BMJ TAG

Elosulfase alfa for treating mucopolysaccharidosis type IVA (re-evaluation of highly specialised technologies guidance 2)

ERG addendum post ECM1

October 2021

1 Introduction

This document provides the Evidence Review Group's (ERG's) addendum after the first committee meeting. The analyses provided in this addendum were requested by the NICE technical team.

2 Additional analyses requested by NICE

The NICE technical team requested ICERs that include the committee's preferred assumptions. The NICE technical team believe scenarios 4 and 5 are most likely to reflect committee's preferred ICER range. All the analyses requested by the NICE technical team include the following assumptions:

- Standard of care (SoC) patients that start in the asymptomatic state of the model are assumed to take 3 years to progress to the symptomatic state, while elosulfase alpha (ESA) patients take 9 years to move from asymptomatic to symptomatic;
- Use the ERG's scenario analysis linking mortality to decreased %FVC predicted in the model (with ERG's 1-year complete case analysis [CCA] estimations for FVC decrease taken from the MAA and MOR-001 data);
- Use the ERG's baseline utility data from the MAA for SoC patients and the ERG's estimations of FVC and 6MWT gains associated with utility increments in the ESA arm;
- The ERG's assumptions for changes in patients' body weight;
- Use a 3.5% discount rate.

The different scenarios requested by NICE (incorporating the assumptions described above) consist of the following:

Scenario 1:

- Company's approach with preferred assumptions described in section 2 above .

Scenario 2:

- Company's approach with preferred assumptions described in section 2 and with the assumption of a 4.86m (instead of a 6.84m) annual loss in 6MWT for SoC patients after year 1 in the model.

Scenario 3:

- Use of company's entrance and exit thresholds from the different WC categories in the model.
- Use the ERG's 1-year CCA data from the MAA and MOR-001 to model change in WC use from baseline to year 1 in the model.
- Assume a 4.86m and 0.1L losses in 6MWT and FVC measures, respectively, for SoC patients after year 1 in the model and assumption that that only 1 in 10,000 patients progresses per year in the ESA arm.

Scenario 4:

- Use the ERG's entrance and exit thresholds from the different WC categories in the model.
- Use the company's 2-year CCA WC transition data to model change in WC use from baseline to year 1 in the model.
- Assume a 4.86m and 0.1L losses for SoC patients after year 1 in the model and assume that that only 1 in 10,000 patients progresses per year in the ESA arm.

Scenario 5:

- Use the ERG's entrance and exit thresholds from the different WC categories in the model.
- Use the ERG's 1-year CCA data from the MAA and MOR-001 to model change in WC use from baseline to year 1 in the model.
- Use the ERG's estimated increase in 6MWT and FVC in the ESA & SoC arms from baseline to year 1 applied in the model according to the MOR-001 and the MAA data.
- Assume a 4.86m and 0.1L losses for SoC patients after year 1 in the model and assumption that that only 1 in 10,000 patients progresses per year in the ESA arm.

Scenario 6:

- Use the ERG's entrance and exit thresholds from the different WC categories in the model.
- Use the ERG's 1-year CCA data from the MAA and MOR-001 to model change in WC use from baseline to year 1 in the model.
- Use the ERG's estimated increase in 6MWT and FVC in the ESA % SoC arms from baseline to year 1 applied in the model according to the MOR-001 and the MAA data.
- Assume a 4.86m and 0.1L losses for SoC patients after year 1 in the model and assume that the effect of ESA observed in the 1-year CCA would be observed for every year of treatment

with ESA in the model. For this scenario, the ERG assumed that after year 1, ESA patients lost 31% less than SoC patients in their 6MWT, (i.e., 3.3m vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost 4% less than SoC patients, (i.e., 0.0957L vs 0.1L, respectively, annually).

Table 1. Deterministic results (discounted except for life years gained)

Scenario		Incremental costs	Incremental QALYs	ICER	Undiscounted incremental QALYs
1	Company's approach with preferred assumptions described in section 2	[redacted]	[redacted]	[redacted]	[redacted]
2	Company's approach with the assumption of a 4.86m (instead of a 6.84m) annual loss in 6MWT for SoC patients after year 1 in the model	[redacted]	[redacted]	[redacted]	[redacted]
3	•Company's entrance and exit thresholds from the different WC categories in the model •Use of ERG's 1-year CCA data from the MAA and MOR-001 to model change in WC use from baseline to year 1 in the model •ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data •Assumption of 4.86m and 0.1L losses for SoC patients after year 1 in the model and assumption that that only 1 in 10,000 patients progresses per year in the ESA arm.	[redacted]	[redacted]	[redacted]	[redacted]
4	•ERG's entrance and exit thresholds from the different WC categories in the model •Company's 2-year WC transition data to model change in WC use from baseline to year 1 in the model •Assumption of 4.86m and 0.1L losses for SoC patients after year 1 in the model and assumption that that only 1 in 10,000 patients progresses per year in the ESA arm.	[redacted]	[redacted]	[redacted]	[redacted]
5	•ERG's entrance and exit thresholds from the different WC categories in the model •Use of ERG's 1-year CCA data from the MAA and MOR-001 to model change in WC use from baseline to year 1 in the model	[redacted]	[redacted]	[redacted]	[redacted]

	•ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data •ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data •Assumption of 4.86m and 0.1L losses for SoC patients after year 1 in the model and assumption that that only 1 in 10,000 patients progresses per year in the ESA arm.				
6	•ERG's entrance and exit thresholds from the different WC categories in the model •Use of ERG's 1-year CCA data from the MAA and MOR-001 to model change in WC use from baseline to year 1 in the model •ERG's increase in 6MWT and FVC in the ESA arm from baseline to year 1 applied in the model according to the MOR-001 and the MAA data •Assumption of 4.86m and 0.1L losses for SoC patients after year 1 in the model and assumption that the effect of ESA observed in the 1-year CCA would be observed for every year of treatment with ESA in the model. For this scenario, the ERG assumed that after year 1 in the model, ESA patients lost 31% less than SoC patients in their 6MWT, (i.e., 3.3m vs 4.86m, respectively, annually). For FVC, the ERG assumed that ESA patients lost 4% less than SoC patients, (i.e., 0.0957L vs 0.1L, respectively, annually).	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

The ERG highlights its concerns around the core assumptions included throughout these five scenarios:

- The assumption that SoC patients starting the model in the asymptomatic state take 3 years to progress to the symptomatic state, while ESA patients take 9 years to become symptomatic – the company based these assumptions on the Montaño *et al.* study for the SoC arm, and on clinical expert opinion for the ESA arm. The ERG notes that the Montaño *et al.* study reported that the mean age of onset of disease was 2.1 years, with initial symptoms recognised between 1 and 3 years. Therefore, the ERG considers that the correct estimate to use for SoC patients in the model is 2 years. Importantly, according to the ERG's clinical experts, even though a delay in the onset of symptoms for ESA patients could be possible, there is no evidence to suggest that such delay would translate into 6 years.

- The ERG received confirmation from the company post-TE that that the utility values used to estimate the utility for SoC patients ([redacted]; [redacted]; [redacted] for NWC; SWC; and WCD, respectively) in the company's model were not based on baseline utility values from the MAA dataset. The company confirmed that the utility values used in the SoC arm are those resulting from a "*composite score from 3 time points (baseline, 12M and 24M), for each wheelchair state*". Therefore, as discussed by the ERG in their response to TE, the ERG disagrees with the use of these utility data in the SoC arm as these reflect the impact of treatment with ESA on patients' quality of life over 2 years. In their response to TE, the ERG reported the results of its additional investigation of the MAA treatment-naïve baseline utility data, using the maximum available baseline data (i.e. including all patients with baseline EQ-5D and WC data), and arrived at the values [redacted] for NWC; SWC; and WCD, respectively.

  The ERG noted that the utility values used in the HST2 (which in turn were taken from the Hendriksz *et al*. 2014 burden of disease study for patients with MPS IVA), were 0.85; 0.58; and 0.06 respectively, in adults (18 years or above) not using a wheelchair, using a wheelchair only when needed, and always using a wheelchair. The ERG also noted that the Hendriksz *et al*. 2014 utility value for WCD adults are [redacted] from that observed in the MAA analysis; however, the WCD and the SWC values in the Hendriksz study are [redacted], for both adults and children. Given the discrepancy in the MAA utilities and the Hendriksz study; the fact that the Hendriksz utilities were accepted in the HST2; and the higher number of adult patients in the published study across each WC category (4 for NWC; 12 for SWC; and 9 for WCD) when compared to the number of adults in the MAA treatment naïve patients (3 for NWC; 3 for SWC; and 2 for WCD), the ERG decided to use the Hendriksz study to estimate the utilities for the SoC arm of the model. Nonetheless, the ERG also acknowledges the relevance of the scenarios provided in this addendum using the baseline utility data collected in the MAA in order to estimate the utility for SoC patients.

Finally, the ERG notes additional concerns around some of the scenarios requested by the NICE technical team. More specifically:

- The use of the company's entrance and exit thresholds from the different WC categories in the model – as discussed in the ERG's response to TE, the company's thresholds lack face validity (as patients progressing from the NWC to the SWC state have an increase of 77m in

their 6MWT) and were based on average values across the baseline, 12-month and 24-month mean 6MWT observed in each time point to estimate the 6MWT value attributable to each WC category in MorCAP1. The ERG noted the inconsistency in the WC thresholds defined in the company's model and the underlying clinical. For example, the threshold used in the company's model of 46m to exit the SWC state (and entering the WCD state) is not consistent with the baseline 6MWT in MOR-001 ([redacted]). Therefore, the ERG's preferred approach remains the use of the entrance and exit threshold re-estimated by the ERG.

- The use of the company's 2-year WC transition data to model change in WC use from baseline to year 1 in the model – given the availability of annual WC change data, the ERG does not agree with the company's approach of using the data on WC change from baseline to year 2 in the MAA and in MorCAP1 to estimate the transition probabilities from baseline to year 1 of the model. The ERG also disagrees with the company's methods of analysis used in the 2-year CCA (i.e. the use of the entire MAA population and of the MorCAP1 population as discussed in the ERG response to TE).
- The assumption that SoC patients in the NWC and the SWC states lose 6.84m in their 6MWT annually – the 6.84m decrease in 6MWT reported in Harmatz *et al*. was that of the matched population to the MOR-005 study, and not for the ITT population. The annual decrease seen in the ITT population in the study was 4.86m (instead of 6.84).
- The assumption that that only 1 in 10,000 ESA patients progresses per year, after year 1 in the model – the ERG has not seen any data to substantiate the company's assumption that ESA patients' 6MWT and FVC values at year 1 do not change for these patients' lifetime. The data in the CCA by 2 years reported in the company's submission show that ESA patients could still progress in their WC dependency from year 1 to year 2, therefore the ERG notes, again, the clinical implausibility in the company's assumption.

The ERG notes that its preferred ICER, making the most possible use of MAA data is based on the following assumptions:

- Assuming that SoC and ESA patients take 2 years to become symptomatic (i.e., no difference in the two arms).
- Using the TPs derived from the ERG's analysis of the 1-year CCA TPs from MOR-001 and the MAA treatment-naïve patients.
- Using the entrance and exit thresholds estimated by the ERG.

- Assuming that after year 1 in the model, SoC patients lose 4.86m and 0.1L in their 6MWT and FVC outcomes, annually, and assuming that ESA has an effect every year in the model, as long as patients are on treatment. Given the lack of data to substantiate any estimate of long-term effectiveness with ESA, the ERG caveats its analysis and notes that the results should be interpreted with caution. For this scenario, the ERG assumed that after year 1 in the model, ESA patients lost [redacted] less than SoC patients in their 6MWT, (i.e., [redacted] vs 4.86m, respectively, annually). This assumption was based on the pooled results from the MAA and MOR-001, which show that ESA patients had an improvement of [redacted] in their 6MWT compared to SoC patients after year 1. For FVC, the ERG assumed that ESA patients lost [redacted] less than SoC patients, (i.e., [redacted] vs 0.1L, respectively, annually). The ERG's assumptions are reported in Table 2, for ease of interpretation.
- Estimating mortality linking changes in FVC predicted to survival. The ERG re-calculated the %FVC predicted values in MOR-001 and assumed an improvement of FVC of [redacted]% associated with ESA as estimated in the ERG's 1-year CCA of FVC data in MOR-001 and the MAA treatment-naïve patients.
- Using the MAA treatment-naïve utility values to estimate utility in the SoC arm of the model and estimating utility increments for the NWC and the SWC utilities for the ESA arm, associated with the 6MWT increase of [redacted] and [redacted] (estimated by the ERG to be the increase in 6MWT results for NWC and SWC patients with ESA, respectively. For the WCD state, the ERG did not apply any utility increments in the ESA arm, as there was no FVC increase observed for ESA patients in the ERG's analysis.
- Using the ERG's assumptions for changes in patients' body weight.
- Replacing the £207 treatments administration cost in the model with the updated £213 estimate.

Table 2. Years to disease progression after year 1 in company's model and ERG's alternative estimates

Outcome by health state at baseline	SoC patients		ESA patients	
	Company's model	**ERG-preferred**	**Company's model**	**ERG-preferred**
Years taken to change from NWC to SWC	[redacted]	14	[redacted]	39
Years taken to change	[redacted]	35	[redacted]	77

from SWC to WCD				
Years taken to change from WCD to paraplegic	[redacted]	7.4	[redacted]	7.7

The resulting ERG-preferred ICER amounts to [redacted] per QALY gained, with incremental discounted costs and QALYs of [redacted], respectively, and incremental undiscounted QALYs of [redacted].

The ERG reiterates that the ICER of [redacted] assumes a life-long benefit associated with ESA, as patients take longer to progress from the all the WC states when compared to SoC patients. For example, as reported in Table 2, it takes ESA patients 77 years to progress from the SWC to the WCD state, compared to 35 years in the SoC arm; and 39 years vs 14 for patients to move from the NWC to the SWC states, respectively.

3 References

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6. Montaño AM, Tomatsu S, Brusius A, Smith M, Orii T. Growth charts for patients affected with Morquio A disease. *Am J Med Genet A* 2008; **146A**: 1286-95.