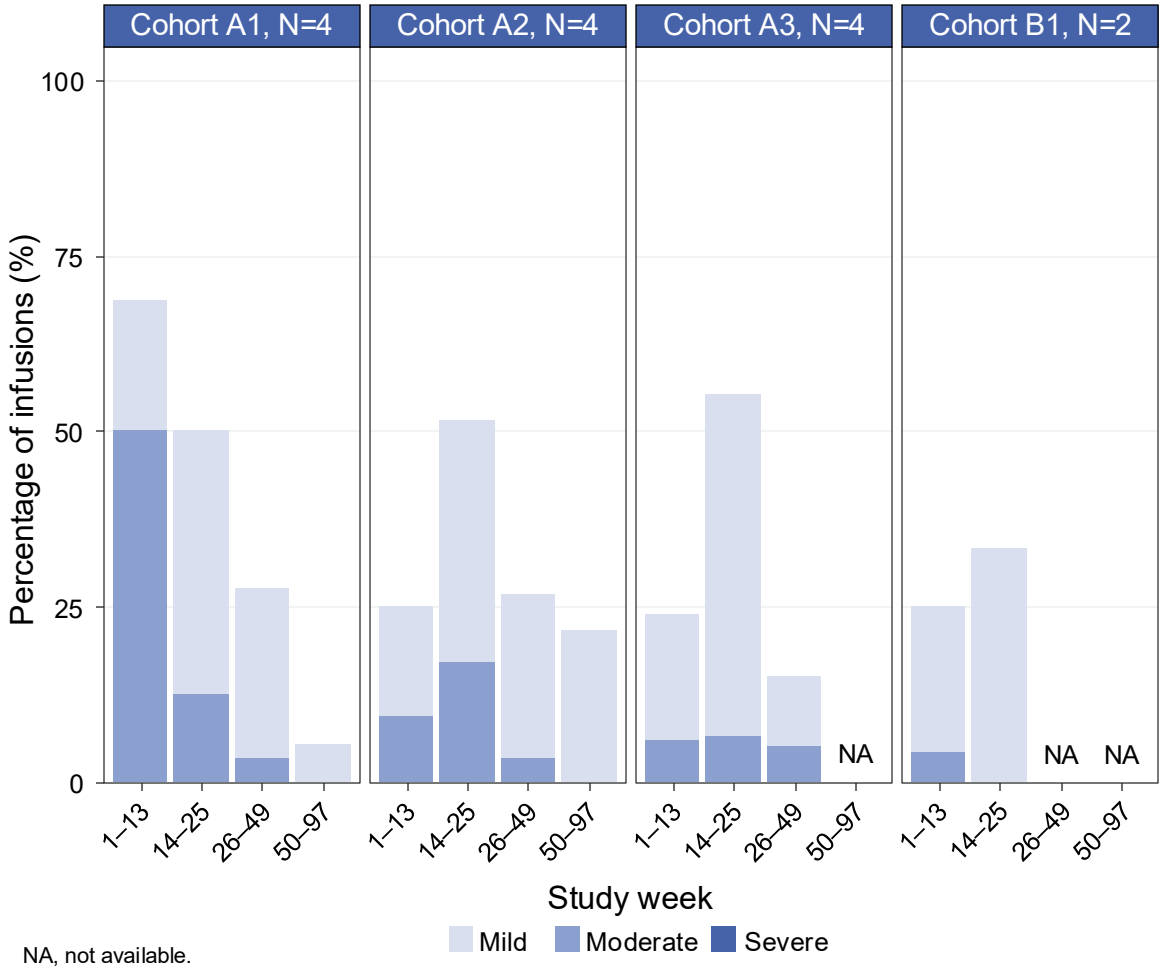
All Cohorts: Infusion-related Reactions

Infusion-related reactions by cohort and study week



- IRR frequency and/or severity decreased after Week 25 in all cohorts (limited data available for Cohorts A3 and B1)
- Reduced IRR severity and/or frequency through Week 25 were observed in cohorts utilizing gradual dose escalation (Cohorts A2, A3 and B1)
- IRRs were manageable with premedications, infusion-rate adjustments, and/or infusion interruptions
  - Slow graduated rates adapted from Castells (2008) were utilized to prevent further IRRs in one participant

NA, not available.

The denominator for the interval is based on the total number of infusions administered during the interval, and the numerator represents the total number of infusions with an IRR during the interval, in which only the most severe one per dosing visit, per participant is counted. As of the data cut date, no Cohort A3 participants had reached Week 50 and no Cohort B1 participants had reached Week 26.

Castells MC et.al. *J Allergy Clin Immunol* 2008;122:574-80.

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Conclusions

Preliminary results from dose-finding cohorts demonstrate that 49 weeks of DNL126 treatment resulted in substantial reductions in CSF and peripheral biomarkers, with some participants achieving normalization

- CSF HS: 80% mean reduction at Week 49, with normalization in 3 of 7 participants
- CSF GM3: 61% mean reduction at Week 49, with normalization in 6 of 7 participants
- Urine HS: 83% mean reduction at Week 49, no participants within normal range
- Improvement in mild hepatomegaly observed as early as Week 25, with normalization in 6 of 6 participants at Week 49

Preliminary safety data in pediatric participants with MPS IIIA treated with DNL126 were generally consistent with established ERTs

- All participants experienced TEAEs; the majority of TEAEs were mild or moderate in severity
- No treatment-related serious TEAEs, treatment discontinuations or study discontinuations were reported
- Frequently reported TEAEs included IRRs, upper respiratory infection, vomiting, nasal congestion, and cough
- IRRs were manageable and decreased in frequency and severity over time
  - Reduced IRR severity and/or frequency was observed in cohorts utilizing gradual dose escalation

Preliminary results support continued evaluation of DNL126 in the ongoing efficacy cohorts

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Acknowledgements

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Thank you for your attention

DNL126 is an investigational drug and has not been approved by any health authority

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Thank You