Impact of elosulfase alfa treatment on patient-reported outcomes in Morquio A Syndrome: results from the first year of an English managed access agreement

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Background

- Morquio A syndrome is an ultra-rare, inherited, multi-systemic disease which, if untreated, results in impaired functioning, mobility, and quality of life (QoL), and early death
- Enzyme replacement therapy with elosulfase alfa is the only approved treatment
- In England, access to elosulfase alfa is granted to all patients on a conditional basis through a managed access agreement (MAA) (Figure 1)
- Patients must fulfil four out of five response criteria to continue receiving treatment; one of the five criteria covers patient-reported outcomes (PROs)
- PROs support continuing treatment if stabilization or improvement are reported in two of the following three domains: QoL, depression, and pain
- PROs for those patients completing the first year of the program are reported herein

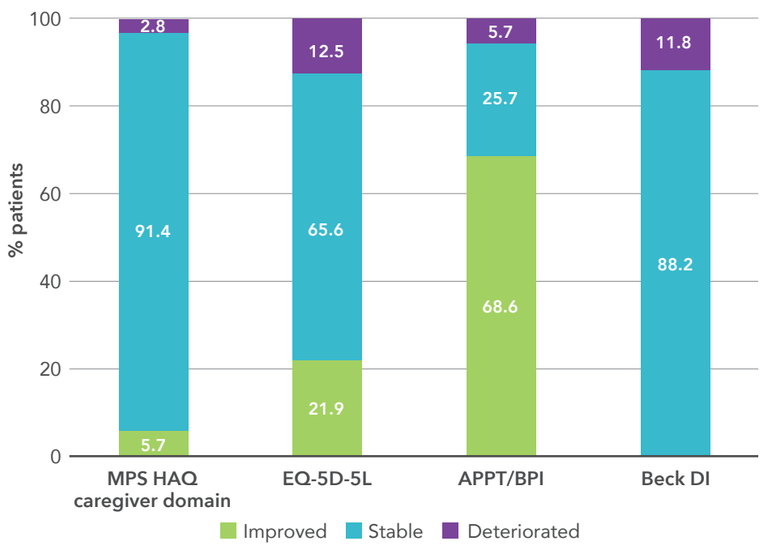
Methods

- All patients completed PRO assessments on entry to the MAA, and at 4, 8 and 12 months (Table 1)
- PRO questionnaires were completed by either the patient or their parent/carer depending on the age of the patient
- Patients or their parent/carer completed the questionnaires either over the telephone or during a face to face interview with a patient organisation representative
- QoL was monitored using the EQ-5D-5L tool and the caregiver assistance domain of the MPS Health Assessment Questionnaire (MPS HAQ)
- The Beck Depression Inventory (BDI; only applicable for patients ≥13 years) was used to assess mood
- Pain was measured using the Adolescent and Paediatric Pain Tool (APPT) for patients under 18 years of age or the Brief Pain Inventory (BPI) for patients aged 18 years and over
- Thresholds for clinically meaningful changes versus inherent assessment variability were established post-hoc by the MAA stakeholders (Table 2)

Results

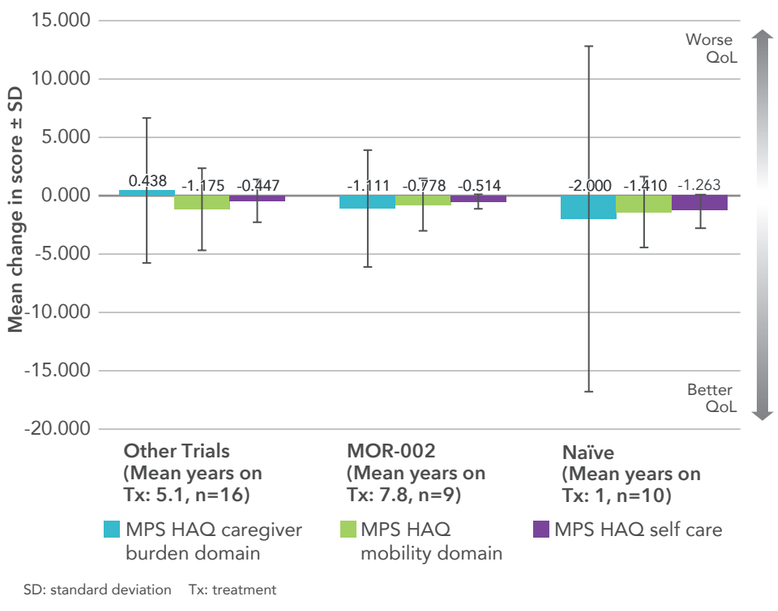
- As of March 2017, 25 children and 10 adults had completed one year of treatment under the MAA
- Ten patients entered the program treatment-naïve, the remainder came from the clinical trial program (mean years on treatment=6.08 [SD 1.36]; n=25)
- The assessment of PROs versus the agreed clinically meaningful changes are summarised in Figure 2

Figure 2. Patient reported outcomes at one year



- Overall, PROs provided evidence supporting continued treatment for 33 of 35 patients
- Results for the individual measures are presented below, results for patients who took part in the MOR 002 study are presented separately as these patients have received elosulfase alfa for the longest period prior to the start of the MAA
- Mean QoL scores for the caregiver burden domain of the MPS HAQ are shown in Figure 3
- MPS HAQ mobility and self care domains were also collected but are not part of the MAA criteria. Changes in mean scores are shown in Figure 3

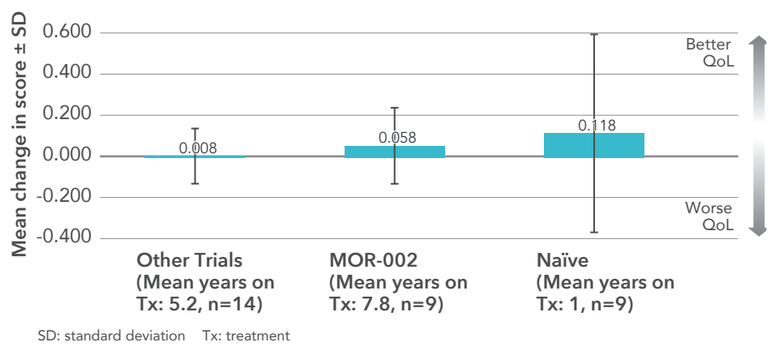
Figure 3. Change in MPS HAQ over 1 year by patient origin



SD: standard deviation Tx: treatment

- Mean changes in EQ-5D-5L were positive in both patient groups (Figure 4)

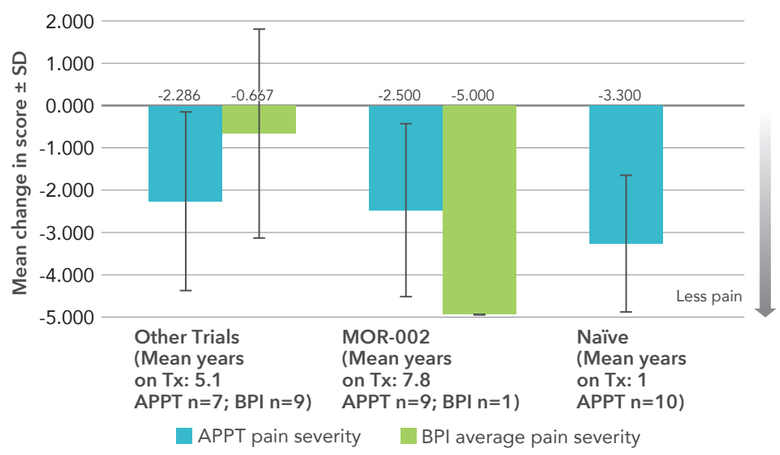
Figure 4. Change in EQ-5D-5L over 1 year by patient origin



SD: standard deviation Tx: treatment

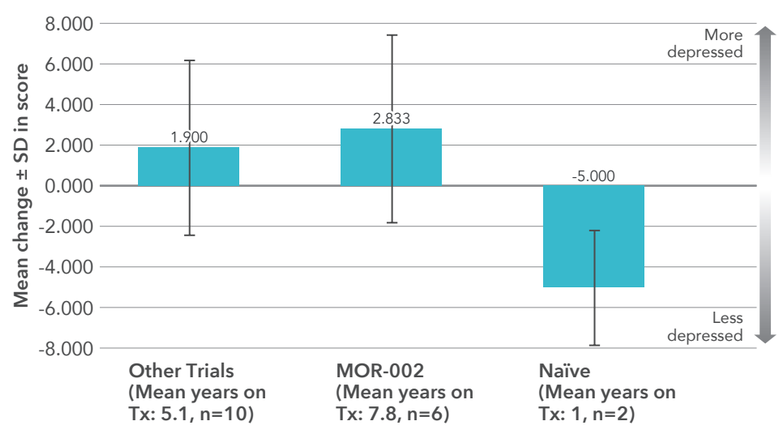
- Mean changes in pain scores showed a pain reduction of over 2 points as measured by the APPT and 1 point as measured by the BPI

Figure 5. Change in pain severity over 1 year by patient origin



- The mean changes in BDI score are shown in Figure 6. A score of 13 or under is considered as normal (i.e. no depression) on the BDI[1] and it is worth noting that no treatment naïve patients and only 1 ex-trial patient scored over 13 on entry to the MAA.

Figure 6. Mean change in BDI over 1 year by patient origin



SD: standard deviation Tx: treatment

Conclusions

- Assessment of multiple domains was a critical component of the program due to patient heterogeneity and the importance of individualized patient management in Morquio A syndrome
- BDI is a new tool for use in this patient cohort and the exact meaning of changes in this measure will have to be further explored in the future. The current changes seen in the naïve patients may be linked to the initial improvement in fatigue which is widely reported and to which patients may adapt over time.
- Based on PROs, the majority of patients met or exceeded the necessary level of treatment benefit established by the MAA stakeholders

Figure 1. The Managed Access Agreement criteria[2]

Start criteria

- Confirmed diagnosis of MPS IVA
- Confirmed enzymatic test, elevated urinary keratan sulfate and mutation analysis
- Sign up to the 'Managed Access Patient Agreement'
- Full set of baseline assessments obtained for patients over 5 years of age

Exclusion criteria

- Patient is diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit e.g. cancer or multiple sclerosis
- Patient has a forced vital capacity of less than 0.3 litres and requires ventilator assistance
- Patient is unwilling to comply with the associated monitoring criteria

Stop criteria

- Non-compliance with assessments for continued therapy (non-compliance is defined as fewer than three attendances for assessment in any 14 month period)
- Patient fails to meet 4 of the 5 treatment response criteria (Table 1)
- Patient is unable to tolerate infusions due to infusion related severe adverse events that cannot be resolved

Patients who are taken off treatment will continue to be monitored for disease deterioration and supported with other clinical measures

Table 1. PRO assessment schedule

Assessment	Baseline	Month 4	Month 8	Month 12
MPS HAQ	X			X
EQ-5D-5L	X			X
BPI/APPT	X	X*	X*	X*
BDI	X		X	

*Day before and day after infusion

Table 2. Thresholds for PRO measurements

	MPS HAQ Caregiver domain	EQ-5D-5L	APPT / BPI	BDI
Clinically meaningful change	Change in point score of 13 or more	Change in value set of 0.2 or more*	Change in 12 month best score versus baseline of 2 or more (APPT) or 3 or more (BPI)	Change in point score of 10 or more

*The EQ-5D-5L threshold for the MAA is still under review, a 0.2 change in value was used for this analysis

References

1 Smarr KL. Measures of Depression and Depressive Symptoms. Arthritis & Rheumatism(Arthritis Care & Research) 2003; 49(5S): S134-46

2 NICE. Managed Access Agreement Elosulfase alfa for treating mucopolysaccharidosis type IVa. 16 December 2015. Available from: https://www.nice.org.uk/guidance/hst2/resources/managed-access-agreement-december-2015-2238935869 (accessed on 19 June 2017)

Acknowledgments

- Patient questionnaires were conducted by MPS Commercial
- Medical writing and editorial support was provided by MPS Commercial and funded by BioMarin Europe Ltd.
- Data analysis and review were provided by BioMarin Europe Ltd. and BioMarin Pharmaceuticals Inc.
- This research was funded by BioMarin Europe Ltd. under the requirements of the MAA