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Infusion rate adjustment in enzyme replacement therapy with pabinafusp alfa for mucopolysaccharidosis II

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INTRODUCTION

- Mucopolysaccharidosis II (MPS II; Hunter syndrome) is a rare genetic lysosomal storage disorder caused by a deficiency of the enzyme iduronate-2-sulfatase (IDS), leading to an accumulation of the glycosaminoglycans (GAGs) heparan sulfate (HS) and dermatan sulfate (DS).[1-3]
- Patients with MPS II often experience progressive central nervous system (CNS) involvement along with somatic symptoms.[4]
- Current enzyme replacement therapy (ERT) targets only somatic symptoms as it cannot cross the blood-brain barrier (BBB) to reach the CNS. Pabinafusp alfa (JR-141) is a novel ERT that can penetrate the BBB, which allows it to target both CNS and somatic symptoms.[5-6]
- Pabinafusp alfa was approved for clinical use in Japan in 2021 and is being further studied in an ongoing global phase III clinical trial (NCT04573023) and its extension study (NCT05594992).
- ERT requires long-term weekly intravenous infusions, often lasting over 3 hours. These infusions pose significant challenges in pediatric clinical practice and can lead to frequent, extended hospital visits that may adversely affect the quality of life of patients and their caregivers and undermine long-term treatment compliance.[7,8]
- Strategies such as shortening infusion time may help manage these challenges; however, modifying infusion parameters could possibly impact enzyme pharmacodynamics and compromise the safety or efficacy of ERT.[9]

OBJECTIVE

- This interim analysis was designed to assess if a shorter infusion duration impacts the long-term efficacy and safety of ERT with pabinafusp alfa in patients with MPS II.

METHODS

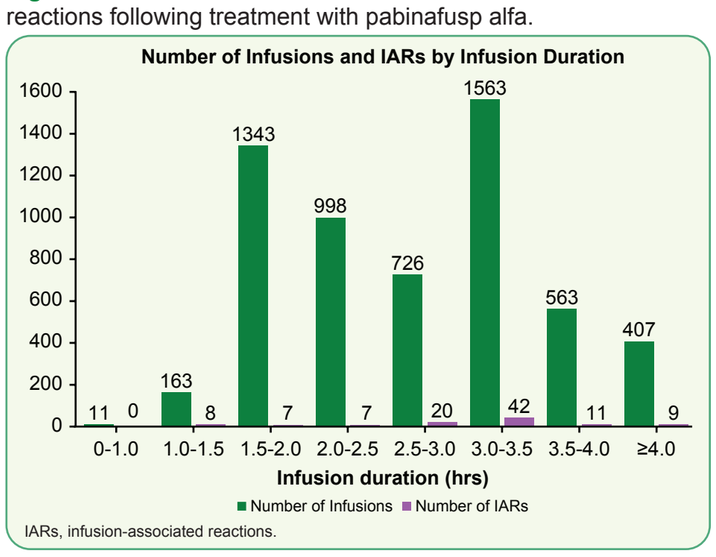
- An interim analysis, with last patient assessment on 24 January 2024, was conducted incorporating 260 weeks of clinical data from 27 Japanese patients with MPS II who received pabinafusp alfa at a dose of 2.0 mg/kg/week during a phase II/III trial (NCT03568175) and its subsequent extension study (NCT04348136).
- From Week 53 onward, following enrollment in the extension phase, infusion rates were allowed to be adjusted on an individual basis per discretion of investigator.
- Patients were categorized by infusion speed as follows:
  - **Fast** (n = 18): **≥66%** of pabinafusp alfa infusions during the extension period were administered at a rate of >33 mL/h (infusion duration predominantly **<3 hours**)
    - In 14/18 subjects, ≥90% of infusions were administered at a rate of >33 mL/h
  - **Slow** (n = 9): **<66%** of pabinafusp alfa infusions during the extension period were administered at a rate of >33 mL/h (infusion duration predominantly **>3 hours**)
- Safety was assessed by measuring the incidence of adverse events (AEs), AEs considered drug-related, and infusion-associated reactions (IARs), as classified by the Investigator.
- Pharmacodynamics were evaluated based on concentrations of HS- and DS-associated GAGs in cerebrospinal fluid (CSF), serum, andurine.
- Liver and spleen volumes were measured by computed tomography and/or magnetic resonance imaging.

RESULTS

Infusion speed was not associated with increased incidence of IARs or other AEs

- Adverse events, including IARs, over each 52-week period are summarized in **Table 1**.
- The incidence of drug-related AEs between the Fast and Slow groups were similar as the study progressed, suggesting that infusion rate adjustments had minimal impact on the overall safety profile of pabinafusp alfa and that many patients tolerated faster infusion rates.
  - Instead of being randomly assigned to the Fast or Slow group, patients were exposed to gradual increases in infusion rates if they did not experience adverse events or IARs. This is reflected by the higher percentage of adverse drug reactions in the Slow group in the first 53 weeks.
- Further evaluation of the safety profile of pabinafusp alfa for each infusion based on infusion duration demonstrated no apparent relationship between shorter infusion times (ie, faster infusion rates) and the incidence of IARs (**Figure 1**).

Figure 1. Number of infusions and infusion-associated reactions following treatment with pabinafusp alfa.



IARs, infusion-associated reactions.

Table 1. Safety-related events observed in those with Fast infusions (≥66% of infusions administered at infusion rate >33 mL/h) and Slow infusions (<66% of infusions administered at infusion rate >33 mL/h).#

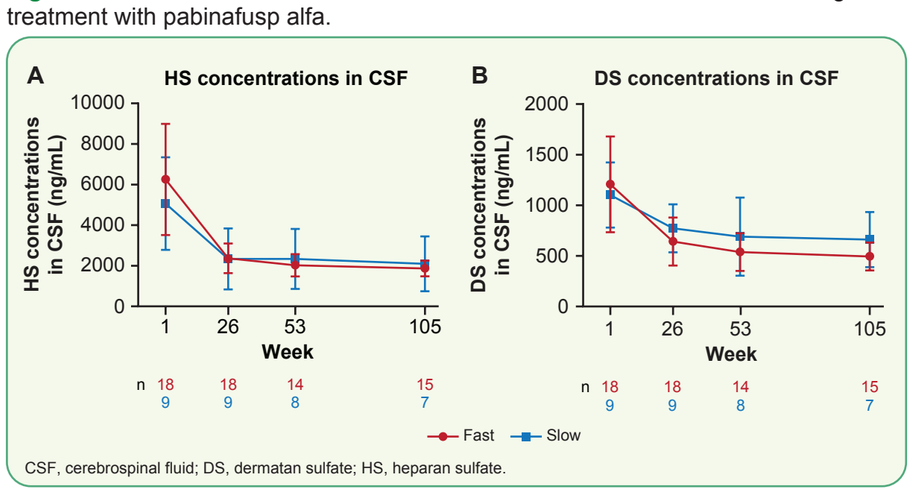
Fast group	1 – 53 weeks (n=18)		53 – 105 weeks (n=18)		105 – 157 weeks (n=15)		157 – 209 weeks (n=13)		209 – 261 weeks (n=12)	
	N (%)	Number of events	N (%)	Number of events	N (%)	Number of events	N (%)	Number of events	N (%)	Number of events
Number of subjects	18	–	18	–	15	–	13	–	12	–
Adverse events	18 (100.0)	196	18 (100.0)	130	15 (100.0)	84	13 (100.0)	90	12 (100.0)	99
Serious adverse events	2 (11.1)	2	1 (5.6)	1	0	0	1 (7.7)	1	1 (8.3)	3
Adverse drug reactions*	7 (38.9)	28	4 (22.2)	15	5 (33.3)	7	4 (30.8)	15	3 (25.0)	3
Serious adverse drug reactions	0	0	0	0	0	0	0	0	0	0
Infusion associated reactions	6 (33.3)	27	4 (22.2)	15	4 (26.7)	5	3 (23.1)	13	2 (16.7)	2
Slow group	**1 – 53 weeks (n=9)**		**53 – 105 weeks (n=9)**		**105 – 157 weeks (n=8)**		**157 – 209 weeks (n=8)**		**209 – 261 weeks (n=8)**	
	N (%)	Number of events	N (%)	Number of events	N (%)	Number of events	N (%)	Number of events	N (%)	Number of events
Number of subjects	9	-	9	-	8	-	8	-	8	-
Adverse events	9 (100.0)	139	9 (100.0)	71	7 (87.5)	75	8 (100.0)	62	7 (87.5)	64
Serious adverse events	3 (33.3)	6	3 (33.3)	5	0	0	0	0	3 (37.5)	3
Adverse drug reactions*	8 (88.9)	31	4 (44.4)	7	4 (50.0)	8	2 (25.0)	2	2 (25.0)	3
Serious adverse drug reactions	0	0	0	0	0	0	0	0	0	0
Infusion associated reactions	8 (88.9)	24	4 (44.4)	6	4 (50.0)	8	1 (12.5)	1	2 (25.0)	3

*Adverse drug reactions considered related to pabinafusp alfa, as classified by Investigator.
#3 patients (2 Fast and 1 Slow) were naive to prior idursulfase treatment.

Concentrations of HS- and DS-associated GAGs in CSF remained stable regardless of infusion rate

- All patients (n = 27) who received pabinafusp alfa demonstrated a marked reduction in HS- and DS-associated GAG levels in the CSF (**Figures 2A and 2B respectively**) from week 1 (baseline) to week 26. This reduction was sustained through week 105.
- Importantly, adjusting the infusion rate did not impact HS or DS concentrations in the CSF.

Figure 2. Concentrations of HS- and DS-associated GAGs in the CSF following treatment with pabinafusp alfa.

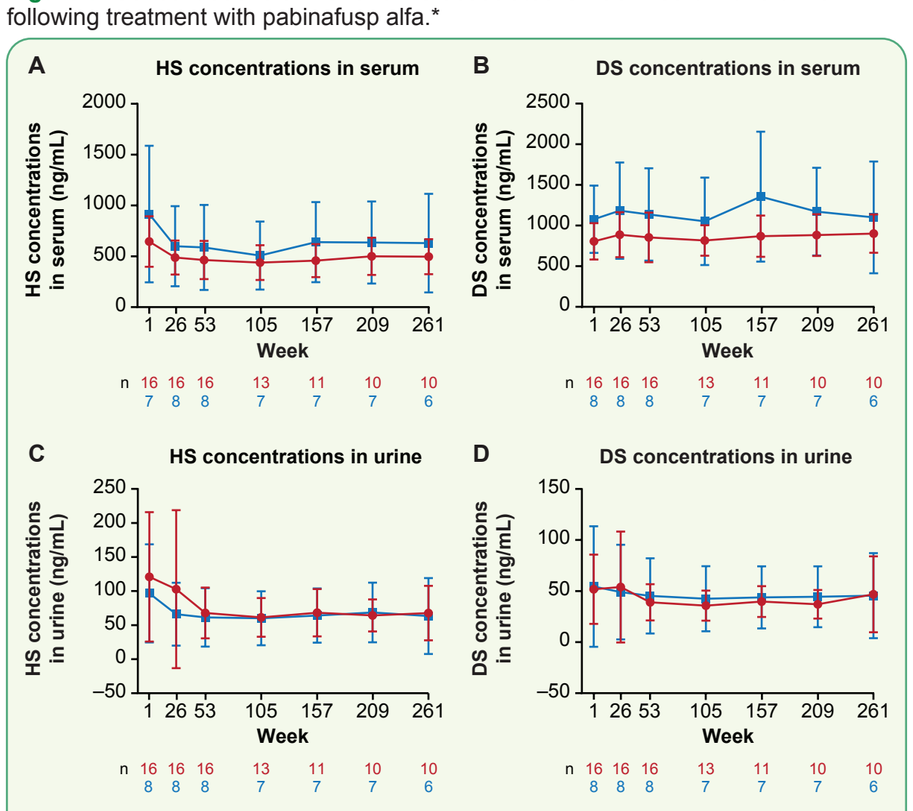


CSF, cerebrospinal fluid; DS, dermatan sulfate; HS, heparan sulfate.

Concentrations of HS- and DS-associated GAGs in serum and urine remained stable regardless of infusion rate

- Patients previously treated with idursulfase who were switched to pabinafusp alfa (n = 24) showed consistently low HS-associated GAG levels in serum (**Figure 3A**), DS-associated GAG levels in serum (**Figure 3B**), HS-associated GAG levels in urine (**Figure 3C**), and DS-associated GAG levels in urine (**Figure 3D**) from week 1 through week 261.
  - This suggests that the somatic efficacy of ERT, reflected by low baseline concentrations of HS and DS in serum and urine, was maintained by pabinafusp alfa.
- Importantly, adjusting the infusion rate did not impact HS or DS concentrations in serum or urine.

Figure 3. Concentrations of HS- and DS-associated GAGs in serum and urine following treatment with pabinafusp alfa.*

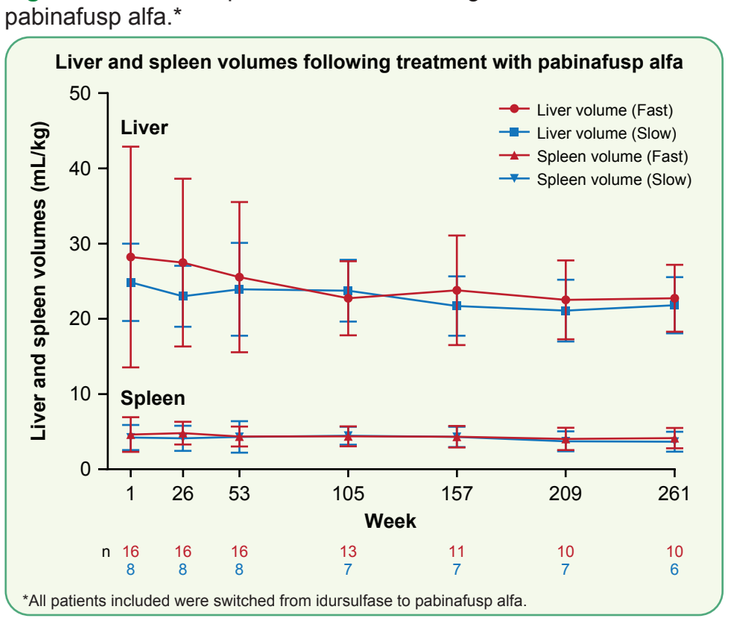


*All patients included were switched from idursulfase to pabinafusp alfa
DS, dermatan sulfate; HS, heparan sulfate.

Liver and spleen volumes remained stable regardless of infusion rate

- In patients switched from idursulfase to pabinafusp alfa (n = 24), liver and spleen volumes (**Figure 4**) remained stable.
  - The absence of hepatosplenomegaly suggests that the somatic efficacy of ERT was maintained by pabinafusp alfa.
- Importantly, adjusting the infusion rate did not impact the somatic benefits of pabinafusp alfa.

Figure 4. Liver and spleen volumes following treatment with pabinafusp alfa.*



*All patients included were switched from idursulfase to pabinafusp alfa.

DISCUSSION

- In a subset of patients with MPS II who were treated with pabinafusp alfa, adjustments to infusion rates did not have a meaningful impact on the safety or pharmacodynamic outcomes of long-term treatment.
  - Infusion rate adjustments had no obvious impact on IARs during treatment with pabinafusp alfa, suggesting that IARs are more closely associated with individual patient characteristics.
- Patients in this study were not randomly assigned to fast or slow groups, but rather, patients who did not experience AEs or IARs were exposed to gradual increases in infusion rates.
  - Thus, the decision to increase ERT infusion rates should be made on an individual patient basis, with close monitoring and careful management.

CONCLUSION

The findings from this study suggest that clinicians may safely consider shorter infusion durations when using pabinafusp alfa to treat MPS II, to accommodate clinical circumstances or individual patient needs, potentially improving quality of life and treatment compliance in pediatric patients.

References

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