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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/P46/006

Note

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

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1. Introduction

On 20 May 2015, the MAH submitted a completed paediatric study for Vimizim, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study MOR-008: A Randomized, Double-Blind, Pilot Study of the Safety and Physiological Effects of Two Doses of BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome) is a stand alone study.

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 obtained for Vimizim (elosulfase alfa; BMN 110) in the European Union on 28 April 2014.

At the time of MAA, study MOR-008 was an ongoing Phase 2, randomized, double-blind, study of BMN 110 2.0 mg/kg/week and 4.0 mg/kg/week administered for an initial treatment period of 27 consecutive weeks in 25 subjects with MPS IVA who are ≥7 years of age with an extension treatment phase of an additional 130 weeks. Interim safety data up till 12 September 2012 were presented and discussed previously, no efficacy data were assessed within the context of the initial MAA.

The currently presented data consists of an interim report and an abbreviated final report for study MOR-008. The interim report dated 22 October 2014 provides a comprehensive summary of safety and efficacy results for the primary treatment phase (27 weeks). The accruing extension phase data were not analysed for the interim study report. This report was generated to evaluate the possibility of a publication, which was not pursued. Because this CSR did not support further clinical conclusions, it was determined that it would be submitted with the final CSR described below.

The abbreviated final CSR presents safety and efficacy data for all subjects through their discontinuation from the study during the extension phase. Safety results are described for the entire study period, while the efficacy results are briefly summarized, with the focus on data through Week 52 for those assessments that Amendment 2 of the protocol included in the extension phase study objectives.

2.3.2. Clinical study

Study MOR-008: A Randomized, Double-Blind, Pilot Study of the Safety and Physiological Effects of Two Doses of BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome).

The study was conducted at 11 study centres in 4 countries (Germany, United Kingdom, Canada, United States).

Description

Methods

Objective(s)

<u>27-week primary treatment phase</u>

The **primary objective** of the study was to evaluate the safety of 2.0 and 4.0 mg/kg/week BMN 110 during the 27-week primary treatment phase of the study.

The **secondary objectives** of the study during the primary treatment period were to evaluate the effect of 2.0 and 4.0 mg/kg/week BMN 110 on endurance (by 6MWT and 3MSCT), overall exercise capacity (by CPET), RFTs, MSTs, cardiac function, pain, uKS levels, and to determine the PK parameters of 2.0 and 4.0 mg/kg/week BMN 110.

The **tertiary objectives** of the primary treatment phase of the study were:

- To evaluate the effect of 2.0 and 4.0 mg/kg/week BMN 110 administered for 24 weeks on growth
- To explore the correlation of the 6MWT and 3MSCT with overall exercise capacity, cardiac function, respiratory function, muscle strength, pain, and plasma and urinary KS levels
- To obtain a subject's self-rating on his or her experiences associated with the 6MWT, the 3MSCT, and with breathing
- To evaluate the effect of 2.0 and 4.0 mg/kg/week BMN 110 administered for 26 weeks on biochemical markers of bone and cartilage metabolism

<u>Extension phase</u>

The **primary objective** of the extension phase of the study was to evaluate the long-term safety of 2.0 mg/kg/week BMN 110 in subjects with MPS IVA.

The **secondary objectives** of the extension phase of the study were to evaluate the effect of 2.0 mg/kg/week BMN 110 on endurance, RFTs, and uKS.

The **tertiary objectives** of the extension phase of the study were:

- To evaluate the effect of 2.0 mg/kg/week BMN 110 on growth
- To explore the correlation of the 6MWT and 3MSCT with respiratory function and urinary KS levels
- To evaluate the effect of 2.0 mg/kg/week BMN 110 on cardiac function
- To evaluate the effect of 2.0 mg/kg/week BMN 110 on biochemical markers of bone and cartilage metabolism

Study design

The study was a phase 2 two-arm, randomized, double-blind study in subjects with MPS IVA who were at least 7 years of age to assess the safety of weekly IV infusions of 2.0 mg/kg/week and 4.0 mg/kg/week BMN 110. The study also evaluated the effect of 2.0 mg/kg/week and 4.0 mg/kg/week BMN 110 on endurance, exercise capacity and various possible determinants of increased endurance, such as cardiac function, respiratory function and pain.

The planned study duration was up to 196 weeks including a 3-week Screening, a 27-week primary treatment phase, and up to a 166-week extension phase.

Study population /Sample size

Study population

Subjects with a documented diagnosis of MPS IVA who were at least 7 years of age, able to walk at least 200 meters in the 6MWT at screening, and had not previously had a hematopoietic stem cell transplant (HSCT) or been previously treated with BMN 110 were eligible to participate in this study. Subjects with severe untreated sleep apnoea (as measured by a home sleep testing device), a requirement for supplemental oxygen or ventilation, or any medical condition, including but not limited to symptomatic cervical spine instability or cord compression that would interfere with study participation as determined by the Investigator, were excluded by the protocol.

Sample size

The planned number of subjects was 25; 15 subjects enrolled in Cohort A and 10 subjects enrolled in Cohort B. Randomization was stratified by cohort (A or B). The 15 subjects enrolled in Cohort A were randomized 2:1 to receive 2.0 or 4.0 mg/kg/week BMN 110 and performed all study procedures, including the CPET. After completion of enrolment in Cohort A, 10 subjects were enrolled in Cohort B and randomized 1:1 to receive 2.0 or 4.0 mg/kg/week BMN 110; Cohort B subjects performed all study procedures except for CPET.

Treatments

All subjects received the active therapy BMN 110 (Vimizim, elosulfase alfa; BMN 110). During the primary treatment phase, subjects received IV infusions of BMN 110 at doses of either 2.0 or 4.0 mg/kg/week for 27 consecutive weeks (Week 0 through Week 26). Each infusion was administered over a period of approximately 4 hours.

In the original protocol, subjects initially randomized to either 2.0 or 4.0 mg/kg/week with BMN 110 were to remain on their dose regimen during the extension treatment phase. Amendment 2 of the protocol standardized the dose for the extension treatment phase to 2.0 mg/kg/week.

Outcomes/endpoints

Safety variables

Safety was assessed through the evaluation of adverse events (AE) including serious adverse events (SAEs) and infusion associated reactions (IARs), clinical laboratory assessments, vital signs assessments, physical examinations, ECG, ECHO, immunogenicity test results, and pregnancy testing.

As subjects may experience hypersensitivity reactions associated with the administration of BMN 110, all subjects were pre-treated with an appropriate dose of antihistamine medication with or without antipyretic medications approximately 30 minutes to 1 hour prior to infusion. Pre-treatment with an antipyretic was allowed at the Investigator's discretion. On infusion days, vital signs were measured immediately (< 30 minutes) before the start of the infusion, immediately prior to each infusion rate increase until maximum infusion rate was achieved, once every 30 minutes (± 5 minutes) for the remainder of the infusion, immediately (< 15 minutes) following the end of the infusion, and at least 60 minutes (± 15 minutes) after the infusion. Subjects also were monitored by continuous pulse oximetry during the infusion and for at least 60 minutes after the infusion had been completed.

For severe events temporally related to a BMN 110 infusion or events requiring cessation of the infusion, blood samples were collected for immunogenicity testing, including drug-specific immunoglobulin E (IgE), complement component 4 (C4), serum tryptase, and total IgE. In the MOR-008 protocol and this report, these temporally-related events were labelled infusion associated reactions (IARs).

Efficacy variable (secondary)

- 6-minute walk test (6MWT)
- 3-minute stair climb test (3MSCT)
- Urine keratan sulfate concentration normalized to creatinine (normalized uKS), plasma keratan sulfate
- Cardiopulmonary exercise testing (CPET)
- Respiratory function tests (RFTs)
- Muscle strength testing (MST)
- Cardiac function (ECHO)
- Home sleep testing
- Pain assessment (Adolescent Paediatric Pain Tool [APPT])
- PK parameters

Efficacy variables (tertiary)

- Anthropometric measurements (standing height or length, sitting height, knee height, and weight)
- Patient Impression Questionnaire (PIQ) associated with 6MWT, 3MSC, and breathing
- Biochemical markers of bone and cartilage metabolism
- Pharmacogenetic analysis (for subjects who had not had genetic testing to confirm diagnosis of MPS IVA)

Primary treatment phase

During the primary treatment phase, endurance was assessed by the 6MWT and 3MSCT. Each test was performed twice during the Screening Period within a 7-day window, with only one test allowed per day. The average distance from the two 6MWTs was used for establishing study eligibility. At Weeks 12 and 24 (or early termination visit [ETV]), the tests were again conducted twice each within the same 7-day window, one test per day, and prior to infusion of study drug. (Note that during the extension phase the 6MWT and 3MSCT were performed only once per timepoint.)

During the primary treatment phase, cardiopulmonary exercise testing (Cohort A only) was performed during the Screening Period and at Week 25, in each case on a separate day and after completion of

the two endurance tests, with a window of +14 days at Week 25 only. A physical examination (including an assessment of skeletal deformities) was performed at Weeks 0 and 24. Overnight monitoring with home sleep testing, anthropometric measurements, ECG, and ECHO, and PIQ performed at Screening were repeated at Week 24 (or ETV). A urine pregnancy test was repeated at Week 26 (or ETV). The APPT, RFTs, and collection of biochemical markers of bone and cartilage metabolism were repeated at Weeks 12 and 24 (or ETV). Clinical laboratory tests were repeated at Weeks 12 and 26 (or ETV). Assessments of plasma and urine GAG and urine creatinine were performed for samples obtained at Weeks 1, 2, 4, 6, 12, and 24 (or ETV).

Blood samples for PK analysis were obtained at Weeks 0 and 23 from all subjects at the following timepoints: pre-dose (within 15 minutes prior to dosing); 60 and 120 minutes after the start of infusion; at the end of infusion (within 5 minutes prior to stopping infusion); and 5, 15, 30, 60, 120, and 180 minutes post-infusion.

Assessment of immunogenicity was performed for samples obtained at Weeks 2, 4, 6, 12, and 24 (or ETV).

Extension phase

Subjects began the extension phase receiving blinded BMN 110, either 2.0 mg/kg/week or 4.0 mg/kg/week, as randomized in the primary treatment phase. However, Amendment 2 of the protocol specified that all subjects in the extension phase transition to open-label 2.0 mg/kg/week BMN 110. This revision was made based on the results of the pivotal Phase 3 study (MOR-004), which showed a statistically significant improvement in the 6MWT for the 2.0 mg/kg/week treatment group compared to placebo. The 2.0 mg/kg/week dose was proposed as an appropriate safe and efficacious dose for patients with MPS IVA. Note that the 5 subjects originally assigned to 4.0 mg/kg/week BMN 110 who were transitioned to 2.0 mg/kg/week BMN 110 per Amendment 2 are included with the 4.0 mg/kg/week treatment group in all the analyses at all timepoints, including those subsequent to the transition. Amendment 2 of the protocol included other changes in the design of the extension phase, including the elimination of 5 efficacy assessments (CPET, MST, APPT, home sleep testing, and PIQ). These assessments were initially performed in the extension phase under Amendment 1 and all data are included, though not described in the text. Amendment 2 removed these evaluations from the study objectives and reporting in this abbreviated final CSR is based on the stated objectives for the extension phase in Amendment 2, the final protocol amendment.

Statistical Methods

The sample size of the study was not determined by statistical power considerations.

Analysis Populations:

The modified intent-to-treat (MITT) population consisted of all subjects who were randomized to study treatment, received at least one dose of study drug, and had at least one post-treatment observation. The primary efficacy analyses for all efficacy endpoints were based on the modified ITT population and data were analysed according to the treatment assigned at randomization. The per-protocol (PP) population is defined as a subset of the MITT population who are reasonably compliant with the protocol. Factors for determining the PP population include major protocol deviations affecting data interpretability and repeated skipped doses of study drug.

Efficacy analysis:

Efficacy analyses include descriptive statistics for all secondary and tertiary efficacy variables.

A baseline value for 6MWT and 3MSCT was determined as the average of the 2 measurements obtained during the Screening period and prior to the first administration of study drug. For the other

efficacy parameters, baseline value is defined as the last measurement taken prior to the first administration of study drug.

Safety analysis:

Safety was assessed by an examination of the type, incidence, severity grade, and relationship to study drug of all treatment-emergent AEs reported during the study period. Baseline summaries and safety analysis are descriptive.

Pharmacokinetic analysis:

Pharmacokinetic parameters were calculated by standard noncompartmental analysis according to current working practices and using WinNonlin version 6.1. Actual sampling times and infusion duration was used in the PK calculation.

Interim analyses:

An unblinded analysis of MOR-008 for an abbreviated CSR was produced after the last subject completed the last visit of the pivotal phase 3 study MOR-004. The abbreviated CSR, dated 5MAR2013, was prepared to support the initial Marketing Application submissions for BMN 110. The abbreviated CSR summarized safety data as of the cutoff date of 14SEPT2012. At the time of data cutoff, no subjects had completed the primary treatment phase.

A second analysis was conducted after the last subject completed the Week 26 visit, the end of the primary treatment phase of the study. That analysis summarized only the primary treatment phase; none of the accruing extension phase data were analysed. The resulting Interim CSR was dated 22OCT2014.

Rapporteur's comment:
Study design has been discussed within the initial MAA. The main objective of the study is to assess the long-term safety. Further, the large number of secondary and tertiary endpoints may lead to chance findings and no firm conclusions are likely to be drawn from this study. This is recognized by the MAH a priori; the goal of the study was to gather pilot data from a wide range of functional tests, to generate hypotheses for potential future studies and to further current understanding of MPS IVA patient's functional impairments, how they interrelate, and how they respond to treatment with BMN 110.
The study was discontinued prior to study end and data are presented for 1 year in a limited number of patients (n=25). Discontinuation after week 52 was due to a rapid reduction in sample size as US subjects discontinued the study and moved into an expanded access program (EAP). By week 96, sample size had been reduced by more than half.

Results

Recruitment / Number analysed

Twenty-five subjects were enrolled at 8 clinical sites, including 4 sites in the US, 2 sites in Canada, and 1 site each in Germany and the UK. The first patient was enrolled at 23 April 2012, the last patient completed the study at 20 November 2014.

A total of 15 subjects were randomized to treatment with BMN 110 at 2.0 mg/kg/week and 10 randomized to treatment with BMN110 at 4.0 mg/kg/week (see Figure 1). All subjects in both treatment groups received BMN 110 and completed the primary treatment phase but then discontinued the study before the planned end of the extension phase at Week 192. Subjects at US sites terminated

the study and entered an expanded access program (EAP) during the extension phase prior to implementation of Amendment 2 of the protocol. Subjects at ex-U.S. sites transitioned from Amendment 1 to Amendment 2 at different times between Week 77 and Week 81, with those randomized to 4.0 mg/kg/week switching to open-label BMN 110 2.0 mg/kg/week as required by Amendment 2. The reason for study discontinuation for all but 2 of the subjects was that the sponsor terminated the study. One subject discontinued because of planned surgery and an expected subsequent transition to the EAP at a site closer to her home, and one subject stopped receiving 2.0 mg/kg/week BMN 110 after Week 24 when she moved further away from the study site.

Numbers analysed: All 25 subjects are included in the safety analyses and in the modified intent-to-treat (MITT) population. Twenty-four subjects were included in the PP population. One subject was excluded from the PP population for the entire study due to the subject having missed 4 infusions, on Weeks 17, 20, 21, 22. Since this subject worsened from Baseline on several efficacy measures (including the 6MWT, 3MSCT, APPT WGRS pain intensity assessment, and all 3 muscle strength tests), the results for those measures appeared to show more efficacy in the PP than in the MITT population.

In addition 2 subjects were excluded from the PP population after Week 24 because each missed ≥ 20% of their scheduled doses during the period they were enrolled in the extension phase. Finally, 2 subjects who underwent orthopaedic surgery on Days 102 and 217, respectively, were excluded from the PP population for all assessments performed following their surgeries. The PP analyses are not presented in the text.

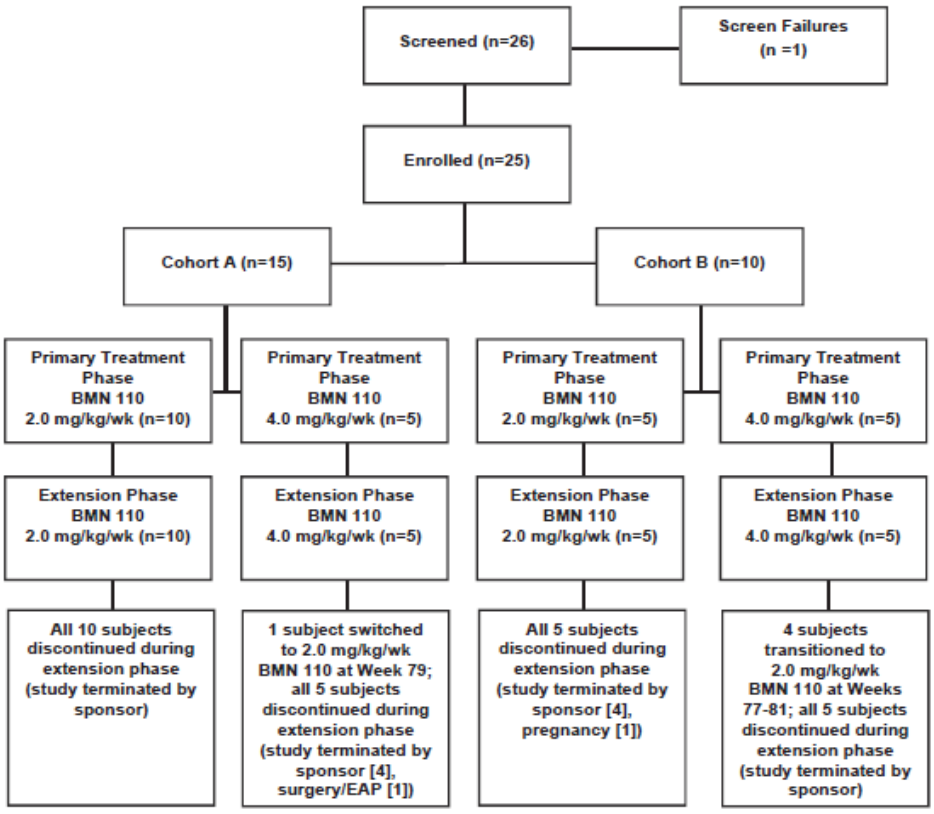

Figure 1. Disposition of subjects

Baseline data

The 2.0 mg/kg/week treatment group included 3 (20.0%) males and 12 (80%) females, while the 4.0 mg/kg/week treatment groups included 6 (60.0%) males and 4 (40.0%) females. The mean ± SD ages of the subjects at Baseline in the 2.0 mg/kg/week and 4.0 mg/kg/week treatment groups were 14.9 ± 9.32 years and 12.0 ± 3.16 years, respectively. A total of 60% of patients was between 7-11 years in the low dose group and 50% in the high dose group.

The mean (± SD) weight of subjects at Baseline in the 2.0 mg/kg/week and 4.0 mg/kg/week treatment groups were 31.0 (± 14.83) kg and 27.4 (± 13.70) kg, respectively (Table 1). Most subjects in both the 2.0 mg/kg/week treatment group (73.3%) and 4.0 mg/kg/week treatment group (90.0%) had heights that were shorter than the 3rd percentile.

Table 1. Baseline characteristics (ITT population)

Characteristics	BMN 110 2.0 mg/kg/week (n = 15)	BMN 110 4.0 mg/kg/week (n = 10)	All Subjects (n = 25)
Weight (kg)			
n	15	10	25
Mean (SD)	31.0 (14.83)	27.4 (13.70)	29.6 (14.20)
Median	26.5	23.4	26.4
25th, 75th Percentile	17, 49	17, 29	17, 36
Min, Max	12, 55	15, 55	12, 55
Height Percentile			
< 3rd percentile	11 (73.3%)	9 (90.0%)	20 (80.0%)
≥ 3rd to < 10th percentile	2 (13.3%)	0	2 (8.0%)
≥ 25th to < 50th percentile	2 (13.3%)	0	2 (8.0%)
≥ 50th percentile	0	1 (10.0%)	1 (4.0%)
6-minute Walk Test (meters)			
Mean (SD)	369.6 (89.19)	376.3 (69.98)	372.2 (80.55)
Median	346.8	393.2	372.3
25th, 75th Percentile	300, 422	326, 444	321, 422
Min, Max	255, 596	267, 453	255, 596
3-minute Stair Climb Test (steps/minute)			
Mean (SD)	65.5 (21.42)	64.2 (23.32)	65.0 (21.73)
Median	65.3	63.6	65.2
25th, 75th Percentile	55, 72	53, 84	55, 78
Min, Max	28, 119	30, 100	28, 119
n (%) using walking aid during 6MWT, 3MSCT	1 (6.7%)	0	1 (4.0%)
Time since MPS IVA Diagnosis (years)			
Mean (SD)	5.5 (3.89)	5.6 (3.93)	5.6 (3.82)
Median	4.4	3.9	4.4
25th, 75th Percentile	3, 10	2, 9	3, 9
Min, Max	1, 13	2, 11	1, 13
Age at Time of MPS IVA Diagnosis (years)			
Mean (SD)	9.4 (10.00)	6.4 (3.31)	8.2 (8.05)
Median	6.2	6.5	6.2
25th, 75th Percentile	4, 9	3, 9	4, 9
Min, Max	2, 35	1, 12	1, 35

The mean (± SD) distances walked by the subjects in the 6MWT at Baseline in the 2.0 mg/kg/week and 4.0 mg/kg/week treatment groups were 369.6 (± 89.19) and 376.3 (± 69.98) meters, respectively (Table 1). The mean (± SD) climbing rates of the subjects in the 3MSCT in the 2.0 mg/kg/week and 4.0 mg/kg/week treatment groups were 65.5 (± 21.42) and 64.2 (± 23.32) stairs/minute, respectively.

The age at MPS IVA diagnosis ranged from 2.0 to 35 years for the 2.0 mg/kg/week treatment group and from 1 to 12 years for the 4.0 mg/kg/week treatment group, with respective means (± SD) of 9.4 (±10.00) and 6.4 (±3.31) years. The mean (± SD) time since MPS IVA diagnosis was 5.5 (±3.89) years for the 2.0 mg/kg/week treatment group and 5.6 (±3.93) years for the 4.0 mg/kg/week treatment group. The mean (± SD) normalized levels of uKS were 16.4 (± 15.23) μg/mg for the 14 subjects with Baseline uKS measurements in the 2.0 mg/kg/week treatment group and 18.8 (±9.03) μg/mg for the 9 subjects with Baseline uKS measurements in the 4.0 mg/kg/week treatment group.

Efficacy results

6-minute Walk Test (6MWT)

There were no meaningful changes from Baseline in walk distance in either dose group at either 12 or 24 weeks, though there was some increase seen at week 52 particularly in the 4.0 mg/kg/week group. At Week 24, the mean and median changes from Baseline were − 13.0 m (95% CI − 43.0, 17.0) and +1.4 m, respectively, in the 2.0 mg/kg/wk group and +0.1 m (95% CI − 24.8, 24.9) and − 1.2 m, respectively, in the 4.0 mg/kg/week group. Some improvement was seen at Week 52, with mean and

median changes from Baseline of +9.0 m (95% CI −18.9, 37.0) and +1.9 m, respectively, in the 2.0 mg/kg/week treatment group and +31.8 m (95% CI −7.2, 70.8) and +22.1 m, respectively, in the 4.0 mg/kg/week treatment group.

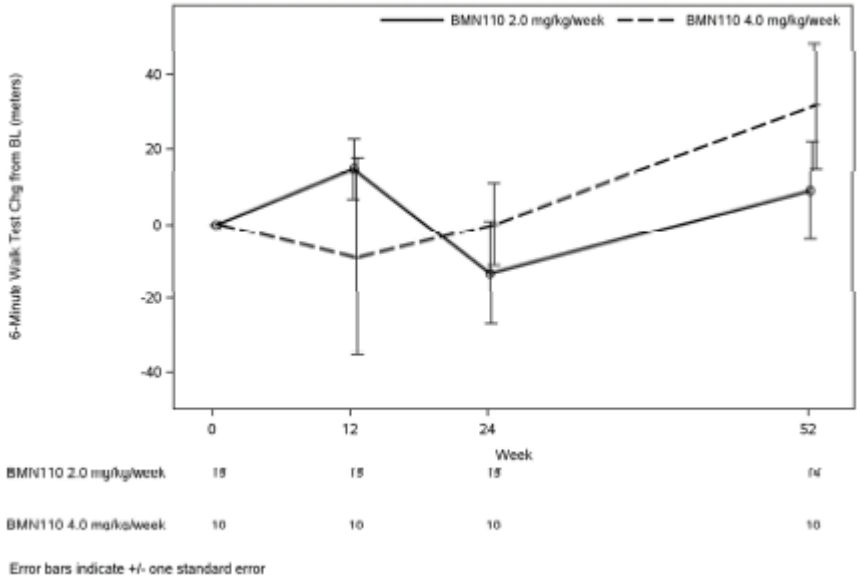

Figure 2. Mean change in 6-Minute Walk Test vs Time (mITT population).

3-minute Stair Climb Test (3MSCT)

There was a numerical improvement from Baseline seen in the 4.0 mg/kg/week treatment group but not in the 2.0 mg/kg/week treatment group. At Week 24, the mean and median changes from Baseline in the number of stairs climbed per minute were − 2.2 (95% CI − 8.6, 4.2) and − 1.3, respectively, in the 2.0 mg/kg/week group and +12.5 (95% CI 1.6, 23.4) and +13.9, respectively, in the 4.0 mg/kg/week group. At Week 52, the mean and median changes from Baseline in the number of stairs climbed per minute were - 4.4 (95% CI - 9.8, 1.0) and - 4.0, respectively, in the 2.0 mg/kg/week group and +10.0 (95% CI - 2.1, 22.0) and +2.3, respectively, in the 4.0 mg/kg/week group.

Urinary Keratan Sulfate (uKS)

Treatment with BMN 110 led to substantial decreases in mean normalized uKS levels in both treatment groups to comparable median values at week 24 (6.7 μg/mg in the 2.0 mg/kg/week group and 6.4 μg/mg in the 4.0 mg/kg/week group), with a more rapid decline observed in the 4.0 mg/kg/week group. The mean and median percent changes from Baseline at Week 24 were − 37.4% (95% CI − 50.8%, − 24.0%) and - 46.3%, respectively, in the 2.0 mg/kg/week treatment group and − 55.5% (95% CI − 65.2%, − 45.8%) and − 55.5%, respectively, in the 4.0 mg/kg/week treatment group. The reductions in mean normalized uKS achieved at Week 24 were largely maintained at Week 52 in the 4.0 mg/kg/week group, while they were somewhat diminished in the 2.0 mg/kg/week group.

The mean and median percent changes from Baseline at Week 52 were − 20.5% (95% CI − 46.9%, 5.9%) and − 23.4%, respectively, in the 2.0 mg/kg/week treatment group and − 52.8% (95% CI − 59.9%, − 45.6%) and − 53.3%, respectively, in the 4.0 mg/kg/week treatment group.

Respiratory Function Tests (RFTs):

There were positive mean and median Week 24 percent changes from Baseline for most of the RFT parameters, with consistently greater percentage increases seen in the 4.0 mg/kg/week group.

Improvements from Baseline for the 4.0 mg/kg/week treatment group were greater at Week 52 than Week 24 for most parameters. Mean and median percent changes from Baseline at Week 52 in forced vital capacity (FVC) were 4.8% (95% CI – 2.2%, 11.8%) and 6.3%, respectively, in the 2.0 mg/kg/week group and 15.1% (95% CI 3.7%, 26.5%) and 13.0%, respectively, in the 4.0 mg/kg/week group. Mean and median percent changes from Baseline at Week 52 in Forced Expiratory Volume (FEV1) were 1.8% (– 8.1%, 11.8%) and – 1.3%, respectively, in the 2.0 mg/kg/week group and 10.3% (– 3.8%, 24.5%) and 9.9%, respectively, in the 4.0 mg/kg/week group.

Anthropometric measurements:

The Baseline mean (SD) and median standing height z scores were slightly higher (i.e., closer to normal) in the 2.0 mg/kg/week group (– 4.1 [3.10] and – 3.1, respectively) than in the 4.0 mg/kg/week group (– 4.5 [2.62] and – 4.0, respectively). Little change was seen at either Week 24, when the mean and median changes in z-scores were – 0.0 (95% CI: – 0.1, 0.1) and – 0.1, respectively, for the 2.0 mg/kg/week group and – 0.1 (95% CI: – 0.3, 0.1) and – 0.1, respectively, for the 4.0 mg/kg/week group, or at Week 52, when the mean and median changes in z-scores were – 0.2 (95% CI: – 0.3, – 0.1) and – 0.2, respectively, for the 2.0 mg/kg/week group and – 0.2 (95% CI: – 0.4, 0.0) and – 0.2, respectively, for the 4.0 mg/kg/week group. Some growth was observed during the study in both treatment groups for standing height, sitting height, length, weight, right knee height, left knee height, and average knee height, with no noteworthy differences between the groups.

Echocardiogram:

There is no clear evidence from echocardiogram data of an effect of BMN 110 on cardiac function.

Cardiopulmonary exercise testing (CPET) – primary treatment phase:

Peak VO2 was only mildly impaired at Baseline compared to normal subjects, but peak Vt was low and an abnormal ventilatory response to exercise was evidenced in the majority of subjects by their minimal Vt increases with exercise. There was no evidence of dynamic cardiac impairment based on relatively stable ejection fraction measurements. The CPET data show trends of positive change in exercise capacity with treatment – exercise duration, workload, and O2 pulse all generally increased with treatment. Aerobic efficiency, which relates oxygen uptake and work, went down, indicating that subjects were performing work at a reduced oxygen cost.

Muscle strength tests (MSTs) – primary treatment phase:

Baseline values for the knee extension test suggest a population with mild to moderate impairment. There were numeric improvements in knee extension, knee flexion, and elbow flexion strength at Week 25 compared to baseline in the 4.0 mg/kg/week group, but not the 2.0 mg/kg/week group. For knee extension, mean and median absolute changes from Baseline were – 0.6 (95% CI – 6.0, 4.8) and 0.0 Nm, respectively, in the 2.0 mg/kg/week group and 5.2 (95% CI – 0.3, 10.7) and 5.0 Nm, respectively, in the 4.0 mg/kg/week group. For knee flexion, the mean and median percent changes from Baseline were – 4.2% (95% CI – 18.5%, 10.2%) and – 0.2%, respectively, in the 2.0 mg/kg/week group and 9.4% (95% CI – 22.7%, 41.5%) and 4.9%, respectively, in the 4.0 mg/kg/week group. For elbow flexion, the mean and median percent changes from Baseline were 12.0% (95% CI – 23.2%, 47.2%) and – 0.5%, respectively, in the 2.0 mg/kg/week group and 17.7% (95%. CI – 21.0%, 56.3%) and 20.6%, respectively, in the 4.0 mg/kg/week group.

Home sleep testing - primary treatment phase:

There are no clear trends evident in the data for Week 24 change from Baseline in the Apnea/Hypopnea Index (AHI), minimum O2 saturation, desaturations ≥ 3% per hour, and the Respiratory Event Index (REI).

Adolescent Pediatric Pain Tool (APPT) – primary treatment phase:

The mean (SD) and median Baseline pain intensity scores were 5.0 (2.88) and 5.3, respectively, in the 2.0 mg/kg/week treatment group and 4.1 (2.46) and 4.5, respectively, in the 4.0 mg/kg/week treatment group. At Week 24 there were mean (SD) and median changes from Baseline in pain intensity score (i.e., improvements) of - 2.2 (3.68) and - 0.7, respectively, in the 2.0 mg/kg/week treatment group and - 1.2 (2.87) and - 0.7, respectively, in the 4.0 mg/kg/week treatment group.

Correlation of 6MWT and 3 MSCT with other secondary endpoints – primary treatment phase:

Correlations between 6MWT and 3MSCT and other secondary variables were estimated at Baseline and Week 24 using the Pearson correlation coefficient for each pair of either 6MWT or 3MSCT and the individual secondary endpoints of VO2 max, ECHOs, RFTs, muscle strength, pain, and urinary KS levels. The purpose of this analysis was to explore which variables contributed to performance on the 6MWT and 3MSCT.

The strongest observed relationships (negative or positive) in the 2.0 mg/kg/week treatment group were between change in the 3MSCT and changes in the 6MWT (r=0.70), muscle strength/knee extension (r=0.58), muscle strength/knee flexion (r=0.50), and WGRS pain intensity (r= − 0.47). The strongest relationships observed in the 4.0 mg/kg/week treatment group were between change in the 6MWT and changes in muscle strength/knee flexion (r=0.69) and WGRS pain intensity (r=− 0.50), and between change in the 3MSCT and changes in ejection fraction (0.71), VO2max (r=0.52), and muscle strength/knee flexion (r=0.45).

Patient Impression Questionnaire (PIQ) – primary treatment phase:

The self-assessed walking ability relative to the beginning of treatment showed improvement in both treatment groups. No subjects reported reduced walking strength, and 15 of 24 reported increased walking strength (10 of 14 in the 2.0 mg/kg/week group and 5 of 10 in the 4.0 mg/kg/week group). The PIQ walk strength results appear to be inconsistent with the results for the associated 6MWT, where 12 of the 24 evaluable subjects had Week 24 walk distance declines. The apparent inconsistency could be explained by the fact that the PIQ asked subjects to rate their strength walking a 30 meter hallway 1 or more times while the 6MWT lasted from a minimum of 255 meters to nearly 600 meters. The self-assessed stair climbing and breathing strength relative to the beginning of treatment also showed improvement in both treatment groups, with only one subject reporting a decline in stair climbing strength and no subjects reporting a decline in breathing strength.

Biochemical markers of bone and cartilage metabolism:

Serum samples were analyzed for levels of procollagen type IIA N-propeptide (PIIANP) and type I collagen C-telopeptides (CTx). The mean (SD) and median Baseline levels of PIIANP were 3456.6 (1364.17) and 3323.6 ng/mL, respectively, in the 2.0 mg/kg/week group and 2558.6 (993.70) and 2363.7 ng/mL, respectively, in the 4.0 mg/kg/week group. At Week 52 the mean (SD) and median levels of PIIANP decreased from Baseline in the 2.0 mg/kg/week group by 407.3 (1134.50) and 480.7 ng/mL, respectively, and increased from Baseline in the 4.0 mg/kg/week group by 290.6 (1130.96) and 235.6 ng/mL, respectively.

The mean (SD) and median Baseline levels of CTx were 1.1 (0.52) and 1.1 ng/mL, respectively, in the 2.0 mg/kg/week group and 1.8 (0.62) and 1.6, respectively, in the 4.0 mg/kg/week group. At Week 52 the mean (SD) and median Baseline levels of CTx decreased from Baseline in the 2.0 mg/kg/week group by 0.3 (0.35) and 0.1, respectively, and decreased from Baseline in the 4.0 mg/kg/week group by 0.4 (0.70) and 0.4, respectively.

Pharmacogenetic analyses

Genetic samples were collected to identify the GALNS mutation and confirm the disease. No specific conclusions can be drawn from the data in this study, but it will be added to data collected in other studies of patients with MPS IVA for further analysis into the genotypic basis of aspects of the disease.

Rapporteur's comment:
In general, the two treatment groups were balanced with regard to baseline characteristics. The study population was generally healthier than in previous studies conducted in this disease, the result of inclusion criteria designed to recruit a study population healthy enough to complete the CPET, muscle strength tests, and other efficacy measures. This is depicted in for instance the baseline measurements of 6MWT; Baseline mean 6MWT ≈ 370 meters in study MOR-008 versus ≈ 205 meters in study MOR-004).

There were no clinical relevant changes from Baseline in walk distance in either dose group at either 12 or 24 weeks, though there was some increase seen at week 52 particularly in the 4.0 mg/kg/week group. This is in contrast to the data from the pivotal study MOR-004 where a statistical significant increase was seen in 6MWT at a dose of 2.0 mg/kg/week. According to the MAH, the baseline distances in the current study are closer to normal and therefore the population included may be less sensitive to detect an effect. Further, the MAH states that according to the ICF the subjects needed to walk at least 200 meters to qualify for the study and this may have been a motivating factor which was not present at 24 weeks or 52 weeks. This appears a reasonable explanation.

A numerical improvement from Baseline in 3MSCT was seen in the 4.0 mg/kg/week treatment group but not in the 2.0 mg/kg/week treatment group. This was seen at week 24 and appeared stable until week 52. The confidence intervals are overlapping; larger controlled studies would be needed to further investigate this observation.

Further, treatment with BMN 110 led to decreases in mean normalized uKS levels in both treatment groups to comparable median values.

Small and clinically irrelevant improvements were seen in RFTs, growth, muscle strength and pain. Also the CPET data (conducted for 10 subjects in the 2.0 mg/kg/week treatment group and 5 subjects in the 5.0 mg/kg/week treatment group) showed trends of improvement in exercise capacity with treatment and improved aerobic efficiency.

Other endpoints did not show improvements.

Overall, the study does not allow to draw robust conclusions for efficacy, given the small size of the treatment groups and the heterogeneity of the relatively less impaired study population. The lack of a placebo control group limits interpretation as untreated patients may have declined in some or all of these functional assessments during the study period, however, this remains unknown. Of more importance, there are no detrimental effects in terms of efficacy that would counteract the results of the previous studies.

Safety results

Extent of exposure

All 25 subjects received at least one dose of BMN 110 and were included in the safety population. The mean (±SD) duration of BMN 110 dosing was 84.38 (30.054) weeks in the 2.0 mg/kg/week treatment group and 76.00 (27.803) weeks in the 4.0 mg/kg/week treatment group. The mean (±SD) number of study drug infusions was 77.7 (29.52) in the 2.0 mg/kg/week treatment group and 73.4 (27.09) in the 4.0 mg/kg/week treatment group. The mean weekly dose of study drug received was 3.51 ± 0.422 (SD) mg/kg per subject in the 2.0 mg/kg/week treatment group and 3.79 ± 0.236 (SD) per subject in the 4.0 mg/kg/week treatment group. The mean total dose received was 291.46 ± 93.538 (SD) mg/kg

per subject in the 2.0 mg/kg/week treatment group and 282.79 ±89.930 (SD) mg/kg per subject in the 4.0 mg/kg/week treatment group.

Adverse events

The overall summary of adverse events is shown in Table xx. No subject permanently discontinued treatment due to an AE. All subjects reported at least one AE while on study. The most common AEs among subjects in the 2.0 mg/kg/week treatment group were headache (86.7%), vomiting (73.3%), nausea (66.7%), pyrexia (60.0%), pain in extremity (53.3%), and fatigue (53.3%). The most common AEs among subjects in the 4.0 mg/kg/week were headache (70.0%), nasopharyngitis (70.0%), vomiting (50.0%), nausea (50.0%), arthralgia (50.0%) and upper respiratory tract infection (50.0%). The most common AEs reported by the investigator as study drug-related in the 2.0 mg/kg/week treatment group were headache (53.3%), pyrexia (46.7%) vomiting (46.7%), and nausea (40.0%). The most common AEs reported by the investigator as drug-related in the 4.0 mg/kg/week treatment group were headache (40.0%), diarrhea (30.0%), and pyrexia, abdominal pain, cough, dizziness, fatigue, and nausea, all reported by 20.0% of subjects.

Deaths and serious adverse events

No deaths occurred during the study.

There were 7 SAEs experienced by a total of 5 subjects in the study, including a medical device removal, enuresis, umbilical hernia, and genua valga each experienced by 1 subject and possible inflammatory bowel disease and 2 SAEs of worsening kyphoscoliosis experienced by 1 subject. All 7 of the SAEs were judged not related to study drug.

Hypersensitivity and infusion associated reactions

Infusion with any biologic agent poses a risk of hypersensitivity events and IARs. There were 8 subjects (53.3%) in the 2.0 mg/kg/week treatment group and 2 subjects (20.0%) in the 4.0 mg/kg/week treatment group with at least one hypersensitivity AE that coded to the Angioedema Standard MedDRA Query (SMQ), whereas there were no subjects in the 2.0 mg/kg/week treatment group and 2 subjects (20.0%) in the 4.0 mg/kg/week treatment group with at least one hypersensitivity AE that coded to the Anaphylactic Reaction SMQ.

At least 1 IAR was reported in all 15 subjects (100.0%) in the 2.0 mg/kg/week treatment group and 10 subjects (100.0%) in the 4.0 mg/kg/week treatment group. No IAR categorized as a SAE was reported in either treatment group. For both the 2.0 mg/kg/week and the 4.0 mg/kg/week treatment groups, headache (66.7% and 50.0%, respectively) was the most commonly reported IAR. The other most commonly reported IARs were nausea (53.3%), vomiting (40.0%), pyrexia (33.3%), fatigue (33.3%) and pain in extremity (33.3%) in the 2.0 mg/kg/week treatment group and vomiting (50.0%), nausea (30.0%), pyrexia (30.0%) and diarrhea (30.0%) in the 4.0 mg/kg/week group. All IARs were mild to moderate in severity, and no IARs led to permanent study drug discontinuation. All subjects who experienced an IAR received and tolerated subsequent infusions.

No clinically significant trends in vital signs, clinical chemistry, hematology, or urinalysis results were observed, and no study subject in either dose group had a shift to a clinically significant abnormal ECG from Baseline to Week 24, 52, or 96.

Table. Overall summary of adverse events (safety population)

	BMN110 2.0 mg/kg/week (n=15)	BMN110 4.0 mg/kg/week (n=10)	All Subjects (n=25)
Any AE	15 (100.0%)	10 (100.0%)	25 (100.0%)
Grade 1	4 (26.7%)	4 (40.0%)	8 (32.0%)
Grade 2	8 (53.3%)	6 (60.0%)	14 (56.0%)
Grade 3	3 (20.0%)	0 (0.0%)	3 (12.0%)
Number of AEs per subject Mean/Median	53.9/50.0	34.0/30.0	48.0/46.0
Any Study Drug-Related AE *	15 (100.0%)	9 (90.0%)	24 (96.0%)
Grade 1	8 (53.3%)	6 (60.0%)	14 (56.0%)
Grade 2	6 (40.0%)	3 (30.0%)	9 (36.0%)
Grade 3	1 (6.7%)	0 (0.0%)	1 (4.0%)
Any SAE	3 (20.0%)	2 (20.0%)	5 (20.0%)
Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 2	2 (13.3%)	2 (20.0%)	4 (16.0%)
Grade 3	1 (6.7%)	0 (0.0%)	1 (4.0%)
Number of SAEs per subject Mean/Median	0.6/0.0	0.2/0.0	0.5/0.0
Any Study Drug-Related SAE *	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any AE Leading to Study Discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any AE Leading to Permanent Study Drug Discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)

AE, adverse event; SAE, serious adverse event.

* AEs that were classified by the investigator as possibly or probably related to study drug.

Mapping was based on MedDRA version 16.1.

Grading (severity) scale based on CTCAE version 4.0 for AE: In MOR-008: 1=Mild; 2=Moderate; 3=Severe or Undesirable; 4=life Threatening or Debilitating; 5=Death.

Subjects who experienced more than one AE within a category in incidence category were counted once within that category at the highest severity level.

Only treatment emergent adverse events (TEAE) are included.

Pharmacokinetic results

The PK parameters of elosulfase alfa were estimated in the 2.0 mg/kg/week and 4.0 mg/kg/week dose groups at Weeks 0 and 23; PK was not assessed in the extension phase of the study. Mean t1/2 was approximately 6 minutes at Week 0 for both dose groups, and increased to 23.2 and 31.1 minutes at Week 23 for the 2.0 mg/kg/week and 4.0 mg/kg/week dose groups, respectively. Following repeat dosing, AUC0-t and C_{max} increased by 48% and 44%, respectively, at Week 23 compared to Week 0 for the 2.0 mg/kg/week dose group, and 69% and 100%, respectively, at Week 23 compared to Week 0 for the 4.0 mg/kg/week dose group. As dose increased from 2.0 mg/kg/week to 4.0 mg/kg/week, increases in the mean values of both C_{max} and AUC0-t were greater than dose proportional, which indicates that the pharmacokinetics of elosulfase alfa are not linear over this dose range.

Immunogenicity results

Serum samples were collected for immunogenicity testing prior to dose administration at Baseline and during the primary treatment phase at Weeks 2, 4, 6, 12, and 24 (or ETV) and Weeks 52, 78, 96, and 120 (or ETV) in the extension phase. The impact of immunogenicity on safety and efficacy in the extension phase were evaluated to Week 52, the latest timepoint from which data on all subjects was collected.

All subjects in the 2.0 mg/kg/week and 4.0 mg/kg/week dose groups tested positive for anti-elosulfase alfa TAb by Week 6 and remained positive for the duration of the study. In general, there was no evidence of a dose dependent increase in TAb titers in the study.

The overall NAb incidence rate at Week 24 was 86.7% for the 2.0 mg/kg/week dose group and 80% for the 4.0 mg/kg/week dose group. The NAb incidence rate declined to 60.0% in both dose groups at Week 52. Each treated subject in the 2.0 mg/kg/week and 4.0 mg/kg/week dose groups tested

positive for NAb antibodies at least once during the study. Approximately 50% of subjects in both dose groups reverted to negative once they tested positive for NAb.

No subjects tested positive for elosulfase alfa IgE during the study.

No relationship was found between higher antibody titers and the incidence of hypersensitivity adverse events. No consistent associations were evident between anti-elosulfase alfa TAb or NAb responses and 6MWT, 3MSCT, or MVV results in either treatment cohort.
Reductions in uKS were detected despite the development of anti-elosulfase alfa TAb and NAb. Within each dose group, there was little to no difference in the decrease of normalized uKS at each study visit in subjects with TAb titers above or below the mean or with NAb positivity rates of less than 50% or greater than 50% by Week 52.

Evaluation of elosulfase alfa PK parameters (AUC0-t, Cmax, t1/2, CL, Vdss) at Week 23 and TAb titer at Week 24 for the elosulfase alfa 2.0 and 4.0 mg/kg/week dose groups showed no association. Similarly, no association was found between elosulfase alfa PK parameters (AUC0-t, Cmax, t1/2, CL, Vdss) at Week 23 and NAb status at Week 24.

Rapporteur's comment:
The study was initially designed to last for a period of 193 weeks to provide long-term safety data for both dosing regimens, but was terminated early and data until week 52 are presented. The most commonly reported study-drug related adverse events for the total population were headache, pyrexia, nausea and vomiting and these were also infusion associated reactions. No dose effect was seen in the limited population. The adverse events were in general of mild to moderate severity and none of the were SAEs were judged related to study drug. No subjects permanently discontinued treatment due to an AE.

There was no (consistent) association between antibody titers and dose, incidence of hypersensitivity adverse events or efficacy measurements, a comparable finding to the previous studies performed.

Overall, no new or unexpected safety signals were observed from the study and the safety results are consistent with prior studies and the established safety profile for BMN 110.

2.3.3. Discussion on clinical aspects

The primary goal of MOR-008 was to evaluate the safety of 2.0 mg/kg/week and 4.0 mg/kg/week BMN 110. The study design and preliminary data have been discussed within the initial MAA for Vimizim. At that time, safety data were available with mean treatment duration (sd) being 11.6 (4.6) and 10.0 (3.5) weeks for the 2.0 mg/kg/week and 4.0 mg/kg/week BMN 110 dosing group, respectively. No efficacy data were previously submitted.

The study was initially designed to last for a period of 193 weeks to provide long-term safety data for both dosing regimens. During the study, it was decided to transition all patients in the extension phase to 2.0 mg/kg/week, based on the results of the pivotal phase 3 study MOR-004. Further, certain efficacy assessments planned for the extension phase were removed (CPET, MST, APPT, home sleep testing, and PIQ) based upon findings and the analysis of data from other BMN 110 studies. This can be considered acceptable as these were mainly included for exploratory analyses.

The most commonly reported study-drug related adverse events for the total population were headache, pyrexia, nausea and vomiting. The most common adverse events were associated with infusions. There was no indication of an increased AEs/IARs at the higher dose, however no firm conclusions can be drawn given the limited number of patients in each dose group. The adverse events were in general of mild to moderate severity and none of the were 7 SAEs among 5 subjects were judged related to study drug. No subjects permanently discontinued treatment due to an AE.

All patients tested positive for anti-BMN 110 total antibody (Tab) titer or Neutralising antibody (Nab). There was no (consistent) association with dose, incidence of hypersensitivity adverse events or efficacy measurements, a comparable finding to the previous studies performed.

Overall, no new or unexpected safety signals were observed from the study and the safety results are consistent with prior studies and the established safety profile for BMN 110.

The secondary goal of the study was to evaluate the effect of both doses on the 6MWT and 3MSCT and investigate changes in the physiological correlates of these functional tests by assessing exercise capacity (CPET), pulmonary function (RFTs), pain (APPT), and strength (MST). In addition, the study assessed cardiac function, urinary keratan sulfate (uKS) levels, and the PK of both doses of BMN 110.

As stated by the MAH, the secondary efficacy analyses were intended to gather pilot data for potentially generating hypotheses for further study. In addition, through the use of specific assessments such as the CPET, MST and APPT, this study was intended to more precisely characterize some of the baseline characteristics of this segment of the MPS IVA population. However, the limited number of patients included (n=25), the known heterogeneity of the disease, and the explorative character of the study all limit the conclusions that can be drawn from this study in terms of efficacy.

There were no meaningful changes from Baseline in the 6MWT walk distance in either dose group at 24 weeks. Some improvement was seen at Week 52, with mean and median changes from Baseline of +9.0 m and +1.9 m, respectively, in the 2.0 mg/kg/week treatment group and +31.8 m and +22.1 m, respectively, in the 4.0 mg/kg/week treatment group. The MAH argues that the fact that less impaired patients were included as compared to for instance the pivotal study MOR-004 (Baseline mean 6MWT ≈ 370 meters in study MOR-008 versus ≈ 205 meters in study MOR-004) may explain the lack of efficacy. The baseline distances in the current study are closer to normal and therefore the population included may be less sensitive to detect an effect. Further, the MAH states that according to the ICF the subjects needed to walk at least 200 meters to qualify for the study and this may have been a motivating factor which was not present at 24 weeks or 52 weeks. This appears a reasonable explanation.

Some other secondary endpoints did show improvements like 3MSCT, uKS, RFTs, growth, pain and muscle strength. However, other endpoints did not. Although some results did suggest a differential effect with dose, the number of patients are to small to draw firm conclusions. Some exploratory endpoints did not show improvement. Of more importance, there are no detrimental effects in terms of efficacy that would counteract the results of the previous studies.

Overall, for all the efficacy measures, the small size of the treatment groups and the heterogeneity of the relatively less impaired study population precluded a meaningful evaluation of the treatment effect of BMN 110 at both doses. Moreover, the lack of a placebo control group limits interpretation as untreated patients may have declined in some or all of these functional assessments during the study period.

3. Rapporteur's overall conclusion and recommendation

The study does not allow to draw robust conclusions for efficacy, given the small size of the treatment groups and the heterogeneity of the relatively less impaired study population. The lack of a placebo control group limits interpretation as untreated patients may have declined in some or all of these functional assessments during the study period, however, this remains unknown.

There are no detrimental effects in terms of efficacy that would counteract the results of the previous studies.

No new or unexpected safety signals were observed from the study and the safety results are consistent with prior studies and the established safety profile for BMN 110.

Therefore the B/R of Vimizim remains positive.

No changes in the SmPC were proposed by the MAH. Given the confirmative or indistinct results of this study no changes in the SmPC are proposed by the Rapporteur.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

4. Additional clarification requested

None