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Long-term outcomes of MPS IVA patients treated with elosulfase alfa: Findings from the Morquio A Registry Study (MARS) after 10 years

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Background

- Mucopolysaccharidosis (MPS) IVA is a rare, progressive lysosomal storage disorder with multisystemic clinical manifestations[1-3]
- The Morquio A Registry Study (MARS) was a multinational, observational study of patients with MPS IVA, with the following key objectives:[4]
  - To characterize the heterogeneity and natural history of disease
  - To evaluate the long-term effectiveness and safety of elosulfase alfa enzyme replacement therapy (ERT)

Methods

- Participants were enrolled at 65 clinical sites located in 16 countries and data were collected between September 2014 and May 2024
  - All patients with a confirmed diagnosis of MPS IVA were eligible to participate
  - Data on medical history, clinical outcomes, and safety assessments were collected as part of routine care
- Safety outcomes were assessed among ERT-treated participants who received at least one dose of elosulfase alfa during MARS
- Change from pre-treatment baseline in clinical outcome variables are summarized for ERT-treated participants with both a baseline measurement and at least one follow-up measurement for the given outcome

Results

- A total of 419 participants were enrolled
  - 54 participants were ERT-naïve (no ERT exposure prior to or during MARS)
  - 365 participants were ERT-treated (≥1 ERT infusion prior to or during MARS)
- Among ERT-treated participants, mean ERT exposure was 7.4 years (range: 0.4–15.0 years), with mean exposure during MARS of 5.2 years (range: 0.0–9.0 years)

Table 1. Disposition

	ERT-naïve (n=54)	**ERT-treated** (n=365)
Enrolled, n (%)	54 (100)	365 (100)
Full Analysis Set, n (%)	54 (100)	364 (99.7)[a]
ERT-treated[b], n (%)	-	365 (100)
Initiated ERT during MARS	-	72 (19.7)
Initiated ERT prior to MARS entry	-	293 (80.3)
Recieved ≥1 ERT infusion during MARS (Safety Population)	-	354 (97.0)
Discontinued from registry, n (%)[c]	17 (31.5)	60 (16.4)
Completed registry, n (%)	37 (68.5)	305 (83.6)

a. One participant was excluded from the full analysis set due to not having a confirmed diagnosis of MPS IVA
b. Participants who have received at least one dose of ERT either prior to or after registry entry
c. Primary reasons for discontinuation from MARS were: death, investigator decision, loss to follow-up, withdrawal by subject, or other

Table 2. Participant Demographics and Characteristics

	ERT-naïve (n=54)	**ERT-treated** (n=364)
Sex, n (%)		
Female	15 (28)	183 (50)
Male	39 (72)	181 (50)
At registry entry:		
Age, years, median (min, max)	21.3 (0, 59)	12.4 (0, 74)
<5 years, n (%)	5 (9)	67 (18)
5 to <12 years, n (%)	6 (11)	112 (31)
12 to <19 years, n (%)	13 (24)	73 (20)
≥19 years, n (%)	30 (56)	112 (31)
Standing height, cm	*n=28*	*n=50*[a]
Mean (SD)	110.0 (19.7)	108.8 (22.9)
Weight, kg	*n=42*	*n=64*[a]
Mean (SD)	32.5 (17.1)	25.9 (15.6)
6-minute walk test (6MWT) distance, m	*n=24*	*n=216*
Mean (SD)	129.0 (174.8)	226.2 (167.8)

a. Weight and standing height data for ERT-treated participants represent pre-ERT baseline values

Safety Outcomes

- Among ERT-treated participants who received ≥1 ERT infusion during the study (n=354), 201 (56.8%) experienced ≥1 adverse event (AE)
- Drug-related AEs were reported in 56 (15.8%) ERT-treated participants; drug-related serious AEs were reported in 7 (2.0%) ERT-treated participants
  - The most common drug-related AEs were hypersensitivity (4.2%), pyrexia (2.8%), urticaria (2.8%)
- 15 ERT-treated participants (4.2%) died during the registry; the most common causes of death were cardiac arrest (n=5) and respiratory failure (n=5)

Table 3. Summary of Drug-Related Adverse Events

Incidence, n (%)	n=354
≥1 drug-related AE[a]	56 (15.8)
Hypersensitivity	15 (4.2)
Pyrexia	10 (2.8)
Urticaria	10 (2.8)
Nausea	6 (1.7)
Infusion-related reaction	6 (1.7)
Vomiting	5 (1.4)
Rash	4 (1.1)
Pruritus	3 (0.8)
Anaphylactic reaction	3 (0.8)
Headache	3 (0.8)
Tachycardia	3 (0.8)
≥1 drug-related serious AE[b]	7 (2.0)
Temporary treatment interruption due to drug-related AEs	14 (4.0)
Permanent treatment discontinuation due to drug-related AEs	8 (2.3)

a. Events that occurred in >2 participants are presented
b. 7 participants experienced 8 drug-related serious AEs: anaphylactic reaction, hypersensitivity, infusion-related hypersensitivity, serum sickness-like reaction, abdominal discomfort, gastritis, pyrexia and infusion-related reaction

Clinical Outcomes

- Urinary keratan sulfate (uKS) levels declined rapidly after ERT initiation and reductions were sustained at subsequent timepoints. Mean percent change from baseline to last follow-up was –40.7% over a mean follow-up of 6.2 years
- 6MWT distance remained relatively stable over time and across treatment durations. Mean change from baseline to last follow-up was –3.5 m over a mean follow-up of 6.6 years
- Respiratory function increased slightly across all treatment durations. Mean change from baseline to last follow-up in forced expiratory volume in 1 second (FEV_1) was +0.2 L over a mean follow-up of 6.9 years
  - Observed increases in FEV_1 were attributable to participants aged <18 years at ERT initiation; FEV_1 was stable among participants who initiated ERT as adults

Figure 1. Normalized urinary keratan sulfate

Pre-ERT baseline and last follow-up (A); change from baseline by treatment duration (B)

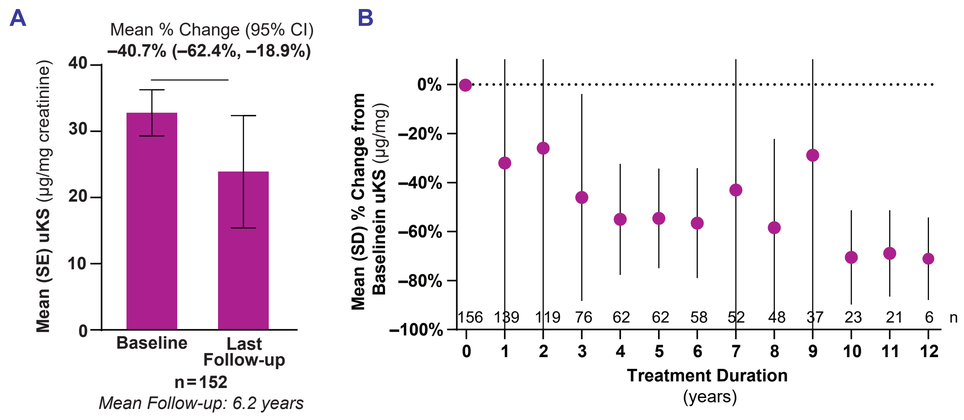


Figure 2. 6-minute walk test

Pre-ERT baseline and last follow-up (A); change from baseline by treatment duration (B)

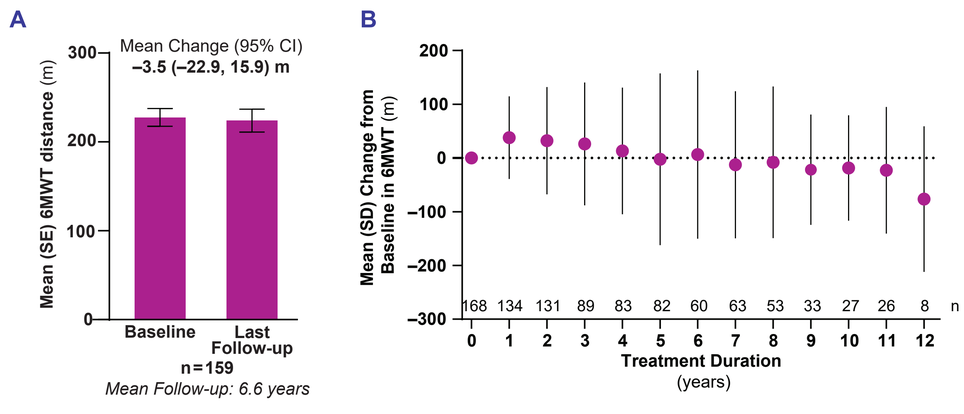
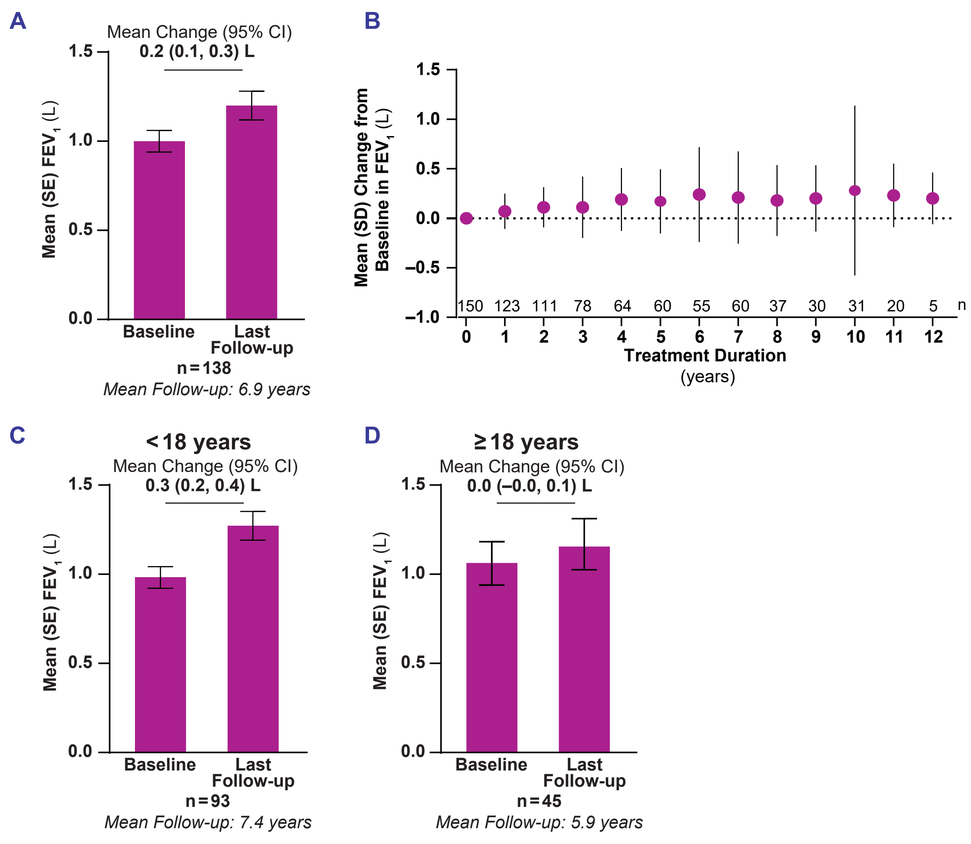


Figure 3. Forced expiratory volume in 1 second

Pre-ERT baseline and last follow-up (A, C, D); change from baseline by treatment duration (B)



Conclusions

- MARS is the largest and longest study of patients with MPS IVA to date, and provides data on the natural history of disease as well as the real-world safety and efficacy of long-term treatment with elosulfase alfa
- Over the 10-year study, ERT-treated participants enrolled in MARS showed sustained reductions in uKS levels and long-term stabilization of endurance and respiratory function
- No new safety concerns associated with elosulfase alfa treatment were identified

References

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