20 August 2015
EMA/592423/2015
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

International non-proprietary name: elosulfase alfa

Procedure No. EMEA/H/C/002779/P46 004

Note

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

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1. Introduction

On 21 April 21015, 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 following study has been provided: study MOR-006; a Phase 2, Open-label, Multinational Study to Evaluate the Efficacy and Safety of BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome) Who Have Limited Ambulation.

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.

The current procedure consists of a study report on Study MOR-006: a Phase 2, Open-label, Multinational Study to Evaluate the Efficacy and Safety of BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome) Who Have Limited Ambulation

2.3.2. Clinical study

Study MOR-006: a Phase 2, Open-label, Multinational Study to Evaluate the Efficacy and Safety of BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome) Who Have Limited Ambulation.

This study was conducted by 7 principal investigators at 7 study centers in 3 countries.

Data until 96 weeks have been presented. No further data beyond 96 weeks are available since the study has been terminated.

The study start date was 10 August 2012 (first subject consented) and Study end date was 22 October 2014 (last subject visit).

The study report date is 21 April 2015.

Description

The purpose of the MOR-006 study was to evaluate the safety and efficacy of 2.0 mg/kg/week BMN 110 in MPS IVA patients who are ≥ 5 years of age and who have limited ambulation, defined as an nability to walk 30 meters as assessed by the 6-minute walk test (6MWT) performed at the Screening Visit.

Methods

Objective(s)

48-week primary treatment phase

The **primary objective** of the initial treatment phase of the study was:

To evaluate the effect of 2.0 mg/kg/week elosulfase alfa (as defined by the domains of upper extremity function and dexterity, mobility, pain, and self-care and functional abilities) in a patient population that has limited ambulation.

The **secondary objectives** of the initial treatment phase of the study were:

To evaluate the effect of 2.0 mg/kg/week elosulfase alfa

- on respiratory function, as measured by the percent increase from baseline in respiratory function tests (RFTs);
- on sleep apnea.
- on urine keratan sulfate (KS) levels.

in patients with MPS IVA who have limited ambulation

The **safety objective** of the initial treatment phase of the study was to evaluate the safety and tolerability of 2.0 mg/kg/week elosulfase alfa administered for up to 48 weeks in patients with MPS IVA who have limited ambulation.

The **tertiary objectives** of the initial treatment phase of the study were to evaluate the effect of 2.0 mg/kg/week elosulfase alfa

- on cardiac function;
- on growth;
- on bone density
- on spine morphology
- on analgesic medication use
- on endurance

in patients with MPS IVA who have limited ambulation

The **exploratory objective** of the initial treatment phase of the study was to evaluate the effect of 2.0 mg/kg/week elosulfase alfa on biochemical markers of bone and cartilage metabolism in patients with MPS IVA who have limited ambulation.

Additional 96 weeks extension phase (up to 144 weeks)

The **primary objective for extending** the Phase 2 study was to evaluate the long-term safety and efficacy of 2.0 mg/kg/week elosulfase alfa in patients with MPS IVA with limited ambulation.

Study design

Phase 2, open-label, multinational study of patients with MPS IVA who are ≥ 5 years of age and who have limited ambulation, defined as an inability to walk ≥ 30 meters as assessed by the 6MWT performed at the Screening Visit. Subjects who met the other study eligibility criteria and provided informed consent were administered weekly infusions of 2.0 mg/kg/week BMN 110 for a total of 48 consecutive weeks during the initial treatment phase. In addition, subjects could continue into the extension phase of the study for up to an additional 96 weeks of study treatment.

Study population /Sample size

Study population

Patients with MPS IVA who are at least 5 years of age and who have limited ambulation abilities, defined using the 6MWT, were eligible to participate in this study.

Individuals eligible to participate in this study must have met all of the **following criteria**:

- Willing and able to provide written, signed informed consent
- Had documented clinical diagnosis of MPS IVA based on clinical signs and symptoms of MPS IVA and documented reduced fibroblast or leukocyte GALNS enzyme activity or genetic testing confirming diagnosis of MPS IVA.
- Was ≥ 5 years of age at the time of enrollment in the study
- If sexually active, was willing to use an acceptable method of contraception while participating in the study.
- Females of childbearing potential must have had a negative pregnancy test at the Screening Visit and been willing to have additional pregnancy tests during the study.
- Was willing and able to perform all study procedures as physically possible.

Individuals who met any of the following **exclusion criteria** were not eligible to participate in the study:

- Was able to walk ≥ 30 meters as assessed by the 6MWT.
- Had previous hematopoietic stem cell transplant (HSCT).
- Received previous treatment with BMN 110.
- Had a known hypersensitivity to any of the components of BMN 110.
- Had major surgery within 3 months prior to study entry or planned to have a major surgery during the first 24 weeks of the study.
- Used any other investigational product or investigational medical device within 30 days prior to the Screening Visit or required any investigational agent prior to completion of all scheduled study assessments.

- Was pregnant or breastfeeding at the Screening Visit or planned to become pregnant (self or partner) at any time during the study.
- Had a concurrent disease or condition, including but not limited to symptomatic cervical spine instability or severe cardiac disease or complete paralysis due to a spinal cord injury (defined as an inability to move arms and legs), that would interfere with study participation or safety as determined by the Investigator.
- Had any condition that, in the view of the Investigator, placed the patient at high risk of poor treatment compliance or of not completing the study.

Sample size

Approximately 20 subjects were to be enrolled into the study. The sample size of the study was not determined by statistical power consideration since no statistical hypotheses were posed.

Treatments

Subjects were to receive weekly IV infusions of 2.0 mg/kg BMN 110 for up to 144 weeks or until one of the following occurred: the subject withdrew consent and discontinued from the study, the subject was discontinued from the study by the Investigator, or the study was terminated.

As subjects may experience hypersensitivity reactions associated with the administration of BMN 110, all subjects were pretreated with an appropriate dose of antihistamine medication approximately 30 minutes to 1 hour prior to infusion.

Outcomes/endpoints

The criteria for evaluation listed below included all efficacy, safety, and pharmacodynamics parameters included in the study protocol.

Primary Efficacy

- FDT; dexterity
- GPT; upper extremity function
- 25FWT; mobility
- BPI (subjects ≥ 18 years old) or APPT (subjects < 18 years old); pain
- SF-36v2 (subjects > 18 years old) or PODCI (subjects ≤ 18 years old); self-care and functional abilities)

Secondary Efficacy

- Respiratory function tests (FET, FEV1, FIVC, FVC, MVV, TLC [optional])
- AHI
- Urine KS concentration (normalized to creatinine)

Tertiary Variables:

- Echocardiograms (to assess cardiac function)
- Anthropometric measurements (standing height or length, sitting height, knee height, weight)
- DXA scans of the lumbar spine and whole body (bone density)
- Radiographs of the lumbar spine, lower extremities, and hand/wrist (growth plate
- morphology, spine morphology, skeletal deformities, bone age)
- Use of analgesic medications
- CGI
- Patient Impression Questionnaire (PIQ)

- 6MWT (endurance)
- MRI scans of the cervical spine (spine and spinal cord morphology)
- Blood and urine biochemical markers of bone and cartilage metabolism

Safety

- Adverse events (AEs), including serious AEs (SAEs)
- Vital signs
- Echocardiograms
- Electrocardiograms
- Physical examination (including neurological examination)
- Standard clinical laboratory tests (serum chemistry, hematology, urinalysis)
- Concomitant medications
- Immunogenicity testing
- Cervical spine radiography
- MRI scans of the cervical spine

Extension phase

During the extension phase, subjects continued to receive 2.0 mg/kg/week BMN 110 for up to an additional 96 weeks. Subjects continued to complete safety and efficacy assessments through the extension phase, according to the following schedule:

Weekly – vital signs, assessment of AEs, concomitant medications, administration of BMN 110

- Every 4 weeks – weight
- Every 12 weeks – physical examination, Brief Pain Inventory short form or Adolescent Pediatric Pain Tool, Pediatric Outcomes Data Collection Instrument or SF-36v2®
- Every 24 weeks – Functional Dexterity Test, Grip/Pinch Test, 25-Foot Walk Test, Clinical Global Impression (CGI), anthropometric measurements, AHI (for subjects in sleep study), clinical laboratory tests, urine KS and creatinine, urine pregnancy test, immunogenicity tests
- Every 48 weeks – 6MWT, ECG, ECHO, RFTs, blood and urine samples for biomarkers of bone and cartilage metabolism
- Early Termination Visit (Extension Phase) – vital signs; 6MWT; Functional Dexterity Test; Grip/Pinch Test; 25-Foot Walk Test; Brief Pain Inventory short form or Adolescent Pediatric Pain Tool; Pediatric Outcomes Data Collection Instrument or SF-36v2; CGI; anthropometric measurements; ECG; ECHO; radiograph/MRI of cervical spine; radiograph of lumbar spine; radiographs of lower extremities, hand/wrist; respiratory function tests; apnea-hypopnea index; clinical laboratory tests; urinary KS and creatinine; urinary pregnancy test; immunogenicity tests; blood and urine biomarkers; AEs; and concomitant medications

In the event of a severe reaction temporally associated with an infusion, or a reaction requiring cessation of the infusion, blood samples were collected for immunogenicity testing, including C4, serum tryptase, total IgE, and drug-specific IgE. An independent Allergic Reaction Review Board (ARRB), appointed by BioMarin and composed of physicians not directly involved with the study (including at least 1 allergist/immunologist), served in a consultant capacity to BioMarin to, at BioMarin's request, review such reactions and make recommendations regarding prevention and management of further reactions. An internal Data Monitoring Committee (DMC) also acted in an advisory capacity to monitor the safety of BMN 110 in subjects who were participating in MOR-006.

Statistical Methods

Sample Size Determination**:** The sample size of the study was not determined by statistical power consideration, as no statistical hypotheses were posed. In addition to the analyses listed below, additional statistical analyses were performed as deemed appropriate.

Safety Analysis: The analyses of safety included all subjects who received any study drug. Safety was assessed by the incidence of AEs and changes in neurologic examinations, vital signs, ECHOs, ECGs, cervical spine radiographs, MRI, immunogenicity tests, clinical laboratory tests, and concomitant medications. All safety data was summarized descriptively.

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs was summarized by System Organ Class (SOC), Preferred Term (PT), relationship to study drug, and severity. Each clinically significant laboratory result was recorded as an AE.

Efficacy Analysis:

The mITT population included all subjects except the one (0018-6010) who was never dosed in MOR-006. Except where specified, all efficacy evaluations were done on the mITT population.

Primary Efficacy Analysis: All enrolled subjects with at least 1 post-treatment efficacy measurement were included.

Analysis of the domains for upper extremity function (GPT), dexterity (FDT), mobility (25FWT), pain (BPI-short form or APPT), and self-care and functional abilities (PODCI or SF-36v2®) were performed.

Secondary Efficacy Analysis: All enrolled subjects with at least 1 post-treatment efficacy measurement were included in the analysis of RFTs and urinary KS levels. Subjects who met the eligibility criteria for the sleep substudy and who had at least 1 post-treatment measurement were included in the AHI analysis.

Percent change in FET, FVC, FEV1, FIVC, MVV, and optional TLC values from Baseline to each scheduled time point and overall were assessed. For each urinary KS concentration measurement, descriptive statistics were provided for Baseline and all subsequent post-treatment scheduled assessment visits (Weeks 2, 4, 6, 12, 24, 36, 48, 72, 96, 120, 144 or Early Termination Visit [ETV]). Change from Baseline and percent change from Baseline to the post-treatment scheduled assessment visits were also be provided at these time points.

Change from Baseline AHI scores were summarized for subjects who participated in the sleep substudy.

Tertiary Analysis:

Descriptive statistics were provided for growth as determined from anthropometric measurements taken at Baseline and at Weeks 24, 48, 72, 96, 120, and 144 (or ETV). The statistical analysis for all other tertiary endpoints were descriptive.

CHMP comment:

The main objective of the study is to assess the long-term safety and efficacy in patients with MPS IVA with limited ambulation. The large number of primary, secondary and tertiary endpoints may lead to chance findings likely precluding the ability to draw firm conclusions from this study. Furthermore, the study was a single arm study, with all it's limitations. Moreover, the primary endpoints chosen are different from earlier studies, which question the usefulness to draw conclusions.

Results

Recruitment / Number analysed

Of the planned enrollment of 20 subjects, only 16 were ultimately enrolled in MOR-006. The enrollment challenge was partially due to the fact that these subjects tended to have more severe disease, making it more difficult for them to tolerate the required travel and safely carry out the required study assessments.

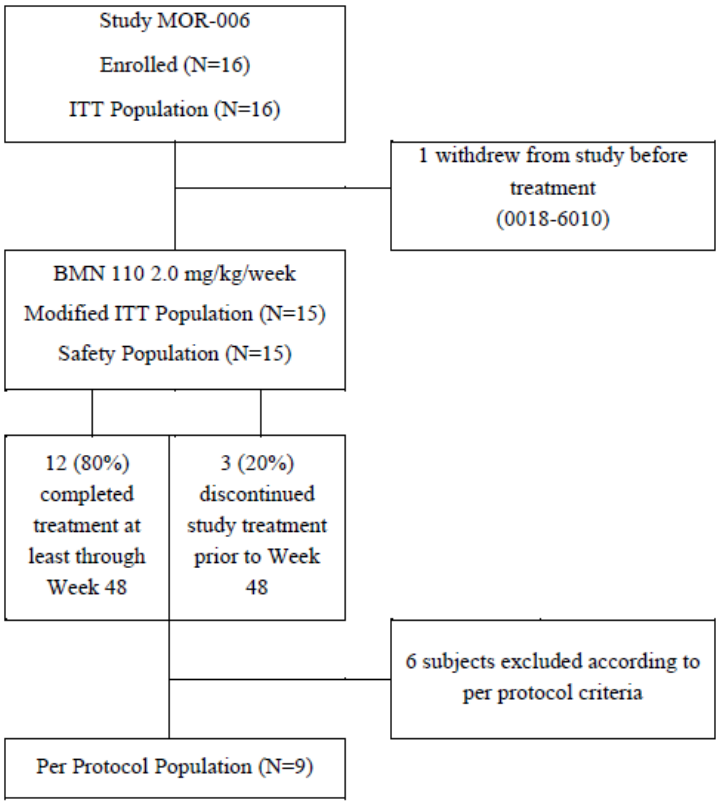
Study MOR-006 began on 10 August 2012; the last subject exited the study on 22 October 2014. Of the 16 subjects who enrolled in MOR-006, 15 received at least one dose of study treatment. The subject who did not receive any study treatment (0018-6010) did so because she could not physically commit to the weekly travel necessary to participate in the study.

Of the 15 subjects treated in MOR-006, 12 completed at least 48 weeks of study treatment.

Three subjects discontinued study drug prior to Week 48, though all 3 remained on the study following drug discontinuation:

- Two subjects (0257-6013 and 0021-6015) experienced serious adverse events (SAEs) related to drug hypersensitivity.
- The third subject (0257-6011) discontinued from study drug after Week 21 because he felt he was having more frequent (non-serious) urinary tract infections during the study; it was recorded as the subject's choice to withdraw from the study treatment, rather than as discontinuation due to an adverse event.

Figure 1. Disposition of subjects



Baseline data

The mean age at enrollment is 20.8 (± 8.67) years. Of the 15 subjects in the mITT population, 9 (60%) were pediatric (< 19 years old), while 6 (40%) were adults. Nine (60%) of the subjects were male. Of the 15 subjects, 7 were non-ambulatory at baseline (meaning that they could not perform the 25FWT). Of the 8 ambulatory subjects, the mean (± SD) speed on the 25FWT test was 40.9 (± 32.76) feet/minute.

Table 1. Baseline characteristics (ITT population)

Demographics	MOR-006 (n = 15)
Age at Enrollment (years)	
n	15
Mean (SD)	20.8 (8.67)
Median	18.7
Min , Max	9.8, 42.4
Age Group	
5-11 years of age	1 (6.7%)
12-18 years of age	8 (53.3%)
≥ 19 years of age	6 (40.0%)
Sex	
Female	6 (40.0%)
Male	9 (60.0%)
Race	
Asian	2 (13.3%)
Black or African American	1 (6.7%)
White	11 (73.3%)
Other	1 (6.7%)
Ethnicity	
Hispanic or Latino	3 (20.0%)
Not Hispanic or Latino	12 (80.0%)

SD, standard deviation.

Table 2: Baseline Characteristics at MOR-006 Baseline (mITT Population)

	MOR-006 (n = 15)
25FWT Speed in Subjects Who were Able to Ambulate (feet/minute)[a]	
n	9
Mean (SD)	40.9 (32.76)
Median	34.7
25th , 75th Percentile	13.5, 70.6
Min , Max	1.2, 88.5
25FWT Number of Subjects Who were Unable to Ambulate[b]	7 (46.7%)
Length (cm)	
n	14
Mean (SD)	99.9 (5.67)
Median	99.7
25th , 75th Percentile	97.0, 102.6
Min , Max	90.2, 110.0
Age at MPS IVA Diagnosis (years)	
n	15
Mean (SD)	6.6 (10.51)
Median	3.0
25th , 75th Percentile	2.7, 4.6
Min , Max	1.4, 42.4
Time since MPS IVA Diagnosis (years)	
n	15
Mean (SD)	14.2 (7.78)
Median	13.8
25th , 75th Percentile	8.0, 21.6
Min , Max	0.0, 27.1

The most common SOCs for which subjects had at least 1 disorder reported as **medical history** were the Musculoskeletal and Connective Tissues Disorder SOC (86.7%) and the Surgical and Medical Procedures SOC (80.0%). The medical history terms of highest frequency were knee deformity and pectus carinatum (each reported in 8 subjects), followed by kyphosis (in 7 subjects), and corneal opacity, body height below normal, and pneumonia (each reported in 6 subjects).

Efficacy results

Primary analyses

The primary analyses were upper extremity function (GPT), dexterity (FDT), mobility (25FWT), pain (BPI-short form or APPT), and self-care and functional abilities (PODCI or SF-36v2®) testing.

- **Dexterity (Functional Dexterity Test: FDT)**

After 48 weeks of treatment with BMN 110, overall the mITT population shows a trend toward increased functional dexterity in both the dominant and non-dominant hand. The increase appears to be sustained through Week 72.

Baseline mean (± SD) speed in the dominant and non-dominant hands was 13.3 (± 10.86) pegs/minute and 13.2 (± 12.49) pegs/minute, respectively. At Week 48, the mean (± SD) speed in

the dominant and non-dominant hands was 17.9 (± 15.18) pegs/minute and 16.8 (± 14.21) pegs/minute, respectively. At Week 48, there is a 23.1% (± 53.88%) increase over baseline in the FDT in the dominant hand, and a 6.0% (± 35.78%) increase in the non-dominant hand. A mean increase of 2.8 pegs/minute (at Week 48) in the dominant hand can also be stated as an increase of approximately 0.047 pegs/second. This rate of increase is generally consistent with the increase observed in developing children (0.04 pegs per second per year of age).

Figure: **Mean Functional Dexterity Test Speed (mITT Population)**

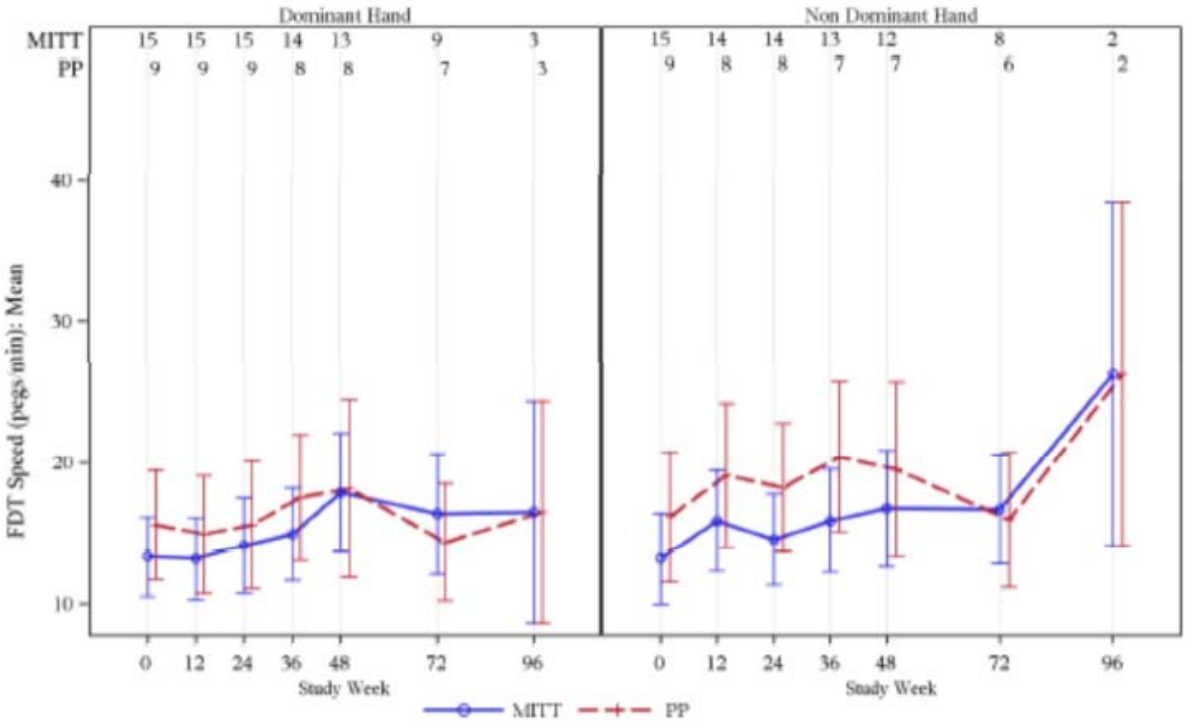


Table: **Descriptive Summary of Functional Dexterity Test (mITT Population)**

	Dominant Hand			Non-dominant Hand		
Study Visit	N	Mean (±SD) Change[a] (pegs/minute) from Baseline	Mean (±SD) % Change[b] from Baseline	N	Mean (±SD) Change[a] (pegs/minute) from Baseline	Mean (±SD) % Change[b] from Baseline
Week 12	15	-0.2 (3.43)	-2.9 (41.37)	14	1.7 (3.23)	11.5 (36.84)
Week 24	15	0.8 (5.38)	1.8 (45.60)	14	0.4 (2.26)	13.8 (32.54)
Week 36	14	1.0 (5.16)	11.2 (48.21)	13	0.9 (3.16)	9.3 (20.55)
Week 48	13	2.8 (8.32)	23.1 (53.88)	12	0.5 (7.10)	6.0 (35.78)
Week 72	9	3.1 (3.79)	37.2 (54.94)	8	0.9 (4.42)	49.3 (126.26)
Week 96	3	1.0 (1.79)	22.5 (42.21)	2	-0.8 (1.13)	-2.0 (2.83)

[a] Change is equal to current value minus the baseline value.

[b] Percent change is equal to 100 times the difference of the current value and baseline value, divided by baseline value.

- **Upper extremity function (Grip/Pinch Test: GPT)**

An electronic grip-strength dynamometer was used in this study to measure grip strength, and an electronic pinch meter was used to measure pinch strength.

After 48 weeks of treatment with BMN 110, overall the mITT population showed no meaningful change in either average grip strength or average pinch strength based on the data available for analysis (n=15). In general, subjects performed better in supported positions than in unsupported for both the pinch and grip test.

Mean grip strength at Baseline was 1.3 (± 0.90) kg (supported) and 1.0 (± 0.77) kg (unsupported) in the dominant hand, and was 1.1 (± 0.85) kg (supported) and 0.9 (± 0.66) kg (unsupported) in the non-dominant hand.

Table: Change from Baseline by Time for Grip Test (mITT Population)

	Dominant Hand				Non-dominant Hand			
Study Visit	N	Mean (±SD) Change[a] (kg) from Baseline Supported	N	Mean (±SD) Change[a] (kg) from Baseline Unsupported	N	Mean (±SD) Change[a] (kg) from Baseline Supported	N	Mean (±SD) Change[a] (kg) from Baseline Unsupported
Week 12	10	0.1 (0.90)	9	0.0 (0.39)	10	0.1 (0.66)	8	0.0 (0.28)
Week 24	10	0.1 (0.89)	9	-0.1 (0.38)	10	-0.0 (0.70)	8	0.1 (0.37)
Week 36	8	-0.1 (0.87)	8	-0.0 (0.56)	8	0.0 (0.73)	8	-0.0 (0.44)
Week 48	9	-0.3 (0.90)	8	-0.1 (0.49)	9	-0.1 (0.66)	8	-0.1 (0.46)
Week 72	6	-0.1 (0.33)	5	-0.1 (0.42)	6	0.1 (0.79)	5	-0.1 (0.52)
Week 96	3	0.3 (0.23)	3	0.1 (0.10)	3	0.4 (0.87)	3	0.5 (0.78)

Mean pinch strength at Baseline was 0.6 (± 0.36) kg (supported) and 0.5 (± 0.37) kg (unsupported) in the dominant hand, and was 0.5 (± 0.39) kg (supported) and 0.5 (± 0.37) kg (unsupported) in the non-dominant hand.

Table: Descriptive Summary of Pinch Test (mITT Population)

Study Visit	Dominant Hand				Non-dominant Hand			
	N	Mean (±SD) Change[a] (kg) from Baseline Supported	N	Mean (±SD) Change[b] (kg) from Baseline Unsupported	N	Mean (±SD) Change[a] (kg) from Baseline Supported	N	Mean (±SD) Change[b] (kg) from Baseline Unsupported
Week 12	9	0.0 (0.26)	9	0.0 (0.19)	9	0.1 (0.21)	9	0.1 (0.20)
Week 24	9	-0.1 (0.32)	9	0.0 (0.13)	9	-0.0 (0.18)	9	0.1 (0.17)
Week 36	8	-0.0 (0.22)	9	-0.1 (0.32)	8	0.0 (0.19)	9	-0.0 (0.34)
Week 48	9	-0.0 (0.30)	9	-0.0 (0.15)	9	0.0 (0.27)	10	0.0 (0.19)
Week 72	7	-0.1 (0.23)	6	-0.0 (0.20	7	-0.1 (0.31)	7	0.0 (0.27)
Week 96	1	-0.6	2	-0.2 (0.27)	2	-0.3 (0.36)	2	-0.0 (0.06)

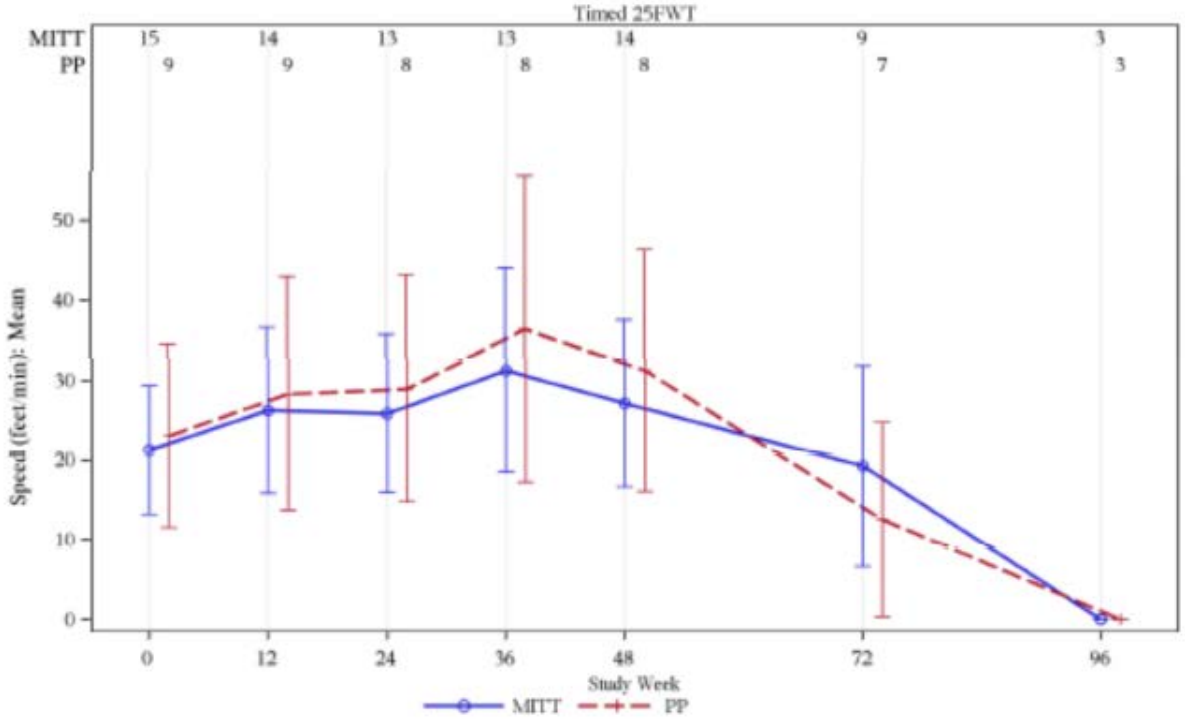
- **Mobility (25-Foot Walk Test)**

The 25FWT is an assessment of mobility and leg function performance based on a timed 25-foot walk. Subjects could use assistive devices when doing this task. In addition, subjects could “walk” (walk, crawl, or roll) on their knees if this was their usual method of ambulation.

At Baseline, 8 of 15 (53.3%) subjects were physically able to perform the 25FWT, either using a walking aid or unassisted. Of the subjects who were able to perform the 25FWT, 3 walked (1 with the assistance of a walking device), 2 crawled, 1 walked on his knees, 1 rolled, and 1 pulled herself along using only her arms. Subjects who were physically unable to performed the test were scored as zero.

At Week 48, there is a 53.5% (± 102.74%) improvement in speed (in feet/minute) of the 25FWT compared with Baseline, and a 48.3% (± 145.01%) improvement at Week 72. In a study of subjects with multiple sclerosis, an increase of more than 20% in the Timed 25FWT was said to be a clinically meaningful improvement. The subset of subjects (n=8) who had a Baseline 25FWT distance > 0 meters (ie, the subset of subjects who were physically capable of performing the 25FWT at Baseline) had a larger absolute numerical improvement in performance on the Timed 25FWT at Week 48 than was seen in the mITT population as a whole.

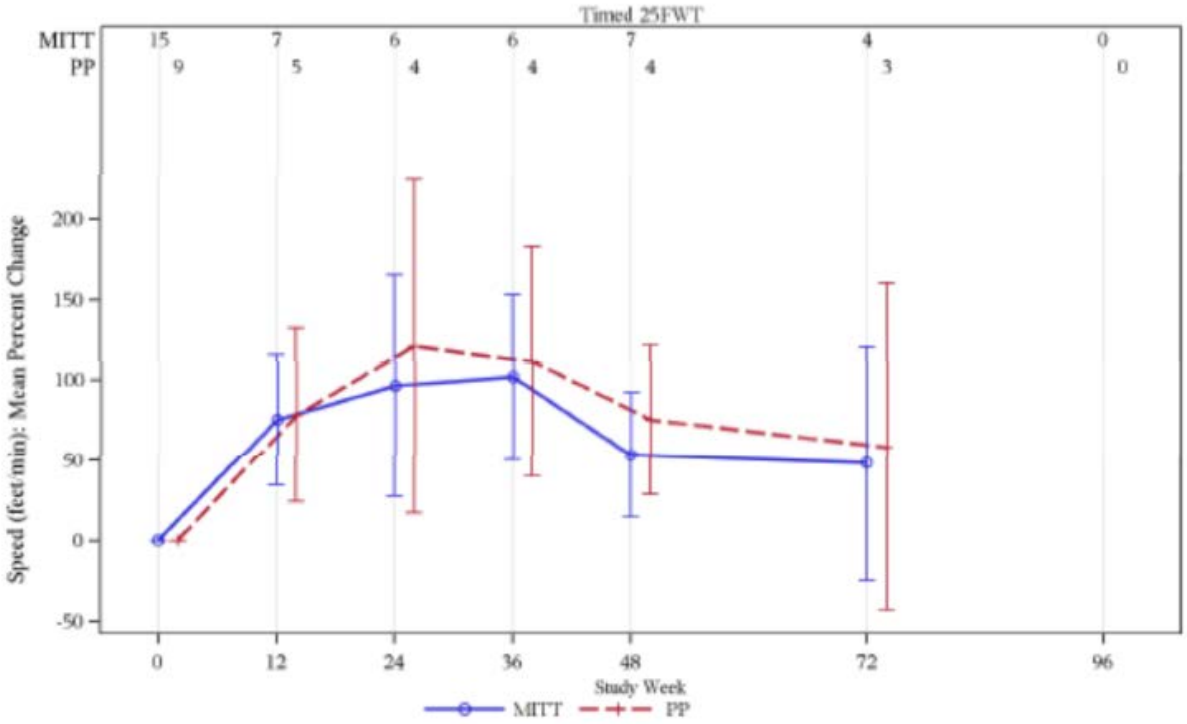
Figure : 25FWT Mean Speed (mITT Population) Visits that Had Ambulation Methods and Walking Aids Consistent with Baseline



All subjects at Week 96 were physically unable to perform the Timed 25FWT.

The subset of subjects (n=8) who had a Baseline 25FWT distance > 0 meters (i.e., the subset of subjects who were physically capable of performing the 25FWT at Baseline) had a larger absolute numerical improvement in performance on the Timed 25FWT at Week 48 than was seen in the mITT population as a whole.

Table: Timed 25FWT Speed: Mean Percent Change from Baseline Visits that Had Ambulation Methods and Walking Aids Consistent with Baseline (mITT Population)



- **Pain (BPI-short form or APPT)**

Pain was assessed using one of two tools, based on the age of the subject:

- The Brief Pain Inventory (BPI) was the tool used for assessing adult subjects (n=8)
- The Adolescent Pediatric Pain Tool (APPT) was used for assessing pediatric or adolescent subjects (n=7).

- **Pain (BPI-short)**

The BPI was developed to provide information on the intensity of pain (the sensory dimension), as well as the degree to which pain interferes with function (the reactive dimension). The BPI was administered to subjects ≥ 18 years old (n=8) every 12 weeks during the study.

At Baseline, 2 subjects reported no pain, 3 reported mild pain, 2 reported moderate pain, and 1 reported severe pain. Overall, adult subjects who were assessed using the BPI showed minimal change between Baseline and Week 48 on any of the scales being assessed, with the possible exception of a small decrease in pain interference with function.

At Week 48:

- Two subjects with mild pain at Baseline now reported no pain, and 1 subject with moderate pain reported mild pain. One subject reported that his ¡§worst¡¨ pain had increased from mild to moderate, and 5 subjects (increased from 3) now reported ¡§non-trivial¡¨ pain.
- For pain interference with function, the average change from Baseline was -0.9 (¡Ó 1.25) (on a 0-10 scale).
- For worst pain in the last 24 hours, the average change from Baseline was +0.3 (¡Ó 0.46) (on a 0-10 scale). No subjects reported any change in their worst pain in the last 24 hours categories between Baseline and Week 48.

- Subject 1099-6012 had large variances in BPI scores across visits and contributed to the fluctuation of the change from Baseline across timepoints. In the per-protocol analysis, when Subject 1099-6012 is removed, the mean change from Baseline is consistently less than 0 during the primary treatment phase, indicating reduced pain in subjects.

- **Pain (APPT)**

The Adolescent Pediatric Pain Tool (APPT) is a validated, multidimensional tool to evaluate pain in children, adolescents, and young adults. The APPT assesses pain on 3 scales: the location(s) of the pain, the severity of the pain, and the subject's use of descriptive terms (from a list of 67 possibilities) to describe his/her pain. The APPT was administered to pediatric/adolescent subjects (n=7) every 12 weeks during the study.

At Baseline, 6 (85.7%) of the 7 subjects assessed reported some pain; the most common sites of pain were the lower torso, abdomen, buttocks, and groin (5 subjects), the chest and back (3 subjects), and lower extremities (2 subjects). The intensity of pain overall was reported as no pain in 2 subjects, mild in 2 subjects, moderate in 2 subjects, and severe in 1 subject. Subjects on average selected 6.7 (± 4.61) descriptive pain words to describe their pain (or 10% of all possible words).

Despite some variability, pediatric/adolescent subjects who were assessed using the APPT did not appear to show any meaningful improvement during the study on either the Words Graphic Rating Scale or the Total Words scale.

At Week 48:

- Two subjects reported pain at fewer locations than at Baseline, 2 reported pain at more locations, and 1 reported no change

- For intensity of pain, the average change from Baseline was +1.8 (¡Ó 3.53) (on a 0-10 scale) (Table 14.2.4.3.1). Of the 6 subjects assessed at that visit, 1 had increased from no pain to severe pain, one had increased from mild to moderate pain, and one had decreased from moderate to mild pain (the others showed no change).

- Subjects selected an average of 5.5 (¡Ó 4.93) descriptive words to describe their pain, a 0.3% (¡Ó 4.50) decrease from Baseline.

- **Self-care and functional abilities (PODCI)**

The PODCI is designed for patients ≤18 years old and assesses the overall health, pain, and ability to participate in normal daily activities, as well as in more vigorous activities associated with young people. The eight scales addressed in the instruments offer a broad view of the physical, mental, and attitudinal condition of the young patient. The PODCI was administered to pediatric/adolescent subjects (n=7) and their parents every 12 weeks during the study.

The scale scores were normalized such that a normal individual will have a score of 50 and SD of 10. Among the four physical health calculated scale scores at Baseline, the transfer and basic mobility normative scores are the worst (-147.0 [± 20.93]) and the pain/comfort scale scores are the best (32.2 [± 22.88]). The happiness score is the only calculated domain score in psychological health; the happiness score at Baseline is 42.8 (± 13.77), indicating a close to normal psychological health in MOR-006 subjects.

Overall, subjects' self-reported assessments on the PODCI showed no meaningful change between Baseline and Week 48 on any of the scales being assessed. Similar results were noted on the parents' PODCI assessments.

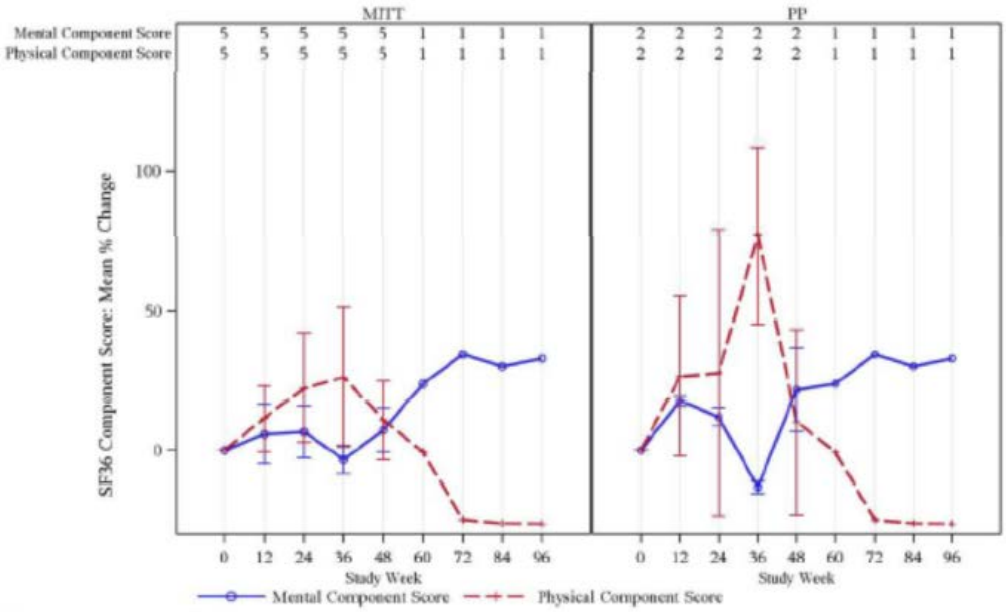
At Week 48, subjects reported a -2.2% (± 20.03) change in the overall global functioning scale normative score, and a -2.7% (± 18.81) change in the happiness scale normative score. Parents reported a -22.3% (± 40.50) change in the overall global functioning scale normative score, and a +0.8% (± 31.80) change in the happiness scale normative score. Cumulative distribution functions (CDF) for the subject's self-reported responses to the PODCI possibly show some improvement at Week 48, particularly in the global functioning and pain/comfort scales. This suggests that, while the overall assessment of PODCI responses shows no change, some subjects are seeing improvement in one or more domains. No meaningful changes are noted in the CDF plot for parent responses to the PODCI.

- **Self-care and functional abilities (SF-36v2®)**

The SF-36 is a validated 36-item questionnaire that yields an 8-scale health profile and summary measures of health-related quality of life. The SF-36 was administered to adult subjects (n=8) every 12 weeks during the study.

Overall, assessments on the SF-36 showed a positive percentage change between Baseline and Week 48 on both the physical and mental health aggregate scores.

Figure: SF36 Component Scores: Mean Change from Baseline



At Week 48, subjects reported a +10.9% (± 31.66) change in the physical health score, and a +7.3% (± 17.24) change in the mental health score. The largest contributor to the increased physical health score came from the physical limitation subscale, where subjects reported a +33.6% (± 33.94) change at Week 48. Subjects' mean mental scores are generally above 50, indicating an above average mental status. This observation is aligned with the higher scores in psychological health domain scales in PODCI.

As with the PODCI, a CDF graph of the responses to the SF36 show that, while the overall results are mixed, some subjects are likely seeing improvement on the physical and/or mental health domains.

Secondary analyses

- **Respiratory Function Tests**: Overall, there were small (8% or less) positive percentage changes for 5 of the 6 parameters (MVV, FVC, FEV1, FIVC, FET, TLC) at Week 48, with absolute measurements showing little to no change.
- **AHI**: A subset of 9 subjects with abnormal overnight pulse oximetry readings at Screening were enrolled in a sleep study. Mean Screening/Baseline AHI for all subjects tested in MOR-006 (n=7) was 14.1 (± 12.49); at Week 48, subjects showed an increase in mean AHI to 28.3 (± 29.28). Mean desaturations of ≥ 3% per hour was 14.6 (± 11.16) at Baseline; the mean increased to 23.7 (± 25.03) at Week 48. Overall, no improvement in sleep apnea was noted after 48 weeks of treatment.
- **Urine KS:** In MOR-006, treatment with BMN 110 for 48 weeks led to a rapid and sustained decrease in urinary KS, which continued in a smaller population at Week 72. At Week 48, urine KS had decreased by a mean of 43.4% (± 24.82%). These findings were consistent with the declines in urinary KS that have been seen in other BMN 110 studies.

Most important tertiary analysis

- **6MWT (6 Minute Walk Test)**

Subjects who could perform the 6MWT during the study were given the opportunity to do soat Screening, Weeks 24 and 48 of the treatment phase, and every 48 weeks during theextension phase. Subjects who were physically unable to perform the 6MWT had thatindicated on their CRFs.

Of the 15 subjects in the mITT population, 3 were physically able to perform the 6MWT atthe Week 24 and/or Week 48 endpoints. One subject (0109-6014) completed the test at Screening/Baseline and Week 48 using the same ambulation/walking aids at each visit; that subject increased his 6MWT distance from 31.7 meters to 66.5 meters at Week 48. All 3 subjects who performed the 6MWT at Week 24 and/or Week 48 were able to complete the test (i.e., were able to perform the test for 6 minutes without stopping early due to pain or other reasons).

CHMP comment:

The study population was generally less healthy than in previous studies conducted in this disease because of limited ambulation, defined as an inability to walk ≥ 30 meters as assessed by the 6MWT performed at the Screening Visit. Consequently the 6 MWT is of less use as an assessment tool and likely therefore not considered as primary endpoint.

The range of primary analyses evaluated demonstrated heterogeneic results. Dexterity and upper extremity function demonstrated different results, with only dexterity by means of the FDT test showing a not so obvious slight trend toward improvement. Such clinically irrelevant improvements have also been observed in previous studies.

The mobility test (25 Foot Walk Test showed some improvement in speed. However, one may argue the relevance of such an observation considering that eventually only one patient was able to perform the (tertiary) endpoint of 6MWT.

Both pain scales did not demonstrate any meaningful effect.

Self-care and functional abilities tests (PODCI and SF-36v2®) showed different results, with only the SF-36 demonstrating some improvement, questioning the relevance of this observation.

Further, treatment with BMN 110 led to decreases in mean normalized Urine KS levels in agreement with other studies.

Overall, the study does not allow robust conclusions for efficacy due to heterogeneous and/or questionable clinical meaningful treatment effects.

Safety results

The mean (± SD) and range of total duration of BMN 110 exposure in MOR-006 were 62.1 (± 31.03) and 5 to 96 weeks, respectively.

The mean (± SD) weekly BMN 110 dose in MOR-006 was 1.7 (± 0.25) mg/kg; the mean (± SD) total BMN 110 dose/subject was 108.7 (± 56.75) mg/kg. One subject missed more than 40% of her scheduled infusions, and 6 other subjects missed between 7 and 18 doses. These missed infusions are the primary reason why the mean weekly dose (1.7 mg/kg) is markedly lower than the 2.0 mg/kg prescribed weekly dose.

None of the 15 subjects who received at least one dose (mITT population) withdrew from the study as a result of adverse events. Two subjects experienced adverse events related to drug hypersensitivity that led to permanent discontinuation of study treatment, though both subjects remained on the study. There were no deaths in the study.

All 15 (100.0%) subjects in MOR-006 had at least 1 treatment-emergent AE, and SAEs were reported for 7 (46.7%) subjects.

The most commonly reported AEs were headache (73.3%), nasopharyngitis (60.0%), and pyrexia (60.0%). Most AEs were reported in only 1 or 2 subjects.

Table. Overall summary of adverse events (safety population)

	MOR-006 (n=15)
Any AE	15 (100.0%)
Grade 1	1 (6.7%)
Grade 2	8 (53.3%)
Grade 3	6 (40.0%)
Grade 4	0
Number of AEs per subject Mean/Median	36.3/25.0
Any Study Drug-Related AE [a]	13 (86.7%)
Grade 1	5 (33.3%)
Grade 2	6 (40.0%)
Grade 3	2 (13.3%)
Any SAE	7 (46.7%)
Grade 1	1 (6.7%)
Grade 2	1 (6.7%)
Grade 3	5 (33.3%)
Number of SAEs per subject Mean/Median	1.1/0
Any Study Drug-Related SAE [a]	2 (13.3%)
Grade 3	2 (13.3%)
Any AE Leading to Study Discontinuation[b]	0
Any AE Leading to Permanent Study Drug Discontinuation	2 (13.3%)
Grade 3	2 (13.3%)
Death	0

Study drug-related AEs were reported for 13 (86.7%) subjects in MOR-006, including 2 subjects who experienced CTCAE grade 3 drug-related AEs (infusion related reaction and hypersensitivity). The most commonly reported related AEs were headache (40.0%), nausea, pyrexia, and vomiting (20.0% each).

Table: AE Incidence in ≥20% of Subjects (Safety Population)

	MOR-006 (n=15)
Subjects with at Least 1 Reported AE	15 (100%)
Headache	11 (73.3%)
Nasopharyngitis	9 (60.0%)
Pyrexia	9 (60.0%)
Diarrhoea	7 (46.7%)
Nausea	7 (46.7%)
Upper respiratory tract infection	7 (46.7%)
Abdominal pain upper	6 (40.0%)
Cough	6 (40.0%)
Vomiting	6 (40.0%)
Arthralgia	5 (33.3%)
Back pain	5 (33.3%)
Nasal congestion	5 (33.3%)
Pain in extremity	5 (33.3%)
Dizziness	4 (26.7%)
Fatigue	4 (26.7%)
Myalgia	4 (26.7%)
Oropharyngeal pain	4 (26.7%)
Pain	4 (26.7%)
Abdominal pain	3 (20.0%)
Lower respiratory tract infection	3 (20.0%)
Poor venous access	3 (20.0%)
Rash	3 (20.0%)
Rhinorrhoea	3 (20.0%)
Sinusitis	3 (20.0%)

Table: Study Drug-Related AEs; Incidence in ≥ 10% of Subjects (Safety Population)

	MOR-006 (n=15)
Subjects with at Least 1 Reported Study Drug-Related[a] AE	13 (86.7%)
Headache	6 (40.0%)
Nausea	3 (20.0%)
Pyrexia	3 (20.0%)
Vomiting	3 (20.0%)
Abdominal pain upper	2 (13.3%)
Hypersensitivity	2 (13.3%)
Rash	2 (13.3%)
Tachycardia	2 (13.3%)

Study drug-related SAEs were reported in 2 (13.3%) subjects. Six subjects experienced a total of 7 grade 3 AEs (poor venous access, hypersensitivity, increased blood bilirubin, cervical cord compression, infusion related reaction, pneumonia mycoplasmal, and respiratory failure). No grade 3 AE was reported in more than one subject. Two of these events (hypersensitivity and infusion related reaction) were assessed as related to study treatment. No subjects experienced a grade 4 event during MOR-006.

Sixteen SAEs were reported for 7 (46.7%) subjects. Four study drug-related SAEs were reported in 2 (13.3%) subjects. No SAE was reported in more than one subject. Most SAEs were consistent with orthopedic disease complications or cannulation difficulties. Six (40.0%) subjects experienced a total of 12 hypersensitivity AEs. With the exception of 2 SAEs of hypersensitivity occurring in the same subject, all hypersensitivity AEs were non-serious. The 12 potential hypersensitivity events were medically assessed against the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) 2006 criteria for anaphylaxis. Of the 12 events, 10 were found to be single events which did not satisfy the NIAID/FAAN criteria. The remaining two events (both in Subject 0020-6005) were reported as grade 2 events of anaphylactic reaction and anaphylactoid reaction; however, the information received from the investigator on these events was insufficient to permit assessment against the NIAID/FAAN criteria. Of note, neither of these events was assessed as severe, both resolved, and the subject remained on the study and continued to receive BMN 110 without the recurrence of similar events.

Six (40.0%) subjects had at least one infusion interrupted or discontinued due to an AE that required medical intervention. Less than 2% of total infusions were interrupted or discontinued due to an AE that required medical intervention. Events were effectively managed with infusion rate changes and medications.

Overall, changes from baseline in clinical laboratory tests were not notable. Clinically significant vital signs and abnormal physical examination findings were reported as AEs. One subject experienced a grade 3 event of increased blood bilirubin (along with non-serious grade 2 elevated ALT), both of which resolved within 2 weeks. Vital signs AEs included pyrexia, tachycardia, body temperature increased, hypotension, sinus tachycardia, and tachypnoea. Most events were grade 1 in severity, and all events were non-serious. Three events of grade 2 pyrexia resulted in infusion interruptions; all resolved within 1-7 days following treatment with antipyretic and/or antibiotic medications.

Eleven subjects (73.3%) reported corneal clouding as part of their medical history at Baseline. Overall, no meaningful change in corneal clouding was noted. No adverse events related to echocardiogram findings were reported during MOR-006. One subject had AE reports of grade 1 first degree atrioventricular block and prolonged PR interval on ECG. The subject was noted to have had complete right bundle branch block and left anterior fascicular block at baseline ECG. Review of shift tables reveals little change in either radiographic or MRI findings.

Deaths

No deaths occurred during the study.

Immunogenicity Results

Serum samples were collected for immunogenicity testing prior to dose administration at Baseline and at Weeks 2, 4, 6, 12, 24, 36, 48, 72, and 96 (or ETV).

All treated subjects (Safety) tested positive for anti-BMN 110 TAb by Week 4 and remained positive for the duration of the study. Each of the three subjects who discontinued study drug prior to Week 48 tested positive for TAb and NAb following treatment initiation. During the initial treatment phase (Baseline to Week 48), mean TAb titers peaked at Week 48 in the Safety and PP populations. Of those subjects that remained on treatment, TAb responses decreased or remained stable in the extension phase (post-Week 48) in 5/9 subjects and increased in 4/9 subjects. All treated subjects tested positive for neutralizing antibodies during the study. Most subjects (11/14, 78.6%) were NAb positive by Week 4. NAb responses were sustained (remained positive once detected) in 9 (60%) and were transiently positive in 6 (40%) subjects. The overall incidence of NAb positivity at Week 48 was 66.7% (10/15). The earliest NAb positive result occurred at Week 2, and the latest time point for a subject to first test positive for NAb was Week 24. No subjects tested positive for BMN 110 IgE during the study.

Despite the universal development of anti-drug antibodies, urine KS decreased from Baseline in all treated subjects. Overall, subjects with higher TAb titers had similar reductions in urine KS at Weeks 24 and 48 compared to subjects with lower TAb titers and no consistent association was detected between TAb titer and percent change in uKS from Baseline. In addition, subjects with higher NAb positivity rates had similar reductions in urine KS at Weeks 24 and 48 compared to subjects with lower NAb positivity rates and no overall association was detected between NAb positivity rate and percent change in uKS from Baseline.

Subjects with higher antibody titers (> mean) at Weeks 24 and 48 did not have a higher incidence of Hypersensitivity AEs compared to subjects with lower antibody titers. There was no relationship between TAb titers and the occurrence of anaphylactic reactions or study drug discontinuation. Due to the exploratory nature of the efficacy assessments performed in this study and the low sample numbers, no analysis was performed to determine the relationship between immunogenicity and efficacy outcomes in MOR-006.

Table: Incidence of Antibody Positivity by Study Visit (Safety Population)

	TAb Titer Positive[a]	NAb Titer Positive[b]
Baseline	3/15 (20.0%)	0/15
Week 2	6/15 (40.0%)	1/15 (6.7%)
Week 4	14/14 (100.0%)	11/14 (78.6%)
Week 6	13/13 (100.0%)	11/13 (84.6%)
Week 12	15/15 (100.0%)	11/15 (73.3%)
Week 24	14/14 (100.0%)	12/14 (85.7%)
Week 36	15/15 (100.0%)	12/15 (80.0%)
Week 48	15/15 (100.0%)	10/15 (66.7%)
Week 72	9/9 (100.0%)	4/9 (44.4%)
Week 96	3/3 (100.0%)	2/3 (66.7%)

[a] TAb (total antibody) titer result equal to or greater than minimum required dilution (1:10)

[b] Positive NAb (neutralizing antibody) screening value

CHMP comment:

All subjects experienced 1 or more AEs, however, only 13% of these events were considered a drug-related SAE. The most commonly reported study-drug related adverse events for the total population were headache, pyrexia, nausea and vomiting, which are known to be associated with BMN 110 treatment. Two subjects permanently discontinued treatment due to an AE (but remained on the study)which can be considered acceptable.

There was no association between antibody titers and incidence of hypersensitivity adverse events or discontinuation, as comparable 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 purpose of the MOR-006 study was to evaluate the safety and efficacy of 2.0 mg/kg/week BMN 110 in MPS IVA patients who are ≥ 5 years of age and who have limited ambulation, defined as an nability to walk 30 meters as assessed by the 6-minute walk test (6MWT) performed at the Screening Visit.

The study population was generally less healthier than in previous studies conducted in this disease because of limited ambulation, defined as an inability to walk ≥ 30 meters as assessed by the 6MWT performed at the Screening Visit. Consequently the 6 MWT is of less use as an assessment tool and likely therefore not considered as primary endpoint.

The range of primary analyses evaluated demonstrated heterogenic results. Dexterity and upper extremity function demonstrated different results, with only dexterity by means of the FDT test showing a not so obvious slight trend toward improvement. Such clinically irrelevant improvements have also been observed in previous studies.

The mobility test (25 Foot Walk Test showed some improvement in speed. However, one may argue the relevance of such an observation considering that eventually only one patient was able to perform the (tertiary) endpoint of 6MWT.

Both pain scales did not demonstrate any meaningful effect.

Self-care and functional abilities tests (PODCI and SF-36v2®) showed different results, with only the SF-36 demonstrating some improvement, questioning the relevance of this observation.

Further, treatment with BMN 110 led to decreases in mean normalized Urine KS levels in agreement with other studies.

Overall, the study does not allow to draw robust conclusions for efficacy, because of heterogeneous and/or questionable clinical meaningful treatment effects.

In terms of safety, 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.

In detail, all subjects experienced 1 or more AEs, however, only 13% of these events were considered a drug-related SAE. The most commonly reported study-drug related adverse events for the total population were headache, pyrexia, nausea and vomiting, which are known to be associated with BMN 110 treatment. Two subjects permanently discontinued treatment due to an AE (but remained on study) which can be considered acceptable. There was no association between antibody titers and incidence of hypersensitivity adverse events or discontinuation, as comparable to the previous studies performed.

3. Rapporteur's overall conclusion and recommendation

The study does not allow to draw robust conclusions for efficacy, due to limitations in study design and the observed heterogeneous and/or questionable clinical meaningful treatment effects . However, there are no efficacy findings that are not in line with 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