14 September 2017
EMA/711038/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Vimizim

elosulfase alfa

Procedure no: EMEA/H/C/002779/P46/008

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Introduction

On 22 December 2016, the MAH submitted a completed paediatric study for Vimizim (active substance recombinant human n-acetylgalactosamine-6-sulfatase; elosulfase alfa; or BMN 110), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. On July 20th 2017 the response to the outstanding issues were received. The assessment of the responses can be found in section 5 and the updated overall conclusion and recommendation in section 3 of this report.

A short clinical overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH submitted the results of study MOR-005: *A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome).*

Study MOR-004 is the pivotal study which formed the basis for approval (see EPAR). Participants who completed MOR-004 were eligible to continue treatment in the 24-week extension study MOR-005 (part I) and continue up to 240 weeks (part II).

2.2. Information on the pharmaceutical formulation used in the study

Not applicable.

2.3. Clinical aspects

2.3.1. Introduction

MPS IVA is a rare inherited disorder caused by mutations of the gene that codes for the lysosomal enzyme N-acetylgalactosamine-6-sulfatase (GALNS), which degrades glycosaminoglycans（GAGs) including keratan sulfate (KS) and chondroitin sulfate. With insufficient GALNS, GAGs progressively accumulate in multiple organs and tissues. The pervasive and progressive accumulation of GAGs leads to significant morbidities and multi-systemic clinical impairments resulting in diminished functional capacity, decreased endurance, impaired quality of life, and early mortality. The most common features of patients with MPS IVA are progressive skeletal dysplasia requiring frequent surgical procedures mostly related to musculoskeletal or respiratory dysfunction, and a significant limitation in mobility, endurance, and respiratory function. In addition, pain is frequently reported by patients with MPS IVA.

Vimizim is a formulation of elosulfase alfa, which is a purified enzyme produced by recombinant DNA technology in a Chinese hamster ovary cell line. Vimizim is an enzyme replacement therapy (ERT) intended to provide exogenous enzyme GALNS allowing cellular uptake by the mannose-6-phosphate receptor and transportation to the lysosomes. This enzyme uptake into the lysosomes promotes increased catabolism of KS in tissue macrophages, hyaline cartilage, other connective tissues, and heart valve, and reduces the progressive accumulation of KS which is responsible for the clinical manifestations of MPS IVA.

Marketing Authorisation was granted for Vimizim (elosulfase alfa; BMN 110) in the European Union on 28 April 2014.

At the time of MAA, study MOR-005 was an ongoing phase 3 extension Study to Evaluate the Long-Term Efficacy and Safety of elosulfase alfa in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome). For study MOR-005 data up to week 24 have been assessed during the MAA. Now data up to week 168 are submitted.

No SmPC changes are proposed by the applicant.

2.3.2. Clinical study

Study MOR-005: *A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome).*

Both the interim result and final study results of the MOR-005 study were published as:

- Hendriksz *et al.* Impact of long-term elosulfase alfa treatment on respiratory function in patients with Morquio A syndrome. J Inherit Metab Dis (2016) 39:839–847.
- Hendriksz *et al.* Long-term endurance and safety of elosulfase alfa enzyme replacement therapy in patients with Morquio A syndrome. Molecular Genetics and Metabolism 119 (2016) 131–143.

Description

Methods

- **Study participants**

Individuals with MPS IVA who completed MOR-004, who did not have any conditions that would interfere with study completion, and who were expected to be able to comply with the treatment schedule, were eligible to participate in this study.

Rapporteur's comment

The methods and patients selection of study MOR004/005 are already described in the initial day 80 clinical assessment report during the Marketing authorisation application (MAA).
The included patient population is characteristic for a population of patients suffering from Morquio disease. Patients with (stem cell) transplantation are excluded because the transplanted patients are capable to produce acetylgalactosamine; thus those patients would not benefit from treatment. The study was limited to patients 5 years of age and over.

- **Treatments**

Figure 1 present the design of the MOR-004 and MOR-005 study. The combination of MOR-004 and MOR-005 data creates 4 treatment cohorts as described below. Cohorts in Part 1 were:

- Cohort PBO-QOW: Patients received placebo in MOR-004 and a BMN 110 dose regimen of 2.0 mg/kg/qow (every other week) in MOR-005
- Cohort PBO-QW: Patients received placebo in MOR-004 and a BMN 110 dose regimen of 2.0 mg/kg/qw (every week) in MOR-005

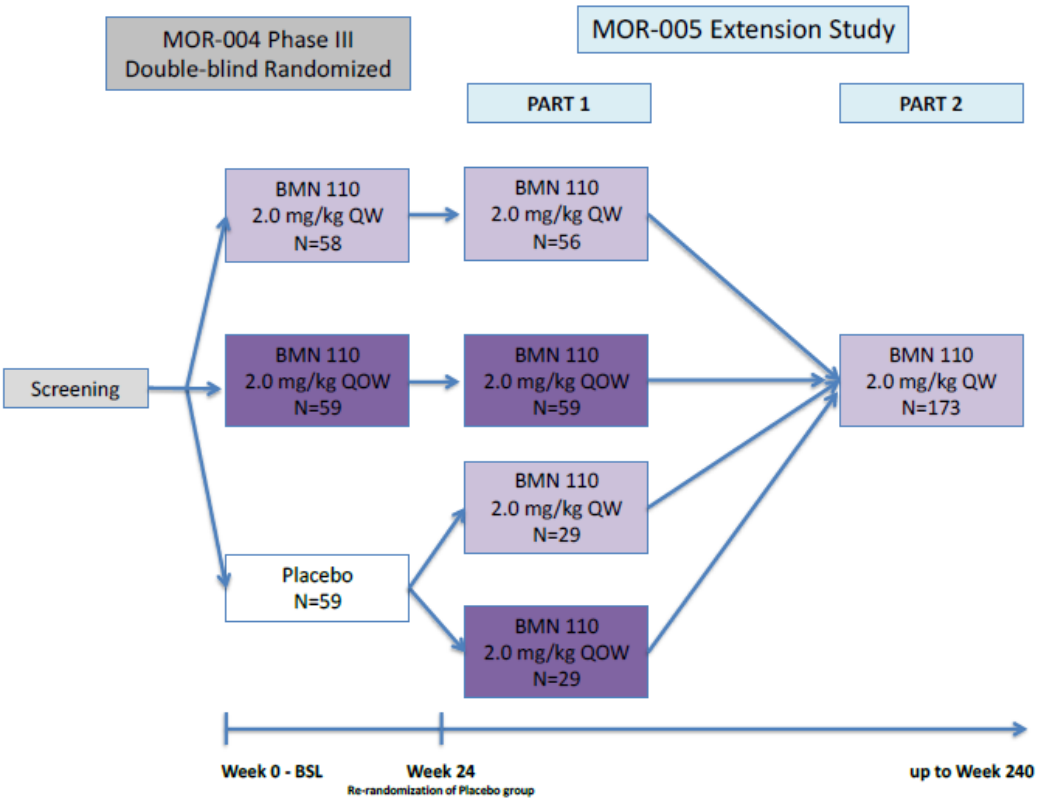
- Cohort QOW-QOW: Patients received BMN 110 dose regimens of 2.0 mg/kg/qow in MOR-004 and MOR-005
- Cohort QW-QW: Patients received BMN 110 dose regimens of 2.0 mg/kg/qw in MOR-004 and MOR-005

With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the 2.0 mg/kg/qw dosing regimen.

During Part 1 (the double-blind phase of the study), patients received intravenous (IV) infusions of BMN 110 at a dose of 2.0 mg/kg/qw or 2.0 mg/kg/qow until 30NOV2012. Patients randomized to the 2.0 mg/kg/qow arm received infusions of placebo on alternating weeks, to mask active drug weeks.

In Part 2 (as of 01DEC2012), all patients receive 2.0 mg/kg/qw for the remainder of the study.

Figure 1: Study design of MOR-004 and MOR-005.



PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw With the initiation of Part 2 of MOR-005 on 01DEC2012, all subjects were transitioned to the 2.0 mg/kg/qw dosing regimen.

The specific time of transition for each subject depended on date of study enrolment, ranging from Week 39 to Week 96.

The following BMN 110 manufacturing lots were utilized in the study

In Part 1, placebo solution was administered IV, at a volume equivalent to that needed for a 2.0 mg/kg dose of BMN 110 diluted in 0.9% sodium chloride, on alternating weeks for the 2.0 mg/kg/qow arm to mask active drug weeks. Each infusion was administered over a period of approximately 4 hours.

The placebo formulation consisted of the same excipients as, was identical in appearance to, and was prepared in the same manner as BMN 110.

The following placebo manufacturing lots were utilized in the study (note that lot numbers were identical to those of BMN 110 to maintain blind):

Placebo solution is not used in Part 2.

Rapporteur's comment
Note that part 1 of this study was already discussed during the MAA assessment. Therefore, the assessment report will mainly focus on the data of part 2 (week 72/48), where relevant the complete study data will be taken into account. Results obtained after the completion of part 1 of study MOR005 indicated that the BMN 110 2.0 mg/kg/qw regimen is superior to placebo (study MOR004) whereas the BMN 110 2.0 mg/kg/qow regimen - based on the 6MWT results - could not demonstrate superiority over placebo(study MOR 005, part 1).

The placebo-QW and QW-QW groups are the most relevant groups, the results from these two groups will contribute to the knowledge on the long term treatment.

In the other groups (QOW-QOW and PBO-QOQ) conclusions should be drawn with caution, as these groups switched to the approved SmPC dosing not earlier than at the start of part 2 of the study. As the specific time of transition for each patient depended on date of study enrolment, ranging from Week 39 to Week 96, there is variation in time on a specific dosing. This hampers the assessment of the long term effect in these two groups.

Duration of Treatment:
Patients receive treatment up to Week 240 or until one of the following occurs: the patient (or their parent or legally authorized representative) withdraws consent and the patient discontinues from the study or study treatment, the patient is discontinued from the study or study treatment at the discretion of the Investigator or BioMarin, or the study is terminated.

Rapporteur's comment
A follow-up of 240 weeks is an acceptable period; any clinically relevant improvement should be observable within this interval.

Study MOR-005 was planned to continue up to Week 240, however it was prematurely terminated by the MAH. The timing of the termination as well as justification for this should be provided by the applicant (**OC**).

- **Outcomes/endpoints**

Efficacy:

- endurance tests:
  - 6MWT
  - 3MSCT
- urine keratan sulfate concentration (normalized to creatinine)

- respiratory function tests:
    - maximum voluntary ventilation (MVV)
    - forced vital capacity (FVC)
    - forced expiratory volume in 1 second (FEV1)
    - forced inspiratory vital capacity (FIVC)
    - forced expiratory time (FET)
- anthropometric measurements (standing height, length, sitting height, and weight)
- skeletal radiographs of lumbar spine and lower extremity (lower extremity radiographs are done only for patients ≤20 years of age)
- MPS Health Assessment Questionnaire
- audiometry examinations

Rapporteur's comment
The endpoints for study MOR-005 are similar to those used in study MOR-004.

Exploratory Efficacy Endpoints:
- blood inflammatory biomarkers
- biochemical markers of bone and cartilage metabolism
- PIQ

Safety:
The safety population consisted of all patients who were enrolled and received at least one dose of study drug in MOR-005. The safety population was analysed according to the treatment received and for the Total population. All safety analyses are presented based on the safety population. Safety data were summarized descriptively by study week. Safety was evaluated by monitoring AEs, changes in physical examination, vital signs, laboratory tests, ECGs, ECHOs, immunogenicity tests, and concomitant medications after the initial study drug administration.

A hypersensitivity AE was defined as any AE that coded to a PT included in the Standardized MedDRA (v. 16.1) for the Total population) Queries (broad) for anaphylactic reaction and angioedema. To obtain the Total population incidence of hypersensitivity AEs, duplicate patient records were deleted.

In fusion associated reactions (IARs) were defined broadly per protocol any AE occurring after start of the infusion and within 1 day following the end of the infusion, regardless of the investigator's assessment of relatedness to study drug administration.

Immunogenicity:
Routine immunogenicity testing included assays for anti-BMN 110 total TAb, NAb, and anti-BMN 110 IgE. Serum sample collection for immunogenicity testing was scheduled at Baseline, Weeks 12, and every 12 weeks thereafter in Part 1 and every 24 weeks in Part 2. The total antibody assay measures multiple anti-drug antibody isotypes in one assay, eliminating the need for multiple isotype-specific assays to assess the anti-drug antibody response.

Pharmacokinetics:
During this study, pharmacokinetic samples are collected from all Japanese patients to fulfil the Japanese health authority request.

Rapporteur's comment
There are many endpoints in this relative small patient population.

The 6MWT, respiratory function, anthropometric measures and the MPS Health Assessment Questionnaire together are considered indicative for observing a clinically relevant effect in these patients. As elosulfase alfa is a lifelong treatment, the results of these endpoints will be especially important in the paediatric population. As these children are still in the development phase, the aforementioned endpoints will be indicative whether in the long run these patients will benefit from treatment. This benefit should be clinically relevant for these patients, e.g. anthropometric measures (z-scores) showing a positive trend or stable trend towards normal values. This also applies to the respiratory function, and the patients should have benefit in terms of self-care and mobility. As mentioned above, the population that received the 2 mg/kg/QW (QW-QW and PBO-QW) dosing is considered the most important population to demonstrate any sustained effect of long-term treatment.

- **Sample size**

Planned: up to 175
Enrolled: 173; 2 patients who completed MOR-004 did not enrol in MOR-005.
Part 1 of the study was completed on 30NOV2012; 172 patients completed Part 1 (1 patient withdrew consent) and remain on study as of the data cut-off date of 04JAN2013. Part 2 was initiated on 01DEC2012 and was completed on 16JUN2016.

- **Statistical methods**

A per-protocol (PP) population was previously used to perform sensitivity analyses for the efficacy endpoints in Part 1. The analyses based on the PP population were performed for the abbreviated CSR (18 March 2013), but given that the final CSR is based on follow-up of 120 weeks or more for most patients, the amount of data omitted in a PP analysis would be large using the same criteria. For this reason, a MPP population was defined for this longer term study, replacing the PP population.

The MPP population was used for this final report to perform sensitivity analysis for the efficacy endpoints. The MPP criteria are to omit from the ITT population the following patients from analysis:

1. Patients with any orthopaedic surgery in the first 120 weeks of MOR-004/005, based on medical monitor review.

2. Patients who were administered less than 80% of dosing within the first 120 weeks of MOR-004/005.

In Part 1, available efficacy variables including endurance tests, urine keratan sulfate, RFTs, and anthropometric measurements are compared between treatment groups. Due to the nature of this ongoing study, all statistical comparisons were for descriptive purposes only.

Anthropometric measurements assessed at MOR-004 Baseline, Week 24, and every 24 weeks in Part 1 and Part 2 of MOR-005 were summarized. Normalized standing height (z-score) was computed using Centers for Disease Control (CDC) normal population values. Change from Baseline in all anthropometric measurements (length, standing height, sitting height, weight) were summarized. Graphical displays showing the mean and standard error of the mean were supplied.
Baseline summaries and safety analysis are descriptive. Descriptive statistics for continuous variables consist of mean, standard deviation, median, and range and also include count and percentage for categorical variables.

Patients who received any dose of study drug and had any post-treatment safety information were included in the safety analysis. Adverse events were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA v. 15.0). The number and percentage of patient incidences of all AEs, AEs related to study drug, serious adverse events (SAEs), SAEs related to study drug, deaths during the study, study drug discontinuations due to an AE, or study withdrawals due to an AE were tabulated by System Organ Class (SOC) and Preferred Term (PT). Patient listings are provided for SAEs, deaths, and AEs leading to study drug discontinuation or study withdrawals. All AE summaries include only treatment-emergent AEs reported during the study period. Infusion associated reactions are summarized by SOC, PT, and severity. The following safety measures are summarized descriptively: concomitant medications, clinical laboratory tests, vital signs, and immunogenicity results. Cervical spine (flexion–extension) X-ray data and results from routine physical examinations will be presented as listings.

Serum samples were collected for immunogenicity testing at Baseline, Week 12, and every 12 weeks thereafter in Part 1 and are collected every 24 weeks in Part 2. Routine immunogenicity testing includes assays for anti-BMN 110 total antibody (TAb), neutralizing antibody (NAb), which here and throughout the document refers to antibodies capable of inhibiting binding of BMN 110 to the cation-independent mannose-6-phosphate receptor, and anti-BMN 110 immunoglobulin E (IgE). When TAb was negative, NAb was not assessed. Anti-BMN 110 IgE, total IgE, complement component 4, and serum tryptase were assessed when patients experienced a severe (grade 3 according to CTCAE, v.4.0) IAR or an IAR requiring infusion interruption or discontinuation.

Study MOR-005 includes the same patients, routes of administration, dosage regimens, and safety and efficacy assessments as MOR-004. Given these similarities, combining the safety and efficacy data from the 2 studies was considered appropriate.

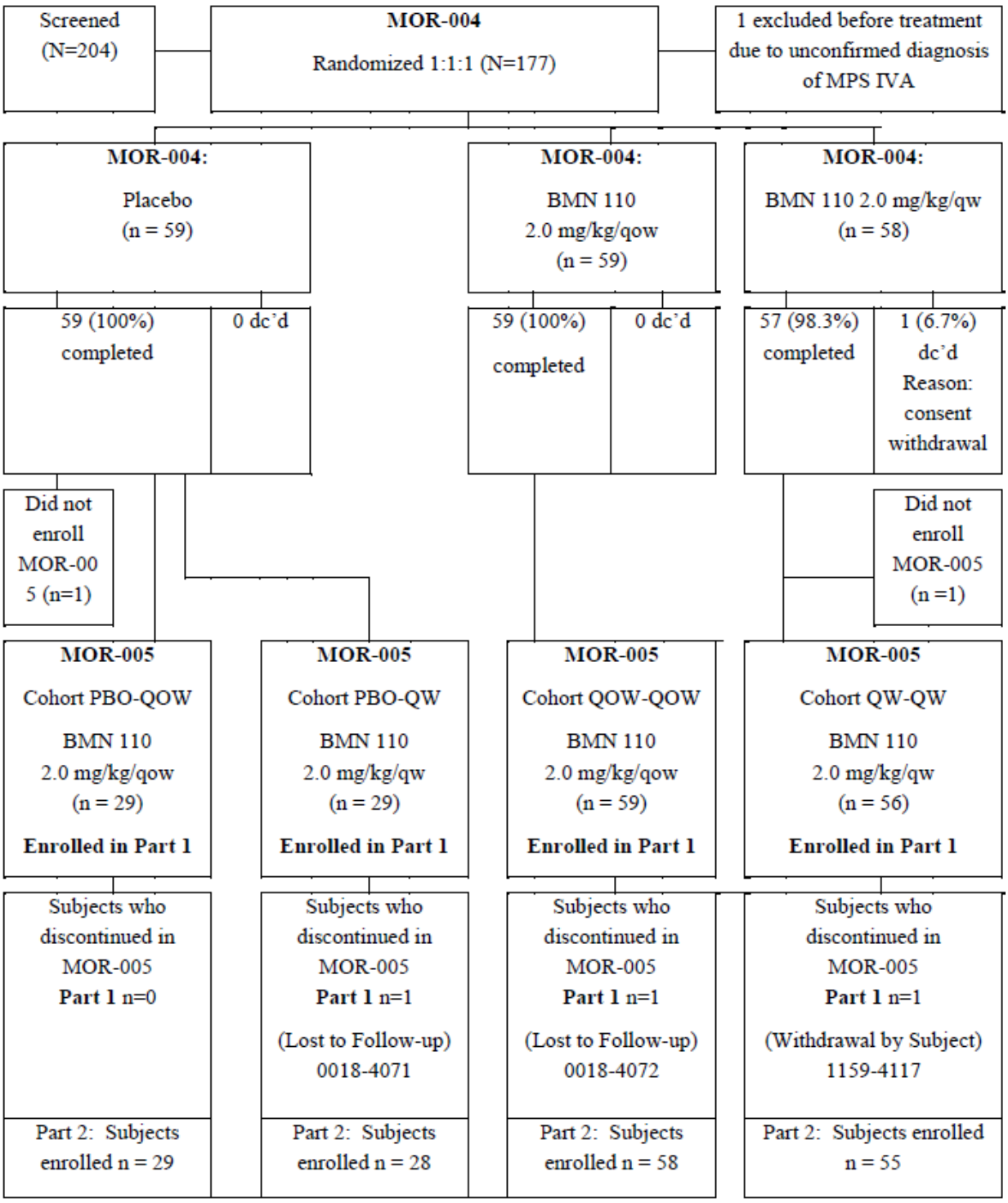
Rapporteur's comment

The applicant proposes to replace the PP criteria reported in the MAA with the MPP criteria which omit patients with orthopaedic surgery in the first 120 weeks of MOR-004/005, based on medical monitor review and patients who were administered less than 80% of dosing within the first 120 weeks of MOR-004/005 from the ITT. In total 55 patients were excluded in the MPP population (Listing 16.2.3.2).The applicant's rationale for using a MPP population instead of the PP can be accepted.

Further, it is acceptable to combine the results of study MOR-004 and MOR-005 as patients, routes of administration, dosage regimens, and safety and efficacy assessments were identical. This was already accepted during the MAA where the interim results of study MOR-005 were submitted (data up to week 48).

Results

- **Participant flow**



Subjects who discontinued in MOR-005 **Part 2**	Subjects who discontinued in MOR-005 **Part 2**	Subjects who discontinued in MOR-005 **Part 2**	Subjects who discontinued in MOR-005 **Part 2**
n = 29	n = 28	n = 58	n = 55
n = 28 due to Study Termination by Sponsor n = 1 due to Withdrawal by Subject	n = 28 due to Study Termination by Sponsor	n = 49 due to Study Termination by Sponsor n = 4 due to Withdrawal by Subject n = 3 due to AE n = 1 due to lost to Follow-up n = 1 "other"	n = 53 due to Study Termination by Sponsor n = 2 due to AE

- **Baseline data**

There were no meaningful imbalances in the ITT population between the continuous-treatment (QOW-QOW and QW-QW) cohorts at Baseline in demographic and other baseline characteristics.

Although some variability in demographic and baseline characteristics was evident, there is no indication that the continuous-treatment cohorts in the ITT population were substantially different at Baseline in demographic or disease state characteristics, as expected, as nearly all of these patients continued into MOR-005.

There were imbalances in the ITT population between the placebo-switch cohorts at Baseline in demographic and other baseline characteristics. Upon re-randomization of the placebo cohort in MOR-004 (n=59) to either the weekly (n=29) or every other week (n=29) dose regimens in MOR-005, imbalances between the MOR-005 cohorts PBO-QOW and PBO-QW were noted in endurance measures and age at Week 24 (MOR-005 Week 0). Because this re-randomization was not stratified by age or 6MWT categories, as was the case at the time of randomization into MOR-004, imbalances of the MOR-005 placebo-switch cohorts by chance is highly plausible.

In the continuous-treatment cohorts QOW-QOW and QW-QW, age of study patients at enrolment ranged from 5.0 to 49.1 years. Distribution of age groups was generally similar between cohorts. Mean age (15.3, 12.8 years) and proportion of males (57.6%, 46.4%) were similar in the QOW-QOW and QW-QW cohorts, respectively. In the placebo-switch cohorts PBO-QOW and PBO-QW, age of study patients at enrolment ranged from 5.0 to 57.4 years. Mean age (16.7, 13.5 years) and proportion of males (51.7%, 37.9%) were higher in the PBO-QOW cohort compared to the PBO-QW cohort, respectively. As expected in this patient population, the most commonly represented age group was 5 to 11 years in each of the 4 cohorts.

Table 1: Demographic Characteristics (Intent-To-Treat Population – MOR-005).

Demographics	PBO-QOW[a] (n = 29)	PBO-QW[a] (n = 29)	QOW-QOW[a] (n = 59)	QW-QW[a] (n = 56)
Age at Enrolment (years)				
n	29	29	59	56
Mean (SD)	16.7 (13.66)	13.5 (8.50)	15.3 (10.79)	12.8 (8.01)
Median	11.1	11.9	12.0	10.6
Min , Max	5.0 , 57.4	5.0 , 33.2	5.0 , 49.1	5.0 , 41.9
Age Group (years)				
5 - 11	15 (51.7%)	15 (51.7%)	31 (52.5%)	32 (57.1%)
12 – 18	7 (24.1%)	7 (24.1%)	16 (27.1%)	16 (28.6%)
≥ 19	7 (24.1%)	7 (24.1%)	12 (20.3%)	8 (14.3%)
Sex				
Female	14 (48.3%)	18 (62.1%)	25 (42.4%)	30 (53.6%)
Male	15 (51.7%)	11 (37.9%)	34 (57.6%)	26 (46.4%)
Race				
Asian	4 (13.8%)	7 (24.1%)	15 (25.4%)	14 (25.0%)
Black or African American	0	0	2 (3.4%)	2 (3.6%)
White	25 (86.2%)	18 (62.1%)	35 (59.3%)	35 (62.5%)
Other	0	4 (13.8%)	7 (11.9%)	5 (8.9%)
Ethnicity				
Hispanic or Latino	4 (13.8%)	8 (27.6%)	16 (27.1%)	9 (16.1%)
Not Hispanic or Latino	25 (86.2%)	21 (72.4%)	43 (72.9%)	47 (83.9%)

a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw; SD, standard deviation
Include patients who entered MOR-005 using MOR-004 baseline values

Baseline disease characteristics for patients enrolled in MOR-005, using the parent study MOR-004 Baseline values, are provided in Table 2.

Due to the heterogeneity of the disease, patients had a wide variation in their functional impairment and organ system involvement (Table 2).

Table 2: Baseline Characteristics (Intent-To-Treat Population – MOR-005).

	PBO-QOW[a] (n = 29)	PBO-QW[a] (n = 29)	QOW-QOW[a] (n = 59)	QW-QW[a] (n = 56)
6-Minute Walk Test (meters)				
n	29	29	59	56
Mean (SD)	219.7 (74.22)	207.2 (64.87)	205.7 (81.19)	209.4 (71.80)
Median	239.5	217.2	218.0	218.7
Min , Max	36.2 , 309.9	93.0 , 312.2	47.1 , 319.6	56.3 , 321.5
Walk Category				
<= 200m	11 (37.9%)	11 (37.9%)	24 (40.7%)	21 (37.5%)
> 200m	18 (62.1%)	18 (62.1%)	35 (59.3%)	35 (62.5%)
Walking Aids Used[b]	5 (17.2%)	6 (20.7%)	16 (27.1%)	8 (14.3%)
3-Minute Stair Climb Test (stairs/minute)				
n	29	29	59	56
Mean (SD)	33.1 (15.60)	26.9 (12.08)	27.1 (15.80)	30.1 (16.24)
Median	33.0	29.0	25.5	30.7
Min , Max	0.0 , 59.0	0.0 , 50.0	0.0 , 66.8	0.0 , 71.9
Normalized Urine KS[c] (ug/mg)				
n	28	29	59	56
Mean (SD)	22.7 (15.27)	28.5 (14.89)	28.6 (21.17)	27.2 (14.22)
Median	25.0	30.3	27.4	25.0
Min , Max	3.1 , 50.5	2.5 , 52.8	2.4 , 117.3	2.1 , 59.0
Age at the Time of MPS IVA Diagnosis (years)				
n	29	29	59	56
Mean (SD)	5.9 (5.79)	6.9 (7.20)	7.5 (8.43)	6.8 (7.18)
Median	3.9	4.4	5.2	4.3
Min , Max	1.2 , 31.2	1.6 , 31.3	-0.3 , 48.2	0.1 , 37.4
Time since MPS IVA Diagnosis (years)				
n	29	29	59	56

Mean (SD)	10.8 (11.25)	6.7 (7.35)	7.8 (7.59)	6.0 (5.78)
Median	6.1	3.5	5.5	4.6
Min , Max	0.0 , 37.7	0.3 , 27.4	0.2 , 32.0	0.2 , 26.0
Height Percentile Groups				
< 3rd percentile	26 (89.7%)	27 (93.1%)	52 (88.1%)	54 (96.4%)
≥ 3rd to < 10th percentile	3 (10.3%)	1 (3.4%)	2 (3.4%)	0
≥ 10th to < 25th percentile	0	0	0	0
≥ 25th to < 50th percentile	0	0	0	0
≥ 50th percentile	0	0	1 (1.7%)	0
Baseline height not available	0	1 (3.4%)	4 (6.8%)	2 (3.6%)

a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw
SD, standard deviation
b walking aids used in 6MWT include crutches, walker/walking frame and cane/walking stick.
c urine KS (keratan sulfate) is calculated as urine keratan sulfate divided by urine creatinine.
Include patients who entered MOR-005 using MOR-004 baseline values.

Rapporteur's comment

As already concluded during the MAA assessment, in the double blind phase of study MOR-004 there were imbalances in the placebo controlled groups. After enrolment in MOR-005 part 1 this imbalance has been solved for the previous on placebo patients. The applicant's interim report (cut off 18 March 2013), submitted during the MAA, summarizes the results for the entire Part 1 study efficacy data.

The majority of the patient's ITT population (n=173) are paediatric patients; 5-11 years, 93/173 (53.8%); 12-18 years 46/173 (26.6%), over 19 years 31/173 (19.7%). The youngest patient enrolled was 5 years old and the eldest 57 years.

The applicant is requested to submit the baseline data and efficacy results for the paediatric patients and paediatric subpopulation separately (**OC**).

The applicant is requested to submit the baseline demographics and characteristics for the MPP population, paediatric, adult and paediatric subpopulations separately (**OC**).

- **Outcomes and estimation**

Efficacy results are first presented for patients who received the same BMN 110 treatment regimen from Baseline of the parent study (MOR-004) to Week 48 (QW-QW and QOW-QOW [continuous-treatment] cohorts), followed by results from patients who switched from placebo treatment in MOR-004 to BMN 110 treatment in MOR-005 (PBO-QW and PBO-QOW [placebo-switch] cohorts).

The primary efficacy variable of this extension study was distance walked in a 6MWT, which provides a measure for endurance. The 3MSCT, also a measure of endurance, and normalized urine KS were secondary efficacy variables. The urine KS measurements were normalized by dividing by urine creatinine levels, resulting in µg/mg creatinine units. In Part 1 of MOR-005, the 6MWT and the 3MSCT were performed at Week 12 and Week 24, and at 24-week intervals thereafter. Normalized urine KS was assessed every 12 weeks. In Part 2 of MOR-005, the 6MWT and 3MSCT were performed at 48-week intervals; normalized urine KS was assessed every 24 weeks. Endurance tests were performed in duplicate (on separate days) and the average of the 2 measurements was used as the score for that week. Patients who were physically unable to perform the endurance tests were scored as zero meters or stairs/minute.

With the initiation of Part 2 (01DEC2012), all patients in QOW-QOW cohort began receiving BMN 110 2.0 mg/kg weekly; the specific time of transition for each patient depended on date of study enrolment, ranging from Week 39 to Week 96 (Figure 1).

6MWT:

For Part 1, patients showed sustained improvement in 6MWT distance through Weeks. The interim report (18MAR2013) summarizes results for the Part 1. Continued treatment with weekly BMN 110 in MOR-005 Part 2 demonstrated further improved 6MWT results for the Total population in the ITT population (n=173) (Figure 2) and for the MPP population (n=124) (Figure 3). Mean (SE) change from baseline in 6MWT distance over 168 weeks for ITT and MPP populations are shown. Not all patients reported results for all time points (including MOR-005 Week 0); the number of patients with data available are shown for each time point. Discussion of data after Week 168 is not included due to the relatively low number of patients that continued on the study after Week 168.

Table 3 displays a descriptive summary of the 6MWT distance change from baseline for the ITT population. A descriptive summary of the 6MWT distance change from baseline for MPP population are provided in Table 4.

The main reason reported for not performing the tests was that the patients were physically unable to perform them. Patients who could not complete a 6MWT (including the primary reason) are presented by time point. The primary reasons for failing to complete a test were fatigue and pain. For patients that used walking aids, they were required to use the same type of walk aid throughout the study to avoid adding uncontrolled variation and introducing bias in estimation of treatment effect.

Table 3: Descriptive Summary of 6-Minute Walk Test Change from Baseline (Intent-to-Treat Population - MOR-004 and MOR-005).

6-Minute Walk Test (meters)	PBOa	PBO-QOW[a]	PBO-QW[a]	QOW-QOW[a]	QW-QW[a]	Total (n = 176)
	(n = 59)	(n = 29)	(n = 29)	(n=59)	n=58)	
Baseline						
n	59	29	29	59	58	176
Mean (SD)	211,9 (69,88)	219,7 (74,22)	207,2 (64,87)	205,7 (81,19)	203,9 (76,32)	207,2 (75,58)
Median	228,9	239,5	217,2	218	216,5	217,6
Min, Max	36,2 , 312,2	36,2 , 309,9	93,0 , 312,2	47,1 , 319,6	42,4 , 321,5	36,2 , 321,5
Week 24 (MOR-005 Week 0) -Change from Baseline[b]						
n	59	29	29	59	57	175
Mean (SD)	13,5 (50,63)	23,8 (56,21)	5,0 (43,27)	11,1 (49,95)	36,5 (58,49)	20,2 (54,02)
Median	9,9	13,9	0,4	15,6	20	14,3
Min, Max	-99,2 , 220,5	-87,8 , 220,5	-99,2 , 95,1	-210,0 , 114,2	-57,8 , 228,7	-210,0 , 228,7
Week 36 (MOR-005 Week 12) -Change from Baseline[b]						
n	NA	28	28	58	54	168
Mean (SD)		31,2 (55,36)	4,0 (68,48)	23,1 (48,70)	42,2 (52,13)	27,4 (55,65)
Median		23,3	3,1	18,8	41,7	22,8
Min, Max		-62,2 , 181,5	-183,5 , 128,1	-93,5 , 129,9	-61,5 , 228,9	-183,5 , 228,9
Week 48 (MOR-005 Week 24) -Change						

from Baseline[b]						
nc	NA	14	13	26	26	79
Mean (SD)		15,8 (119,49)	-4,2 (105,85)	3,7 (68,46)	33,4 (64,89)	14,3 (84,68)
Median		18,9	30	13,5	32,3	17,5)
Min, Max		-309,9 , 241,5	-234,1 , 143,4	-238,5 , 120,0	-120,0 , 181,5	-309,9 , 241,5
Week 72 (MOR-005 Week 48) -Change from Baseline[b]						
n	NA	28	27	57	55	167
Mean (SD)		41,5 (89,24)	-1,5 (112,07)	27,2 (56,66)	30,6 (73,66)	26,1 (79,26)
Median		31	17,9	29,8	32	30,4
Min, Max		-101,0 , 336,0	-312,2 , 171,1	-125,4 , 173,2	-149,4 , 229,3	-312,2 , 336,0
Week 120 (MOR-005 Week 96) -Change from Baseline[b]						
n	NA	28	27	54	54	163
Mean (SD)		32,3 (92,13)	-2,9 (95,69)	6,0 (86,28)	29,7 (81,37)	16,9 (87,67)
Median		34	20,5	3,5	41	27,8
Min, Max		-309,9 , 227,5	-245,2 , 199,4	-277,4 , 150,5	-321,5 , 211,3	-321,5 , 227,5
Week 168 (MOR-005 Week 144) -Change from Baseline[b]						
n	NA	10	13	32	26	81
Mean (SD)		52,2 (100,07)	20,1 (80,79)	5,2 (81,54)	-8,8 (101,24)	8,9 (90,81)
Median		41,4	27	-0,9	8,1	19,8
Min, Max		-70,6 , 307,5	-166,0 , 134,0	-200,9 , 159,8	-309,0 , 133,6	-309,0 , 307,58

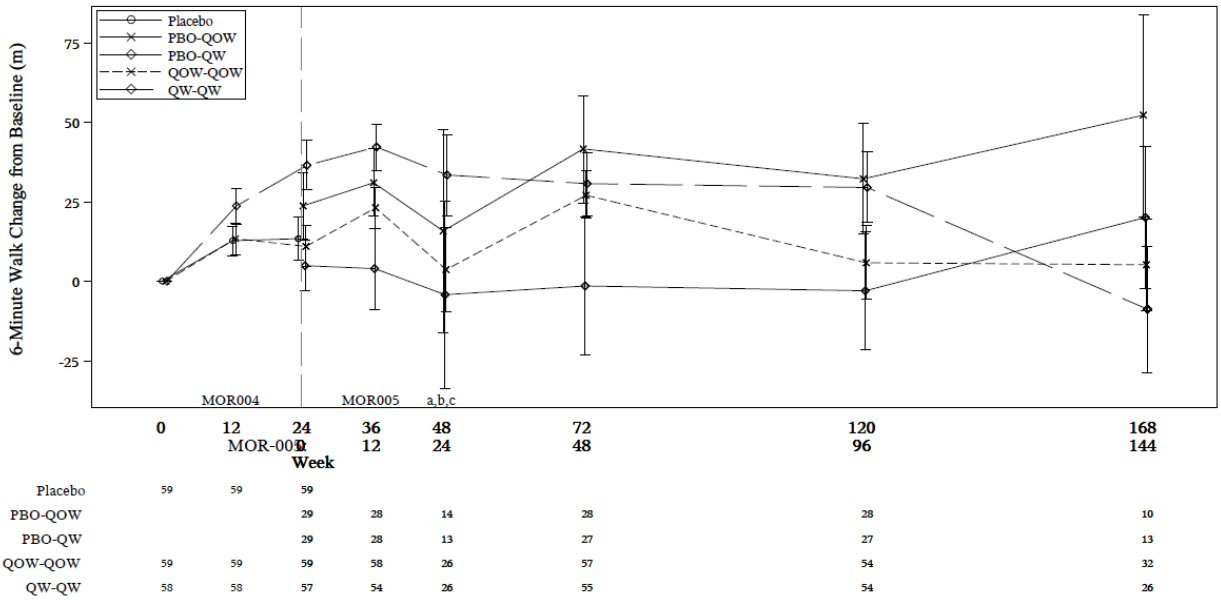
Table 4: Descriptive Summary of 6-Minute Walk Test at Scheduled Visits (Analysis Population: Modified Per Protocol).

Distance Walked Average, meters	PBO[a] (n = 39)	PBO-QOW[a] (n = 20)	PBO-QW[a] (n = 19)	QOW-QOW[a] (n = 42)	QW-QW[a] (n = 43)	Total (n = 124)
Baseline						
n	39	20	19	42	43	124
Mean (SD)	199.7 (71.94)	208.7 (78.12)	190.2 (65.54)	195.9 (80.40)	208.8 (73.24)	201.6 (74.94)
Median	209.6	224.5	183.5	207.2	226.9	210.6
Min, Max	36.2 , 304.4	36.2 , 304.4	93.0 , 286.5	47.1 , 319.6	56.3 , 309.0	36.2 , 319.6
Week 24 (MOR-005 Week 0) - Change from Baseline[b]						
n	39	20	19	42	43	124
Mean (SD)	20.2 (52.43)	30.3 (56.53)	9.6 (46.87)	13.6 (52.65)	41.5 (59.89)	25.4 (56.08)
Median	13.5	14.0	0.4	17.0	22.8	17.3
Min, Max	-99.2 , 220.5	-35.9 , 220.5	-99.2 , 95.1	-210.0 , 90.4	-41.4 , 228.7	-210.0 , 228.7
Week 36 (MOR-005 Week 12) - Change from Baseline[b]						
n	NA	19	19	42	42	122
Mean (SD)		32.1 (58.57)	12.0 (79.64)	32.2 (48.66)	44.4 (53.94)	33.2 (57.94)
Median		28.2	13.5	29.3	40.8	32.1
Min, Max		-62.2 , 181.5	-183.5 , 128.1	-93.5 , 129.9	-37.5 , 228.9	-183.5 , 228.9
Week 48 (MOR-005 Week 24) - Change from Baseline[b]						
nc	NA	8	7	15	19	49
Mean (SD)		39.6 (90.14)	22.5 (104.50)	14.5 (53.55)	37.4 (73.05)	28.6 (74.20)
Median		26.0	30.9	16.1	26.5	26.5
Min, Max		-48.8 , 241.5	-183.5 , 143.4	-105.0 , 120.0	-120.0 , 181.5	-183.5 , 241.5
Week 72 (MOR-005 Week 48) - Change from Baseline[b]						
n	NA	20	18	42	43	123
Mean (SD)		54.5 (85.19)	37.7 (69.35)	35.3 (58.19)	37.5 (72.17)	39.6 (69.11)
Median		36.4	24.6	35.3	32.0	32.0
Min, Max		-87.0 , 336.0	-87.4 , 171.1	-125.4 , 173.2	-120.0 , 229.3	-125.4 , 336.0
Week 120 (MOR-005 Week 96) -Change from Baseline[b]						
n	NA	20	19	41	43	123
Mean (SD)		60.8 (64.45)	19.8 (86.69)	19.7 (77.29)	38.6 (66.65)	33.0 (73.94)
Median		46.6	42.3	30.0	42.6	36.0
Min, Max		-25.4 , 227.5	-172.5 , 199.4	-277.4 , 150.5	-321.5 , 211.3	-277.4 , 227.5
Week 168 (MOR-005 Week 144) -Change from Baseline[b]						
n	NA	5	8	26	22	61
Mean (SD)		346.9 (146.38)	225.1 (112.40)	10.0 (84.66)	-12.3 (106.34)	8.8 (98.69)
Median		321.5	276.9	13.3	8.1	23.3

Min, Max		196.2 , 588.0	10.0 , 333.5	-200.9 , 159.8	-309.0 , 133.6	-309.0 , 307.5

N, number of patients; SD, standard deviation; QW, every week; QOW, every other week.
With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the2.0 mg/kg/qw dosing regimen.
a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
b Change is equal to current value minus the baseline value.
c Week 48 endurance assessment results included only patients who reached Week 48 while in Part 1 of the study as there was no Week 48 assessment in Part 2. This led to a reduced sample size at Week 48.

Figure 2: Mean Change in 6-Minute Walk Test (Intent-to-Treat Population - MOR-004 & MOR-005).

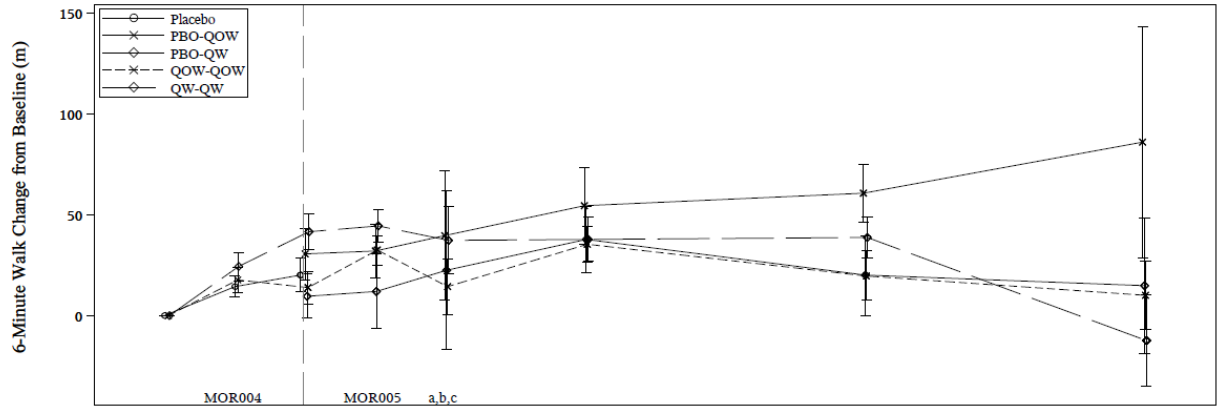


PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
a Due to different assessment schedule in Part 2, not all patients have Week 48 endurance assessments available.
b With start of Part 2 of MOR-005 (01DEC2012), patients in QOW-QOW cohort began receiving 2.0 mg/kg weekly; the specific time of transition for each patient depended on date of study enrolment, ranging from Week 39 to Week 96
c Week 48 results for the QOW-QOW cohort include only patients who reached Week 48 while still in Part 1 of the study as there was no Week 48 endurance assessment in Part 2.

In the PBO-QW cohort of the ITT population, the mean change in 6MWT distance from MOR-004 Baseline was 4.0 (±68.48) meters at Week 36 and 15.0 (±83.78) meters at Week 48.

Results in patients previously treated with placebo in MOR-004 are difficult to interpret for several reasons. Patients who had received placebo in MOR-004 were randomized without stratification to BMN 110 for Part 1 of MOR-005, resulting in a substantial between-cohort imbalance in age and endurance measures at Week 24. The numbers of patients in the placebo-switch cohorts at Week 48 were only half the size of the continuous-treatment cohorts. The overall small sample sizes resulted in large standard errors and overlapping confidence intervals. In addition, during MOR-005, 3 patients in the PBO-QW group experienced lower limb fracture (n=1) and orthopaedic surgeries (n=2) which may have skewed the group mean test results, as evidenced by substantial differences between results from the ITT and MPP analyses.

Figure 3: Mean Change in 6-Minute Walk Test (Intent-to-Treat Population - MOR-004 & MOR-005).

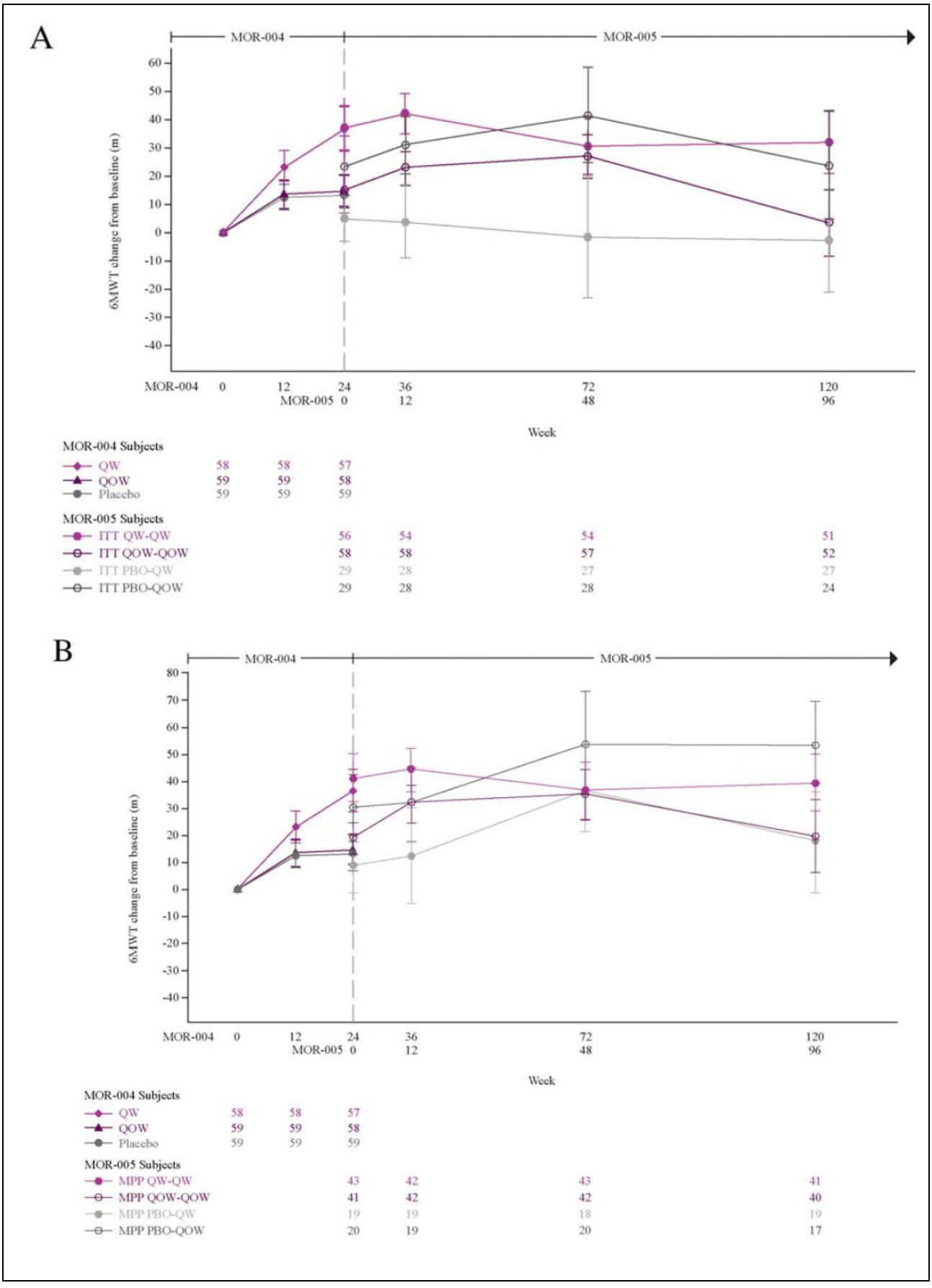


Placebo	39	39	39					
PBO-QOW			20	19	8	20	20	5
PBO-QW			19	19	7	18	19	8
QOW-QOW	42	42	42	42	15	42	41	26
QW-QW	43	43	43	42	19	43	43	22

PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
a Due to different assessment schedule in Part 2, not all patients have Week 48 endurance assessments available.
b With start of Part 2 of MOR-005 (01DEC2012), patients in QOW-QOW cohort began receiving 2.0 mg/kg weekly; the specific time of transition for each patient depended on date of study enrolment, ranging from Week 39 to Week 96
c Week 48 results for the QOW-QOW cohort include only patients who reached Week 48 while still in Part 1 of the study as there was no Week 48 endurance assessment in Part 2.

Rapporteur's comment

General remark: the figures in the dossier are difficult to interpret, as no clearly distinctive legend is used as in the published results of this study Hendriksz *et al.* (2016). For clarity the figures (A and B) from this publication have been inserted below.


A
MOR-004
MOR-005
6MWT change from baseline (m)
60
50
40
30
20
10
0
-10
-20
-30
-40
MOR-004 0 12 24 36 72 120
MOR-005 0 12 48 96
Week
MOR-004 Subjects
QW 58 58 57
QOW 59 59 58
Placebo 59 59 59
MOR-005 Subjects
ITT QW-QW 56 54 54 51
ITT QOW-QOW 58 58 57 52
ITT PBO-QW 29 28 27 27
ITT PBO-QOW 29 28 28 24
B
MOR-004
MOR-005
6MWT change from baseline (m)
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
MOR-004 0 12 24 36 72 120
MOR-005 0 12 48 96
Week
MOR-004 Subjects
QW 58 58 57
QOW 59 59 58
Placebo 59 59 59
MOR-005 Subjects
MPP QW-QW 43 42 43 41
MPP QOW-QOW 41 42 42 40
MPP PBO-QW 19 19 18 19
MPP PBO-QOW 20 19 20 17

It is important to realise that in part 2 (start at week 72/48) all patients were switched to 2.0 mg/kg QW dose (approved per SmPC), however this transition was not at a prespecified time point but varied per patient. This complicates the assessment of the treatment effect for those patients on the QOW regimen (e.g. QOW-QOW and PBO-QOW). Therefore, conclusions in these two groups should be drawn with caution. For the assessment of the long term effects the patients that received the 2 mg/kg/QW and those switched from placebo to QW dosing are considered most important. The long term data in the QW-QW groups seems to indicate that with continued treatment the effect on the 6MWT somewhat declines. In the placebo-QW group a similar trend is observed.

Further, the assessment of the (long term) 6MWT and 3MSCT data is hampered, as submitted data appear not to be corrected for age and gender. At baseline the mean (SD) for the 6MWT was 209.5 (74.0) meter. As such it is unknown whether the observed improvements for 6MWT approximately 50 meters (mean change) are due to treatment or whether other confounding factors ("training effect" or patient' s growth) contribute to this effect. Note that patients were required to use their walking aids (if applicable) throughout the study.

In addition, it should be noted that the presented data in the figures are a mean value for the total study population (n=173, all age groups). The applicant is requested to submit analyses for 6MWT corrected for age and gender (using z-scores (Z-6MWT)). As the QW-QW and placebo-QW groups are considered the most relevant populations (see above), these analyses should be submitted for these two groups only. These data should be compared to the normalized 6MWT in healthy peers (**OC**).

The applicant is requested to discuss whether there are patient characteristics that could help to determine if a patient could be a non-responder to elosulfase alfa treatment. The applicant should explore the possibility to include stopping rules in the SmPC for those patients not benefitting from treatment (anymore) (**OC**).

The applicant is requested to also plot the results of the treated population as well as the natural history population as z-scores of the 6MWT, FEV1, standing height and, growth velocity. For each measurement a separate graph should be submitted. For the growth velocity the applicant should plot the actual data against the CDC growth and the published MPS IV growth curves (**OC**).

Furthermore, it is of scientific and clinical interest to verify whether there is an association between the 6MWT, lung capacity and MPS HAQ. The applicant is requested to submit these analyses (**OC**).

3MSCT:

For Part 1, patients showed sustained improvement in 3MSCT through Week 36. The interim report (18MAR2013) summarizes results for the Part 1. Continued treatment with weekly BMN 110 in Part 2 of MOR-005 further improved 3MSCT results for the Total population for the ITT population (n=176) (Figure 11.4.1.2.2) and for the MPP population (n=124) (Figure 11.4.1.2.2). Mean (SE) change from baseline in 3MSCT over 168 weeks for the ITT and MPP populations are shown. Not all patients reported results for all time points (including MOR-005 Week 0); the number of patients with data available are shown for each time point. Discussion of data after Week 168 is not included due to the relatively low number of patients that continued in the study after Week 168.

Table 5 displays a descriptive summary of the 3MSCT rate change from baseline for the ITT population. A descriptive summary of the 3MSCT rate change from baseline for MPP population are provided in Table 6.

The main reason reported for not performing the tests was that the patients were physically unable to perform. Patients who performed but could not complete a 3MSCT (including the primary reason) are presented by time point. The primary reasons for failing to complete a test were fatigue and pain.

Table 5: Descriptive Summary of 3-Minute Stair-Climb Test Rate Change from Baseline (Intent-to-Treat Population - MOR-004 and MOR-005).

Stair Climb Rate (stairs/min)	PBO[a] (n = 59)	PBO-QOW[a] (n = 29)	PBO-QW[a] (n = 29)	QOW-QOW[a] (n=59)	QW-QW[a] (n=58)	Total (n = 176)
Baseline						
n	59	29	29	59	58	176
Mean (SD)	30.0 (14.05)	33.1 (15.60)	26.9 (12.08)	27.1 (15.80)	29.6 (16.44)	28.9 (15.42)
Median	30.8	33.0	29.0	25.5	30.5	29.1
Min, Max	0.0 , 59.0	0.0 , 59.0	0.0 , 50.0	0.0, 66.8	0.0, 71.9	0.0 , 71.9
Week 24 (MOR-005 Week 0) - Change from Baseline[a]						
n	59	29	29	59	57	175
Mean (SD)	3.6 (8.51)	4.7 (9.65)	2.9 (7.30)	2.9 (10.94)	4.8 (8.06)	3.8 (9.25)
Median	0.9	0.9	1.3	1.5	4.3	1.7
Min, Max	-13.0 , 32.4	-8.8 , 32.4	-13.0 , 21.8	-27.8 , 45.8	-12.4, 20.5	-27.8 , 45.8
Week 36 (MOR-005 Week 12) - Change from Baseline[a]						
n	NA	28	28	58	54	168
Mean (SD)		6.8 (10.81)	2.3 (10.55)	4.4 (11.78)	6.1 (8.43)	5.0 (10.45)
Median		3.8	0.1	3.6	4.5	3.2
Min, Max		-8.7 , 31.8	-19.0 , 30.6	-35.9, 45.8	-16.2, 27.2	-35.9 , 45.88
Week 48 (MOR-005 Week 24) - Change from Baseline[a]						
nc	NA	14	13	26	26	79
Mean (SD)		3.1 (21.66)	3.2 (14.70)	4.3 (15.62)	7.7 (11.02)	5.0 (15.25)
Median		0.4	5.7	2.0	4.4	3.8
Min, Max		-55.6 , 42.5	-22.8 , 35.5	-38.2 , 60.5	-22.0 , 30.4	-55.6 , 60.55
Week 72 (MOR-005 Week 48) - Change from Baseline[a]						
n	NA	28	26	56	54	164
Mean (SD)		8.9 (15.44)	1.2 (14.95)	5.5 (11.96)	5.3 (9.88)	5.3 (12.60)
Median		7.1	0.9	3.1	4.7	4.0
Min, Max		-35.5 , 47.9	-36.2 , 38.1	-13.9 , 53.6	-22.0 , 24.7	-36.2 , 53.6
Week 120 (MOR-005 Week 96) -Change from Baseline[a]						
n	NA	28	27	54	53	162
Mean (SD)		6.0 (17.05)	1.7 (14.80)	4.7 (14.60)	5.8 (13.42)	4.8 (14.65)
Median		7.2	0.0	2.7	5.5	4.4
Min, Max		-55.6 , 44.7	-23.7 , 35.8	-24.2 , 43.1	-42.0 , 41.5	-55.6 , 44.7
Week 168 (MOR-005 Week 144) -Change from Baseline[a]						

n	NA	10	13	32	25	80
Mean (SD)		8.9 (17.57)	5.5 (15.44)	4.6 (13.64)	0.4 (20.96)	4.0 (16.90)
Median		2.4	6.2	0.9	1.3	1.2
Min, Max		-11.7 , 40.5	-19.9 , 35.0	-27.2 , 35.5	-61.2 , 59.7	-61.2 , 59.7

N, number of patients; SD, standard deviation; QW, every week; QOW, every other week.
With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the2.0 mg/kg/qw dosing regimen.
a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
b Change is equal to current value minus the baseline value.
c Week 48 endurance assessment results included only patients who reached Week 48 while in Part 1 of the study as there was no Week 48 assessment in Part 2. This led to a reduced sample size at Week 48.

Figure 4: Mean Change in 3-Minute Stair-Climb Test Rate (Intent-To-Treat Population MOR-004 & MOR-005).

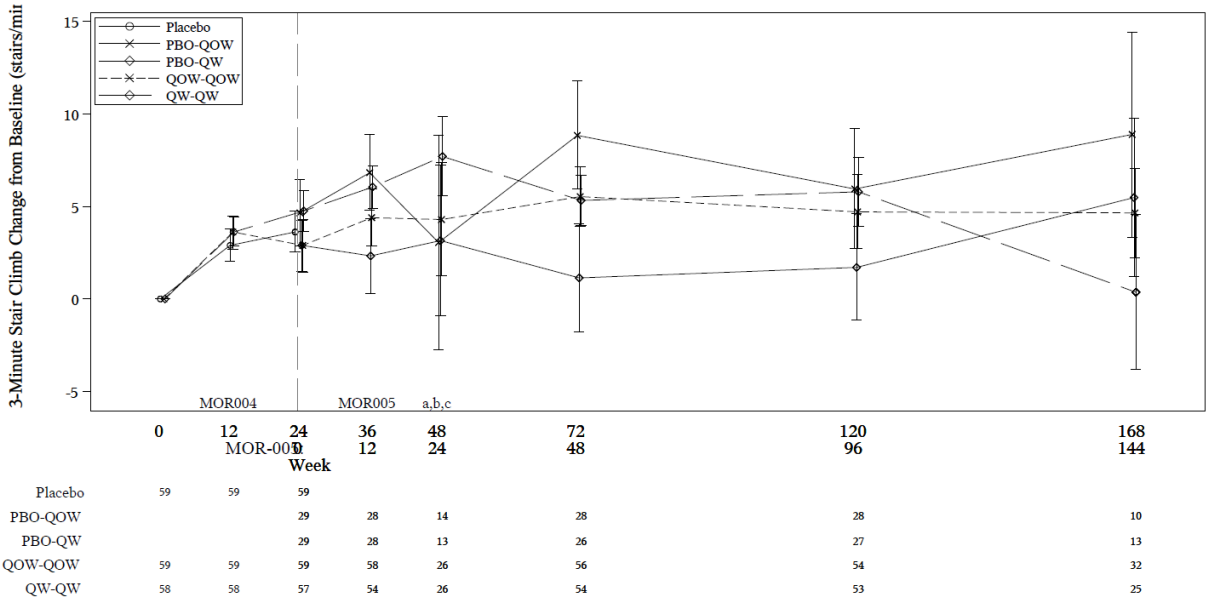


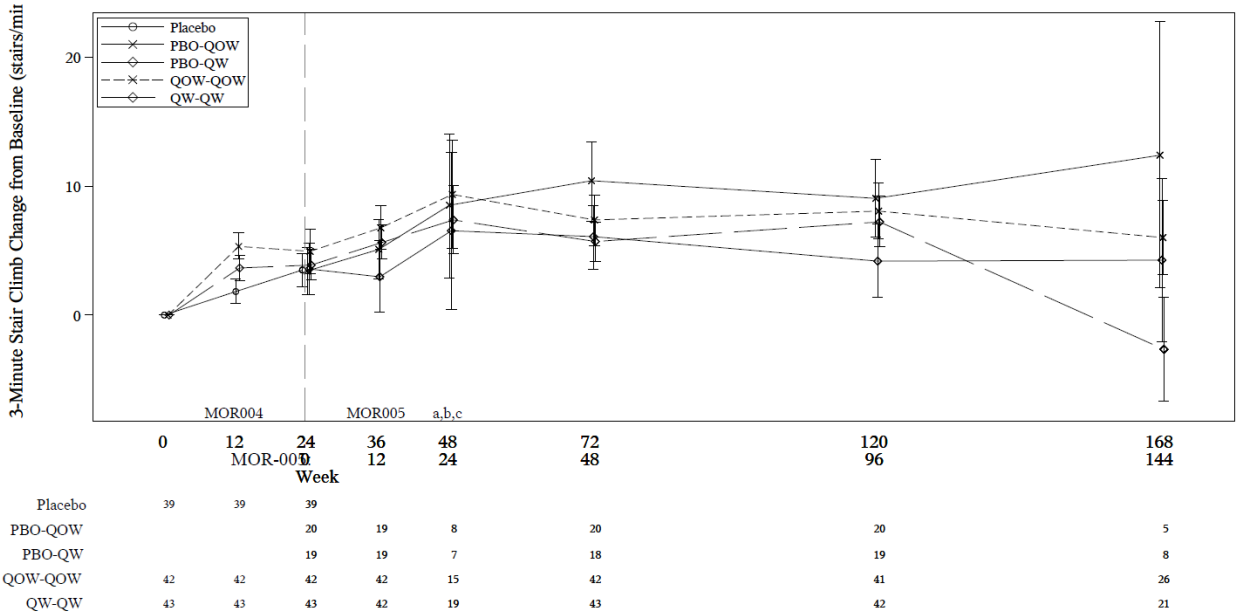
Table 6: Descriptive Summary of 3-Minute Stair-Climb Test Rate at Scheduled Visits (Analysis Population: Modified Per Protocol).

Stair Climb Rate Average, stairs/min	PBO[a] (n = 39)	PBO-QOW[a] (n =20)	PBO-QW[a] (n =19)	QOW-QOW[a] (n = 42)	QW-QW[a] (n = 43)	Total (n=124)
Baseline						
n	39	20	19	42	43	124
Mean (SD)	29.1 (14.46)	33.1 (14.12)	24.8 (13.92)	25.6 (13.73)	31.3 (16.22)	28.7 (14.93)
Median	30.0	32.8	25.5	25.7	31.3	29.6
Min, Max	0.0 , 59.0	6.5 , 59.0	0.0 , 50.0	0.0 , 60.0	0.0 , 71.9	0.0 , 71.9
Week 24 (MOR-005 Week 0) -Change from Baseline[b]						
n	39	20	19	42	43	124
Mean (SD)	3.5 (8.25)	3.4 (8.09)	3.6 (8.63)	5.0 (11.46)	3.9 (7.67)	4.1 (9.23)
Median	0.9	1.0	0.3	2.3	4.3	2.1

Min, Max	-13.0 , 23.9	-5.3 , 23.9	-13.0 , 21.8	-27.8 , 45.8	-12.4 , 17.8	-27.8 , 45.8
Week 36 (MOR-005 Week 12) -Change from Baseline[b]						
n	NA	19	19	42	42	122
Mean (SD)		5.1 (9.84)	3.0 (12.15)	6.8 (11.09)	5.7 (8.69)	5.6 (10.26)
Median		3.4	0.2	4.0	4.1	3.4
Min, Max		-8.7 , 29.6	-19.0 , 30.6	-5.0 , 45.8	-16.2 , 27.2	-19.0 , 45.8
Week 48 (MOR-005 Week 24) -Change from Baseline[b]						
nc	NA	8	7	15	19	49
Mean (SD)		8.5 (15.79)	6.6 (16.01)	9.4 (16.18)	7.4 (11.35)	8.1 (13.93)
Median		2.5	6.3	4.2	4.8	4.3
Min, Max		-4.7 , 42.5	-19.0 , 35.5	-3.5 , 60.5	-22.0 , 26.7	-22.0 , 60.5
Week 72 (MOR-005 Week 48) -Change from Baseline[b]						
n	NA	20	18	42	43	123
Mean (SD)		10.4 (13.77)	6.1 (10.56)	7.4 (12.53)	5.7 (9.98)	7.1 (11.61)
Median		7.1	3.2	4.3	5.3	4.7
Min, Max		-3.0 , 47.9	-6.6 , 38.1	-8.0 , 53.6	-22.0 , 24.7	-22.0 , 53.6
Week 120 (MOR-005 Week 96) -Change from Baseline[b]						
n	NA	20	19	41	42	122
Mean (SD)		9.1 (13.38)	4.2 (12.49)	8.1 (13.83)	7.2 (12.58)	7.4 (13.05)
Median		7.6	0.0	4.7	5.9	5.8
Min, Max		-10.3 , 44.7	-15.8 , 35.8	-12.5 , 43.1	-22.0 , 41.5	-22.0 , 44.7
Week 168 (MOR-005 Week 144) -Change from Baseline[b]						
n	NA	5	8	26	21	60
Mean (SD)		12.4 (23.03)	4.3 (17.82)	6.0 (14.59)	-2.6 (18.47)	3.3 (17.39)
Median		4.8	3.3	2.4	0.0	2.1
Min, Max		-11.7, 40.	-19.9 , 35.0	-27.2 , 35.5	-61.2, 25.5	-61.2 , 40.5

N, number of patients; SD, standard deviation; QW, every week; QOW, every other week.
With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the2.0 mg/kg/qw dosing regimen.
a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
b Change is equal to current value minus the baseline value.
c Week 48 endurance assessment results included only patients who reached Week 48 while in Part 1 of the study as there was no Week 48 assessment in Part 2. This led to a reduced sample size at Week 48.

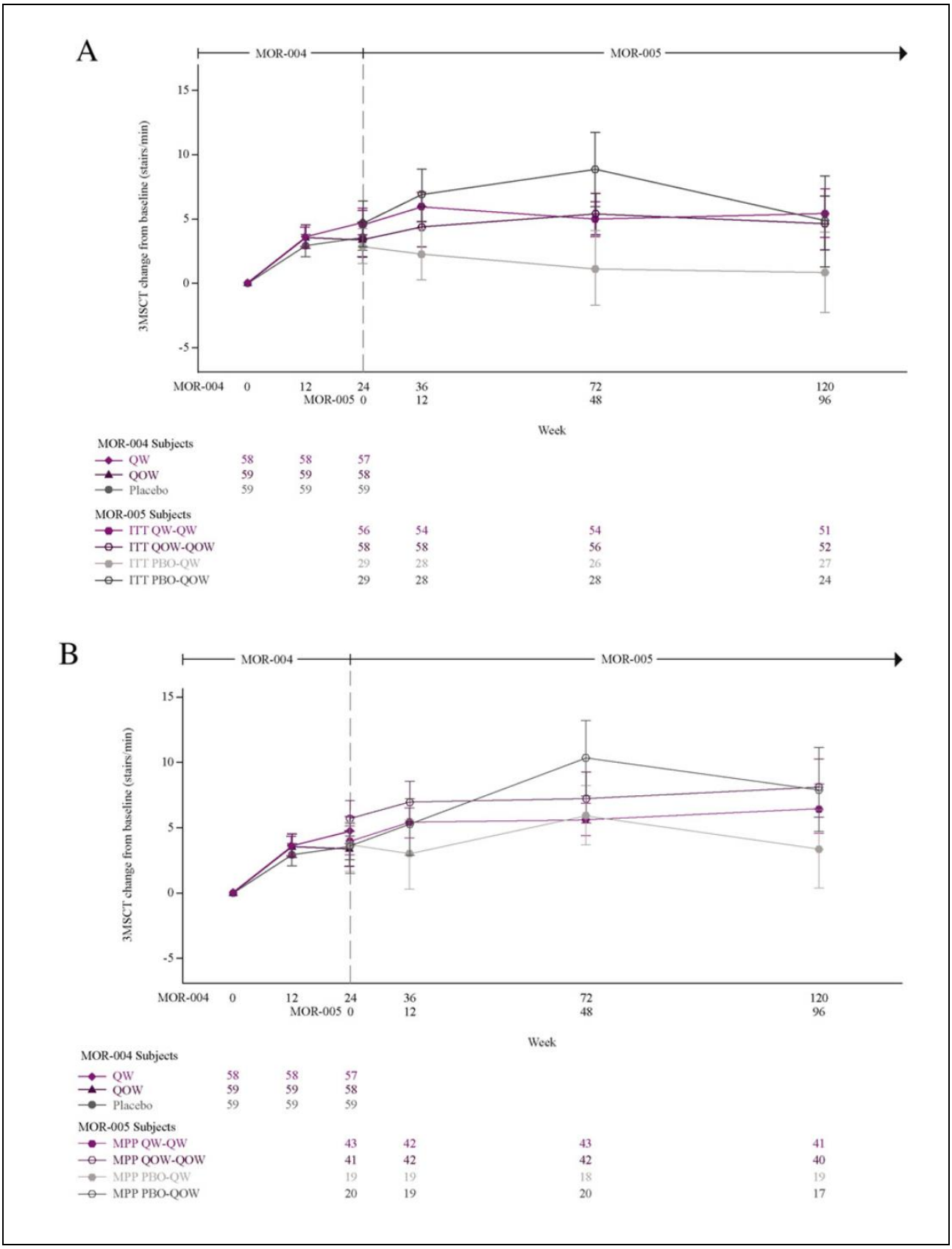
Figure 5: Mean Change in 3-Minute Stair-Climb Test Rate (Modified Population MOR-004 & MOR-005).



Rapporteur's comment

The beneficial effects on the 3MSCT seen in study MOR-004 are confirmed in this study. The clinical relevance of the observed improvement remains to be established. The figures A and B below are taken from Hendriksz *et al.* (2016) for clarity.

In part 2 all patients were switched to 2 mg/kg QW treatment, however the transition occurred at different time points. Therefore, conclusions for the QOW-QOW and PBO-QOW groups can only be drawn cautiously. For the QW-QW population there seems to be a sustained effect on the 3MSCT, similar for the PBO-QW population. However, it is to be noted that this is a mean of the overall population. The applicant does not seem to have taken into account the difference in age groups and gender.


A
MOR-004
MOR-005
3MSCT change from baseline (stairs/min)
15
10
5
0
-5
MOR-004 0 12 24 36 72 120
MOR-005 0 12 48 96
Week
MOR-004 Subjects
QW 58 58 57
QOW 59 59 58
Placebo 59 59 59
MOR-005 Subjects
ITT QW-QW 56 54 54 51
ITT QOW-QOW 58 58 56 52
ITT PBO-QW 29 28 26 27
ITT PBO-QOW 29 28 28 24
B
MOR-004
MOR-005
3MSCT change from baseline (stairs/min)
15
10
5
0
-5
MOR-004 0 12 24 36 72 120
MOR-005 0 12 48 96
Week
MOR-004 Subjects
QW 58 58 57
QOW 59 59 58
Placebo 59 59 59
MOR-005 Subjects
MPP QW-QW 43 42 43 41
MPP QOW-QOW 41 42 42 40
MPP PBO-QW 19 19 18 19
MPP PBO-QOW 20 19 20 17

Urine keratan sulfate

For Part 1, patients showed sustained reduction in urine KS through Weeks 36 (**Figure 6**). The interim CSR (18MAR2013) summarizes results for the Part 1. Continued treatment with weekly BMN 110 in Part 2 of MOR-005 resulted in further reduction in normalized urine KS for the Total ITT population (n=176) (Figure 11.4.1.3.1), and for the MPP population (n=124) (Figure 11.4.1.3.2). Mean (SE) percent change from baseline in normalized urine KS over 168 weeks for the ITT and MPP populations are shown. Not all patients reported results for all time points (including MOR-005 Week 0); the number of patients with data available are shown for each time point. Since patients transitioned to Part 2 with a variable amount of BMN 110 treatment and follow-up, over the range Weeks 39 through 96 (MOR005 Week 15–72), a large percentage of patients were not required to be assessed at Week 60 (MOR005 Week 36) for urine KS.

Discussion of data after Week 168 is not included due to the relatively low number of patients that continued on the study after Week 168.

Table 7 displays a descriptive summary of normalized urine KS percent change from baseline for the ITT population (Table 14.2.3.1). A descriptive summary of normalized urine KS percent change from baseline for the for MPP population are provided in **Table 8**.

Patients in both the Total ITT and the MPP populations continued to show sustained reduction in urine KS through Week 168. The slight increase starting at Week 144 and continuing to Week 168 may have been due to the decrease in sample size at Week 144 and further decrease at Week 168. The reduction in normalized urine KS was similar for the Total ITT and MPP populations because, unlike endurance measures, normalized urine KS is not influenced by factors such as orthopaedic surgeries.

Descriptive summaries using the ITT population (**Figure 6** [mean change], and for the MPP population (**Figure 7** [mean change]) yielded results consistent with the mean percent change from baseline results.

Table 7: Descriptive Summary of Normalized Urine Keratan Sulfate Percent Change from Baseline (Intent-To-Treat Population - MOR-004 and MOR-005).

Normalized Urine KS (µg/mg)	**PBO[a] (n = 59)**	**PBO-QOW[a] (n = 29)**	**PBO-QW[a] (n = 29)**	**QOW-QOW[a] (n=59)**	**QW-QW[a] (n=58)**	**Total (n = 176)**
Baseline						
n	58	28	29	59	58	175
Mean (SD)	25.7 (15.09)	22.7 (15.27)	28.5 (14.89)	28.6 (21.17)	26.9 (14.11)	27.1 (17.05)
Median	26.7	25.0	30.3	27.4	24.1	25.7
Min, Max	2.5 , 52.8	3.1 , 50.5	2.5 , 52.8	2.4, 117.3	2.1, 59.0	2.1, 117.3
Week 24 (MOR-005 Week 0) -Percent Change from Baseline[b]						
n	55	26	28	57	54	166
Mean (SD)	-4.4 (27.03)	3.4 (29.15)	-11.3 (23.68)	-35.2 (20.70)	-45.1 (19.89)	-28.2 (28.46)
Median	-12.3	-2.5	-13.6	-35.8	-50.8	-28.9
Min, Max	-50.0 , 73.6	-28.2 , 73.6	-50.0 , 45.8	-91.7, 45.0	-79.4, 5.3	-91.7 , 73.6
Week 36 (MOR-005 Week 12) -Percent Change from Baseline[b]						
n	NA	27	28	56	52	163
Mean (SD)		-33.6 (18.55)	-48.2 (15.57)	-36.4 (21.58)	-48.0 (17.49)	-41.7 (19.76)

Median		-38.3	-49.9	-39.7	-52.7	-45.3
Min, Max		-60.0 , 0.7	-72.5 , -13.9	-92.1 , 45.1	-78.5 , 4.2	-92.1 , 45.1
Week 48 (MOR-005 Week 24) -Percent Change from Baseline[b]						
n	NA	28	27	56	52	163
Mean (SD)		-40.8 (21.11)	-53.6 (11.96)	-46.6 (22.18)	-49.5 (16.70)	-47.7 (19.17)
Median		-42.4	-52.2	-48.4	-53.9	-51.0
Min, Max		-66.6 , 20.6	-81.2 , -32.3	-93.9 , 32.8	-72.9 , -0.3	-93.9 , 32.8
Normalized Urine KS (µg/mg)	PBOa (n = 59)	PBO-QOWa (n = 29)	PBO-QWa (n = 29)	QOW-QOWa (n=59)	QW-QWa (n=58)	Total (n = 176)
Week 60 (MOR-005 Week 36) -Percent Change from Baseline[b]						
nc	NA	7	6	16	11	40
Mean (SD)		-30.0 (23.53)	-48.2 (10.45)	-35.5 (15.12)	-29.9 (17.94)	-34.9 (17.56)
Median		-30.5	-47.3	-39.1	-37.1	-39.1
Min, Max		-65.5 , 4.2	-64.2 , -33.6	-59.7 , 1.5	-57.1 , -0.1	-65.5 , 4.2
Week 72 (MOR-005 Week 48) -Percent Change from Baseline[b]						
n	NA	26	28	57	51	162
Mean (SD)		-54.1 (17.21)	-56.8 (13.69)	-55.6 (14.23)	-53.7 (17.45)	-55.0 (15.61)
Median		-56.3	-60.4	-55.3	-56.6	-56.5
Min, Max		-80.5 , 0.3	-74.1 , -9.3	-91.8 , -18.7	-94.8 , -18.0	-94.8 , 0.3
Week 96 (MOR-005 Week 72) -Percent Change from Baseline[b]						
n	NA	27	25	55	51	158
Mean (SD)		-50.2 (17.20)	-58.5 (14.46)	-56.7 (14.21)	-46.9 (54.43)	-52.7 (33.42)
Median		-52.4	-58.4	-55.5	-57.0	-56.5
Min, Max		-74.9 , -14.3	-78.1 , -15.3	-96.1 , -16.1	-78.7 , 300.8	-96.1 , 300.8
Week 120 (MOR-005 Week 96) -Percent Change from Baselineb						
n	NA	26	24	53	53	156
Mean (SD)		-55.5 (18.60)	-62.2 (15.39)	-55.8 (26.56)	-61.5 (20.59)	-58.7 (21.88)
Median		-59.3	-65.6	-58.1	-63.5	-60.6
Min, Max		-82.4 , -9.1	-95.4 , -32.1	-97.3 , 90.2	-100.0 , 23.3	-100.0 , 90.2
Week 144 (MOR-005 Week 120) -Percent Change from Baseline[b]						
n	NA	15	16	38	31	100
Mean (SD)		-50.9 (26.43)	-65.9 (15.71)	-51.5 (25.56)	-38.7 (106.94)	-49.8 (62.67)
Median		-53.3	-68.6	-55.9	-60.1	-57.2
Min, Max		-78.7 , 21.3	-98.8 , -42.0	-95.7 , 21.8	-84.7 , 519.9	-98.8 , 519.9
Week 168 (MOR-005 Week 144) -Percent Change from Baseline[b]						
n	NA	8	11	27	18	64
Mean (SD)		-31.9 (31.20)	-38.3 (47.43)	-28.5 (35.14)	-39.3 (47.39)	-33.7 (40.06)
Median		-29.9	-55.6	-38.1	-61.2	-45.5

Min, Max		-68.9 , 21.8	-98.4 , 52.4	-95.4 , 47.6	-85.8 , 96.4	-98.4 , 96.4

N, number of patients; SD, standard deviation; QW, every week; QOW, every other week.
With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the2.0 mg/kg/qw dosing regimen.
a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-
BMN 110 2.0 mg/kg/qw.
b Percent change is equal to 100 times the difference of current value and baseline value and then divided by baseline value
c Since patients transitioned to Part 2 with a variable amount of BMN 110 treatment and follow-up, over the range Weeks 39 – 96 (MOR005 Week 15 – 72), a large percentage of patients were not required to be assessed at Week 60 (MOR005 Week 36) for uKS.

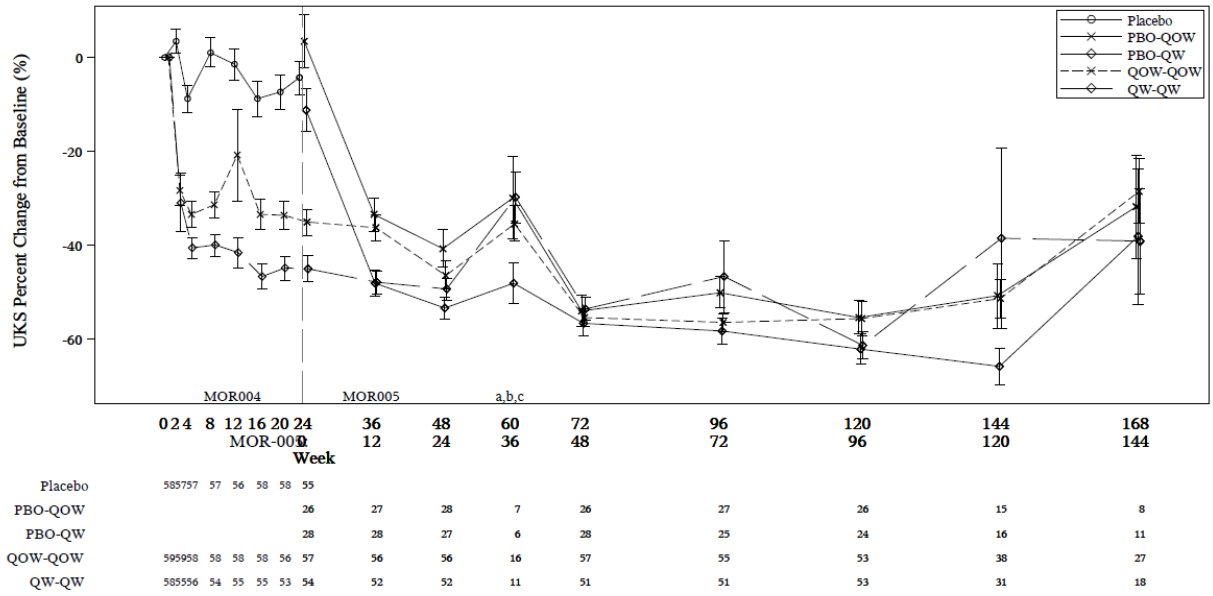
Table 8: Descriptive Summary of Normalized Urine Keratan Sulfate Percent Change from Baseline (Modified Per Protocol).

Normalized Urine KS (µg/mg)	**PBO[a] (n = 39)**	**PBO-QOW[a] (n = 20)**	**PBO-QW[a] (n = 19)**	**QOW-QOW[a] (n = 42)**	**QW-QW[a] (n = 43)**	**Total (n = 124)**
Baseline						
n	38	19	19	42	43	123
Mean (SD)	24.3 (15.52)	21.2 (15.55)	27.5 (15.24)	27.2 (22.90)	24.9 (13.13)	25.5 (17.61)
Median	25.0	23.8	27.9	22.2	23.4	23.4
Min, Max	2.5 , 52.8	3.1 , 50.5	2.5 , 52.8	2.4 , 117.3	2.1 , 52.8	2.1 , 117.3
Week 24 (MOR-005 Week 0) -Percent Change from Baseline[b]						
n	36	17	19	41	40	117
Mean (SD)	-6.2 (25.01)	1.2 (24.34)	-12.9 (24.29)	-35.5 (22.62)	-44.9 (19.60)	-29.7 (27.52)
Median	-12.0	0.1	-16.4	-37.5	-50.8	-28.9
Min, Max	-50.0 , 59.1	-27.8 , 59.1	-50.0 , 45.8	-91.7 , 45.0	-79.4 , 5.3	-91.7 , 59.1
Week 36 (MOR-005 Week 12) -Percent Change from Baseline[b]						
n	NA	18	19	40	42	119
Mean (SD)		-32.1 (21.74)	-49.8 (16.06)	-35.5 (23.27)	-47.2 (18.73)	-41.4 (21.37)
Median		-36.7	-51.3	-37.9	-51.1	-45.5
Min, Max		-60.0 , 0.7	-72.5 , -21.0	-92.1 , 45.1	-78.5 , 4.2	-92.1 , 45.1
Week 48 (MOR-005 Week 24) -Percent Change from Baseline[b]						
nc	NA	19	18	41	41	119
Mean (SD)		-38.7 (22.24)	-55.4 (10.20)	-48.8 (23.58)	-48.5 (17.28)	-48.1 (20.07)
Median		-40.2	-57.1	-50.4	-51.8	-51.6
Min, Max		-66.6 , 20.6	-69.8 , -32.3	-93.9 , 32.8	-71.8 , -0.3	-93.9 , 32.8
Normalized Urine KS (µg/mg)	PBOa (n = 39)	PBO-QOWa (n = 20)	PBO-QWa (n = 19)	QOW-QOWa (n = 42)	QW-QWa (n = 43)	Total (n = 124)
Week 60 (MOR-005 Week 36) -Percent Change from Baseline[b]						
n	NA	2	3	9	9	23
Mean (SD)		-13.2 (24.53)	-47.8 (15.37)	-33.9 (19.57)	-29.2 (19.00)	-32.1 (19.77)
Median		-13.2	-45.8	-39.7	-37.1	-38.2
Min, Max		-30.5 , 4.2	-64.2 , -33.6	-59.7 , 1.5	-57.1 , -0.1	-64.2 , 4.2
Week 72 (MOR-005 Week 48) -Percent Change from Baseline[b]						
n	NA	18	19	41	41	119

Mean (SD)		-51.7 (19.34)	-58.8 (14.60)	-56.9 (13.55)	-53.7 (17.87)	-55.3 (16.21)
Median		-53.7	-62.0	-55.3	-56.6	-56.6
Min, Max		-80.5 , 0.3	-74.1 , -9.3	-91.8 , -26.3	-94.8 , -18.0	-94.8 , 0.3
Week 96 (MOR-005 Week 72) -Percent Change from Baseline[b]						
n	NA	19	17	41	42	119
Mean (SD)		-50.7 (16.99)	-61.7 (12.69)	-59.1 (13.67)	-46.2 (57.39)	-53.6 (36.25)
Median		-53.6	-59.6	-60.2	-54.7	-57.5
Min, Max		-70.6 , -18.8	-78.1 , -37.8	-96.1 , -32.5	-78.7 , 300.8	-96.1 , 300.8
Week 120 (MOR-005 Week 96) -Percent Change from Baseline[b]						
n	NA	18	17	40	42	117
Mean (SD)		-58.3 (15.87)	-64.2 (16.58)	-62.1 (15.97)	-61.8 (21.28)	-61.7 (17.98)
Median		-59.8	-67.1	-60.6	-63.1	-62.0
Min, Max		-78.6 , -28.0	-95.4 , -32.1	-97.3 , 90.2	-100.0 , 23.3	-100.0 , 90.2
Week 144 (MOR-005 Week 120) - Percent Change from Baseline[b]						
n	NA	9	10	30	26	75
Mean (SD)		-51.5 (19.64)	-66.9 (17.26)	-54.3 (25.09)	-37.2 (114.89)	-49.7 (69.92)
Median		-49.9	-68.6	-56.7	-57.0	-56.8
Min, Max		-78.7 , -26.2	-98.8 , -42.0	-95.7 , 21.8	-84.7 , 519.9	-98.8 , 519.9
Week 168 (MOR-005 Week 144) - Percent Change from Baseline[b]						
n	NA	4	7	22	15	48
Mean (SD)		-9.9 (23.48)	-41.6 (46.05)	-27.1 (37.28)	-43.0 (34.07)	-32.8 (37.11)
Median		-13.2	-45.9	-28.1	-59.6	-40.7
Min, Max		-34.9 , 21.8	-98.4 , 52.4	-95.4 , 47.6	-77.3 , 52.6	-98.4 , 52.6

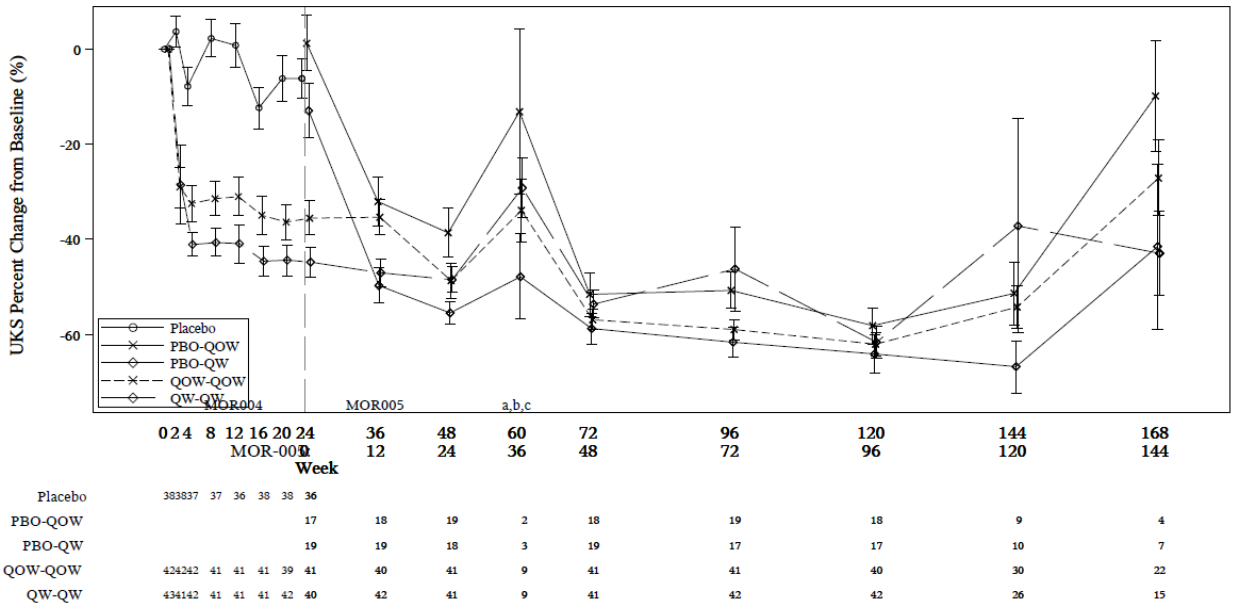
N, number of patients; SD, standard deviation; QW, every week; QOW, every other week.
With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the2.0 mg/kg/qw dosing regimen.
a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
b Percent change is equal to 100 times the difference of current value and baseline value and then divided by baseline value.
c Week 48 endurance assessment results included only patients who reached Week 48 while in Part 1 of the study as there was no Week 48 assessment in Part 2. This led to a reduced sample size at Week 48. Since patients transitioned to Part 2 with a variable amount of BMN 110 treatment and follow-up, over the range Weeks 39 – 96 (MOR005 Week 15 – 72), a large percentage of patients were not required to be assessed at Week 60 (MOR005 Week 36) for uKS.

Figure 6: Mean Percent Change in Normalized Urine Keratan Sulfate at Scheduled Visits Analysis Population, ITT – MOR-004 and MOR-005.



PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-
BMN 110 2.0 mg/kg/qw.
a Due to different assessment schedule in Part 2, not all patients have Week 48 endurance assessments available.
b With start of Part 2 of MOR-005 (01DEC2012), patients in QOW-QOW cohort began receiving 2.0 mg/kg weekly; the specific time of transition for each patient
depended on date of study enrolment, ranging from Week 39 to Week 96
c Week 48 results for the QOW-QOW cohort include only patients who reached Week 48 while still in Part 1 of the study as there was no Week 48 endurance assessment in Part 2.

Figure 7: Mean Percent Change in Normalized Urine Keratan Sulfate at Scheduled Visits (analysis Population, Modified Per Protocol).



PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
a Due to different assessment schedule in Part 2, not all patients have Week 48 endurance assessments available.

b With start of Part 2 of MOR-005 (01DEC2012), patients in QOW-QOW cohort began receiving 2.0 mg/kg weekly; the specific time of transition for each patient depended on date of study enrolment, ranging from Week 39 to Week 96
c Week 48 results for the QOW-QOW cohort include only patients who reached Week 48 while still in Part 1 of the study as there was no Week 48 endurance assessment in Part 2.

Rapporteur's comment
The results obtained for KS further support the observation that with continued elosulfase alfa treatment the pharmacodynamic effect is maintained.

Patients previously on placebo treatment in MOR-004 who switched to active treatment in MOR-005, showed a similar reduction for KS as those patients on active treatment in MOR-005, thus confirming the pharmacodynamic activity of elosulfase alfa.

Respiratory Function Tests (RFTs):
In Part 1 of MOR-005, the RFTs were performed at Week 24 and at Week 48. Patients sustained numerical improvements in all RFTs (MVV, FET, FEV1, FIVC) that had been achieved in MOR-004. The interim CSR (18MAR2013) summarizes results for the Part 1.

The number of patients in each cohort with Week 48 assessments was approximately half than at Baseline due to the change in RFT assessment schedule with the transition to Part 2 of MOR-005. RFTs were performed every 48 weeks in MOR-005 Part 2. Not all patients reported results for all time points (including MOR-005 Week 0); the number of patients with data available are shown for each time point. Discussion of data after Week 168 is not included due to the relatively low number of patients that continued on the study after Week 168.

Long-term data for the Total population (ITT and MPP) shows numerical improvements in RFTs from MOR-004 baseline and sustained over time.

Patients who did not perform the RFT (including the primary reason) are listed (the primary reason for patients not performing the RFTs was insufficient developmental maturity).

Patients who could not complete the RFTs are presented by time point.

Maximum Voluntary Ventilation
Results for the Total population (ITT and MPP) are as follows: Mean percent changes (±SD) from MOR-004 Baseline in MVV at Week 48 for ITT (n=63) and for the MPP population (n=41) were 8.5% (±32.08) and 2.5% (±23.05), respectively. At Week 72, values for the ITT population (n=144) and for the MPP population (n=111) were 10.9% (±32.48) and 9.6% (±28.97), respectively. At Week 120 values for the ITT population (n=133) and for the MPP population (n=106) were 11.1% (±51.61) and 5.7% (32.62), respectively. At Week 168 values for the ITT population (n=67) and for the Total MPP population (n=53) were 7.1% (±30.11) and 7.7% (±31.74), respectively.

Forced Vital Capacity
Mean percent changes (±SD) from MOR-004 Baseline in FVC at Week 48 (n=71), Week 72 (n=157), Week 120 (n=147), and Week 168 (n=71) for the Total ITT population were 3.2% (±12.62), 7.3% (±16.57), 9.4% (±21.33), and 14.5% (±24.90), respectively. The descriptive summaries show that with continued treatment with BMN 110 in MOR-005, numerical improvement in FVC was sustained over time in the Total ITT population.

Forced Expiratory Time
Mean percent changes (±SD) from MOR-004 Baseline in FET at Week 48 (n= 69), Week 72 (n=151), Week 120 (n=140), and Week 168 (n=64) for the Total ITT population were 22.9% (±128.91), 29.0

(±89.25), 50.9% (±190.78), and 69.1% (±121.15), respectively. The descriptive summaries show that with continued treatment with BMN 110 in MOR-005, numerical improvement in FET was sustained over time in the Total ITT population.

Forced Inspiratory Vital Capacity

Mean percent changes (±SD) from MOR-004 Baseline in FIVC at Week 48 (n= 68), Week 72 (n=147), Week 120 (n=135), and Week 168 (n=64) for the Total ITT population were 2.2% (±31.56), 6.8% (±35.97), 21.2% (±151.51), and 11.9% (±26.71), respectively. The descriptive summaries show that with continued treatment with BMN 110 in MOR-005, numerical improvement in FIVC was sustained over time in the Total ITT population.

Forced Expiratory Volume in 1 Second

Mean percent changes (±SD) from MOR-004 Baseline in FEV1 at Week 48 (n= 71), Week 72 (n=156), Week 120 (n=147), and Week 168 (n=71) for the Total ITT population were 2.9% (±12.58), 6.2% (±19.27), 8.3% (±24.79), and 9.9% (±25.00), respectively. The descriptive summaries (see also Table 9) show that with continued treatment with BMN 110 in MOR-005, numerical improvement in FEV1 was sustained over time in the Total ITT population.

Table 9: Descriptive Summary of Forced Expiratory Volume for 1 Second at Scheduled Visits (Analysis Population: ITT- MOR-004 and MOR-005).

Forced Expiratory Volume, L	**PBO[a] (n = 59)**	**PBO-QOW[a] (n = 29)**	**PBO-QW[a] (n = 29)**	**QOW-QOW[a] (n=59)**	**QW-QW[a] (n=58)**	**Total (n = 176)**
Baseline						
n	54	29	24	54	56	164
Mean (SD)	1.0 (0.72)	1.1 (0.70)	0.9 (0.76)	1.0 (0.54)	0.8 (0.42)	0.9 (0.57)
Median	0.8	0.8	0.7	0.8	0.7	0.8
Min, Max	0.3 , 3.8	0.3 , 2.7	0.3 , 3.8	0.3 , 2.6	0.3 , 2.5	0.3 , 3.8
Week 24 (MOR-005 Week 0) -Percent Change from Baseline[b]						
n	52	28	23	54	55	161
Mean (SD)	2.1 (17.50)	3.3 (19.95)	0.3 (14.67)	3.4 (13.87)	5.2 (11.81)	3.6 (14.50)
Median	-2.5	-2.1	-3.8	3.6	4.3	1.8
Min, Max	-25.6 , 75.7	-25.6 , 75.7	-15.6 , 56.8	-43.2 , 42.1	-17.2 , 39.5	-43.2 , 75.7
Week 48 (MOR-005 Week 24) -Percent Change from Baseline[b]						
nc	NA	14	9	24	24	71
Mean (SD)		3.3 (13.98)	-1.7 (17.98)	4.8 (10.60)	2.5 (11.58)	2.9 (12.58)
Median		1.0	-4.5	2.7	4.1	2.8
Min, Max		-23.5 , 28.1	-20.0 , 31.4	-11.3 , 31.6	-17.9 , 20.7	-23.5 , 31.6
Week 72 (MOR-005 Week 48) -Percent Change from Baseline[b]						
n	NA	28	23	52	53	156
Mean (SD)		10.9 (21.05)	8.1 (22.86)	3.4 (17.53)	5.6 (18.22)	6.2 (19.27)
Median		7.3	4.8	2.4	5.4	4.7
Min, Max		-12.0 , 89.2	-27.0 , 86.5	-75.3 , 34.0	-24.6 , 88.4	-75.3 , 89.2

Week 120 (MOR-005 Week 96) -Percent Change from Baseline[b]						
n	NA	28	22	48	49	147
Mean (SD)		13.8 (28.29)	16.5 (29.46)	7.2 (19.18)	2.7 (24.45)	8.3 (24.79)
Median		9.9	11.6	5.6	6.8	8.1
Min, Max		-40.7 , 91.9	-24.2 , 97.3	-38.9 , 48.4	-83.8 , 42.6	-83.8 , 97.3
Week 168 (MOR-005 Week 144) -Percent Change from Baseline[b]						
n	NA	9	11	29	22	71
Mean (SD)		10.8 (16.99)	7.3 (26.21)	10.0 (19.72)	10.7 (33.51)	9.9 (25.00)
Median		11.4	9.2	6.1	3.1	6.1
Min, Max		-11.0 , 35.7	-28.3 , 57.1	-26.8 , 55.6	-16.0 , 147.7	-28.3 , 147.7

N, number of patients; SD, standard deviation; QW, every week; QOW, every other week.
With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the2.0 mg/kg/qw dosing regimen.
a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
b Percent change is equal to 100 times the difference of current value and baseline value and then divided by baseline value.
c Week 48 endurance assessment results included only patients who reached Week 48 while in Part 1 of the study as there was no Week 48 assessment in Part 2. This led to a reduced sample size at Week 48.

Rapporteur's comment

Respiratory function, including MVV, FET, FEV1, FIVC, and FVC, were evaluated. With continued elosulfase alfa treatment respiratory function seems to improve numerically. It is expected that an improvement in respiratory function would also influence the endurance capacity of a patient (and thus a possible contribution to improvement of 6MWT, 3MSCT). However, given the somewhat disappointing results for the 6MWT, it is very likely that other pathophysiological features play a role in the observed deterioration. This remains unknown. The applicant is requested to submit the predicted values for FEV1 and FVC. Further, an analysis should be performed using z-scores. In addition, the applicant should plot the mean results for FEV1 and FVC against the data from the natural history population (**OC**).

Anthropometric measurements:

Analyses of Normalized Standing Height and Growth Rate

Results from the interim CSR report (MOR-005, 18MAR2013) suggested that the positive treatment effect observed in MOR-004 on normalized standing height and growth rate z-scores in males ≤18 years and females ≤15 years (i.e., age-restricted) was maintained with longer treatment on the weekly regimen of BMN 110. Long-term data summarized in this report show continued positive treatment effect in the Total population (ITT and MPP).

Descriptive Statistics: Normalized Growth Rate and Standing Height Z-Scores In the age-restricted population, the MOR-004 Baseline mean (±SD) normalized growth rate z-scores were -0.5 (±0.63; n = 59) for the ITT population (Table 10) and -0.4 (±0.62; n = 39) for the MPP population (with age restriction; restricted to Females age <=15 years and Males age <= 18 years), indicating that both treatment groups at Baseline were within 1 standard deviation below normal age-adjusted growth rate z-scores. In the Total ITT population (with age restriction), the mean change in normalized growth rate z-scores from MOR-004 Baseline was 0.4 (±0.85, n = 59) at Week 24, -0.4 (±0.79, n = 118) at Week 48, 0.2 (±0.90, n = 57) at Week 72, 0.1 (±1.17, n = 54) at Week 120, and 0.0 (±0.97, n = 33) at Week 144. In the Total MPP population (with age restriction), the mean change in normalized growth

rate z-scores from MOR-004 Baseline was 0.4 (±0.82, n = 39 at Week 24, 0.2 (±0.81, n = 38) at Week 48, 0.0 (±0.97, n = 39) at Week 72, 0.0 (±1.27, n = 38) at Week 120. and, -0.2 (±0.99, n = 22) at Week 144.

Mean (±SD) change in the normalized growth rate z-score from MOR-004 Baseline to Week 24 in the age-restricted Total ITT and MPP populations were positive and remained positive at Week 72, and Week 120, which is suggestive of a continued trend toward a more normal growth rate with long-term treatment. In the Total ITT population, mean change from MOR-004 Baseline to Week 120 in the normalized growth rate z-score was also positive.

In the age-restricted population, the MOR-004 Baseline mean (±SD) normalized standing height z-scores were -5.5 (± 2.16; n = 123) for the Total ITT population indicating that at Baseline it was more than 5 standard deviations below normal age-adjusted standing height z-scores (Table 10). In the ITT population (age restricted), the mean change from MOR-004 Baseline was -0.1 (±0.40, n = 122) at Week 24, -0.3 (±0.61, n =117) at Week 48, -0.4 (±0.69, n = 116) at Week 72, and -0.7 (±1.03, n = 112) at Week 120. Normalized standing height z-scores change from baseline were less than 1 SD for Week 24 through Week 120 in the age-restricted and Total ITT population.

Table 10: Descriptive Summary of Growth Rate at Scheduled Visits (with age restriction; Analysis Population: ITT- MOR-004 and MOR-005).

Growth rate z-score	**PBO[a] (n =39)**	**PBO-QOW[a] (n = 20)**	**PBO-QW[a] (n = 19)**	**QOW-QOW[a] (n =41)**	**QW-QW[a] (n = 44)**	**Total (n = 125)**
Baseline						
n	18	10	8	19	22	59
Mean (SD)	-0.7 (0.58)	-0.4 (0.45)	-1.0 (0.62)	-0.3 (0.52)	-0.6 (0.72)	-0.5 (0.63)
Median	-0.7	-0.3	-0.8	-0.3	-0.7	-0.5
Min , Max	-2.3 , 0.5	-1.1 , 0.5	-2.3 , -0.3	-1.4 , 0.8	-1.6 , 1.3	-2.3 , 1.3
Week 24 (MOR-005 Week 0) -Change from Baseline[b]						
n	18	10	8	19	22	59
Mean (SD)	0.3 (0.70)	0.3 (0.42)	0.3 (0.98)	0.4 (0.86)	0.6 (0.95)	0.4 (0.85)
Median	0.2	0.3	0.1	0.5	0.7	0.5
Min , Max	-0.7 , 1.9	-0.5 , 0.9	-0.7 , 1.9	-1.3 , 1.8	-1.7 , 1.9	-1.7 , 1.9
Week 48 (MOR-005 Week 24) -Change from Baseline[b]						
n	NA	10	6	19	22	57
Mean (SD)		-0.1 (0.77)	0.4 (0.89)	0.1 (0.98)	0.4 (0.87)	0.2 (0.90)
Median		0.1	0.2	0.1	0.4	0.3
Min , Max		-1.6 , 0.7	-0.5 , 2.1	-2.5 , 2.0	-1.4 , 2.2	-2.5 , 2.2
Week 72 (MOR-005 Week 48) -Change from Baseline[b]						
n	NA	10	8	19	20	57
Mean (SD)		0.4 (0.79)	0.9 (0.69)	0.1 (0.74)	-0.2 (1.18)	0.2 (0.98)
Median		0.4	0.8	0.1	-0.1	0.2
Min , Max		-1.1 , 1.9	0.2 , 2.4	-1.3 , 1.4	-2.0 , 1.9	-2.0 , 2.4
Week 120 (MOR-005 Week 96) -Change from Baseline[b]						

n	NA	9	7	19	19	54
Mean (SD)		0.1 (0.80)	0.3 (1.00)	-0.2 (1.41)	0.2 (1.14)	0.1 (1.17)
Median		0.3	0.4	-0.2	0.1	0.1
Min , Max		-1.8 , 0.9	-1.4 , 1.6	-4.2 , 2.6	-2.0 , 2.1	-4.2 , 2.6
Week 144 (MOR-005 Week 120) -Change from Baseline[b]						
n	NA	4	4	12	13	33
Mean (SD)		0.0 (0.47)	0.4 (0.84)	-0.2 (0.89)	0.0 (1.21)	0.0 (0.97)
Median		0.0	0.6	-0.1	-0.1	0.3
Min , Max		-0.5 , 0.4	-0.8 , 1.2	-1.7 , 0.8	-2.2 , 1.8	-2.2 , 1.8
Week 168 (MOR-005 Week 144) -Change from Baseline[b]						
n	NA	4	2	8	7	21
Mean (SD)		-0.4 (1.14)	2.5 (0.30)	0.4 (1.62)	0.0 (0.98)	0.3 (1.43)
Median		-0.3	2.5	0.2	0.0	0.1
Min , Max		-1.6 , 0.6	2.3 , 2.7	-1.4 , 3.7	-1.8 , 1.2	-1.8 , 3.7

SD, standard deviation
With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the2.0 mg/kg/qw dosing regimen.
a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw
b Change is equal to current value minus the baseline value.

Restricted to Females age <=15 years and Males age <= 18 years.

Table 11: Descriptive Summary of Normalized Standing Height at Scheduled Visits (with age restriction; Analysis Population: ITT- MOR-004 and MOR-005).

Standing height z-score	PBO[a] (n = 40)	PBO-QOW[a] (n = 20)	PBO-QW[a] (n = 19)	QOW-QOW[a] (n = 41)	QW-QW[a] (n = 44)	Total (n = 125)
Baseline						
n	39	20	18	41	43	123
Mean (SD)	-5.1 (2.17)	-5.2 (2.69)	-4.9 (1.49)	-5.8 (2.22)	-5.6 (2.07)	-5.5 (2.16)
Median	-5.3	-5.1	-5.1	-6.0	-5.6	-5.6
Min , Max	-11.3 , -1.4	-11.3 , -1.4	-7.2 , -2.2	-9.6 , 0.1	-10.9 , -2.1	-11.3 , 0.1
Week 24 (MOR-005 Week 0) -Change from Baseline[b]						
n	39	20	18	40	43	122
Mean (SD)	-0.2 (0.30)	-0.1 (0.24)	-0.3 (0.36)	-0.1 (0.56)	0.0 (0.29)	-0.1 (0.40)
Median	-0.2	-0.2	-0.3	-0.1	-0.1	-0.1
Min , Max	-0.9 , 0.4	-0.5 , 0.3	-0.9 , 0.4	-1.2 , 2.5	-0.6 , 0.8	-1.2 , 2.5
Week 48 (MOR-005 Week 24) -Change from Baseline[b]						
n	NA	20	15	40	42	117
Mean (SD)		-0.4 (0.43)	-0.3 (0.52)	-0.3 (0.81)	-0.2 (0.48)	-0.3 (0.61)
Median		-0.4	-0.3	-0.3	-0.2	-0.2
Min , Max		-1.3 , 0.3	-1.4 , 0.4	-2.5 , 2.5	-1.4 , 0.8	-2.5 , 2.5
Week 72 (MOR-005 Week 48) -Change from Baseline[b]						
n	NA	20	17	39	40	116
Mean (SD)		-0.4 (0.49)	-0.5 (0.53)	-0.3 (0.82)	-0.4 (0.71)	-0.4 (0.69)
Median		-0.5	-0.5	-0.4	-0.4	-0.4
Min , Max		-1.1 , 0.4	-1.5 , 0.5	-1.8 , 2.4	-2.0 , 1.2	-2.0 , 2.4
Week 120 (MOR-005 Week 96) -Change from Baseline[b]						
n	NA	19	16	38	39	112
Mean (SD)		-0.5 (0.73)	-0.9 (0.82)	-0.6 (1.25)	-0.7 (1.01)	-0.7 (1.03)
Median		-0.5	-0.8	-0.7	-0.8	-0.7
Min , Max		-1.6 , 0.8	-2.6 , 0.9	-3.0 , 3.1	-2.4 , 1.1	-3.0 , 3.1
Week 144 (MOR-005 Week 120) -Change from Baseline[b]						
n	NA	12	10	27	22	71
Mean (SD)		-0.5 (1.26)	-1.0 (0.89)	-0.8 (1.31)	-0.7 (1.30)	-0.7 (1.23)
Median		-1.0	-1.0	-0.8	-0.6	-0.9
Min , Max		-1.8 , 2.8	-2.1 , 1.0	-2.9 , 2.5	-2.8 , 1.4	-2.9 , 2.8
Week 168 (MOR-005 Week 144) -Change from Baseline[b]						
n	NA	7	5	21	13	46
Mean (SD)		-1.3 (0.97)	-1.4	-0.7	-0.8	-0.9

			(0.51)	(1.57)	(1.51)	(1.39)
Median		-1.8	-1.1	-0.7	-0.4	-1.0
Min , Max		-2.3 , 0.5	-2.2 , -1.0	-3.1 , 2.6	-2.5 , 1.8	-3.1 , 2.6

SD, standard deviation
With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the 2.0 mg/kg/qw dosing regimen.
a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110- BMN 110 2.0 mg/kg/qw
b Change is equal to current value minus the baseline value.

Restricted to Females age <=15 years and Males age <= 18 years.

Rapporteur's comment
Note that the data were restricted to females age ≤15 years and males age ≤ 18 years.
On continued treatment with elosulfase alfa, the anthropologic measures show a normalised growth rate, SD between -1 and +1. It appears that in these patients there is no catch up growth.

Other Anthropometric Measures

In Part 1, positive changes in the absolute values in most anthropometric measurements were observed in patients who received continuous treatment with BMN 110; however, standard deviations were large. The mean (±SD) changes in absolute values for the anthropometric measures from MOR-004 Baseline to Week 48 in the entire ITT population were similar between cohorts.

Continued treatment with weekly BMN 110 in Part 2 through Week 120 showed similar findings. Discussion of data after Week 120 is not included due to the relatively low number of patients that continued on the study after Week 120.

Mean (±SD) changes in absolute values for the Total population:

- standing height values at Week 48 (n=158), Week 72 (n=158), and Week 120 (n= 150) were 1.8 cm (±2.36), 2.5 cm (±2.62), and, 3.5 cm (±3.64), respectively.
- sitting height values at Week 48 (n=161), Week 72 (n=161), and Week 120 (n=155) were -2.3 cm (±11.95), -1.8 cm (±12.82), and, -1.5 cm (±11.61), respectively.
- length values at Week 48 (n=157), Week 72 (n=158), and Week 120 (n= 150) were 2.2 cm (±2.67), 2.6 cm (±3.52), and 3.6 cm (±9.06), respectively.
- weight values at Week 48 (n=167), Week 72 (n=168), and Week 120 (n= 160) were 1.7 kg (±2.18), 2.2 kg (±2.34), and 3.3 kg (±3.24), respectively.

To explore these findings further, analyses were performed using the age-restricted population (males ≤18 years and females ≤15 years). In general, a numerically larger change was observed in the absolute values of these 4 anthropometric measures in the younger (growing) population compared to the Total study population.

Mean (±SD) changes in absolute values for the Total population:

- standing height values at Week 48 (n=117), Week 72 (n=116), and Week 120 (n= 112) were 2.2 cm (±2.42), 3.3 cm (±2.38), and, 4.7 cm (±3.34) respectively.
- sitting height values at Week 48 (n=120), Week 72 (n=118), and Week 120 (n= 115) were -1.5 cm (±10.87), -0.5 cm (±11.78), and -0.3 cm (±11.02), respectively.

- length values at Week 48 (n=116), Week 72 (n=117), and Week 120 (n= 112) were 2.5 cm (±2.70), 3.1 cm (±3.56), 5.2 cm (±4.21), respectively.
- weight values at Week 48 (n=124), Week 72 (n=125), and Week 120 (n= 121) were 1.9 kg (±2.16), 2.4 kg (±2.18), 3.9 kg (±3.07), respectively.

Rapporteur's comment
Numerical anthropometric data should some positive effects, however SD-values are large and therefore, no firm conclusion can be drawn.

The applicant is requested to also plot the results of standing height z-score, growth velocity z-score, and standing height against data for the natural history population (**OC**).

Radiographs of Lumbar Spine and Lower Extremity

Radiographs of the lower extremity were performed for patients ≤20 years old only. Data from radiographs performed in MOR-004, or within 72 weeks prior to enrolment, may have been used for the Baseline radiographs. Subsequent radiographs were performed at 72-week intervals from the time of the most recent radiograph.

The mean (± SD) change from Baseline for the Total population in the left lower extremity length was 0.7 cm (± 1.36) at Week 24 (n=87), 1.7 cm (± 3.74) at Week 96 (n=75). Changes in the right lower extremity were similar to those in the left.

The mean (± SD) change from Baseline for the Total population in the right lower extremity length was 0.7 cm (± 1.57) at Week 24 (n=86), 2.0 cm (± 2.21) at Week 96 (n=76).

Rapporteur's comment
The data on the radiographs of the lumbar spine and lower extremities showed some minimal improvement. The numerical values are in line with the values for height, indicating some improvement. The clinical relevance of these changes remain to be demonstrated.

Other Measurements
No meaningful treatment effects or negative signals were observed in corneal clouding, audiometry, PIQ, CTX1, or PIIANP. No definitive conclusions can be drawn from results obtained for these measurements.

Rapporteur's comment
The MPS HAQ was developed to assess the self-care and mobility skills of patients with MPS I. The questionnaire includes self-care (eating/drinking, dressing, bathing, grooming, tooth brushing, and toileting) and mobility domains (dexterity, mobility, walking, stair climbing, and gross motor skills). Caregiver assistance items were also to be included to assess the extent to which assistance was required for the performance of activities related to the self-care and mobility domains. This is considered an important part of the assessment, as improvement in this domain of self-care and mobility could also add to the possible benefit of elosulfase alfa in these patients.

It is important to realise that a higher Domain score signifies more impaired functionality and therefore, results in a negative direction indicate improvement in functionality.

Based on the data submitted in the appendices of the dossier (table 14.2.7.1 and 14.2.7.3, inserted below) it can be concluded that patients mobility scores thus show a small positive trend over time for all treatment groups (note only the change from baseline to week 120 is taken, but this improvement is visible throughout the treatment period). Similar results were observed for the self-care domain. The clinical relevance of this marginal improvement is unknown. Note that the placebo group (PBO) in the table below does not exist anymore in study MOR-005, thus are not applicable (NA) in these tables.

Table 14.2.7.3
Descriptive Summary of MPS HAQ Mobility Domain Score at Scheduled Visits
Analysis Population: ITT- MOR004 and MOR005

Test, unit Study Visit Statistic	PBO (n = 59)	PBO-QOW (n = 29)	PBO-QW (n = 29)	QOW-QOW (n = 59)	QW-QW (n = 58)	Total (n = 176)
Mobility Domain Score (cont.)						
Change from Baseline to Week 14 4 (MOR-005 Week 120)						
n	NA	14	15	35	26	90
Mean (SD)		-0.4 (1.73)	-0.1 (2.05)	-0.7 (2.60)	-0.9 (1.70)	-0.6 (2.14)
Median		-0.4	0.3	-0.4	-0.9	-0.6
25th , 75th Percentile		-1.3 , 0.3	-0.9 , 1.3	-2.1 , 0.9	-1.8 , 0.4	-1.7 , 0.5
Min , Max		-3.7 , 4.1	-5.4 , 2.7	-6.2 , 6.0	-5.3 , 2.1	-6.2 , 6.0

Table 14.2.7.1
Descriptive Summary of MPS HAQ Self-Care Domain Score at Scheduled Visits
Analysis Population: ITT- MOR004 and MOR005

Test, unit Study Visit Statistic	PBO (n = 59)	PBO-QOW (n = 29)	PBO-QW (n = 29)	QOW-QOW (n = 59)	QW-QW (n = 58)	Total (n = 176)
Self-Care Domain Score (cont.)						
Change from Baseline to Week 14 4 (MOR-005 Week 120)						
n	NA	14	15	35	26	90
Mean (SD)		-0.8 (1.76)	-0.1 (1.47)	-0.3 (1.92)	-0.7 (1.57)	-0.5 (1.72)
Median		-0.5	-0.5	-0.4	-0.6	-0.4
25th , 75th Percentile		-2.5 , -0.1	-1.2 , 0.9	-1.3 , 0.3	-1.4 , 0.0	-1.3 , 0.1
Min , Max		-3.9 , 2.4	-2.0 , 3.5	-4.4 , 6.0	-3.9 , 3.6	-4.4 , 6.0

Safety results

BMN 110 was generally well-tolerated in patients younger than 5 years. There were no deaths during the study and no patients withdrew from the study or permanently discontinued treatment due to an AE.

Extent of Exposure

The mean (±SD) total duration of BMN 110 exposure was 120.7 (±37.5) weeks. Mean (±SD) weekly study drug dose/patient was 2.00 (0.026) mg/kg. Mean (±SD) total study drug exposure was 228.12 (77.738) mg/kg.

Adverse Events

All patients (100%) experienced at least one AE during the study (Table 13). The most commonly reported AEs were pyrexia (68.8%), vomiting (66.5%), and headache (65.9%).

Table 12: Overall Summary of Adverse Events: (Safety Population).

	PBO-QOW[a] (n = 29)	**PBO-QW[a] (n = 29)**	**QOW-QOW[a] (n = 59)**	**QW-QW[a] (n = 56)**	**Total (n=173)**
Any AE	29 (100.0%)	29 (100.0%)	59 (100.0%)	56 (100.0%)	173 (100.0%)
Number of AEs per patient Mean/Median	58.2/46.0	40.1/26.0	50.5/39.0	59.0/45.5	52.8/42.0
Any Study Drug-Related AEb	28 (96.6%)	21 (72.4%)	49 (83.1%)	51 (91.1%)	149 (86.1%)
Any SAE	17 (58.6%)	15 (51.7%)	26 (44.1%)	31 (55.4%)	89 (51.4%)
Number of SAEs per patient Mean/Median	0.9/1.0	0.8/1.0	0.9/0.0	1.1/1.0	0.9/1.0
Any Study Drug-Related SAE	2 (6.9%)	0 (0.0%)	1 (1.7%)	2 (3.6%)	5 (2.9%)
Any AE Leading to Study Discontinuation	0 (0.0%)	0 (0.0%)	2 (3.4%)	2 (3.6%)	4 (2.3%)
Any AE Leading to Permanent Study Drug Discontinuation	0 (0.0%)	0 (0.0%)	3 (5.1%)	2 (3.6%)	5 (2.9%)
Death	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (0.6%)

a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW,BMN 110-BMN 110 2.0 mg/kg/qw
b AEs that were classified by the investigator as possibly or probably related to study drug
With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the2.0 mg/kg/qw dosing regimen.
AEs coded by MedDRA version 16.1;
Patients who experienced more than one AE within a category in incidence category were counted once within that category

Table 13: Adverse Events Reported in ≥ 20% of Total Population (Analysis Population: Safety- MOR-004 and MOR-005).

	PBO-QOW[a] (n = 29)	**PBO-QW[a] (n = 29)**	**QOW-QOW[a] (n = 59)**	**QW-QW[a] (n = 56)**	**Total (n = 173)**
Patients with at Least 1 Reported AE	29 (100.0%)	29 (100.0%)	59 (100.0%)	56 (100.0%)	173 (100.0%)
Pyrexia	22 (75.9%)	19 (65.5%)	39 (66.1%)	39 (69.6%)	119 (68.8%)
Vomiting	20 (69.0%)	17 (58.6%)	39 (66.1%)	39 (69.6%)	115 (66.5%)
Headache	23 (79.3%)	16 (55.2%)	39 (66.1%)	36 (64.3%)	114 (65.9%)
Arthralgia	20 (69.0%)	16 (55.2%)	40 (67.8%)	29 (51.8%)	105 (60.7%)
Cough	21 (72.4%)	14 (48.3%)	37 (62.7%)	28 (50.0%)	100 (57.8%)
Pain in extremity	16 (55.2%)	12 (41.4%)	27 (45.8%)	31 (55.4%)	86 (49.7%)
Nasopharyngitis	13 (44.8%)	13 (44.8%)	29 (49.2%)	28 (50.0%)	83 (48.0%)
Nausea	15 (51.7%)	10 (34.5%)	26 (44.1%)	28 (50.0%)	79 (45.7%)
Oropharyngeal pain	13 (44.8%)	11 (37.9%)	23 (39.0%)	27 (48.2%)	74 (42.8%)
Diarrhoea	11 (37.9%)	11 (37.9%)	25 (42.4%)	23 (41.1%)	70 (40.5%)
Upper respiratory tract infection	13 (44.8%)	8 (27.6%)	24 (40.7%)	24 (42.9%)	69 (39.9%)
Abdominal pain	12 (41.4%)	6 (20.7%)	22 (37.3%)	24 (42.9%)	64 (37.0%)

Fatigue	10 (34.5%)	13 (44.8%)	16 (27.1%)	19 (33.9%)	58 (33.5%)
Gastroenteritis	6 (20.7%)	9 (31.0%)	24 (40.7%)	17 (30.4%)	56 (32.4%)
Ear pain	10 (34.5%)	7 (24.1%)	19 (32.2%)	19 (33.9%)	55 (31.8%)
Back pain	10 (34.5%)	4 (13.8%)	19 (32.2%)	18 (32.1%)	51 (29.5%)
Rash	8 (27.6%)	8 (27.6%)	15 (25.4%)	19 (33.9%)	50 (28.9%)
Nasal congestion	10 (34.5%)	4 (13.8%)	15 (25.4%)	16 (28.6%)	45 (26.0%)
Abdominal pain upper	8 (27.6%)	9 (31.0%)	9 (15.3%)	18 (32.1%)	44 (25.4%)
Pruritus	7 (24.1%)	3 (10.3%)	8 (13.6%)	19 (33.9%)	37 (21.4%)
Otitis media	8 (27.6%)	5 (17.2%)	11 (18.6%)	11 (19.6%)	35 (20.2%)
Rhinitis	9 (31.0%)	6 (20.7%)	11 (18.6%)	9 (16.1%)	35 (20.2%)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term
a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW,BMN 110-BMN 110 2.0 mg/kg/qw
With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the2.0 mg/kg/qw dosing regimen.
AEs coded by MedDRA version 16.1. Patients with more than 1 AE within a given MedDRA PT were counted once within that PT
Patients who experienced more than one AE within a category were counted once within that category.

Table is sorted in decreasing frequency by PT in the Total population

Rapporteur's comment

No (noteworthy) major differences in AEs between the different treatment groups were observed.

Drug-Related Adverse Events

Overall, 149 (86.1%) patients reported study drug-related AEs (Table 13). The most commonly reported study drug-related AE was pyrexia (35.8%) followed by headache (30.6%).

Table 14: Study Drug-Related Adverse Events by Preferred Term in ≥ 10% of Total Population Analysis Population: Safety- MOR-004 and MOR-005.

	PBO-QOW[a] (n = 29)	PBO-QW[a] (n = 29)	QOW-QOW[a] (n = 59)	QW-QW[a] (n = 56)	Total (n = 173)
Patients with at Least 1 Reported Study Drug-Related AE	28 (96.6%)	21 (72.4%)	49 (83.1%)	51 (91.1%)	149 (86.1%)
Pyrexia	12 (41.4%)	10 (34.5%)	13 (22.0%)	27 (48.2%)	62 (35.8%)
Headache	12 (41.4%)	7 (24.1%)	13 (22.0%)	21 (37.5%)	53 (30.6%)
Vomiting	7 (24.1%)	6 (20.7%)	12 (20.3%)	24 (42.9%)	49 (28.3%)
Nausea	9 (31.0%)	5 (17.2%)	11 (18.6%)	20 (35.7%)	45 (26.0%)
Rash	4 (13.8%)	4 (13.8%)	10 (16.9%)	11 (19.6%)	29 (16.8%)
Pruritus	5 (17.2%)	0	5 (8.5%)	15 (26.8%)	25 (14.5%)
Urticaria	6 (20.7%)	1 (3.4%)	7 (11.9%)	11 (19.6%)	25 (14.5%)
Fatigue	5 (17.2%)	4 (13.8%)	5 (8.5%)	10 (17.9%)	24 (13.9%)
Diarrhoea	3 (10.3%)	5 (17.2%)	5 (8.5%)	9 (16.1%)	22 (12.7%)
Abdominal pain	5 (17.2%)	1 (3.4%)	4 (6.8%)	10 (17.9%)	20 (11.6%)
Tachycardia	7 (24.1%)	3 (10.3%)	5 (8.5%)	5 (8.9%)	20 (11.6%)
Abdominal pain upper	4 (13.8%)	2 (6.9%)	1 (1.7%)	11 (19.6%)	18 (10.4%)

Chills	3 (10.3%)	1 (3.4%)	5 (8.5%)	9 (16.1%)	18 (10.4%)

a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW,BMN 110-BMN 110 2.0 mg/kg/qw
With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the2.0 mg/kg/qw dosing regimen.
A drug-related AE was classified by investigator as possibly or probably related to study drug; AEs coded by MedDRA version 16.1.
Table is sorted in decreasing frequency of the Total column by PT
Patients with more than one AE within a MedDRA PT were counted once.

Rapporteur's comment

Patients in the PBO-QOW groups seem to experience more AE's related to the respiratory system. In general, respiratory issues in Morquio patients are well known from literature. The applicant is requested to submit the "Drug-Related Adverse Events by Preferred Term in ≥ 10%" stratified by age-groups (<18 years and ≥18 years). This to confirm that the safety profile in paediatric patients is similar to those observed in the adults. If appropriate the applicant is requested to update SmPC section 4.8 (**OC**).

Death and Serious Adverse Events

Deaths

One patient (Patient 0024-4173; female age 11 years at time of enrolment) died during the study during Part 2 due to an AE (MedDRA Preferred Term: lung disorder), which was considered not related to study drug as assessed by the investigator and attributable to underlying disease. The patient suffered a serious Grade 4 event of myelopathy and was scheduled for laminectomy plus spinal fusion, and hospitalised (28 October 2013). Following the surgery, the patient remained hospitalized with a left pleural effusion requiring a chest tube; she had no sensation or mobility below T3-T4. On an unreported date, her pulmonary function declined, becoming a serious Grade 5 lung disorder. On 15 November 2013, the patient died; the cause of death was reported as postoperative pulmonary complications.

Rapporteur's comment

One patient died during part 2 of the MOR-005 study. The patient died due to post operative pulmonary complications. It is plausible that this was related to the underlying disease.

Serious adverse events

Overall, 89 patients (51.4%) reported at least one SAE. The most commonly reported SAE was knee deformity (29 patients [16.8%]) followed by poor venous access (12 patients [6.9%]). Other SAEs reported by more than 1 patient included central venous catheterization, joint instability, medical device removal (each 5 patients), lower respiratory tract infection, spinal cord compression, vomiting (each 4 patients), cervical cord compression, developmental hip dysplasia, device dislocation, gastroenteritis, pneumonia (each 3 patients), anaphylactic reaction, asthma, back pain, medical device implantation, middle ear effusion, otitis media, sleep apnoea syndrome, and tonsillar hypertrophy (each 2 patients). Most SAEs were reported by one patient each.

Five patients (2.9%) reported study drug-related SAEs, which included anaphylactic reaction (2 patients), haematuria, hypersensitivity, and vomiting (each 1 patient).

Rapporteur's comment
Five patients (2.9%) reported study drug-related SAEs, which included anaphylactic reaction (2 patients), haematuria, hypersensitivity, and vomiting (each 1 patient). This is already covered in the warning section of the approved SmPC. No further action is deemed necessary at this moment.

Hypersensitivity Adverse Events

Overall, 89 (51.4%) patients reported hypersensitivity AEs. The most commonly reported hypersensitivity AE PT was urticaria (30 patients [17.3%]) followed by wheezing (20 patients [11.6%]), nasal obstruction (15 patients [8.7%]), and hypersensitivity (10 patients [5.8%]) (all in Angioedema SMQ (Standardized MedDRA Query)) (Table 15).

Other hypersensitivity AE PTs (Angioedema or Anaphylactic Reaction SMQ) reported in more than 1 patient included cough (9 patients), peripheral oedema (8 patients), dyspnoea (each 6 patients), obstructive airways disorder, rash, pruritus (each 5 patients), flushing (4 patients), throat tightness, eye swelling, lip swelling, erythema, (each 3 patients), stridor, swelling face, choking, drug hypersensitivity, oedema, hypotension, anaphylactic reaction, bronchospasm, and chest discomfort (each 2 patients). Forty-nine patients (28.3%) experienced reported study drug-related hypersensitivity AEs. The most commonly reported study drug-related hypersensitivity AE PT was urticaria (Angioedema SMQ 25 patients [14.5%]). Two patients each experienced an AE coded to the PT anaphylactic reaction (Patient 0021-4005 and Patient 1075-4007); both events were study-drug related SAEs.

Twenty patients were identified as having events of anaphylaxis during MOR-005 using the anaphylactic reaction SMQ (Table 15).

Table 15: Hypersensitivity Adverse Events Using Standardized MedDRA Queries (Analysis Population: Safety- MOR-004 and MOR-005).

	PBO-QOW[a] (n = 29)	PBO-QW[a] (n = 29)	QOW-QOW[a] (n = 59)	QW-QW[a] (n = 56)	Total (n=173)
Patients with at Least 1 Hypersensitivity AE[b]	17 (58.6%)	11 (37.9%)	32 (54.2%)	29 (51.8%)	89 (51.4%)
Anaphylactic Reaction SMQ[b]	5 (17.2%)	2 (6.9%)	7 (11.9%)	6 (10.7%)	20 (11.6%)
Cough	2 (6.9%)	2 (6.9%)	2 (3.4%)	3 (5.4%)	9 (5.2%)
Urticaria	4 (13.8%)	0 (0%)	1 (1.7%)	1 (1.8%)	6 (3.5%)
Dyspnoea	1 (3.4%)	1 (3.4%)	2 (3.4%)	2 (3.6%)	6 (3.5%)
Rash	1(3.4%)	1(3.4%)	2(3.4%)	1(1.8%)	5(2.9%)
Pruritus	2 (6.9%)	0 (0%)	1 (1.7%)	2 (3.6%)	5 (2.9%)
Flushing	1 (3.4%)	0 (0%)	1 (1.7%)	2 (3.6%)	4 (2.3%)
Erythema	0 (0%)	0 (0%)	0 (0%)	3 (5.4%)	3 (1.7%)
Anaphylactic reaction	1(3.4%)	0 (0%)	1 (1.7%)	0 (0%)	2 (1.2%)
Bronchospasm	0 (0%)	1 (3.4%)	1 (1.7%)	0 (0%)	2 (1.2%)
Chest discomfort	2(6.9%)	0 (0%)	0 (0%)	0 (0%)	2(1.2%)
Nasal obstruction	1 (3.4%)	0 (0%)	1 (1.7%)	0 (0%)	2 (1.2%)
Patients with at Least 1 Hypersensitivity AE[b]	17 (58.6%)	11 (37.9%)	32 (54.2%)	29 (51.8%)	89 (51.4%)
Angioedema SMQ[b]	17 (58.6%)	11 (37.9%)	30 (50.8%)	27 (48.2%)	85 (49.1%)
Urticaria	6 (20.7%)	1 (3.4%)	11 (18.6%)	12 (21.4%)	30 (17.3%)

Wheezing	5 (17.2%)	5 (17.2%)	6 (10.2%)	4 (7.1%)	20 (11.6%)
Nasal obstruction	3 (10.3%)	3 (10.3%)	6 (10.2%)	3 (5.4%)	15 (8.7%)
Local swelling	3 (10.3%)	0 (0%)	5 (8.5%)	4 (7.1%)	12 (6.9%)
Hypersensitivity	1 (3.4%)	0 (0%)	5 (8.5%)	4 (7.1%)	10 (5.8%)
Oedema peripheral	1 (3.4%)	0 (0%)	4 (6.8%)	3 (5.4%)	8 (4.6%)
Obstructive airways disorder	0 (0%)	1 (3.4%)	1 (1.7%)	3 (5.4%)	5 (2.9%)
Throat tightness	0 (0%)	0 (0%)	1 (1.7%)	2 (3.6%)	3 (1.7%)
Eye swelling	0 (0%)	0 (0%)	2 (3.4%)	1 (1.8%)	3 (1.7%)
Lip swelling	0 (0%)	1 (3.4%)	2 (3.4%)	0 (0%)	3 (1.7%)
Oedema	0 (0%)	2 (6.9%)	0 (0%)	0 (0%)	2 (1.2%)
Drug hypersensitivity	0 (0%)	1 (3.4%)	1 (1.7%)	0 (0%)	2 (1.2%)
Choking	1 (3.4%)	1 (3.4%)	0 (0%)	0 (0%)	2 (1.2%)
Swelling face	1 (3.4%)	0 (0%)	0 (0%)	1 (1.8%)	2 (1.2%)
Stridor	0 (0%)	0 (0%)	1 (1.7%)	1 (1.8%)	2 (1.2%)

a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW,BMN 110-BMN 110 2.0 mg/kg/qw
With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the 2.0 mg/kg/qw dosing regimen.
Preferred Terms coded by MedDRA version 16.1
Patients with more than one AE within a MedDRA PT were counted once; maximum severity is summarized by patient
b Hypersensitivity adverse events were identified by utilizing the broad Anaphylactic Reaction algorithmic Standardized MedDRA query and the broad Angioedema
Standardized MedDRA query

Table is sorted in decreasing frequency of the Total column

Rapporteur's comment

89 patients (54.9%) reported hypersensitivity reactions. Most reported was urticaria, followed by wheezing. Hypersensitivity reaction appears well manageable with infusion rate adjustments and/or medical intervention. The approved SmPC section 4.4 (warnings) already includes the occurrence of infusion related reactions and severe allergic reactions, and how to respond to these. Therefore, at this moment no action seems necessary.

Infusion-Associated Reactions

IARs are summarized in Table 16. Nearly all patients (98.3%) reported IARs. The most common IARs were similar to the most common AEs overall and included pyrexia (51.4%), vomiting (49.1%), and headache (46.8%).

Most of the IARs that occurred during the study were Grade 2 (58.4% of patients) in severity. Nineteen patients (11.0%) reported Grade 3 IARs. Three patients (1.7%) reported Grade 4 IARs, which included asthma (Patient 1075-4084), anaphylactic reaction (Patient 0021-4005), and status asthmaticus (Patient 1017-4075); these Grade 4 IARs were also classified as SAEs. The Grade 4 IAR of anaphylactic reaction (Patient 0021-4005) was also classified as a hypersensitivity AE and was considered possibly related to study drug. Twenty-two patients (12.7%) experienced severe IARs.

A subset of IARs led to interruption or discontinuation of infusion during the study visit. Infusions were interrupted due to AEs for 46 patients (26.6%). Infusions were discontinued during a study visit due to AEs for 41 patients (23.7%) (Table 16). One patient (Patient 1159-4096; 41 year old male) permanently discontinued study drug due to a Grade 1 IAR AE of proteinuria. The proteinuria did not resolve after discontinuation. The investigator assessed the event of proteinuria as not related to study treatment.

Most IARs in all patients were either tolerated by patients with no change to infusion rate, or were successfully managed by either interrupting or discontinuing infusion at that visit, and in some cases, additional medical intervention.

Table 16: Overall Summary of Infusion Associated Reactions Analysis (Population: Safety-MOR004 and MOR005).

	PBO-QOW[a] (n = 29)	PBO-QW[a] (n = 29)	QOW-QOW[a] (n =59)	QW-QW[a] (n = 56)	Total (n=173)
Any IAR[b] AE	29 (100.0%)	27 (93.1%)	58 (98.3%)	56 (100.0%)	170 (98.3%)
Any IAR[b] AE during infusion	29 (100.0%)	25 (86.2%)	58 (98.3%)	56 (100.0%)	168 (97.1%)
Any IAR[b] SAE during infusion	3 (10.3%)	3 (10.3%)	4 (6.8%)	8 (14.3%)	18 (10.4%)
Any IAR[b] AE leading to infusion interruption	4 (13.8%)	3 (10.3%)	21 (35.6%)	18 (32.1%)	46 (26.6%)
Any IAR[b] AE leading to infusion discontinuation	8 (27.6%)	4 (13.8%)	12 (20.3%)	17 (30.4%)	41 (23.7%)
Any IAR[b] AE leading to infusion interruption or discontinuation requiring medical intervention	8 (27.6%)	3 (10.3%)	18 (30.5%)	22 (39.3%)	51 (29.5%)
Any IAR[b] AE leading to permanent study drug discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (0.6%)
Any AE Leading to Permanent Study Drug Discontinuation	0 (0.0%)	0 (0.0%)	3 (5.1%)	2 (3.6%)	5 (2.9%)
Death	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (0.6%)

a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW,BMN 110-BMN 110 2.0 mg/kg/qw
b IAR, infusion-associated reaction.
With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the2.0 mg/kg/qw dosing regimen.
IARs are considered associated with the administration of study drug if they occur after the onset of the infusion or within one day following the end of the infusion. IARs coded by MedDRA 16.1
For infusion interruption, the infusion was completed; for infusion discontinuation, the infusion was not completed.
Patients with more than one AE within a category were counted once.

Rapporteur's comment

Nearly all patients (98.3%) reported IARs. The most common IARs were similar to the most common AEs overall and included pyrexia (51.4%), vomiting (49.1%), and headache (46.8%). One patient permanently discontinued treatment due to persisting proteinuria.

The SmPC in section 4.8 mentions "…Infusion reactions (IRs) occurring in ⩾ 10% of patients treated with Vimizim." and "IRs were generally mild or moderate, and the frequency was higher during the first 12 weeks of treatment and tended to occur less frequently with time." However, in the combined safety population of studies MOR-004 and MOR-005, nearly all patients (98.3%) reported Infusion Associated Reactions (IARs). The MAH should discuss whether the frequency of IRs in this study was higher than already described in the SmPC and, if needed, propose amendments of the SmPC wording (**OC**).

Infusion Associated Reactions Resulting in Infusion Interruption or Discontinuation and Requiring Medical Intervention

AEs that resulted in infusion interruption or infusion discontinuation and also required medical intervention were reported by 42 (24.3%) and 19 (11.0%) patients, respectively. Most of these patients had the AEs managed with IV antihistamines (33 patients [19.1%]) or IV steroids (30 patients [17.3%]).

Table 17: Patient Incidence of Adverse Events During Infusion Requiring Medical Intervention (Population: Safety- MOR004 and MOR005).

	PBO-QOW[a] (n = 29)	PBO-QW[a] (n = 29)	QOW-QOW[a] (n = 59)	QW-QW[a] (n = 56)	Total (n= 173)
Patients with infusion interrupted or discontinued due to an AE that required medical intervention	8 (27.6%)	3 (10.3%)	18 (30.5%)	22 (39.3%)	51 (29.5%)
Number of Patients with infusions interruption	7 (24.1%)	3 (10.3%)	14 (23.7%)	18 (32.1%)	42 (24.3%)
Number of Patients with infusions discontinuation	4 (13.8%)	0	7 (11.9%)	8 (14.3%)	19 (11.0%)
Medical Intervention					
IV Antihistamines	6 (20.7%)	0	2 (20.3%)	15 (26.8%)	33 (19.1%)
IV Steroids	5 (17.2%)	2 (6.9%)	13 (22.0%)	10 (17.9%)	30 (17.3%)
IV Fluids	1 (3.4%)	0	4 (6.8%)	8 (14.3%)	13 (7.5%)
Oxygen	0	1 (3.4%)	4 (6.8%)	7 (12.5%)	12 (6.9%)

AE, adverse event; IV, intravenous
a PBO-QOW, Placebo-BMN 110 2.0 mg/kg/qow; PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw
With the initiation of Part 2 of MOR-005 on 01DEC2012, all patients were transitioned to the 2.0 mg/kg/qw dosing regimen.
Denominators are the numbers of patients in the safety population.
Medical intervention is defined as at least one of the following: IV antihistamine, IV steroids, IV fluids, or oxygen, as determined from WHO Drug coding.
Only adverse events which were interrupted or discontinued were considered.

For infusion interruption, the infusion was completed; for infusion discontinuation, the infusion was not completed.

Rapporteur's comment:
It is known for this product that patients can experience infusion related reactions and require medical intervention. Measurements to be taken when an infusion related reaction occurs or how to pre-treat the patient prior to elosulfase alfa infusion with antihistaminics are already stated in the SmPC (posology and warning section).

Pregnancy

Patient 0025-4010 (QW-QW cohort; 37 years old female) had an ectopic pregnancy that was reported as an SAE (20 Feb 2014 to 22 Feb 2014). The patient had no previous pregnancy history prior to enrolment in MOR-004. She started treatment with BMN 110 2.0 mg/kg/week in MOR-004 on 24 June 2011, and started treatment in MOR-005 on 9 December 2011. On an unspecified date, the subject became pregnant while receiving BMN 110. The date of her last menstrual period was 15 July 2013. BMN 110 therapy continued during the pregnancy. On 5 September 2013, an ultrasound revealed a gestational sac without an embryo (serious Grade 2 blighted ovum), and the diagnosis was confirmed with additional testing on 13 September 2013. Treatment for the event included an unspecified procedure, and the event was considered resolved on 25 September 2013. No action was taken with study medication in response to the event, and the subject continued to received BMN 110.

The date of her last menstrual period was 25 December 2013. On 14 February 2014, an ultrasound showed an empty uterus with suspicion of an ectopic pregnancy. She was hospitalized on 20 February 2014 for a serious Grade 3 ectopic pregnancy with hemoperitoneum. On that date, she underwent a therapeutic abortion via right salpingectomy. The patient was discharged home on 22 February 2014, and the event was considered resolved on that date. No action was taken with study medication in response to the event. The investigator assessed the events of blighted ovum and ectopic pregnancy as not related to study treatment.

The patient received her last infusion of study drug on 04 Jul 2014 (Part 2, Week 134) and exited the study on 12 Sep 2014.

Rapporteur's comment
During the study 1 patient became pregnant twice. Both pregnancies were ectopic. The conclusion of the investigator that the ectotopic pregnancies were not related to the study drug seems plausible.

Clinical Laboratory Evaluation

No clinically meaningful changes in vital signs, clinical chemistry, haematology, or urinalysis results were observed.

Vital Signs, Physical Findings, and Other Observations Related to Safety

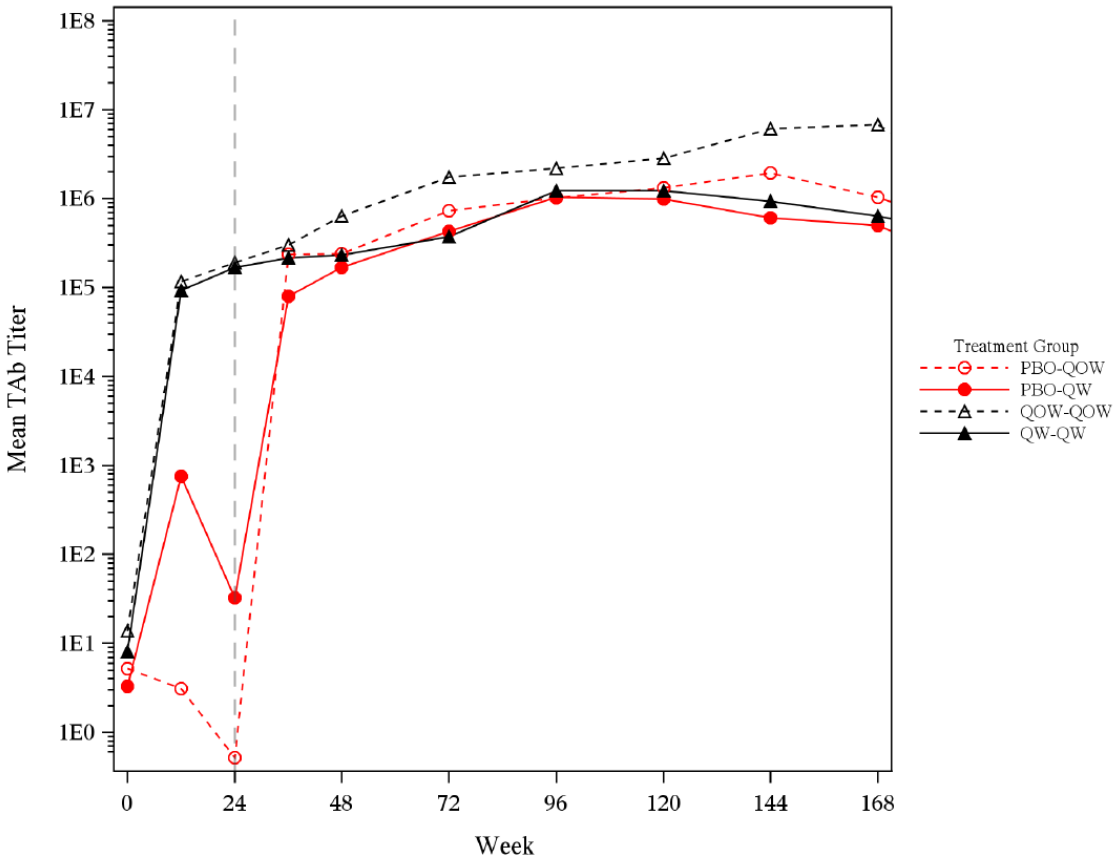
There were no clinically significant trends in vital signs, ECG, ECHOs in the total population, based on review of changes in vital signs from pre-infusion to during or post-infusion.

Immunogenicity and Efficacy

All patients treated with BMN 110 developed antidrug total antibody (Tab) by Week 24 of MOR-004. In the extension study, all treatment groups, including patients who had previously been on placebo, were TAb positive by study Week 36 (MOR-005 Week 12). All patients remained TAb positive throughout the study and TAb titers were similar across treatment groups at Week 120. Nearly all patients tested positive for elosulfase alfa specific neutralizing antibodies (Nab) at least once, with incidence of Nab positivity peaking at 85.9% at study Week 36, then steadily declining to 66.0% at study Week 120. In all treatment groups, mean urine KS remained below treatment-naive baseline despite the presence of antidrug antibodies. No relationship was observed between TAb titers or NAb positivity and changes in urine KS, 6MWT, or 3MSCT from Baseline to Week 120.

All patients treated with BMN 110 developed anti-BMN 110TAb by study Week 36 and remained positive for TAb throughout MOR-005. Patients who received placebo in MOR-004 initiated BMN 110 treatment upon entering MOR-005, and all patients in this group tested positive for TAb following 12 weeks of BMN 110 treatment. From study Week 36 through to study end, all patients remained TAb positive and mean titer values remained similar across all treatment groups through Week 120 (Figure 8). There were no apparent differences in TAb titer between the ITT and MPP populations.

Figure 8: Mean TAb Titer and Treatment Duration (Analysis Population: ITT- MOR004 and MOR005).



Rapporteur's comment:
All patients treated with elosulfase alfa developed antidrug TAb by Week 24 of MOR-004. In the extension study, all treatment groups, including patients who had previously been on placebo, were TAb positive by study Week 36 (MOR-005 Week 12). All patients remained TAb positive throughout the study and TAb titers were similar across treatment groups at Week 120.

After switching to elosulfase alfa treatment, patients previously on placebo all showed an increase in Nab titers, following the same trend as observed during study MOR-004.

No relationship was observed between TAb titers or NAb positivity and changes in urine KS, 6MWT, or 3MSCT from Baseline to Week 120.

Mean TAb titer was not associated with either the presence or severity of hypersensitivity AEs. Through the end of MOR-005, 89 of 172 patients (51.7%) experienced a hypersensitivity AE (Table 18). There was no difference in mean TAb titer between patients that experienced hypersensitivity AEs vs those that did not.

Table 18: Mean TAb Titer and HAE Severity (Modified ITT)

Statistic	
AE Severity	**All Patients (n=172)**
Mean TAb Titer (Range)	
None n=83	534367.7 (2754.0 – 5461400.0)

Grade 1 n=63	893084.5 (10212.0 – 13933120.0)
Grade 2 n=21	615448.0 (33536.0 – 4360000.0)
Grade 3 n=3	120059.3 (74400.0 – 179280.0)
Grade 4 n=2	67849.0 (61298.0 – 74400.0)

Rapporteur's comment:
The data indicate that there is no association between Tab titers and AE severity or efficacy. This is in line with the data assessed during the initial MAA.

2.3.3. Discussion on clinical aspects

Based on the submitted uncontrolled data of the extension study MOR-005 no firm conclusions can be drawn at this moment. Study MOR-005 is the long-term extension study of study MOR-004, which is partially discussed during the initial MAA (data up to week 48 (week 24) were already assessed in the MAA).

Data up to week 168 have now become available. In total 173 patients were included in the study. The majority of the population were paediatric patients over 5 years of age (5-11 years, 93/173 (53.8%); 12-18 years 46/173 (26.6%), over 19 years 31/173 (19.7%)).

The results obtained for urine keratin sulphate (KS) indicate that with continued elosulfase alfa treatment the pharmacodynamic effect is maintained. This is confirmed in patients previously on placebo treatment in MOR-004 who switched to active treatment in MOR-005.

The 6MWT, respiratory function (capacity), anthropometric measures and the MPS Health Assessment Questionnaire are considered important indicators for observing a clinically relevant effect in these patients. As elosulfase alfa is a life-long treatment, it will be especially important for the paediatric patient population that in due time a clear relevant clinical benefit for these patients is observed/demonstrated.

As all patients on the 2 mg/kg every other week (QOW) dosage were switched to the approved dosage (2 mg/kg every week (QW)) in accordance with the SmPC, the results of the patients in the QOW-QOW and Placebo-QOW should be interpreted with caution. The patients who received the QW regimen during the whole study (QW-QW and placebo-QW) are considered the most important groups, as these data will add to the knowledge of the long term treatment effect of elosulfase alfa.

In the QW-QW group, the results of the 6MWT from MOR-005 show some initial improvement up to week 48 (part 1 of the study), but the long term data suggests that the effect decline under continued treatment (part 2 of the study). A similar trend is observed in the placebo-QW group. As the respiratory function seems to improve numerically in the patients with continued elosulfase alfa treatment, it is expected that this would also influence the endurance capacity of a patient resulting in an improvement of 6MWT. The interpretation of the data is hampered as the results are not normalized. For this reason the applicant should submit the results of the 6MWT, FEV1, FVC, height and height velocity based on z-scores for the QW-QW and placebo-QW groups.

On continued treatment with elosulfase alfa, the anthropologic measures show a normalised growth rate, SD between -1 and +1.

Data from the MPS Health Assessment Questionnaire (MPS HAQ), both self-care and mobility domain, showed a marginal positive trend for all treatment groups. The clinical relevance of this marginal improvement is unknown.

Altogether, taken the above observations, there seems to be limited clinical benefit of continued elosulfase alfa treatment on the 6MWT, lung capacity and MPS HAQ. It is therefore of scientific and clinical interest to verify whether there is an association between the 6MWT, lung capacity and MPS HAQ. The applicant is requested to explore this relationship.

Elosulfase alfa was generally well-tolerated in patients over 5 years. Hypersensitivity reactions appear to be well manageable with infusion rate adjustments and/or medical intervention. This is in line with the approved SmPC. No new or unexpected adverse events were observed. With respect to the drug-related AEs the applicant should submit the data stratified by age groups to confirm the statement that the safety in patients over 5 years of age is similar to those observed in adults. One patient died due to post operative pulmonary complications. During the study one patient became pregnant twice. Both pregnancies were ectopic. This is not considered to be related to the study drug.

All patients treated with elosulfase alfa developed antidrug total antibody (Tab) by week 24 of MOR-004. In the extension study, all treatment groups, including patients who had previously been on placebo, were TAb positive by study Week 36 (MOR-005 Week 12). All patients remained TAb positive throughout the study and TAb titers were similar across treatment groups at Week 120. Data indicate that there is no association between Tab titers and AE severity. This is in line with the data assessed during the initial MAA.

3. Rapporteur's updated overall conclusion and recommendation

In the previous assessment round the MAH was requested to submit additional analyses for baseline adjusted characteristics (e.g. age, gender). The rationale of this request was based on the need to examine whether there were any possible stopping rules for those patients that may not benefit from treatment. As requested the additional analyses were submitted by the MAH. However, in these analyses no clear difference between the age-groups (5-11 years and 12-18 years) were observed. Furthermore, when stratified by walking distance at baseline and use of walking aids, again no difference could be observed.

The data for 6MWT and 3MSCT showed that in both age groups treatment showed comparable results after 96 weeks. Initially an improvement is observed, however, at a later time point a decline in treatment effect is noticed in the younger population. With respect to the lung function (FEV1 and FVC) it is shown that the younger patients (5-11 years) showed slightly more improvement than the older patients (12-18 years).

In general patients in study MOR-005 had, besides an improvement in oligosaccharides (i.e. a decline), a better pulmonary function, endurance and daily self-care when compared to the natural history cohort. However, no firm conclusions can be drawn as the data were gathered in an open label study.

In order to investigate whether there was a correlation between the 6MWT and lung capacity with the MPS HAQ, the MAH performed a correlation analysis. The association is considered weak. Within the time-frame of the study the positive effect on the lung function and endurance apparently does not translate into a clear improvement of QoL.

In conclusion, based on data comparing the patients in study MOR-005 to the natural history cohort, there is no direct evidence for introducing stopping rules.

No new or unexpected safety signals were observed from the study. The safety results are consistent with prior studies and the safety profile for elosulfase alfa within the scope of the current knowledge. At this moment, there is no need to update SmPC section 4.8.

The benefit/risk of elosulfase alfa remains positive.

Data from the registry are awaited due time.

☒ **Fulfilled:**

No regulatory action is required.

4. Request for supplementary information

1. With respect to the 6MWT, FEV1, FVC, height and height velocity the MAH is requested to submit analyses using z-scores. These data should be submitted for the patient-groups that received 2.0 mg/kg QW during study 004 and 005, as the (QW-QW and placebo-QW groups separately) are the most relevant populations in this regard. Further, these data should be compared to the natural history population (study MOR-001). For each measurement (6MWT, FEV1, FVC, height and height velocity) a separate graph should be submitted. On the x-axis the time on treatment should be plotted, on the y-axis the z-score. The data of the natural history group should be incorporated in each graph.
2. For height and growth velocity (y-axis) the MAH should plot against age (x-axis), and the CDC and the published MSP growth curves should be incorporated (refer to the publication by *P. Harmatz et al., Molecular Genetics and Metabolism 109 (2013) 54–61*). Graphs should be submitted for males and females separately.
3. The MAH is requested to submit the baseline data and efficacy results for the paediatric patients and paediatric subpopulation separately.
4. The MAH is requested to submit the baseline demographics and characteristics for the MPP population, paediatric, adult and paediatric subpopulations separately.
5. In the MPS HAQ a marginal positive improvement was observed. The clinical relevance is unknown. The MAH is requested to submit the results for both MPS HAQ domains stratified by age groups, as this may provide insight on whether there is a difference in impact between the age groups.
6. As elosulfase alfa is for life-long treatment, presumably starting early in life (after diagnosis), it is clear that a clinically relevant benefit for the patient is to be expected. In this case the 6MWT, lung capacity and MPS HAQ are considered important indicators for observing a clinically relevant effect in these patients, although other factors are important as well. It is therefore important to verify whether there is an association between the 6MWT, lung capacity and MPS HAQ. The MAH is requested to submit these analyses.

7. The MAH is requested to discuss whether there are any patient characteristics that could help to determine, *a priori*, those patients that will not benefit from elosulfase alfa treatment. The MAH should explore the possibility to include stopping rules in the SmPC for those patients not (or no longer) having a benefit from treatment.
8. Study MOR-005 was planned to continue up to Week 240, however it was prematurely terminated by the MAH. The timing of the termination as well as justification for this should be provided by the MAH.
9. The MAH is requested to submit the "Drug-Related Adverse Events by Preferred Term in ≥ 10%" stratified by age-groups (<18 years and ≥18 years), to confirm that the safety profile in paediatric patients is similar to that observed in the adult population. When appropriate SmPC section 4.8 should be updated accordingly.
10. The SmPC in section 4.8 mentions "…. Infusion reactions (IRs) occurring in ⩾ 10% of patients treated with Vimizim." and "IRs were generally mild or moderate, and the frequency was higher during the first 12 weeks of treatment and tended to occur less frequently with time." However, in the combined safety population of studies MOR-004 and MOR-005, nearly all patients (98.3%) reported Infusion Associated Reactions (IARs). The MAH should discuss whether the frequency of IRs in this study was higher than already described in the SmPC and, if needed, propose amendments of the SmPC wording.

5. MAH responses to Request for supplementary information

Question 1.
Study MOR-005 was planned to continue up to Week 240, however it was prematurely terminated by the MAH. The timing of the termination as well as justification for this should be provided by the MAH.

MAH Response
The primary objective of MOR-005 was to evaluate long-term safety and efficacy of a *2.0 mg/kg dose of BMN 110, administered weekly or every other week, in subjects with* MPS IVA. MOR-004 was the pivotal study. Extension study MOR-005 allowed the MOR-004 MPS IVA patient population to continue on therapy in a clinical trial setting; as the drug was approved country by country, patients would discontinue study MOR-005 and move on to commercially available treatment.

The 240-week maximum study duration was originally proposed by the Sponsor to allow for a long extension period of continued patient treatment, without need for additional protocol amendments, until commercial product could be made available, and was written at a time when the timing for availability of commercial product could not be accurately predicted. As such the 240-week maximum study duration was not driven by scientific considerations, but to simplify the clinical management of the studies. It is for this reason the study duration was described in MOR-005 clinical protocols as 'Up to 240 weeks'. Following the European Commission Decision on the Vimizim Marketing Authorisation Application in 2014, and as Member States finalised Pricing and Reimbursement/Continued Access, patients were transitioned to commercial treatment and the study sites were closed.

Assessment of the MAH's response
The MAH explained that due to the availability of the commercial products patients could be transitioned from study MOR-005 to the commercial product. In the protocol it was stated that patients

could receive up to 240 weeks of treatment in study MOR-005, as no accurate prediction could be made when the Vimizim was commercial available.

Issue resolved.

Question 2.
The MAH is requested to discuss whether there are patient characteristics that could help to determine if a patient could be a non-responder to elosulfase alfa treatment. The MAH should explore the possibility to include stopping rules in the SmPC for those patients not benefitting from treatment (anymore).

MAH Response:
MPS IVA is a rare, devastating, inherited disorder caused by mutations of the gene that codes for the lysosomal enzyme N-acetylgalactosamine-6-sulfatase (GALNS), which degrades glycosaminoglycans (GAGs) including keratan sulfate (KS) and chondroitin-6- sulfate (C6S). With insufficient GALNS, GAGs progressively accumulate in multiple organs and tissues.

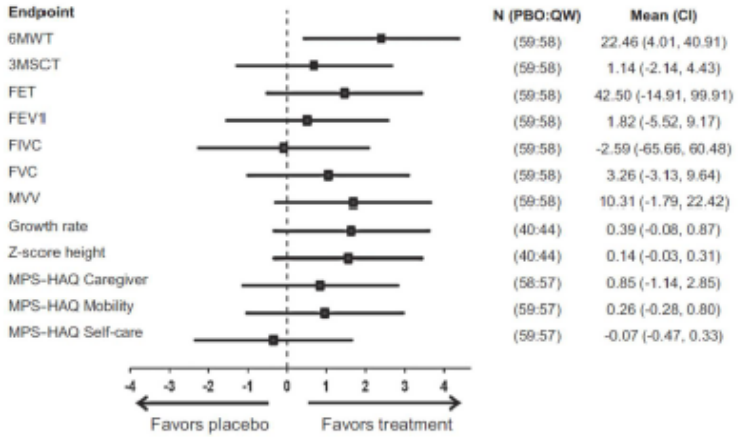
The pervasive and progressive accumulation of GAGs leads to significant morbidities and multisystemic clinical impairments resulting in diminished functional capacity, decreased endurance, impaired quality of life, and early mortality.

Patients with Morquio A suffer from a progressive decline in endurance as measured by the 6 Minute Walk Test (6MWT) (−6.84m ±5.38m per year), lung function (on average, FVC and MVV increased in patients aged ⩽14 years [FVC: 9.06%; MVV: 10.25%], but decreased in older patients [FVC: -2.34%; MVV: -9.58%]), and activities in daily living (significant decline in all domains of MPS HAQ) (Harmatz 2015; Hendriksz 2014a; Hendriksz 2017). It has also been shown that not all patients respond to treatment in the same way (Hendriksz 2014a). Therefore, when assessing the data on effectiveness, it is important that more than one endpoint is taken into account to determine whether or not a patient is benefitting from therapy.

In study MOR-005 patient randomisation was stratified according to the baseline walk distance (6MWT ⩽ 200m ⩾) and age group (5-11, 12-18 and ⩾19 years). Exploratory analyses were performed to obtain an indication of whether treatment effects differed across several baseline covariates, including the screening 6MWT, age category, sex, race and region. Subgroup analyses did not provide strong evidence of differences in treatment effect according to any of the categories of age group, sex, race and geographic region (Hendriksz 2014b, supplementary Table 5).

Regarding the first 24 weeks of elosulfase alfa treatment, although only the 6MWT showed a significantly greater treatment effect compared to placebo, the majority of the remaining estimates fell to the right of zero (positive), indicating numerically higher treatment effects for weekly elosulfase alfa over 24 weeks (Hendriksz 2014a). Efficacy results for the MOR-004 primary (6MWT), secondary (3MSCT), and tertiary endpoints (respiratory, anthropometric, MPS-HAQ) for elosulfase alfa QW treatment versus placebo over 24 weeks are summarised in the forest plot in Figure 2.1 which demonstrates numerical improvements across multiple domains in favour of treatment.

Figure 2.1: Forest Plot of Primary, Secondary and Tertiary Efficacy Endpoints for Study MOR-004: elosulfase alfa QW Treatment Versus Placebo for 24 weeks – ITT.



In the MOR-005 extension study, the initial 24-week efficacy of elosulfase alfa treatment (as displayed in Figure 2.1) was demonstrated to continue over 120 weeks across the treatment groups: treatment with once-weekly elosulfase alfa sustained the positive treatment effects on uKS, endurance and pulmonary function measures (Hendriksz 2016a). For the 120 week analysis, two main populations were analyzed, the intention to treat (ITT) population, which included all patients who received a dose of elosulfase alfa, and the modified per protocol (MPP) population, which controlled for confounding by excluding those patients who had surgeries after week 24, and/or had missed more than three doses of elosulfase alfa. Hence the data below includes the MPP analysis.

There was almost identical improvement in endurance over 120 weeks for patients who at baseline had endurance categorised as substantially limited (6MWT ⩽200 m) and less limited (6MWT >200 m) (Figure 2.2) as was the improvement in endurance of patients both with and without the use of walking aid at baseline (Figure 2.3).

Figure 2.2: Mean (SE) Change from Baseline in 6MWT for Patients Treated With elosulfase alfa QW Over 120 Weeks, By Baseline 6MWT (⩽ 200 m >) – MPP.

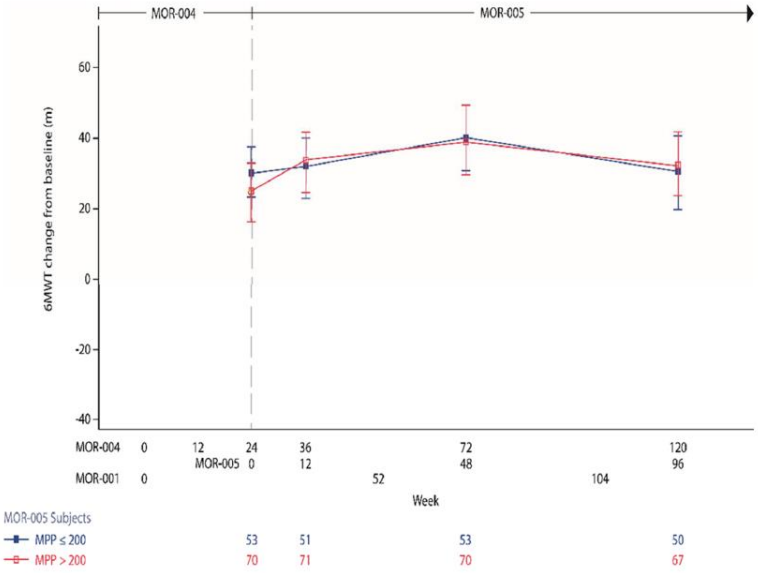
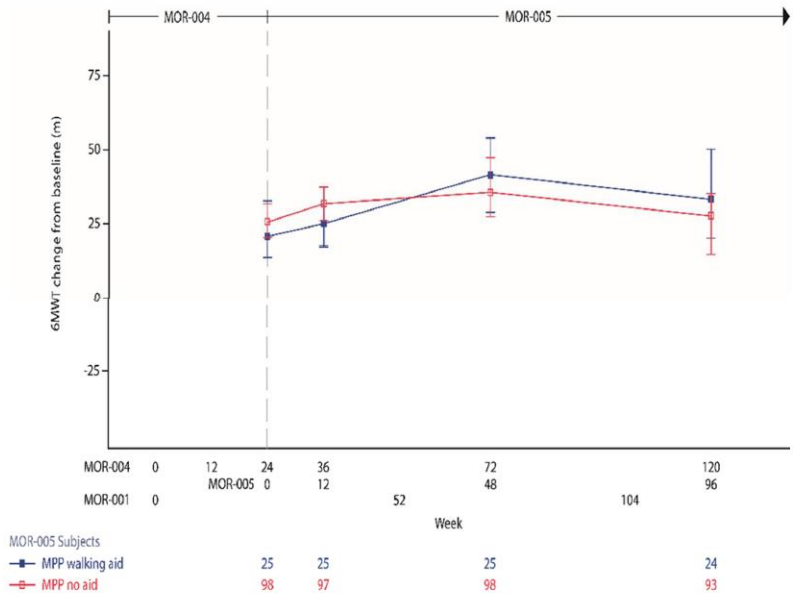


Figure 2.3: Mean (SE) Change from Baseline in 6MWT for Patients Treated with elosulfase alfa QW Over 120 Weeks, by Baseline Use of Walking Aid During 6MWT – MPP.



As there was no placebo arm after 24 weeks, the MOR-005 outcomes were compared to matched patients from the natural history study, MOR-001 (MorCAP). Patients receiving elosulfase alfa over 120 weeks demonstrated significant overall improvements in uKS levels ($p<0.0001$), endurance ($p=0.005$) (Hendriksz 2016a), pulmonary function (FVC $p= 0.04$; FEV1 $p=0.03$) (Hendriksz 2016b) and activities of daily living (ADL) that were significantly greater compared with untreated patients (Hughes 2017, Hendriksz, 2017). Increases in FVC and FEV1 were greater in treated patients than in untreated patients overall, but also in ERT-treated patients ⩽ 14 years of age. It could be argued that this may have been caused in part by enzyme replacement therapy (ERT)-induced growth acceleration, as treated patients showed a mean (SE) increase in height of +5.1 (3.5) cm over 2 years compared to only +2.8 (2.8) cm in the untreated patients. However, FVC and FEV1 also improved in ERT-treated patients >14 years of age (when growth is much more limited), while the untreated MorCAP patients in this age group showed considerable decline (Hendriksz 2016b, Figure 3c). Mean (SE) growth in this older patient age group was +1.3 (3.2) cm in treated vs -0.0 (0.9) cm in untreated patients, suggesting that the increase in respiratory function by ERT was most likely mediated by other mechanisms, such as decreased upper airway obstruction, increased chest wall compliance, improved respiratory muscle strength, and/or improved diaphragmatic movement due to a reduction in liver size and a reduction in GAG tissue storage (Hendriksz 2016a, Hendriksz 2016b, Hughes 2017).

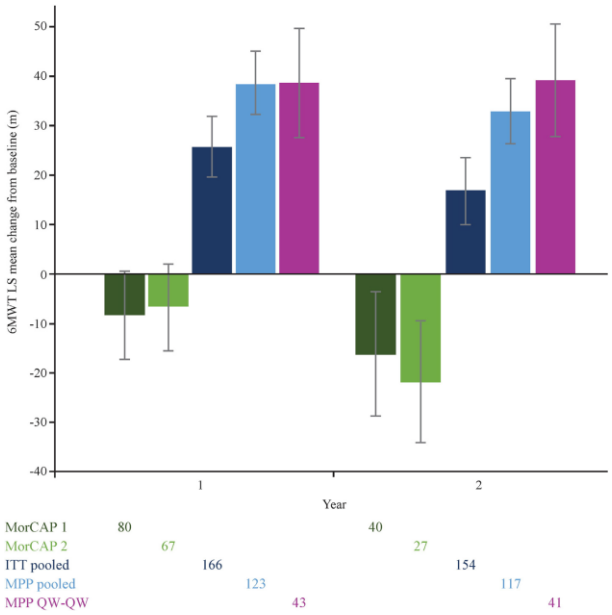
In conclusion the results of MOR-005 do not provide any conclusive evidence regarding patient characteristics that allow the determination of patient response to elosulfase alfa treatment. Patients with MPS IVA show considerable heterogeneity of disease; there is no single measure of efficacy that captures all benefit. Some patients will show benefit on functional tests but not on respiratory function tests and vice versa. In addition, efficacy outcomes are highly variable. For example, patients can show large decreases in the 6MWT in the event of orthopaedic surgery. Given these conditions, it is challenging to determine stopping rules at this time. Stratification using a baseline walk test cut off of >200m does not suggest a difference in response. Please also see responses to Question 3 for a more detailed assessment of stratification using age groups 5-11 and 12-18 with respect to 6MWT, 3MSC, Lung Function Tests and uGAGs.

The current expert consensus is that all patients with MPS IVA should be treated with elosulfase alfa in order to determine response. Therefore, given the above factors, we are currently unable to propose any stopping rules in the SmPC.

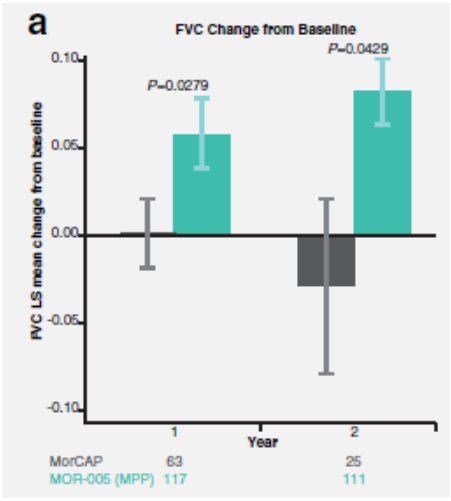
Assessment of the MAH's response

It is agreed with the MAH that the treatment effectiveness should not be based on one single endpoint, especially in a heterogeneous disease such as Morquio A. It is also understandable that within this patient population the youngest patients may show more improvement in endurance than the older patients.

The MAH was requested to discuss whether there are any patient characteristics that could help to determine if a patient could be a non-responder to elosulfase alfa treatment. For this question the MAH showed that based on stratification to patients capable of walking >200m at baseline compared to ≤200m, no difference in response could be observed. Similar for stratification by walking aid or no aid. The difference in scaling of the figures is noted, but improvement is comparable. Further, the publication by Hendriksz *et al.* (2016a) showed that patients in MOR-005 had more improvement in uKS and endurance compared to matched patients from the historical control (MorCap) (6MWT; figure below).



In addition, pulmonary function in treated patients was also better than in the matched patients from the historical control (MorCap) (Hendriksz *et al.* 2016b). As discussed by the MAH patients ≤14 years of age showed more improvement than those >14 years of age. Both age groups showed more improvement than the historically matched population.



Hughes *et al* (2017) showed that in daily living patients on treatment showed better result than those from the MorCAP population. However, it should be noted that the patient numbers are limited and this hampers drawing firm conclusions.

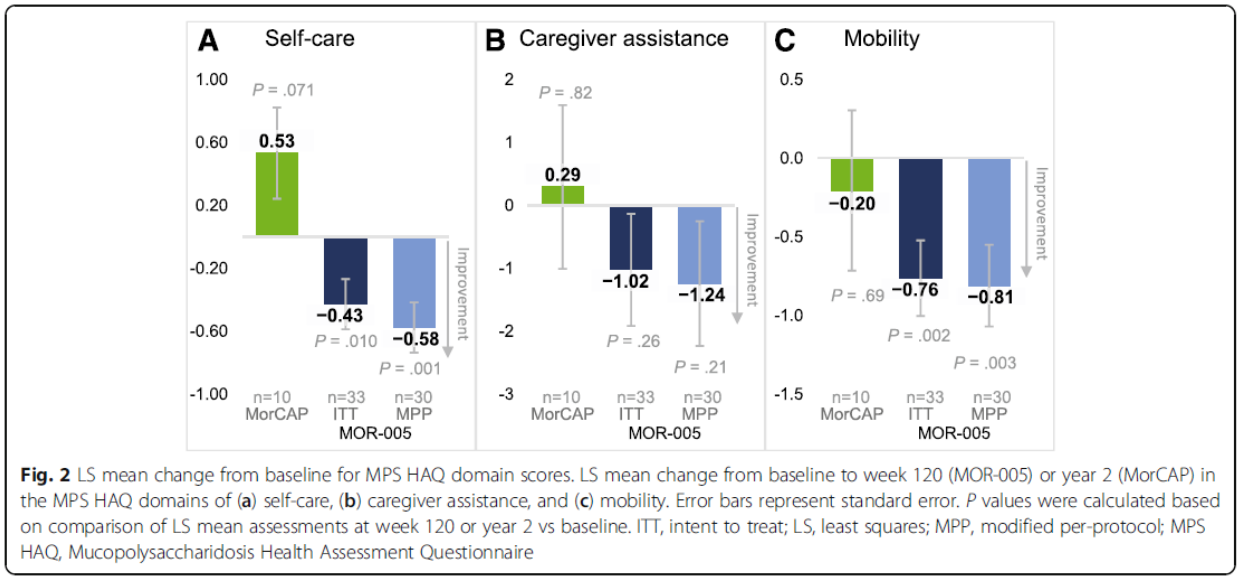


Fig. 2 LS mean change from baseline for MPS HAQ domain scores. LS mean change from baseline to week 120 (MOR-005) or year 2 (MorCAP) in the MPS HAQ domains of (**a**) self-care, (**b**) caregiver assistance, and (**c**) mobility. Error bars represent standard error. *P* values were calculated based on comparison of LS mean assessments at week 120 or year 2 vs baseline. ITT, intent to treat; LS, least squares; MPP, modified per-protocol; MPS HAQ, Mucopolysaccharidosis Health Assessment Questionnaire

It is agreed with the MAH that based on data comparing the patients in study MOR-005 and the MorCAP, there is no direct evidence for stopping rules.

Issue resolved

Question 3.
The MAH is requested to submit the baseline data and efficacy results for the paediatric patients and paediatric subpopulation separately.

MAH Response (shortened by Rapporteur):
Baseline efficacy data and change from baseline to Weeks 96 and 144 (for the cohort initially on placebo in MOR-004 and transferred to active treatment [PBW-QW]) and change from baseline to Weeks 120 and 168 (for the cohort initially on active treatment in MOR-004 and continuing on active treatment [QW-QW]) for the paediatric population as a whole (<19 years) and for the paediatric sub-

populations (5-11 years and 12-18 years) are presented in this section, according to efficacy assessment.

The 6MWT and 3MSCT data are presented in Table 3.1, respiratory function data are presented in Table 3.2, and uKS data are presented in Table 3.3. HAQ data are discussed in response to Question 7. Overall, improvements in efficacy endpoints seen in the MOR-005 total population were reflected in the paediatric sub-populations: improvements of a similar magnitude to the overall population were observed in endurance tests, respiratory function and uKS. However, any interpretation of data by paediatric sub-group should be done with caution. Given the small numbers of patients in some sub-groups and the high variability of the data, it was not possible to draw any meaningful conclusions on differences in response between paediatric sub-populations.

Baseline data for the **6MWT** were comparable between treatment cohorts. The 6MWT was lower in the 12-18 years sub-population (187.2 m in the PBO-QW group and 185.0 m in the QW-QW group) than the 5-11 years sub-population (208.9 m for the PBO-QW group and 232.8 m for the QW-QW group), which is reflective of the natural history data which shows a gradual decline over time. In the total population, improvements were seen in the 6MWT, with an overall mean increase of 33.0 m from baseline to Week 120 (MPP, n=123). For the paediatric subpopulations, change from baseline data for the 6MWT were highly variable and difficult to interpret. Note that given the small n for the 5-11 years subpopulation (n=11 at week 168), one patient who had a substantial decline (-309m) had a very large impact on the mean. It is also important to remember that not every patient will respond to treatment in the same manner and therefore important to assess all results for each individual patient (Hendriksz 2014b Figure 1 A & B).

Baseline data for the **3MSCT** were comparable between treatment cohorts and paediatric sub-populations (mean 3MSCT ranged from 26.3 and 36.5 stairs/min). In the total population, improvements were seen in the 3MSCT, with an overall mean increase of 7.4 stairs/min from baseline to Week 120 (MPP, n=122). Change from baseline data for the 3MSCT were highly variable and difficult to interpret. Baseline data for the 3MSCT were comparable between treatment cohorts and paediatric sub-populations (mean 3MSCT ranged from 26.3 and 36.5 stairs/min).

In the total population, improvements were seen in the 3MSCT, with an overall mean increase of 7.4 stairs/min from baseline to Week 120 (MPP, n=122). Change from baseline data for the 3MSCT were highly variable and difficult to interpret. In the PBOQW group, median change to Week 96 (n=13) was positive in the 12-18 years subpopulation (2.9 stairs/min) and showed no change in the 5-11 years sub-population; low patient numbers at Week 144 (n=4) did not allow any meaningful interpretation. As discussed above, one patient may be driving the decline in the mean for the 5-11 sub-group.

Table 3.1: Subgroup Analysis of 6MWT and 3MSCT by Treatment MPP - MOR004 and MOR005.

	6MWT (m)			3MSCT (stairs/min)		
Treatment Group Study Visit Statistic	**Paediatric (<19)**	**Paediatric (5-11)**	**Paediatric (12-18)**	**Paediatric (<19)**	**Paediatric (5-11)**	**Paediatric (12-18)**
PBO-QW						
Baseline						
n	13	9	4	13	9	4
Mean (SD)	202.2 (70.13)	208.9 (64.81)	187.2 (89.65)	26.6 (13.50)	26.3 (12.92)	27.4 (16.80)
Week 96						
n	13	9	4	13	9	4
Mean (SD)	205.3 (115.74)	201.6 (121.99)	213.4 (117.33)	29.0 (17.80)	28.1 (18.44)	31.0 (18.78)
Change from Baseline[a]						

to Week 96						
n	13	9	4	13	9	4
Mean (SD)	3,0 (95,89)	-7,2 (79,97)	26,2 (136,74)	2,4 (11,30)	1,9 (12,17)	3,6 (10,63)
Week 144						
n	4	3	1	4	3	1
Mean (SD)	220,5 (141,97)	188,3 (154,99)	317,0 (NA)	32,1 (24,46)	21,8 (16,16)	63,0 (NA)
Change from Baseline[a] to Week 144						
n	4	3	1	4	3	1
Mean (SD)	-21,8 (100,33)	-39,2 (115,22)	30,5 (NA)	-3,6 (15,74)	-9,2 (13,68)	13,0 (NA)
QW-QW						
Baseline						
n	36	23	13	36	23	13
Mean (SD)	215,5 (69,65)	232,8 (62,37)	185,0 (73,76)	33,2 (16,00)	36,5 (16,45)	27,4 (13,88)
Week 120						
n	36	23	13	35	23	12
Mean (SD)	251,3 (96,96)	258,4 (97,49)	238,7 (98,65)	41,6 (21,40)	42,0 (22,28)	40,8 (20,53)
Change from Baseline[a] to Week 120						
n	36	23	13	35	23	12
Mean (SD)	35,8 (71,63)	25,6 (76,37)	53,7 (61,04)	8,3 (13,25)	5,5 (12,24)	13,7 (13,99)
Week 168						
n	17	11	6	16	11	5
Mean (SD)	210,4 (119,52)	209,9 (133,85)	211,2 (99,39)	32,6 (24,00)	30,0 (25,95)	38,2 (20,46)
Change from Baseline[a] to Week 168						
n	17	11	6	16	11	5
Mean (SD)	-16,5 (113,24)	-34,4 (134,96)	16,3 (51,09)	-3,4 (21,02)	-9,5 (21,45)	9,9 (13,56)

SD, standard deviation.
a Change is equal to current value minus the baseline value.
PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
For PBO-QW, in order to remove the placebo effect, the first 24 weeks data have been excluded and subsequent visits have been re-labeled, such as week 48 become to week 24 etc.

Baseline FEV1 and FVC data and change from baseline to Weeks 96, 144, 120 and 168 for the paediatric population as a whole (<19 years) and for the paediatric sub-populations (5-11 years and 12-18 years) are discussed here and presented in MPP Table 3.2.

Baseline data for **FEV1** were comparable between treatment cohorts and between the paediatric sub-populations (mean FEV1 ranged from 0.5 L in the PBO-QW group for the 5-11 years sub-population to 1.4 L in the PBQ-QW group for the 12-18 years subpopulation). In the total population, improvements were seen in FEV1, with an overall mean (SD) increase of 8.3% (24.79%) from baseline to Week 120 (MPP, n=147). For the paediatric sub-populations, change from baseline data for FEV1 were highly variable. Note that given the small n for the 12-18 years sub-population (n=6 at Week 168), one patient who had a substantial decline (-16%) may have had a large impact on the summary data.

Baseline data for **FVC** were comparable between treatment cohorts; mean FVC ranged from 0.6 L in the PBO-QW group for the 5-11 years sub-population to 1.6 L in the PBQQW group for the 12-18 years sub-population. Mean FVC in the PBO-QW group was higher for the 12-18 years sub-population (1.6 L) than the 5-11 years sub-population (0.6 L); this difference was not observable in the QW-QW group.

In the total population, improvements were seen in FVC, with an overall mean (SD) increase of 9.4% (21.33%) from baseline to Week 120 (MPP, n=147). For the paediatric sub-populations, change from

baseline data for FVC were highly variable, but positive across treatment cohorts and paediatric sub-populations.

Table 3.2: Subgroup Analysis of FEV1 and FVC by Treatment MPP - MOR004 and MOR005.

	FEV1 (L)			FVC (L)		
Treatment Group Study Visit Statistic	**Paediatric (<19)**	**Paediatric (5-11)**	**Paediatric (12-18)**	**Paediatric (<19)**	**Paediatric (5-11)**	**Paediatric (12-18)**
PBO-QW						
Baseline						
n	10	6	4	10	6	4
Mean (SD)	0.9 (0.67)	0.5 (0.11)	1.4 (0.84)	1.0 (0.75)	0.6 (0.10)	1.6 (0.97)
Week 96						
n	13	9	4	13	9	4
Mean (SD)	1.0 (0.64)	0.7 (0.14)	1.7 (0.78)	1.1 (0.78)	0.7 (0.19)	1.9 (1.05)
% Change from Baseline[a] to Week 96						
n	10	6	4	10	6	4
Mean (SD)	26.9 (38.47)	23.1 (40.18)	32.5 (40.95)	21.8 (25.64)	16.4 (21.89)	29.8 (32.10)
Week 144						
n	3	2	1	1.5 (1.20)	0.8 (0.06)	2.9 (NA)
Mean (SD)	1.3 (1.01)	0.7 (0.04)	2.5 (NA)	0.9	0.8	2.9
% Change from Baseline[a] to Week 144						
n	3	2	1	3	2	1
Mean (SD)	29.7 (24.71)	33.2 (33.88)	22.7 (NA)	31.2 (16.71)	29.1 (23.08)	35.3 (NA)
QW-QW						
Baseline						
n	34	21	13	34	21	13
Mean (SD)	0.8 (0.40)	0.8 (0.25)	0.9 (0.57)	0.9 (0.47)	0.9 (0.30)	1.0 (0.65)
Week 120						
n	35	22	13	35	22	13
Mean (SD)	0.8 (0.44)	0.8 (0.30)	0.9 (0.62)	1.0 (0.53)	0.9 (0.31)	1.1 (0.76)
% Change from Baseline[a] to Week 120						
n	33	20	13	33	20	13
Mean (SD)	4.7 (23.44)	6.5 (27.59)	1.9 (15.66)	8.4 (22.22)	9.7 (25.90)	6.3 (15.71)
Week 168						
n	15	9	6	15	9	6
Mean (SD)	1.0 (0.47)	1.0 (0.39)	0.9 (0.61)	1.1 (0.51)	1.1 (0.45)	1.1 (0.64)
% Change from Baseline[a] to Week 168						
n	14	8	6	14	8	6
Mean (SD)	18.0 (40.21)	31.8 (48.64)	-0.4 (13.45)	23.1 (41.53)	35.2 (49.86)	7.0 (21.43)

SD, standard deviation.
a Change is equal to current value minus the baseline value.
PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
For PBO-QW, in order to remove the placebo effect, the first 24 weeks data have been excluded and subsequent visits have been re-labeled, such as week 48 become to week 24 etc.

Baseline uKS data and change from baseline to Weeks 96, 144, 120 and 168 for the paediatric population as a whole (<19 years) and for the paediatric sub-populations (5-11 years and 12-18 years) are discussed here and presented in MPP Table 3.3.

Baseline data for urine keratan sulfate (uKS, normalized to creatinine) were comparable between treatment cohorts in the overall paediatric population. Mean uKS was lower in the 12-18 years sub-population (17.5 µg/mg in the PBO-QW group and 20.5 µg/mg in the QW-QW group) than the 5-11

years sub-population (41.1 µg/mg for the PBO-QW group and 31.7 µg/mg for the QW-QW group) reflective of the natural history of uKS.

In the total population, decreases were seen in uKS, with an overall mean (SD) decrease of -61.7% (17.98%) from baseline to Week 120 (MPP, n=117).

Table 3.3: Subgroup Analysis of uKS by Treatment of PBO-QW and QW-QW MPP- MOR004 and MOR005.

	uKS (ug/mg) PBO-QW			uKS (ug/mg) QW-QW		
Treatment Group Study Visit Statistic	Paediatric (<19)	Paediatric (5-11)	Paediatric (12-18)	Paediatric (<19)	Paediatric (5-11)	Paediatric (12-18)
Baseline						
n	13	9	4	36	23	13
Mean (SD)	34,0 (13,55)	41,3 (7,76)	17,5 (7,15)	27,9 (11,98)	32,0 (12,19)	20,5 (7,30)
Week 96						
n	13	9	4	35	22	13
Mean (SD)	12,7 (9,70)	16,1 (9,86)	4,9 (0,93)	16,8 (28,50)	21,4 (35,16)	9,0 (5,78)
% Change from Baseline[a] to Week 96						
n	13	9	4	35	22	13
Mean (SD)	-64,1 (18,48)	-61,3 (21,75)	-70,3 (5,44)	-44,0 (62,35)	-36,5 (76,30)	-56,8 (23,40)
Week 120						
n	6	4	2	35	22	13
Mean (SD)	8,2 (6,25)	10,0 (7,18)	4,6 (0,99)	11,2 (7,17)	12,9 (5,95)	8,2 (8,29)
% Change from Baseline[a] to Week 120						
n	6	4	2	35	22	13
Mean (SD)	-70,4 (18,37)	-72,4 (23,35)	-66,3 (0,57)	-60,5 (22,20)	-59,6 (16,53)	-61,9 (30,25)
Week 144						
n	3	2	1	22	14	8
Mean (SD)	12,7 (14,30)	14,6 (19,71)	9,0 (NA)	20,3 (43,57)	27,1 (53,92)	8,3 (6,00)
% Change from Baseline[a] to Week 144						
n	3	2	1	22	14	8
Mean (SD)	-62,0 (31,56)	-72,2 (37,09)	-41,8 (NA)	-33,0 (124,68)	-15,6 (155,16)	-63,6 (15,72)
Week 168						
n	NA	NA	NA	10	6	4
Mean (SD)				18,1 (14,02)	21,0 (16,92)	13,6 (8,26)
% Change from Baseline[a] to Week 168						
n	NA	NA	NA	10	6	4
Mean (SD)				-40,6 (39,72)	-37,7 (50,96)	-45,1 (19,00)

SD, standard deviation.
a Change is equal to current value minus the baseline value.
PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
For PBO-QW, in order to remove the placebo effect, the first 24 weeks data have been excluded and subsequent visits have been re-labeled, such as week 48 become to week 24 etc.

Assessment of the MAH's response

As requested the MAH presented the baseline data and the efficacy data stratified by the paediatric subgroups (5-11 years; 12-18 years) separately. Baseline values for 6MWT, 3MSCT, FEV1, FVC and uKS were balanced.

The data for 6MWT and 3MSCT showed that in both age groups treatment showed comparable results after 96 weeks. Initially an improvement is observed, however, at a later time point in the younger

population a decline is noticed. With respect to the lung function (FEV1 and FVC) it can be observed that the younger patients (5-11 years) showed slightly more improvement, compared to the older patients. This seems to be in line with the publication of Hughes *et al.* (2017) (see above).

As in the overall population a decrease in uKS was also observed in the age groups in both study arms (e.g. PBO-QW and QW-QW).

Note that due to the open-label character and the limited number of patients no conclusion can be drawn.

For the assessment of data on the Health Assessment Questionnaire refer to question 7.

Issue resolved.

Question 4.

The MAH is requested to submit the baseline demographics and characteristics for the MPP population, paediatric, adult and paediatric subpopulations separately.

MAH Response:
Table 4.1 provides a summary of the total MPP population and the adult and paediatric sub-populations.

Table 4.1: Baseline demographics – MPP population and sub-populations.

	MPP Total (N=124)	**Total Adult Population (>=19 years) (N=29)**	**Total Paediatric (5-18 years) (N=95)**	**Total Paediatric Pop (5-11 years) (N=61)**	**Total Paediatric Pop (12-18 years) (N=34)**
Age at Enrolment, years					
n	124	29	95	61	34
Mean (SD)	15.4 (10.28)	31.6 (7.99)	10.4 (3.68)	8.2 (2.29)	14.4 (1.78)
5-11 years	61 (49.2%)	0	61 (64.2%)	61 (100.0%)	0
12-18 years	34 (27.4%)	0	34 (35.8%)	0	34 (100.0%)
≥ 19 years	29 (23.4%)	29 (100.0%)	0	0	0
Sex					
Female	58 (46.8%)	18 (62.1%)	40 (42.1%)	27 (44.3%)	13 (38.2%)
Male	66 (53.2%)	11 (37.9%)	55 (57.9%)	34 (55.7%)	21 (61.8%)
Race					
Asian	26 (21.0%)	6 (20.7%)	20 (21.1%)	13 (21.3%)	7 (20.6%)
Black or African American	3 (2.4%)	0	3 (3.2%)	1 (1.6%)	2 (5.9%)
White	84 (67.7%)	23 (79.3%)	61 (64.2%)	41 (67.2%)	20 (58.8%)
Other	11 (8.9%)	0	11 (11.6%)	6 (9.8%)	5 (14.7%)
Ethnicity					
Hispanic or Latino	28 (22.6%)	6 (20.7%)	22 (23.2%)	13 (21.3%)	9 (26.5%)
Not Hispanic or Latino	96 (77,4%)	23 (79,3%)	73 (76,8%)	48 (78,7%)	25 (73,5%)
Region					
Europe	50 (40,3%)	18 (62,1%)	32 (33,7%)	19 (31,1%)	13 (38,2%)
North America	29 (23,4%)	3 (10,3%)	26 (27,4%)	17 (27,9%)	9 (26,5%)
Other	45 (36,3%)	8 (27,6%)	37 (38,9%)	25 (41,0%)	12 (35,3%)

When investigating the PBO-QW and QW-QW arms of each sub-population (See Table 4.2), there do not appear to be any significant discrepancies in the demographic characteristics within sub-populations, indicating a balanced comparison between arms.

Table 4.2: Demographics - MPP population stratified by age and trial arm (PBO-QW and QW-QW).

	MPP		Adults		Paediatric		Paediatric 5-11		Paediatric 12-18	
	PBO-QW (N=19)	QW-QW (N=43)	PBO-QW (N=6)	QW-QW (N=7)	PBO-QW (N=13)	QW-QW (N=36)	PBO-QW (N=9)	QW-QW (N=23)	PBO-QW (N=4)	QW-QW (N=13)
Age at Enrolment, years										
n	19	43	6	7	13	36	9	23	4	13
Mean (SD)	14,6 (9,50)	13,5 (8,62)	26,7 (5,38)	29,7 (8,05)	9,1 (4,19)	10,4 (3,90)	6,6 (1,47)	7,9 (2,12)	14,7 (2,17)	14,7 (2,05)
5-11	9 (47,4%)	23 (53,5%)	0	0	9 (69,2%)	23 (63,9%)	9 (100,0%)	23 (100,0%)	0	0
12-18	4 (21,1%)	13 (30,2%)	0	0	4 (30,8%)	13 (36,1%)	0	0	4 (100,0%)	13 (100,0%)
. 19	6 (31,6%)	7 (16,3%)	6 (100,0%)	7 (100,0%)	0	0	0	0	0	0
Sex										
Female	12 (63,2%)	22 (51,2%)	4 (66,7%)	4 (57,1%)	8 (61,5%)	18 (50,0%)	6 (66,7%)	12 (52,2%)	2 (50,0%)	6 (46,2%)
Male	7 (36,8%)	21 (48,8%)	2 (33,3%)	3 (42,9%)	5 (38,5%)	18 (50,0%)	3 (33,3%)	11 (47,8%)	2 (50,0%)	7 (53,8%)
Race										
Asian	4 (21,1%)	10 (23,3%)	1 (16,7%)	1 (14,3%)	3 (23,1%)	9 (25,0%)	3 (33,3%)	6 (26,1%)	0	3 (23,1%)
Black or African American	0	2 (4,7%)	0	0	0	2 (5,6%)	0	1 (4,3%)	0	1 (7,7%)
White	13 (68,4%)	28 (65,1%)	5 (83,3%)	6 (85,7%)	8 (61,5%)	22 (61,1%)	6 (66,7%)	14 (60,9%)	2 (50,0%)	8 (61,5%)
Other	2 (10,5%)	3 (7,0%)	0	0	2 (15,4%)	3 (8,3%)	0	2 (8,7%)	2 (50,0%)	1 (7,7%)
Ethnicity										
Hispanic or Latino	5 (26,3%)	7 (16,3%)	2 (33,3%)	1 (14,3%)	3 (23,1%)	6 (16,7%)	1 (11,1%)	3 (13,0%)	2 (50,0%)	3 (23,1%)
Not Hispanic or Latino	14 (73,7%)	36 (83,7%)	4 (66,7%)	6 (85,7%)	10 (76,9%)	30 (83,3%)	8 (88,9%)	20 (87,0%)	2 (50,0%)	10 (76,9%)
Region										
Europe	8 (42,1%)	19 (44,2%)	4 (66,7%)	4 (57,1%)	4 (30,8%)	15 (41,7%)	4 (44,4%)	7 (30,4%)	0	8 (61,5%)
North America	3 (15,8%)	9 (20,9%)	0	1 (14,3%)	3 (23,1%)	8 (22,2%)	1 (11,1%)	7 (30,4%)	2 (50,0%)	1 (7,7%)
Other	8 (42,1%)	15 (34,9%)	2 (33,3%)	2 (28,6%)	6 (46,2%)	13 (36,1%)	4 (44,4%)	9 (39,1%)	2 (50,0%)	4 (30,8%)

Table 4.3 Summary of the baseline characteristics of the MPP populations and the requested sub-populations.

	Total MPP Population (N=124)	Total Adult Population (>=19 years) (N=29)	Total Paediatric Population (5-18 years) (N=95)	Total Paediatric Population (5-11 years) (N=61)	Total Paediatric Population (12-18 years) (N=34)
Weight, (kg)					
n	123	29	94	60	34
Mean (SD)	26,5 (12,43)	38,3 (15,28)	22,8 (8,68)	19,7 (6,55)	28,3 (9,37)
Length, (cm)					
n	119	28	91	59	32
Mean (SD)	107,9 (15,89)	116,4 (21,17)	105,4 (12,95)	102,2 (11,23)	111,1 (14,10)
Standing Height, (cm)					
n	118	29	89	58	31
Mean (SD)	105,2 (16,60)	114,9 (21,37)	102,1 (13,43)	99,1 (11,80)	107,7 (14,66)
Sitting Height, (cm)					
n	123	29	94	60	34
Mean (SD)	60,1 (15,63)	67,6 (21,05)	57,8 (12,82)	56,3 (12,19)	60,4 (13,65)
Height Percentile					
< 3rd percentile	113 (91,1%)	28 (96,6%)	85 (89,5%)	54 (88,5%)	31 (91,2%)
. 3rd to < 10th percentile	4 (3,2%)	1 (3,4%)	3 (3,2%)	3 (4,9%)	0
. 10th to < 25th percentile	0	0	0	0	0
. 25th to < 50th percentile	0	0	0	0	0
. 50th percentile	1 (0,8%)	0	1 (1,1%)	1 (1,6%)	0
Baseline height not available	6 (4,8%)	0	6 (6,3%)	3 (4,9%)	3 (8,8%)
6-minute Walk Test, (meter)					
n	124	29	95	61	34
Mean (SD)	201,6 (74,94)	173,7 (72,21)	210,1 (74,04)	225,0 (67,80)	183,3 (78,13)
≤200m	53 (42,7%)	16 (55,2%)	37 (38,9%)	18 (29,5%)	19 (55,9%)
> 200m	71 (57,3%)	13 (44,8%)	58 (61,1%)	43 (70,5%)	15 (44,1%)
Subject who used walking aids during 6MWT –n (%)					
Crutches	7 (5,6%)	5 (17,2%)	2 (2,1%)	1 (1,6%)	1 (2,9%)
Walker/Walking Frame	15 (12,1%)	2 (6,9%)	13 (13,7%)	6 (9,8%)	7 (20,6%)
Cane/Walking Stick	3 (2,4%)	1 (3,4%)	2 (2,1%)	1 (1,6%)	1 (2,9%)
None	99 (79,8%)	21 (72,4%)	78 (82,1%)	53 (86,9%)	25 (73,5%)
3-minute Stair Climb Test, (stairs/minute)					
n	124	29	95	61	34
Mean (SD)	28,7 (14,93)	21,9 (13,51)	30,7 (14,79)	33,4 (14,33)	25,9 (14,54)
Normalized Urine Keratan Sulfate, (ug/mg)					
n	123	29	94	94	34
Mean (SD)	25,5 (17,61)	8,9 (5,72)	30,7 (16,85)	30,7 (16,85)	22,4 (8,98)
Time since MPS IVA Diagnosis, (years)					
n	124	29	95	61	34
Mean (SD)	8,0 (8,38)	17,0 (11,86)	5,3 (4,16)	3,5 (2,60)	8,4 (4,64)
Age at the Time of MPS IVA Diagnosis, (years)					
n	124	29	95	61	34
Mean (SD)	7,4 (7,92)	14,6 (13,26)	5,2 (2,99)	4,7 (2,37)	6,1 (3,73)

A further breakdown of the sub-populations by trial arm showed no significant differences between trial arms within the same population. However, it should be noted that there were fewer patients in the PBO-QW arm when compared to the QW-QW arm (data not shown).

Assessment of the MAH's response

As requested the MAH submitted the baseline demographics and characteristics. No major differences between the different age groups were noticed. Although comparison of the groups should be done with caution, most paediatric patients could walk more than 200 m at baseline. This may be explained by the progressive cause of the disease. Similar for the 3MSCT. Remarkably the adult population had lower ukS values at baseline, which is in line with the natural history of the disease, where older patients showed a decline in uKS with age.

Issue resolved.

Question 5.

With respect to the 6MWT, FEV1, FVC, height and height velocity the MAH is requested to submit analyses using z-scores. These data should be submitted for the patient-groups that received 2.0 mg/kg QW during study 004 and 005, as the (QW-QW and placebo-QW groups separately) are the most relevant populations in this regard. Further, these data should be compared to the natural history population (study MOR-001). For each measurement (6MWT, FEV1, FVC, height and height velocity) a separate graph should be submitted. On the x-axis the time on treatment should be plotted, on the y-axis the z-score. The data of the natural history group should be incorporated in each graph.

MAH Response:

Table 5.1 and 5.2 provides an overview of Z-scores for 6MWT, FEV1, FVC, Height and Growth Velocity for the MOR-001 and the MOR-005 PBO-QW and QW-QW populations in the ITT and MPP population. Anthropometric Z-scores were based on the CDC growth charts (standardised by sex and age). For the 6MWT, FEV1, and FVC, there are no norms available. Therefore, these were calculated by pooling the first measurement of MOR-001 with the baseline of PBO-QW and QW-QW populations, forming six groups stratified by sex and the three age groups of interest, with Z-scores being produced by taking the mean and SD of these groups.

Table 5.1: ITT Z-score change from baseline to 120 weeks for 6MWT, FEV1, FVC, Height, and Growth Velocity.

	6MWT			**FEV1**			**FVC**			**Standing Height**			**Growth Velocity**		
	MOR-001	MOR-005 PBO-QW	MOR-005 QW-QW	MOR-001	MOR-005 PBO-QW	MOR-005 QW-QW	MOR-001	MOR-005 PBO-QW	MOR-005 QW-QW	MOR-001	MOR-005 PBO-QW	MOR-005 QW-QW	MOR-001	MOR-005 PBO-QW	MOR-005 QW-QW
Baseline															
N	163	29	58	146	24	56	147	24	56	180	28	56	142	11	27
Mean (SD)	-0,1 (1,07)	0,1 (0,72)	0,0 (0,92)	0,0 (0,98)	-0,1 (1,12)	-0,1 (0,87)	0,0 (1,00)	-0,1 (1,05)	-0,2 (0,88)	-5,7 (2,50)	-6,4 (2,84)	-6,4 (2,55)	-2,3 (18,91)	-0,7 (0,70)	-0,5 (0,69)
Week 120*															
N	18	27	54	17	27	51	17	27	50	14	25	50	14	25	50
Mean (SD)	0,0 (0,99)	0,0 (1,34)	0,4 (1,32)	0,1 (1,07)	0,0 (1,01)	-0,2 (1,11)	0,2 (1,08)	0,0 (1,01)	-0,1 (1,04)	-6,2 (1,87)	-6,8 (2,49)	-6,8 (2,32)	-0,3 (0,40)	-0,3 (0,64)	-0,3 (0,64)
Change from Baseline															
N	18	27	54	13	22	49	13	22	48	14	24	49	13	10	23
Mean (SD)	-0,1 (0,70)	0,0 (1,21)	0,4 (1,06)	0,1 (0,26)	0,3 (0,49)	0,0 (0,83)	0,1 (0,23)	0,2 (0,36)	0,0 (0,71)	-0,8 (0,76)	-0,6 (0,82)	-0,6 (0,94)	0,9 (1,05)	0,2 (0,86)	0,2 (1,05)

**For MOR-001: 103 weeks due to lack of data at 120 weeks, and for MOR-005 PBO-QW group: 96 weeks (including PBO time period 120 weeks on active therapy)*
Z-score based on log(FVC), log(FEV)
PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
For PBO-QW, in order to remove the placebo effect, the first 24 weeks data have been excluded and subsequent visits have been re-labelled, such as week 48 become to week 24 etc..
Z-scores of 6MWT, log(FEV), log(FVC) were derived from the pooled data of Mor004 (ITT) and Mor001 (subjects with age>=5 and with 6MWT between 30-325 m) based on the age and sex.
Z-scores of height and growth velocity were derived based on the CDC growth data (age between 5 to18).

Table 5.2: MPP Z-Score Change From Baseline to 120 Weeks for 6MWT, FEV1, FVC, Height, and Growth Velocity.

	6MWT			FEV1			FVC			Standing Height			Growth Velocity		
	MOR-001	MOR-005 PBO-QW	MOR-005 QW-QW	MOR-001	MOR-005 PBO-QW	MOR-005 QW-QW	MOR-001	MOR-005 PBO-QW	MOR-005 QW-QW	MOR-001	MOR-005 PBO-QW	MOR-005 QW-QW	MOR-001	MOR-005 PBO-QW	MOR-005 QW-QW
Baseline															
N	163	19	43	146	16	41	147	16	41	180	18	41	142	6	19
Mean (SD)	-0,1 (1,07)	-0,1 (0,74)	0,0 (0,92)	0,0 (0,98)	-0,2 (1,32)	-0,1 (0,97)	0,0 (1,00)	-0,2 (1,23)	-0,1 (0,99)	-5,7 (2,50)	-6,5 (3,30)	-6,2 (2,59)	-2,3 (18,91)	-0,4 (0,40)	-0,5 (0,71)
Week 120*															
N	18	19	43	17	19	41	17	19	40	14	17	41	14	17	41
Mean (SD)	0,0 (0,99)	0,1 (1,35)	0,5 (1,24)	0,1 (1,07)	0,0 (1,17)	-0,1 (1,14)	0,2 (1,08)	0,0 (1,15)	0,0 (1,08)	-6,2 (1,87)	-6,9 (2,87)	-6,7 (2,36)	-0,3 (0,40)	-0,3 (0,45)	-0,3 (0,68)
Change from Baseline															
N	18	19	43	13	16	39	13	16	38	14	16	40	13	5	19
Mean (SD)	-0,1 (0,70)	0,2 (1,09)	0,5 (0,87)	0,1 (0,26)	0,3 (0,48)	0,0 (0,81)	0,1 (0,23)	0,2 (0,38)	0,1 (0,72)	-0,8 (0,76)	-0,6 (0,72)	-0,5 (0,90)	0,9 (1,05)	0,0 (0,57)	0,1 (1,07)

**For MOR-001: 103 weeks due to lack of data at 120 weeks, and for MOR-005 PBO-QW group: 144weeks (including PBO time period 120 weeks on active therapy)*
Z-score based on log(FVC), log(FEV)
PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
For PBO-QW, in order to remove the placebo effect, the first 24 weeks data have been excluded and subsequent visits have been re-labeled, such as week 48 become to week 24 etc..
Z-scores of 6MWT, log(FEV), log(FVC) were derived from the pooled data of Mor004 (ITT) and Mor001 (subjects with age>=5 and with 6MWT between 30-325 m) based on the age and sex.

Z-scores of height and growth velocity were derived based on the CDC growth data (age between 5 to18).

Figure 5.1 to Figure 5.5 provide a graphical representation of the Z-scores for each outcome respectively comparing MOR-001 and MOR-005 MPP populations. The Figures indicate that there was

relatively wide variation in all three populations of interest for each outcome. It should be noted that patients in the MOR-001 study did not have the same assessment schedule as the trial patients and therefore the timing of the measurements varied compared to the MOR-005 populations.

Similarly to the primary and secondary endpoint data presented previously, overall, treated patients improved when compared with natural history.

For the 6MWT, the natural history group saw a decline in Z-score (-0.1, SD 0.70), while the PBO-QW group saw no change in Z-score over time (PBO-QW 0.0, SD 1.21) and the QW QW group saw an increase in Z-score over time (QW-QW 0.4, SD 1.06), indicating a positive treatment effect. However, it should be noted that there are no published 6MWT norms for MPS IVA patients and therefore the Z-score data should be interpreted with caution.

For the respiratory function tests, the data was skewed, and therefore the z-scores were based on log(FEV1) and log(FVC). For FEV1, Z-scores for the natural history cohort improved slightly (0.1, SD 0.26). The Z-score for the PBO-QW improved by 0.3 (SD 0.49). The QW-QW group saw limited change in Z-score (0.0, SD 0.83). It is worth noting that there was a wide range in responses, with many patients on treatment achieving an increase in Z-score (range for treated patients: -4.3 to 1.1). The results for FVC were similar, with the Z-scores for natural history showing a slight improvement (0.1, SD 0.26), PBO-QW group showing an improvement in Z-score (0.2, SD 0.36) and the QW-QW group showing stability (0.0, SD 0.71). Similarly, there was a wide range of FVC Z-score changes in the treated group (-3.7 to 0.9).

For standing height, the natural history cohort showed a clear negative trend, with the patients having a Z-score change of -0.8. Patients in the treated groups also had a negative change in standing height Z-score of -0.6 (SD 0.82) for the PBO-QW group, and -0.6 (SD 0.94) for the QW-QW group. Again, it is worth noting that these Z-scores were derived from CDC population norms, and therefore it is expected that the Morquio A population is less tall (a negative Z-score) compared to the unaffected population. The mean Z-scores for the treated group appear to be closer to the population norm than the untreated group. However, as with the other measures, there is considerable variation in all three populations.

Finally, for growth velocity, the Z-scores showed improvement for the natural history and the treated groups over time. It is unclear whether or not this is due to natural growth patterns in these populations. As with standing height, these Z-scores were derived from CDC population norms, and not Morquio A, so negative Z-scores would be expected for this population. As with the other outcomes, there was considerable variation in all populations.

Figure 5.1: Z-Score of 6MWT MOR001 and ITT – MOR004 and MOR005.

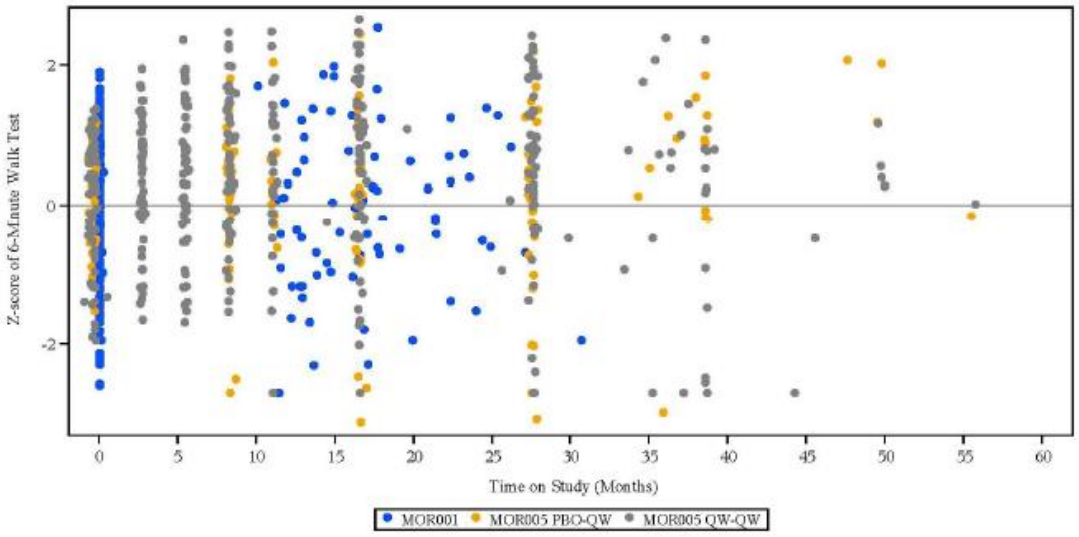
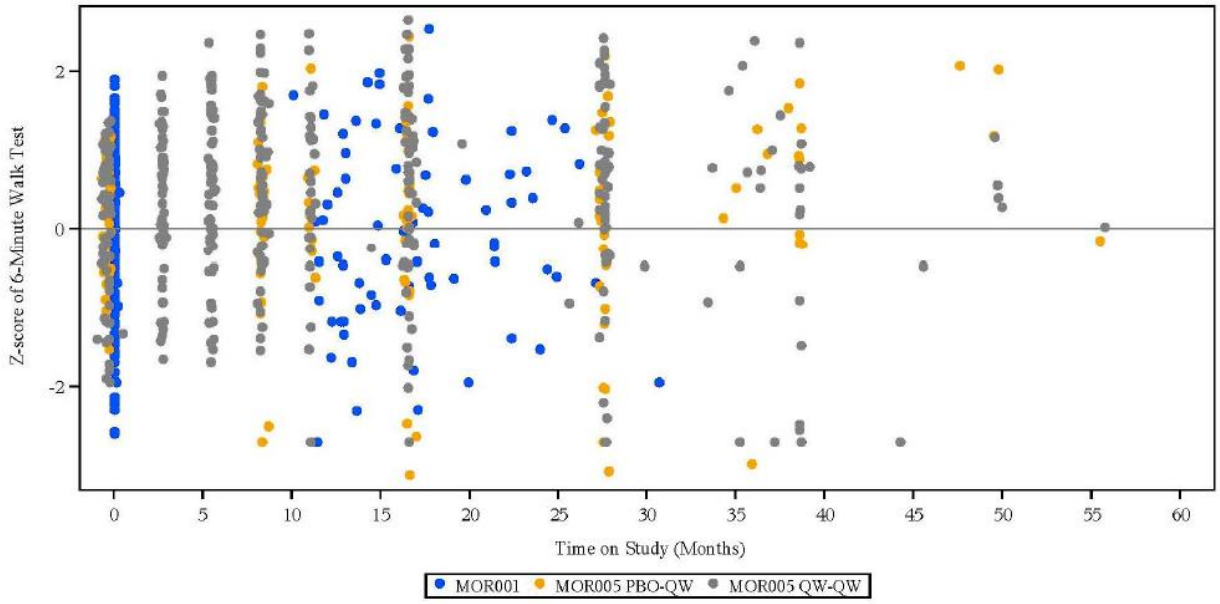
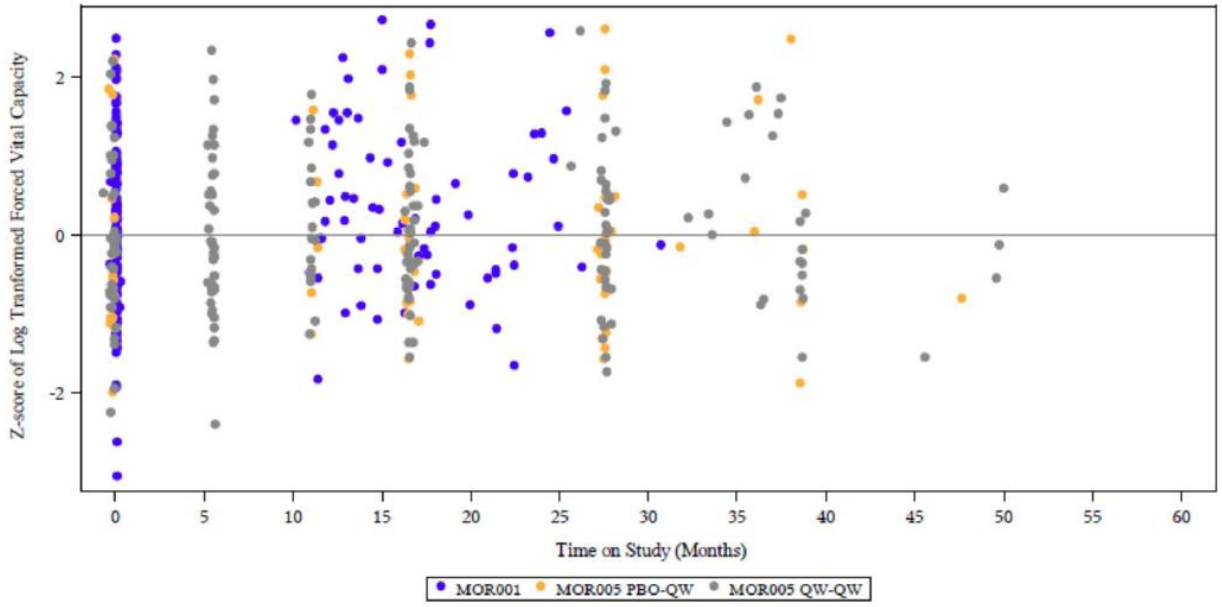


Figure 5.2: Z-Score of log(FEV1) MOR001 and ITT – MOR004 and MOR005.



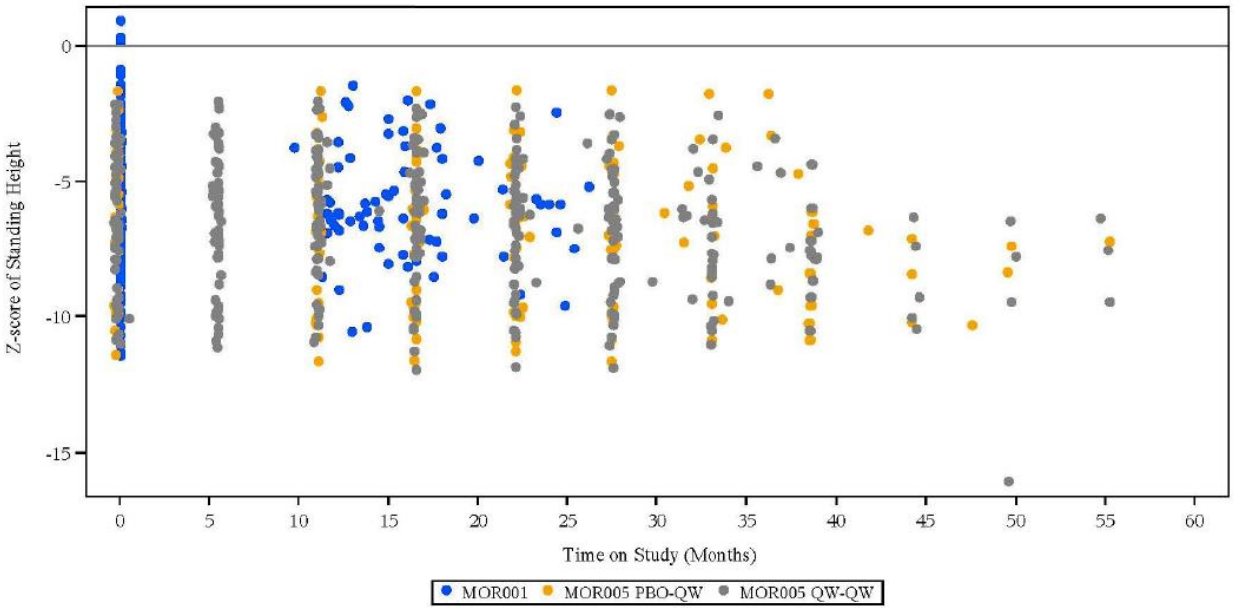
PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
For PBO-QW, in order to remove the placebo effect, the first 24 weeks data have been excluded and subsequent visits have been re-labeled, such as week 48 become to week 24 etc..
Z-scores of 6MWT were derived from the pooled data of Mor004 (ITT) and Mor001 (ITT but age>=5 and with 6MWT between 30-325 m) based on the age and sex.
In scatter plots, the actual visits (by months) were used.
Report: ltsai 02JUN2017 16:25 /ace/acedev/bmn110/mpsiva/mor005/ir201704a/output/stat/fig/g_14.2.01.11.01_eff_zsum_6mwt_itt.pdf+rtf
Source: /ace/acedev/bmn110/mpsiva/mor005/ir201704a/progstat/g_eff_zsum.sas, Database: Unlocked - extracted on 12AUG2016:16:27:28 Page 1 of 1

Figure 5.3: Z-Score of log (FVC) MOR001 and ITT – MOR004 and MOR005.



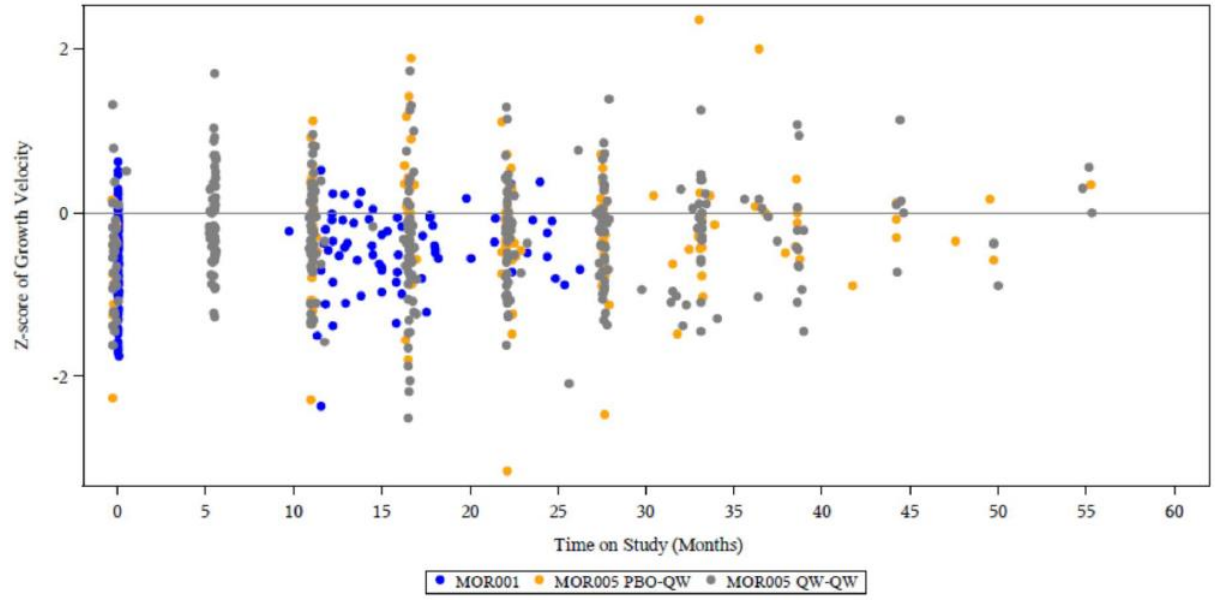
PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
For PBO-QW, in order to remove the placebo effect, the first 24 weeks data have been excluded and subsequent visits have been re-labeled, such as week 48 become to week 24 etc..
Z-scores were derived based on the pooled data from MOR004 (intent to treat population) and MOR001 (intent to treat population, but subjects with baseline of 6-Minute Walk Test in the range of 30m to 325m and age >=5 yrs) adjusted by age and sex.

Figure 5.4: Z-Score of standing height MOR001 and ITT – MOR004 and MOR005.



O-QW, Placebo-BMN 110 2.0 mg/kg/qw; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
r PBO-QW, in order to remove the placebo effect, the first 24 weeks data have been excluded and subsequent visits have been re-labeled, such as week 48 become to week 24 etc..
scores of height were derived based on the CDC growth data (age between 5 to18).
scatter plots, the actual visits (by months) were used.
port: ltsai 02JUN2017 16:25 /ace/acedev/bmn110/mpsiva/mor005/ir201704a/output/stat/fig/g_14.2.01.11.04_eff_zsum_haz_itt.pdf+rtf
urce: /ace/acedev/bmn110/mpsiva/mor005/ir201704a/progstat/g_eff_zsum.sas, Database: Unlocked - extracted on 12AUG2016:16:27:28 Page 1 of 1

Figure 5.5: Z-Score of Growth Velocity MOR001 and ITT – MOR004 and MOR005.



PBO-QW, Placebo-BMN 110 2.0 mg/kg/qw; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
For PBO-QW, in order to remove the placebo effect, the first 24 weeks data have been excluded and subsequent visits have been re-labeled, such as week 48 become to week 24 etc..
Z-scores of growth velocity were derived based on the CDC growth data (age between 5 to18).
In scatter plots, the actual visits (by months) were used.

Figures for the MPP are not shown, but these showed a similar pattern.

Assessment of the MAH's response

The MAH's efforts to submit the requested data are highly appreciated, as it is clear that there are no norms available for the 6MWT, FEV1 and FVC. It is agreed with the MAH that there is a high variability amongst the patients, which is representative for the heterogeneity of the disease. The figures submitted for 6MWT, FEV1, FVC, standing height and growth velocity did not show a distinctive pattern.

Issue resolved.

Question 6.

As elosulfase alfa is for life-long treatment, presumably starting early in life (after diagnosis), it is clear that a clinically relevant benefit for the patient is to be expected. In this case the 6MWT, lung capacity and MPS HAQ are considered important indicators for observing a clinically relevant effect in these patients, although other factors are important as well. It is of scientific and clinical interest to verify whether there is an association between the 6MWT, lung capacity and MPS HAQ. The MAH is requested to submit these analyses.

MAH Response:

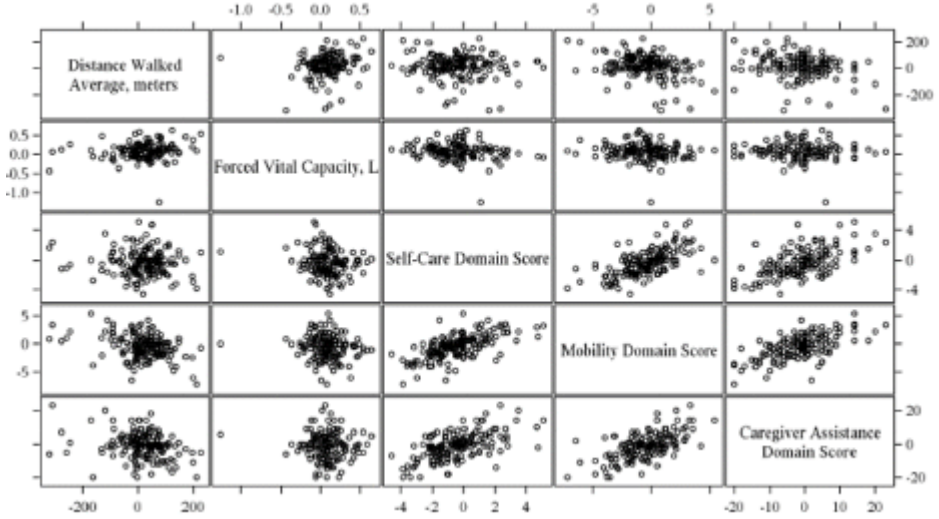
Pearson Correlation Coefficients between 6MWT, FVC (lung capacity), and the three domains of the MPS HAQ (self-care, mobility and caregiver assistance) were performed on MOR-004/005 Week 120 data, and the change from baseline to Week 120 data, to assess the relationship between variables in the ITT population of Study MOR-005.

At Week 120, the analysis showed a significant positive correlation between all variables (Table 6.1 and Figure 6.1). The increases in 6MWT from baseline were associated with increases in lung function (FVC) and decreases in the MPS HAQ domains (Table 6.2). This is perhaps unsurprising, as it would be expected that improved endurance would have a relationship with pulmonary function, and mobility. In addition, the ability to be more ambulatory and to be able to breathe better would be likely to reduce the self-care and caregiver burden, particularly when help was needed with walking even short distances.

Table 6.1: Pearson's correlation coefficients between functional measures and MPS HAQ - ITT population at Week 120.

Tested outcome vs. other relevant outcomes	N	Pearson's Correlation Coefficient	p-value
Distance Walked (6MWT – metres)			
FVC, L	157	0.26372	0.0008
Self-Care domain score	160	-0.32813	<0.0001
Mobility domain score	160	-0.58757	<0.0001
Caregiver assistance domain score	162	-0.44299	<0.0001
FVC, L			
Distance Walked (6MWT, m)	157	0.26372	0.0008
Self-Care domain score	155	-0.46146	<0.0001
Mobility domain score	155	-0.26828	0.0007
Caregiver assistance domain score	146	-0.50739	<0.0001
Self-care domain score			
Distance Walked (6MWT, m)	160	-0.32813	<0.0001
FVC, L	155	-0.46146	<0.0001
Mobility domain score	160	0.74983	<0.0001
Caregiver assistance domain score	160	0.82855	<0.0001
Mobility domain score			
Distance Walked (6MWT, m)	160	-0.58757	<0.0001
FVC, L	155	-0.26828	0.0007
Self-care domain score	160	0.74983	<0.0001
Caregiver assistance domain score	160	0.70904	<0.0001
Caregiver assistance domain score			
Distance Walked (6MWT, m)	162	-0.44299	<0.0001
FVC, L	156	-0.50739	<0.0001
Self-care domain score	160	0.82855	<0.0001
Mobility domain score	160	0.70904	<0.0001

Figure 6.1: Scatterplots at week 120 for 6MWT, FVC, and MPS HAQ.



In the ITT population, the changes from baseline to Week 120 in the 6MWT was significantly correlated with FVC (L), and the Mobility and Caregiver assistance domains suggesting an improvement in endurance is correlated with improvements in lung function, mobility, self-care, and caregiver

assistance. The change in 6MWT was not significantly associated with a change in the self-care domain; however, the coefficient indicated an improvement.

Change in FVC (L) was significantly correlated with improvements in endurance (6MWT). While the correlation coefficients indicated an improvement in the three MPS HAQ domains, the correlation was not significant. As previously mentioned, lung function would be expected to have a positive correlation with improvements in endurance, as the ability to breathe better would allow more physical activity.

The MPS HAQ domains were also significantly correlated with each other.

Table 6.2: Pearson correlation coefficients between the change from baseline to Week 120 in 6MWT, FVC, and MPS HAQ domains - ITT population.

Tested outcome vs. other relevant outcomes	N	Pearson's Correlation Coefficient	p-value
Distance Walked (6MWT – metres)			
FVC, L	147	0.17473	0.0343
Self-Care domain score	160	-0.08319	0.2956
Mobility domain score	160	-0.34456	<0.0001
Caregiver assistance domain score	162	-0.25792	0.0009
FVC, L			
Distance Walked (6MWT, m)	147	0.17473	0.0343
Self-Care domain score	145	-0.16020	0.0543
Mobility domain score	145	-0.11325	0.1750
Caregiver assistance domain score	146	-0.04539	0.5864
Self-care domain score			
Distance Walked (6MWT, m)	160	-0.08319	0.2956
FVC, L	145	-0.16020	0.0543
Mobility domain score	160	0.62951	<0.0001
Caregiver assistance domain score	160	0.58805	<0.0001
Mobility domain score			
Distance Walked (6MWT, m)	160	-0.34456	<0.0001
FVC, L	145	-0.11325	0.1750
Self-care domain score	160	0.62951	<0.0001
Caregiver assistance domain score	160	0.62179	<0.0001
Caregiver assistance domain score			
Distance Walked (6MWT, m)	162	-0.25793	0.0009
FVC, L			
Self-care domain score	146	-0.04539	0.5864
Mobility domain score	160	0.58805	<0.0001
	160	0.62179	<0.0001

Assessment of the MAH's response

It is no surprise that the domains of the MPS HAQ are correlated with each other. For the measurements at week 120 there is only a slight correlation (|Pearson's correlation coefficient| >0.55) between 6MWT and Mobility. The other correlations considering the measurements at week 120 and the changes from baseline to week 120 are considered weak (|Pearson's correlation coefficient| within (0.3, 0.5) and (0.0 and 0.3), respectively).

Within the time-frame of the study the positive effect on the lung function and endurance apparently does not translate into a clear improvement in QoL.

Issue resolved.

Question 7.

In the MPS HAQ a marginal positive improvement was observed. The clinical relevance is unknown. The MAH is requested to submit the results for both MPS HAQ domains stratified by age groups, as this may provide insight on whether there is a difference in impact between the age groups.

MAH Response:

The data shows that patients receiving the licensed dose improved across all three domains, regardless of age, which is consistent with the published data (Hendriksz 2017). Figure 7.1 to Figure 7.3 provide a graphical representation of the change from baseline to 120 weeks for the three MPS HAQ domains (Mobility, Self-Care, and Caregiver Burden, respectively). It is difficult to make any statistical claims of differences between sub-groups given the small number of patients in some sub-groups and the wide range of responses from patients or their caregivers as is consistent with the other sub-group analyses from the MOR-004/005 trials. It is important to remember that a reduction in score is a positive outcome for all three domains of the MPS HAQ.

In terms of changes in mobility, Figure 7.1 highlights that there are no significant differences between adult and paediatric populations, nor between the ITT and MPP populations. However, it appears that those patients who received the licensed dose are consistently showing improvement across populations. The wide confidence intervals are reflective of the small population size in some sub-populations.

A similar pattern was seen for the Self-Care (See Figure 7.2) and Caregiver Burden domains (See Figure 7.3): an improvement in scores over 120 weeks, but no clear differences between age groups, and the QW-QW arms generally performing better than the PBO-QW group in the paediatric sub-groups.

Figure 7.1: MPS HAQ Mobility Domain Change From Baseline Over 120 Weeks.

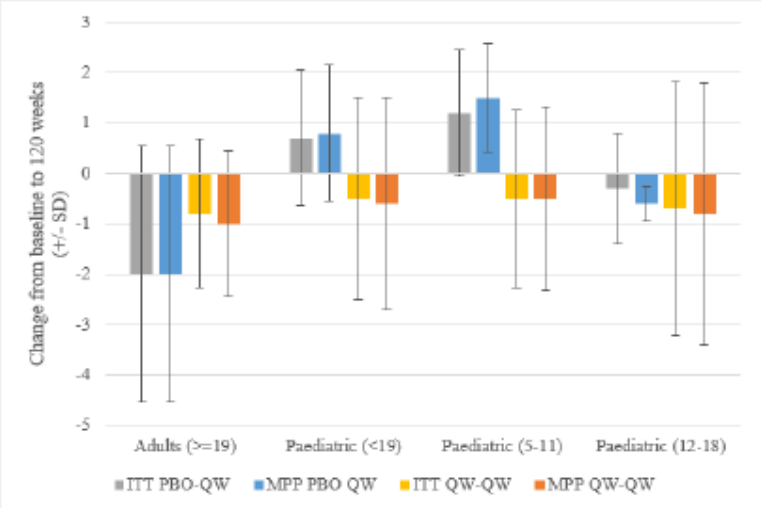


Figure 7.2: MPS HAQ Self-Care Domain Change From Baseline Over 120 Weeks.

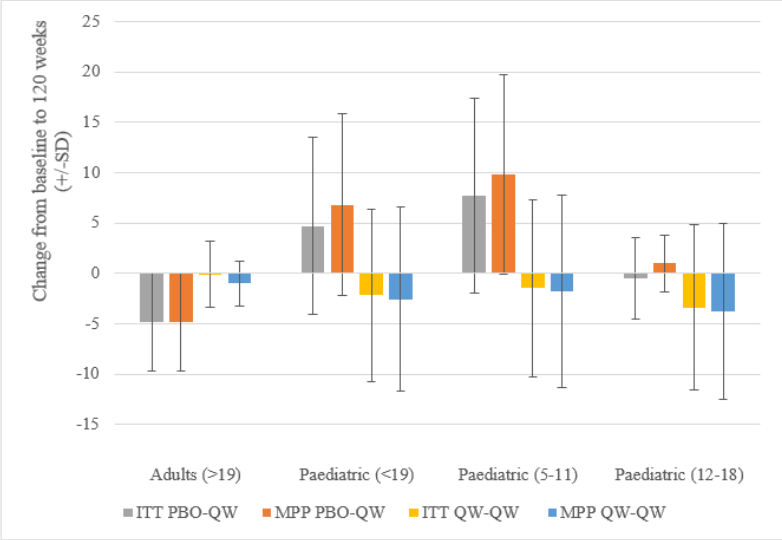
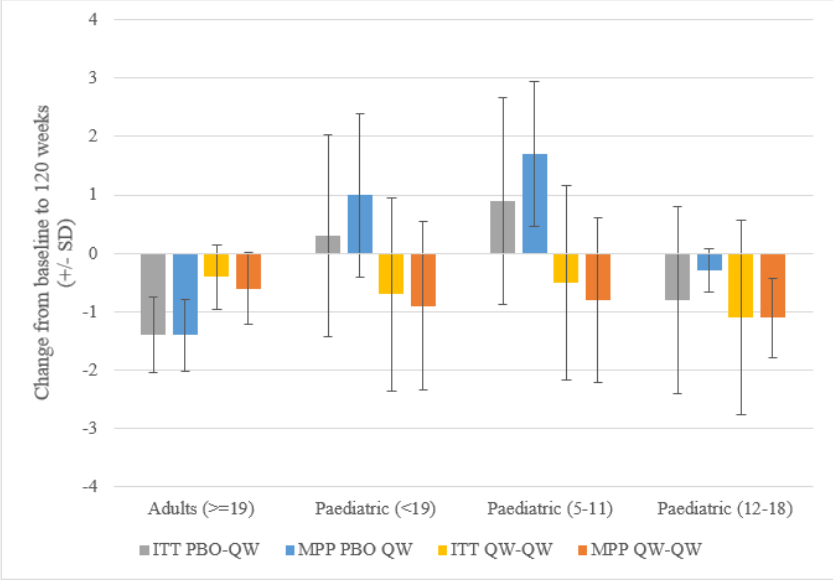


Figure 7.3: MPS HAQ Caregiver Burden Domain Change From Baseline Over 120 Weeks.



Assessment of the MAH's response

As requested the MAH provided the subgroup analysis for the 3 health domains. Note that negative values represent an improvement. There are no apparent differences between the various age groups analysed. Unfortunately it cannot be concluded that one of the age groups profits more from treatment. The preventive effect of the ERT can not be concluded from this (short-term) analysis. The results of the registry are to be awaited to provide more (long-term) data.

Issue resolved.

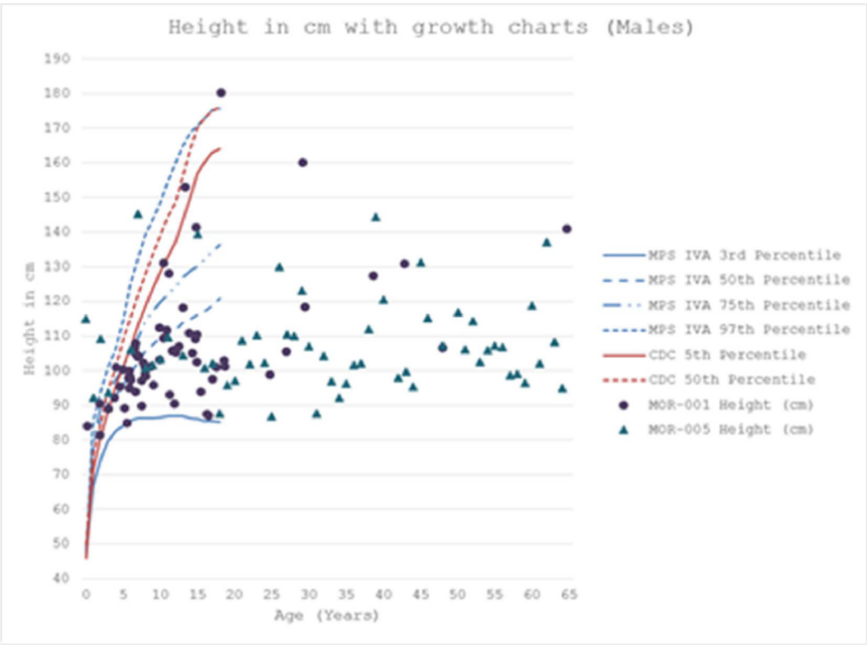
Question 8.

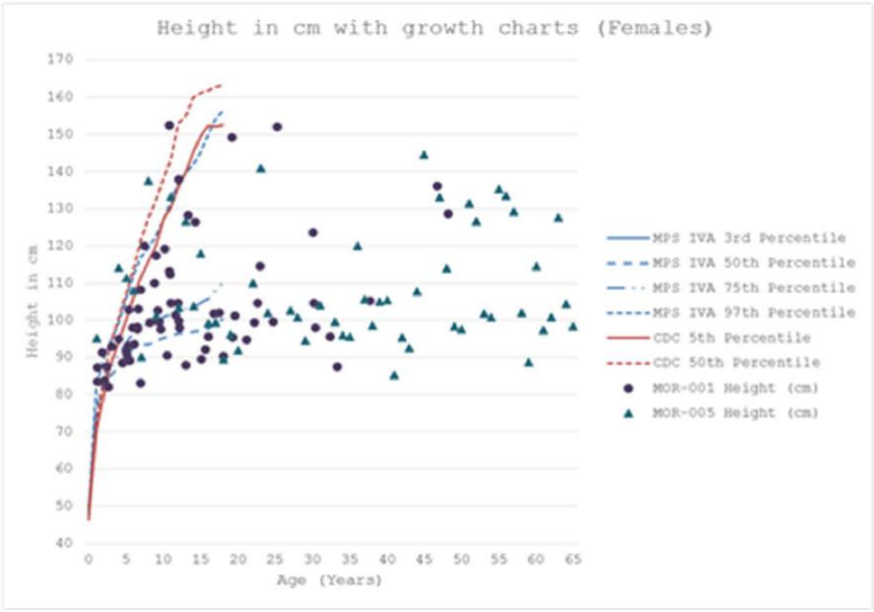
For height and growth velocity (y-axis) the MAH should plot against age (x-axis), and the CDC and the published MSP growth curves should be incorporated (refer to the publication by P. Harmatz et al., Molecular Genetics and Metabolism 109 (2013) 54–61). Graphs should be submitted for males and females separately.

MAH Response:

As requested, the MAH has provided plots for male and female height versus age in the MOR-001 and MOR-005 population with both the published MPS growth curves and the CDC growth curves (see Figure 8.1). As discussed in the publication by Harmatz 2013 (based on MOR-001 data) and Montaño 2007, MPS IVA patients are for the most part significantly shorter than the unaffected population, but show considerable variation. There are no clear differences in height between the MOR-001 population and the MOR-005 population.

Figure 8.1: Male and Female Height from the MOR-001 study and the MOR-005 ITT trial population with CDC and MPS IV growth curves.





Assessment of the MAH's response

It is agreed with the MAH that no distinctive differences in height were observed between the MOR005 study and the natural history (MOR-001). In general, Morquio A patients are smaller than the healthy population.

However, it is curious that the eldest patient in the MOR-005 study was about 49 years of age (see Table 1 in this report) and the figures display patients aged 50 and over. In the placebo controlled phase the eldest patient included was about 57 years.

Issue not resolved, however not further pursued.

Question 9.

The MAH is requested to submit the "Drug-Related Adverse Events by Preferred Term in ⩾ 10%" stratified by age-groups (<18 years and ⩾18 years). This to confirm that the safety profile in paediatric patients is similar to those observed in the adults. If appropriate the MAH is requested to update SmPC section 4.8.

MAH Response:

As reported in section 4.8 of the SmPC, the patients in the placebo-controlled trial were ages 5 to 57 years old. The vast majority (80.3%) of the patients were patients 18 or younger. Amongst these patients the events of pyrexia, rash, and nausea were less than 5% higher in this group than in those 19 or older. With the exception of vomiting, all other events were less common in the younger population. Although vomiting was observed in almost 10% more paediatric patients, it is already classified as very common in the EU SmPC therefore, the frequency would not change and an update would not be required.

Table 9.1 provides the Drug-Related Adverse Events by Preferred Term stratified by adult (⩾19 years) and paediatric (⩽18 years) patient populations. The MAH concludes that the safety profile for both sub-populations is similar, with the most common events related to infusion associated reactions.

There appeared to be a larger proportion (>10% greater) of adult patients with fatigue, chest discomfort, chills, hypertension and arthralgia than in the paediatric population. BioMarin determined events in the MOR 004 study were adverse drug reactions using the following criteria: (1) Events observed in patients receiving active drug must have a 5% or higher incidence than placebo, (2) The event must have a plausible, clinically meaningful relationship to drug (3) Severe events that were plausible and clinically meaningful were included without regards to the number of events. In MOR-004, the events of chest discomfort, rash and urticaria did meet criteria in the context of an infusion related reaction. Based on data provided, the MAH does not believe an update to the SmPC is required at this time.

Table 9.1: Safety profile of MOR-004/5 by Paediatric and Adult Subgroups.

	<=18 years (N=139)		>=19 years (N=34)		Total (N=173)	
	Incidence	Events	Incidence	Events	Incidence	Events
Subjects with at least 1 reported study drug-related treatment-emergent adverse event	101 (72,7%)	847	25 (73,5%)	224	126 (72,8%)	1071
General disorders and administration site conditions	57 (41,0%)	199	16 (47,1%)	49	73 (42,2%)	248
Pyrexia	51 (36,7%)	180	11 (32,4%)	34	62 (35,8%)	214
Chest discomfort[1]	3 (2,2%)	4	6 (17,6%)	6	9 (5,2%)	10
Chills	12 (8,6%)	15	6 (17,6%)	9	18 (10,4%)	24
Gastrointestinal disorders	64 (46,0%)	208	14 (41,2%)	65	78 (45,1%)	273
Nausea	35 (25,2%)	72	10 (29,4%)	37	45 (26,0%)	109
Vomiting	42 (30,2%)	112	7 (20,6%)	18	49 (28,3%)	130
Diarrhoea	17 (12,2%)	24	5 (14,7%)	10	22 (12,7%)	34
Nervous system disorders	45 (32,4%)	147	11 (32,4%)	70	56 (32,4%)	217
Headache	42 (30,2%)	141	11 (32,4%)	62	53 (30,6%)	203
Dizziness	5 (3,6%)	6	4 (11,8%)	8	9 (5,2%)	14
Skin and subcutaneous tissue disorders	38 (27,3%)	267	10 (29,4%)	32	48 (27,7%)	299
Rash[1]	24 (17,3%)	140	5 (14,7%)	22	29 (16,8%)	162
Urticaria[1]	20 (14,4%)	127	5 (14,7%)	10	25 (14,5%)	137
Respiratory, thoracic and mediastinal disorders	12 (8,6%)	26	4 (11,8%)	8	16 (9,2%)	34
Dyspnoea	12 (8,6%)	26	4 (11,8%)	8	16 (9,2%)	34

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term..
1These events were observed in the context of an infusion related reaction
Subjects with more than 1 AE within a given MedDRA PT were counted once within that PT. Mapping was based on MedDRA version 16.1.
a AEs that were classified by the investigator as possibly or probably related to study drug.
QOW-QOW, BMN 110-BMN 110 2.0 mg/kg/qow; QW-QW, BMN 110-BMN 110 2.0 mg/kg/qw.
These events were observed in the context of an IAR or hypersensitivity reactions.

Assessment of the MAH's response

It is agreed with the MAH that the safety profile for both sub-populations is comparable, with the most common events related to infusion associated reactions. There appeared to be a larger proportion (>10% greater) of adult patients with fatigue, chest discomfort, chills, hypertension and arthralgia than in the paediatric population. In the currently approved SmPC these adverse events are already stated, hence there is no need to update section 4.8 at this moment.

Issue resolved.

Question 10.

The SmPC in section 4.8 mentions "…Infusion reactions (IRs) occurring in ⩾ 10% of patients treated with Vimizim." and "IRs were generally mild or moderate, and the frequency was higher during the first 12 weeks of treatment and tended to occur less frequently with time." However, in the combined safety population of studies MOR-004 and MOR-005, nearly all patients (98.3%) reported Infusion Associated Reactions (IARs). The

MAH should discuss whether the frequency of IRs in this study was higher than already described in the SmPC and, if needed, propose amendments of the SmPC wording.

MAH Response:

The current SmPC states that the majority of adverse reactions in clinical trials were Infusion reactions (IRs). The most common symptoms of these IRs were identified as those occurring in ⩾10% of all patients treated with Vimizim and an incidence of ⩾5% more, in the patients receiving active drug when compared to those receiving placebo in MOR-004.

In MOR 004, the most common symptoms of IARs included pyrexia (36.2%) vomiting (37.9%), and headache (32.8%) in patients receiving 2.0 mg/kg/ week. In the combined safety population, the most common symptoms of IRs were pyrexia (51.4%), vomiting (49.1%), and headache (46.8%). These symptoms are currently described in the SmPC with a frequency categorized as very common. Since these events were similar to the most common AEs overall and are already categorized as very common, the sponsor believes that an amendment to the SmPC at this time is not warranted.

Assessment of the MAH's response

It is agreed with the MAH that currently no update for SmPC section 4.8 is needed.

Issue resolved.

REFERENCES

Aldurazyme (Laronidase) Package Insert, [BoMarin]. Aldurazyme (Laronidase) Package Insert. 2011.

Elaprase SmPC [Shire]. Elaprase Summary of Product Characteristics. 2012.

Harmatz, P, Mengel, KE, Giugliani, R, et al. The Morquio A clinical assessment program: baseline results illustrating progressive, multisystemic clinical impairments in Morquio A patients. Mol Genet Metab 109[1], 54-61. 2013.

Kuczmarski, RJ, Ogden, CL, Grummer-Strawn, LM, et al. 2000 CDC growth charts for the United States: methods and development. National Center for Health Statistics, Vital Health Stat 11(246). 2002.

Montano, AM, Tomatsu, S, Gottesman, GS, Smith, M et. al. International Morquio A Registry: clinical manifestation and natural course of Morquio A disease. J Inherit Metab Dis 30[2], 165-174. 2007.

Muenzer, J, Wraith, JE, Beck, M, Giugliani, R et. al. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genet Med 8[8], 465-473. 2006.

Naglazyme Package Insert [BioMarin]. Naglazyme Package Insert. 2012.