Long-term outcomes of MPS IVA patients treated with elosulfase alfa: Findings from the Morquio A Registry Study (MARS) after 6 years

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MARS Study Information

- MARS* is an ongoing, multinational, observational study of patients with MPS IVA

All patients with a confirmed diagnosis of MPS IVA are eligible to participate
Patients are not required to receive elosulfase alfa enzyme replacement therapy (ERT)

Key objectives:

- Characterize the heterogeneity and natural history of disease
- Evaluate long-term effectiveness and safety of elosulfase alfa ERT

Data are collected on clinical assessments that are performed as part of routine care, along with demographic and disease characteristics

Data collection began in Sep 2014 and will continue for a period of up to 10 years

*MARS: Morquio A Registry Study

Subject Disposition

As of 12 February 2021, a total of 381 subjects at 65 clinical sites located in 17 countries had enrolled

As of 12 Feb 2021	ERT-Naïve	ERT-Treated*
Subjects enrolled in registry (**Full Analysis Set**)	58	323
Subjects treated with ERT during registry (**Safety Population**)		314 (97%)
Subjects who discontinued from the registry**	5 (9%)	23 (7%)
Previous trial enrollment	6 (10%)	130 (40%)

*Received at least one dose of ERT, before or after registry entry
**Reasons for discontinuation included death (n=11), investigator decision (n=3), lost to follow-up (n=2), withdrawal by subject (n=3), and other (n=9)

Subject Demographics & Characteristics

	ERT-Naïve	ERT-Treated
Sex		
Female	18 (31.0%)	160 (49.5%)
Male	40 (69.0%)	163 (50.5%)
Age at MPS IVA diagnosis		
Median	6.5 years	3.4 years
Mean	8.9 years	6.3 years
At registry entry:		
Age, median	21.4 years	13.0 years
<5 years	4 (6.9%)	58 (18.0%)
≥19 years	34 (58.6%)	101 (31.3%)
Standing height, mean (SD)	112.0 (21.3) cm	107.3 (19.4) cm
Weight, mean (SD)	34.4 (18.3) kg	26.3 (13.1) kg
6MWT distance, mean (SD)*	165.6 m (229.3)	224.5 m (161.9)

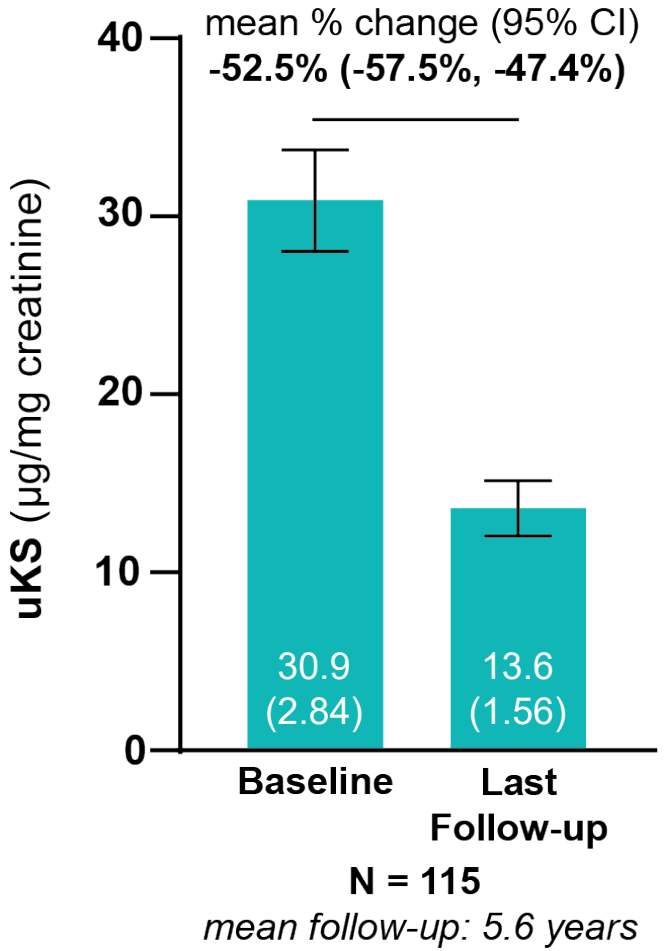
*Note: more than 50% of ERT-naïve subjects were unable to complete the 6MWT (distance imputed as 0); <10% unable to complete among ERT-treated

6MWT: 6-minute walk test; SD: standard deviation

ERT Exposure

	ERT-Treated (N=323)
ERT exposure, years	
Total	
mean	5.47
min, max	0.11, 11.98
During MARS	
mean	3.26
min, max	0.06, 5.97
Age at ERT initiation, years	
median	9.8
min, max	0.3, 69.4
Age group ERT initiation, n (%)	
<5 years	83 (25.7%)
5 to <12 years	105 (32.5%)
12 to <19 years	54 (16.7%)
≥19 years	81 (25.1%)

Normalized uKS: Change from Baseline in ERT-Treated Subjects



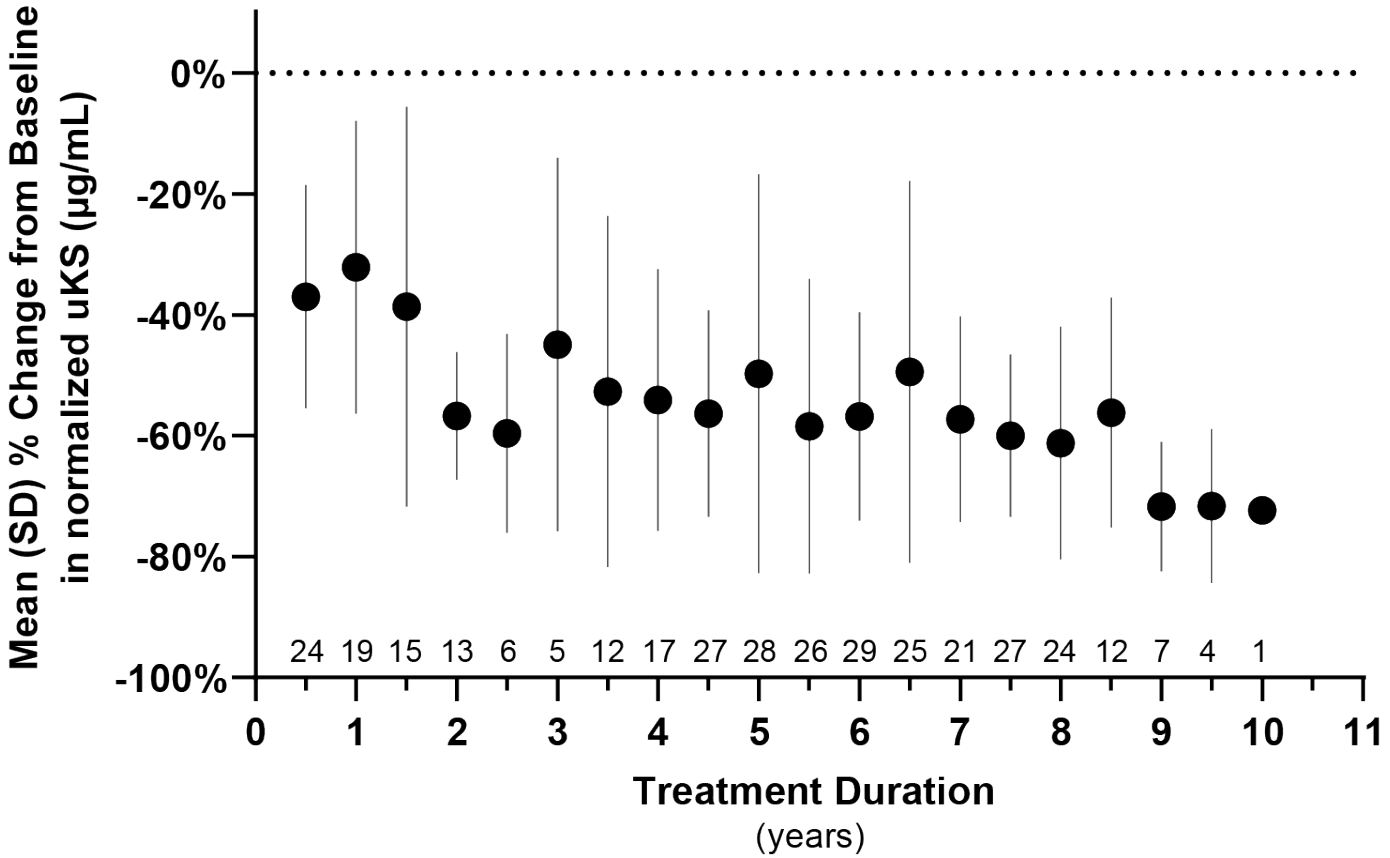
- Mean % change from baseline to last follow-up was -52.5% (*P*<0.0001)
  - Decrease from baseline was consistent with findings from MOR-004/005 clinical trials[1,2]

Error bars represent standard errors (SE)

CI: confidence interval; uKS: urine keratan sulfate

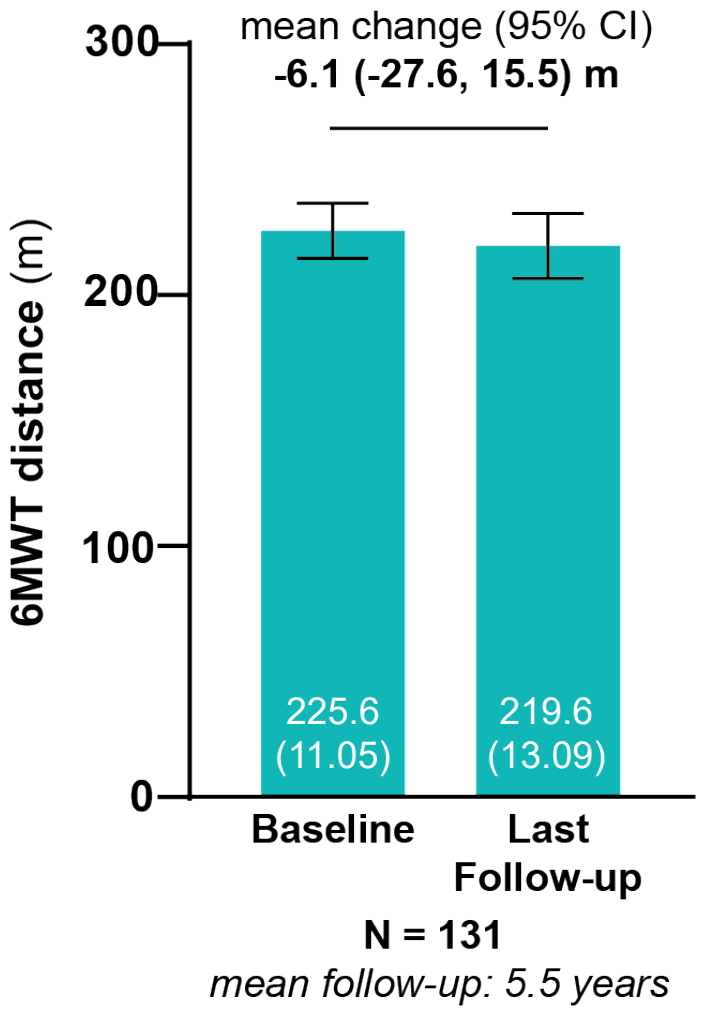
1. Hendriksz CJ et al. J Inherit Metab Dis 2014;37:979-90; 2. Hendriksz CJ et al. Mol Genet Metab 2016;119:131-43

Normalized uKS: Change from Baseline by Treatment Duration



- uKS levels declined rapidly after ERT initiation
- After 2 years on treatment, uKS levels were ≈60% lower than at baseline
- Reductions were sustained at subsequent time points

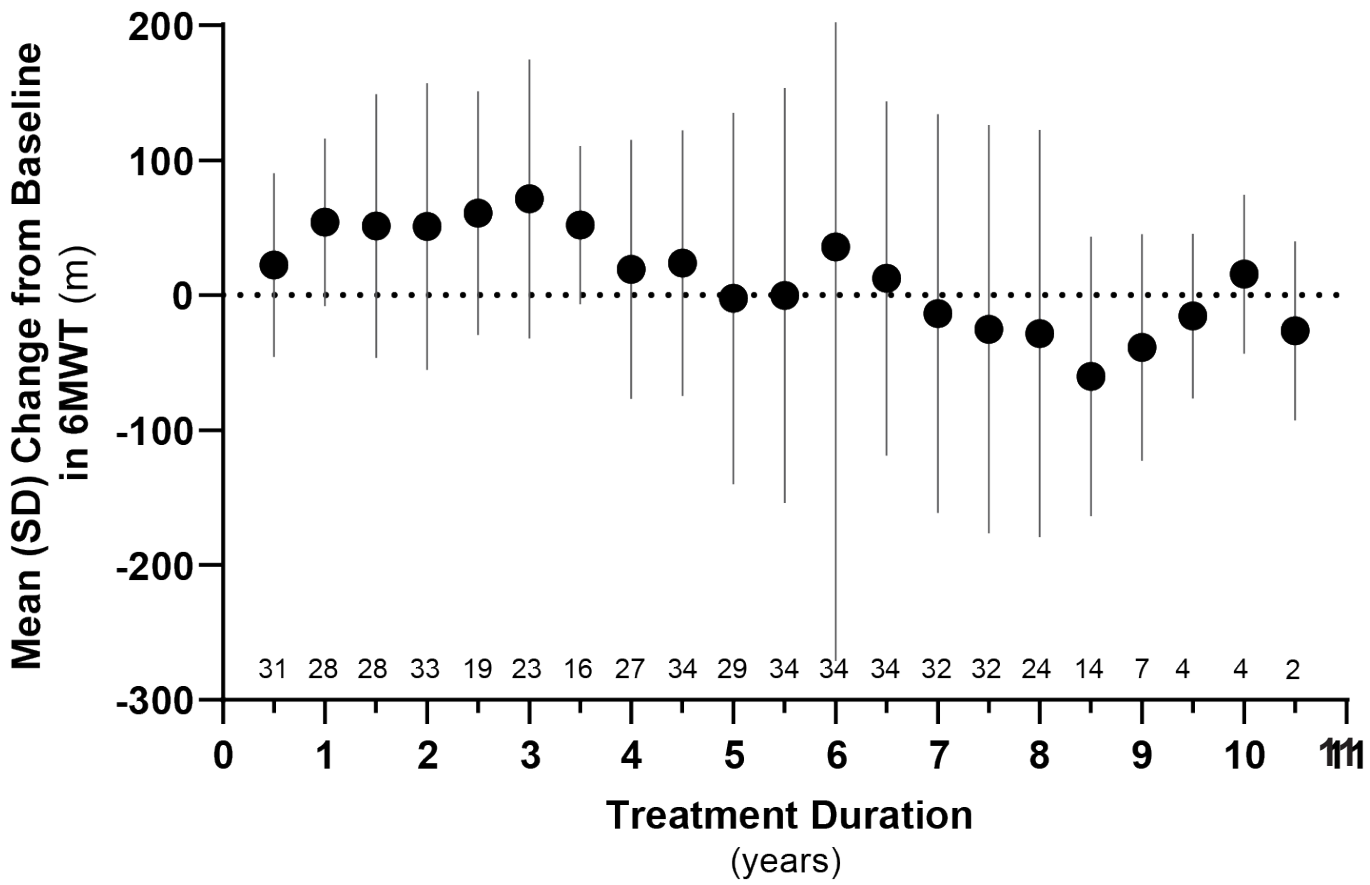
6-Minute Walk Test: Change from Baseline in ERT-Treated Subjects



- Mean change from baseline to last follow-up in the 6MWT was -6.1 m, over a mean treatment duration of 5.5 years

Error bars represent SE

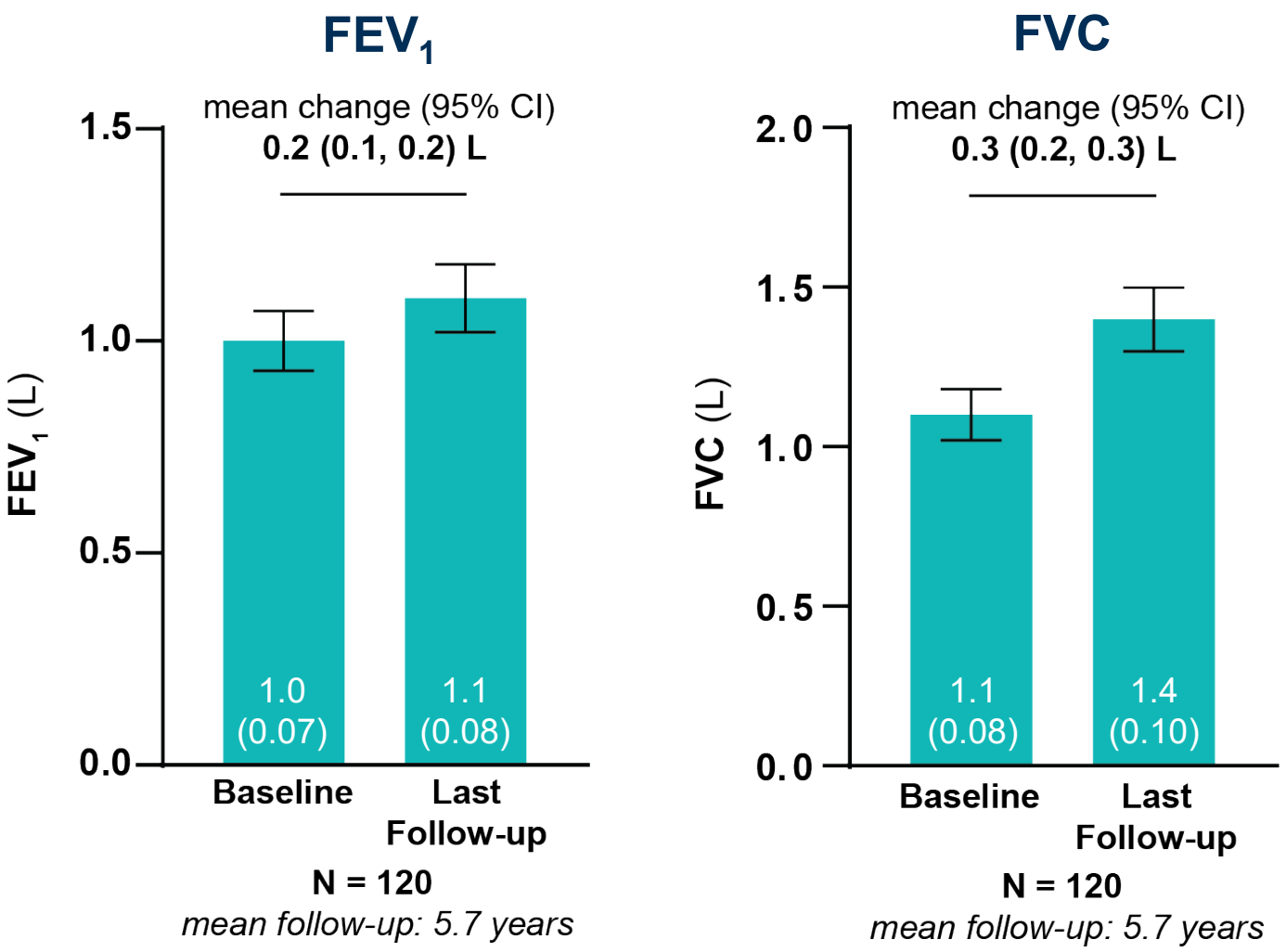
6-Minute Walk Test: Change from Baseline by Treatment Duration



- 6MWT distance remained relatively stable over time
  - In contrast, untreated subjects in the MorCAP natural history study showed a gradual decline of 4.9-6.8 m/year in endurance[1]
  - Initial mean increase from baseline was comparable in magnitude to that observed in the phase 3 studies[2,3]

1. Harmatz PR et al. Mol Genet Metab 2015;114:186-94; 2. Hendriksz CJ et al. J Inherit Metab Dis 2014;37:979-90; 3. Hendriksz CJ et al. Mol Genet Metab 2016;119:131-43

Respiratory Function: Change from Baseline in ERT-Treated Subjects



- Respiratory outcomes were improved or stabilized over the duration of follow-up
- Increases observed after 2 years of treatment were similar in magnitude to those observed in clinical trials[1,2]

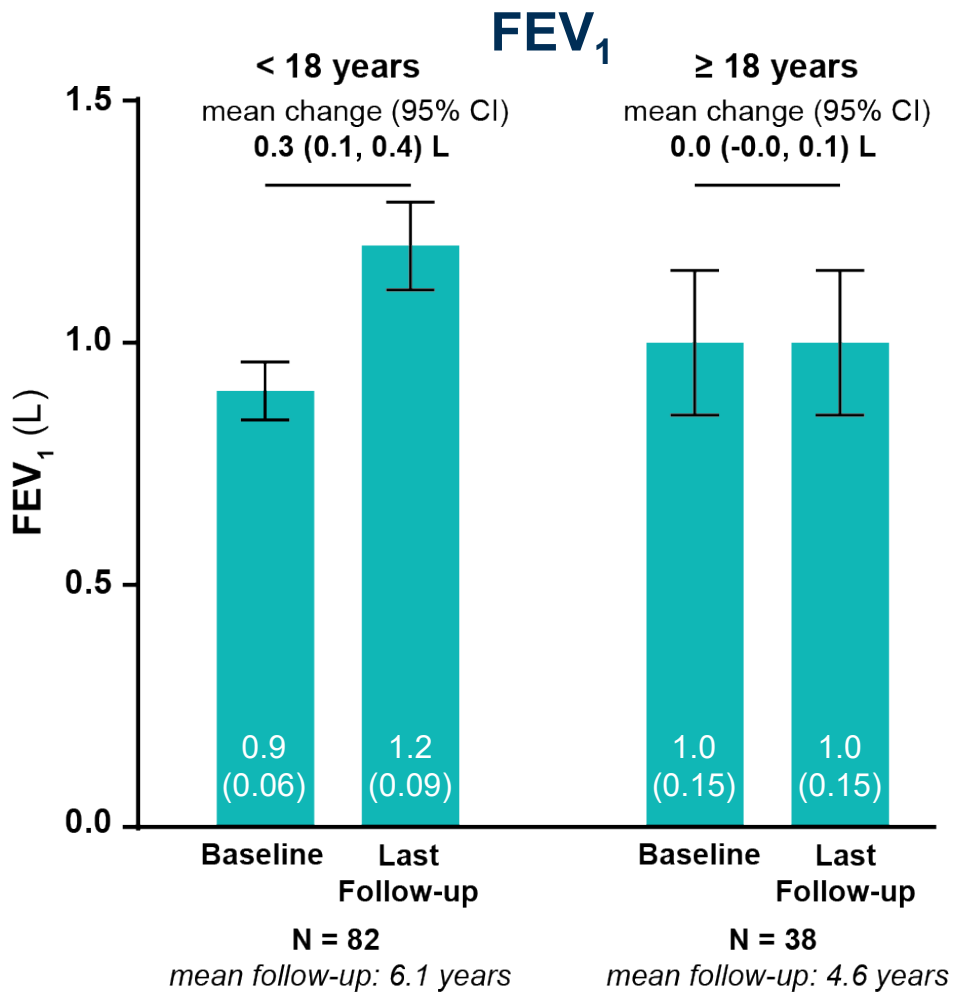
Error bars represent SE

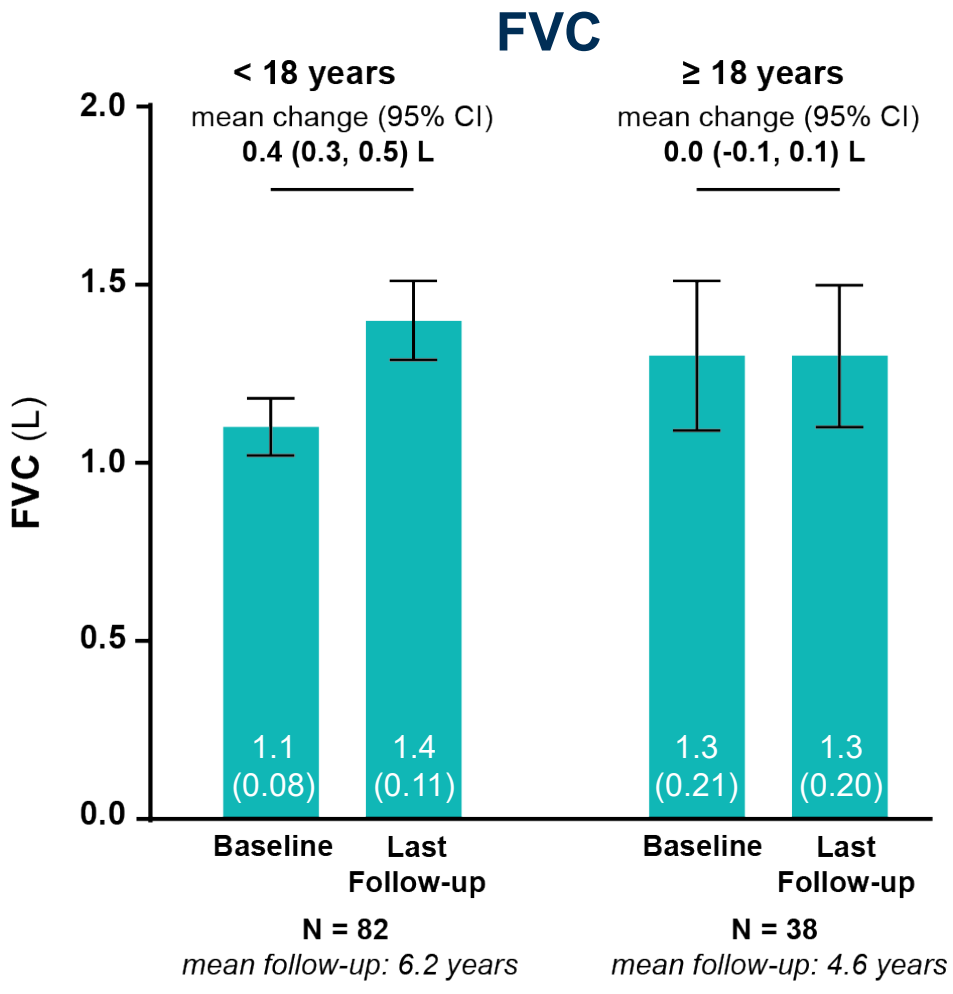
FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity

1. Hendriksz CJ et al. J Inherit Metab Dis 2014;37:979-90; 2. Hendriksz CJ et al. Mol Genet Metab 2016;119:131-43

Respiratory Function: Change From Baseline by Age at Treatment Initiation

- Respiratory function increased in subjects <18 years and remained stable in older subjects

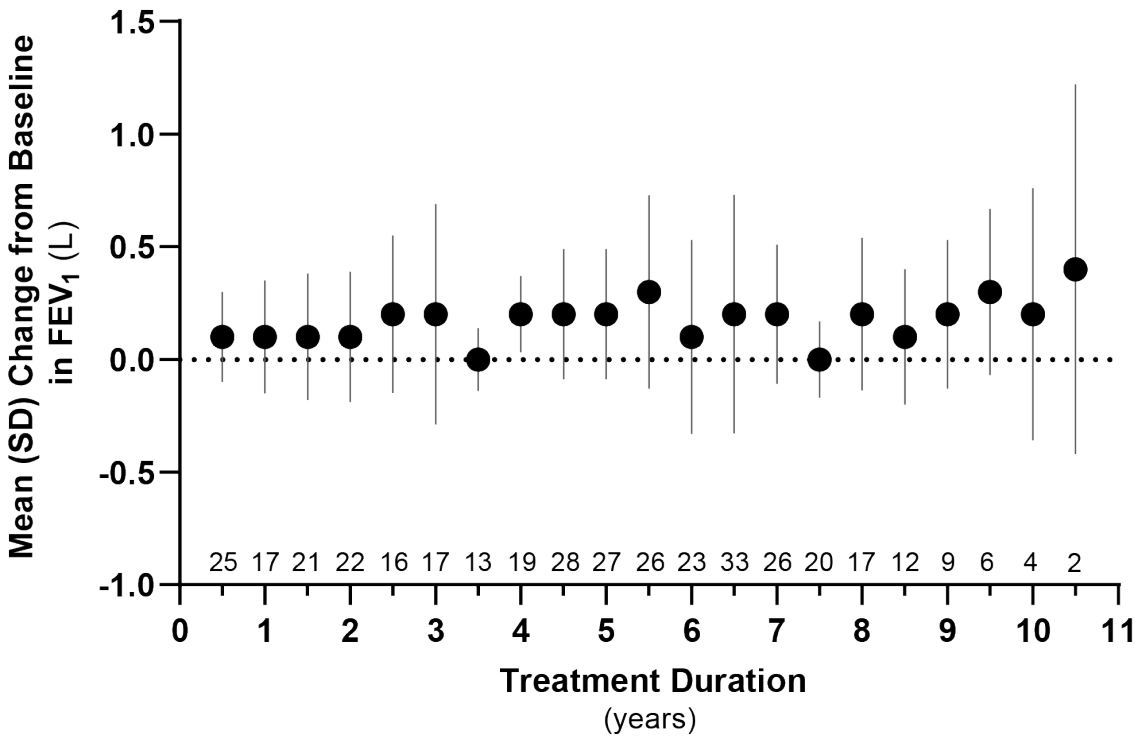




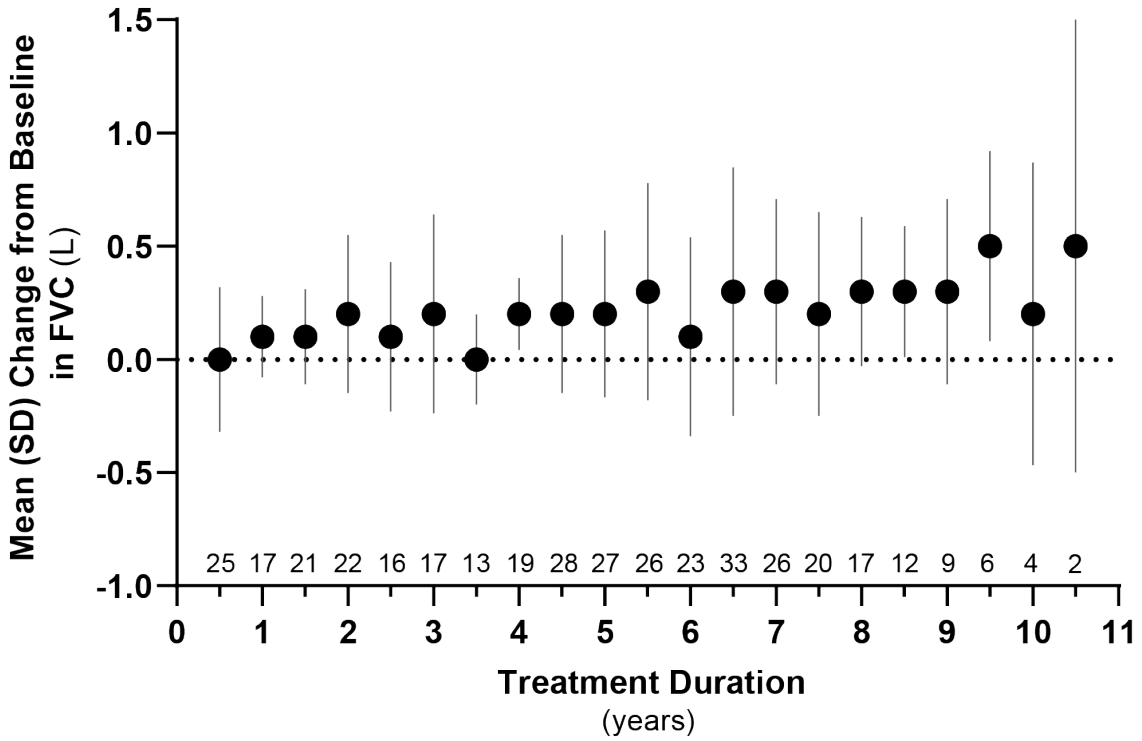
Error bars represent SE

Respiratory Function: Change from Baseline by Treatment Duration

FEV_1



FVC



Safety Summary: ERT-Treated Subjects

	ERT-Treated (Safety Population) N=314*
Subjects with ≥1 Reported AE	148 (47.1%)
Subjects with ≥1 Reported Drug-Related AE**	39 (12.4%)
Hypersensitivity	9 (2.9%)
Urticaria	8 (2.5%)
Pyrexia	7 (2.2%)
Infusion-related reaction	6 (1.9%)
Nausea	4 (1.3%)
Rash	4 (1.3%)
Headache	3 (1.0%)
Vomiting	3 (1.0%)

	ERT-Treated (Safety Population) N=314*
Subjects with ≥1 Reported SAE	110 (35.0%)
Subjects with ≥1 Reported Drug-Related SAE	5 (1.6%)
Hypersensitivity	2 (0.6%)
Anaphylactic reaction	1 (0.3%)
Infusion-related reaction	1 (0.3%)
Serum sickness	1 (0.3%)

*Safety population: subjects treated with ERT during MARS

**Includes drug-related AEs occurring in >1 subject; only AEs occurring in ≥1% of subjects are presented

AE, adverse event; SAE, serious adverse event

Safety Summary: ERT-Treated Subjects

- **No new safety concerns and no unexpected drug-related AEs were reported over 6 years of follow-up in MARS to date**
- Temporary treatment interruptions due to an AE were reported for 36 subjects
  - ERT treatment was subsequently resumed successfully in these subjects
- AEs led to permanent ERT discontinuation in 1 subject
- 10 ERT-treated subjects died during the registry:
  - None of the deaths were assessed by investigators as related to ERT

Conclusions

- MARS is the longest real-world study of elosulfase alfa, with a heterogenous population representative of the MPS IVA population overall
- Data collected over the first 6 years of MARS provide real-world evidence for sustained reduction in uKS levels and long-term stabilization of endurance and respiratory function among ERT-treated patients
- Findings to date support efficacy and safety findings from clinical trials[1,2]
- Continued collection and analysis of real-world data in MARS will provide further insights into the natural history of MPS IVA and the long-term impact of treatment

1. Hendriksz CJ et al. J Inherit Metab Dis 2014;37:979-90; 2. Hendriksz CJ et al. Mol Genet Metab 2016;119:131-43

Children and families with MPS IVA

MARS (NCT02294877)

Study sponsor: BioMarin Pharmaceutical, Inc.

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