ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

BIOMARIN®

Vimizim (elosulfase alfa) for the treatment of Mucopolysaccharidosis Type IVA (Morquio A syndrome)

BRIEFING DOCUMENT FOR THE ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

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ABBREVIATIONS

Abbreviation	Definition
3MSCT	3-minute stair-climb test
6MWT	6-minute walk test
AE	adverse event
ANCOVA	analysis of covariance
ARRB	Allergic Reaction Review Board
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to the time of last measurable concentration
BMN	BioMarin Pharmaceutical Inc.
BMN 110	recombinant human N-acetylgalactosamine-6-sulfatase
BMN 110 2.0 mg/kg/qow	every other week cohort
BMN 110 2.0 mg/kg/week	weekly cohort
°C	degree Celsius
CDF	cumulative distribution function
CI-M6PR	cation-independent mannose-6-phosphate receptor
C_{max}	observed maximum plasma concentration
CL	total clearance of drug after intravenous administration
CSR	Clinical Study Report
CTX1	type I collagen C-terminal crosslinked C-telopeptide
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECHO	echocardiogram
ERT	enzyme replacement therapy
FDA	Food and Drug Administration
FET	forced expiratory time
FEV_1	forced expiratory volume in 1 second
FIVC	forced inspiratory vital capacity
FVC	forced vital capacity
GAG	glycosaminoglycan
GALNS	N-acetylgalactosamine-6-sulfatase
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
IAR	Infusion associated reaction

Abbreviation	Definition
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IgG	immunoglobulin G
ITT	Intent-to-treat
IV	intravenous
KS	keratan sulfate
K_{uptake}	the concentration of enzyme/ligand that yields half the maximal uptake value
LS	least square
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MPS	mucopolysaccharidosis
MPS HAQ	MPS health assessment questionnaire
MPS IVA	MPS IV type A; Morquio A Syndrome
MVV	maximum voluntary ventilation
NAb	BMN 110-specific neutralizing antibodies (that inhibit cellular receptor binding)
PBO	placebo
PIIANP	type IIA collagen N-propeptide
PK	pharmacokinetics
PP	per-protocol
PRO	patient-reported outcomes
qow	every other week
RFTs	respiratory function tests
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQ	Standardised MedDRA Query
SOC	system organ class
$t_{1/2}$	elimination half-life
T_{max}	time to reach C_{max}
TAb	total antibody

Abbreviation	**Definition**
urine KS	urine keratan sulfate
US	United States
V_{dz}	apparent volume of distribution based upon the terminal phase
V_{dss}	apparent volume of distribution at steady state
WHO	World Health Organization

1 EXECUTIVE SUMMARY

BMN 110 is a proposed enzyme replacement treatment for Mucopolysaccharidosis IV Type A (MPS IVA, Morquio A Syndrome), a severely debilitating and progressive disease with an entirely unmet medical need. The disease occurs as a result of a deficiency of activity in an enzyme involved in glycosaminoglycan (GAG) metabolism. The pervasive and progressive accumulation of GAGs leads to significant morbidities and multisystemic clinical impairments resulting in diminished functional capacity, impaired quality of life, and early mortality. The most common features of the disease are progressive skeletal dysplasia, the need for frequent surgical procedures related primarily to musculoskeletal or respiratory dysfunction, and significant limitations in mobility, endurance, and breathing. These patients have no approved treatment options.

In summarizing data from the clinical development program in the marketing application, BioMarin has provided evidence to support the clinical meaningfulness of the treatment effect, the generalizability of the results in the overall patient population, the reliability of the clinical trial data, and the long-term safety and efficacy, thus supporting an overall positive risk-benefit profile in the target patient population.

The pivotal Phase 3 trial, MOR-004, a randomized, double-blind, placebo-controlled study in 176 patients with Morquio A Syndrome, examined two different dose regimens (2.0 mg/kg weekly and 2.0 mg/kg every other week (qow)) infused intravenously compared with placebo. The primary efficacy finding in MOR-004 was that BMN 110, at a dose of 2.0 mg/kg/week, demonstrated a statistically significant improvement at Week 24 in the primary efficacy measure, 6-minute walk test (6MWT) distance, compared with placebo. The modeled treatment effect was 22.5 meters (CI_{95}, 4.0, 40.9; p=0.0174) for this regimen. This result is consistent across a variety of pre-specified sensitivity and subgroups analyses. The 2.0 mg/kg/qow regimen resulted in 6MWT distances comparable to placebo.

While drugs have been approved with both larger and smaller treatment effects on 6MWT in other disease settings, BioMarin has provided evidence to support the position that the observed magnitude of effect is clinically meaningful in Morquio A Syndrome. Data from a large natural history study (MorCAP) indicate that untreated patients with similar baseline characteristics to subjects in MOR-004 decline by approximately 7 meters in their 6MWT distance per year of life. Thus, the observed treatment effect represents a clinically meaningful improvement and a reversal to the unrelenting disease progression and the chronic effects caused by years of damage due to accumulated GAGs.

It has been suggested that a method to assess the meaningfulness of walk improvement is to determine a minimal clinically important difference (MCID), and test for significant improvement by either ruling out the MCID in hypothesis testing or through a responder comparison at an MCID threshold. In response, BioMarin undertook efforts to define *a priori* an MCID that could be applied to Morquio A Syndrome, but no definitive conclusion could be reached. Research on MCID reveals that at lower levels of baseline function, smaller improvements can result in clinically meaningful changes, while at higher levels of function, larger increases may be necessary to achieve the same degree of clinical benefit (Henricson, 2013, PLoS Curr). This principle makes defining a MCID by an absolute threshold difficult in a heterogeneous disease such as Morquio A Syndrome, which presents with a wide spectrum of symptoms and disease severity.

Patients with Morquio A Syndrome present with varying levels of functional endurance. In general these patients perform at approximately 1/3 the level of an age-matched healthy population. In MOR-004, where the baseline mean 6MWT was approximately 200 meters, the mean treatment effect of 22.5 meters represents a clinically meaningful benefit for Morquio A Syndrome patients. Further, across all levels of change as represented by a cumulative distribution function (CDF), clear separation demonstrated consistent advantage of the weekly treatment group from the placebo group across various levels of response.

Additional efficacy findings from the clinical development program were obtained from other tests of endurance, respiratory function, pharmacodynamic measures, and growth. A secondary endpoint of MOR-004, 3-minute stair climb test (3MSCT), was selected on the basis of prior evaluations in related MPS syndromes and results from the Phase 1/2 study (MOR-002). The response in 3MSCT in BMN 110- treated patients observed in the MOR-002 study was not repeated in MOR-004. Although small numerical improvements in stair climbing were observed in the pivotal trial, these changes did not reach statistical significance. It is unknown why the 3MSCT did not parallel the statistically significant improvement in 6MWT distance. Notably, there is substantially less experience with this test from a clinical trial and regulatory standpoint, and due to severe skeletal impairments most Morquio A patients have difficulty climbing stairs.

Evidence of pharmacologic activity of BMN 110 comes from reductions in the pathologic GAGs that accumulate as a consequence of the inherited deficiency of enzyme activity. Moreover, numerical improvements in almost all respiratory function tests, as well as numerical improvements in growth, were observed. In totality, this evidence is supportive of the existence of a treatment effect.

Results from the ongoing open-label Phase 3 extension study, MOR-005, show that patients receiving BMN 110 2.0 mg/kg/week for 72 weeks experienced stable and sustained improvements in 6MWT and 3MSCT, as well as sustained reduction in the pharmacologic marker of urinary KS. In the absence of a placebo control in the extension phase, these data must be interpreted with caution, but the observed long-term durability of effect is clinically meaningful given that progressive decline in endurance and overall function is expected as part of the natural history of Morquio A Syndrome.

The overall data reveal an acceptable safety profile consistent with other approved enzyme replacement therapies. Safety analyses over time show that short-term and long-term treatment with BMN 110 is well tolerated. Evaluation of safety data by duration of treatment showed that the subject-year adjusted incidence of adverse events (AEs) decreased over time. Infusion-associated reactions (IARs) were generally mild to moderate in severity and manageable. No patient in the pivotal Phase 3 study discontinued due to an adverse event, and all of these patients with IARs went on to receive subsequent infusions. Patients will benefit from appropriate prophylaxis and infusion management to reduce infusion-related symptoms. Serious adverse events (SAEs) and hypersensitivity adverse events occurred infrequently, and generally consisted of Morquio A-related symptoms and associated necessary medical/surgical procedures. As of the data cutoff date for the marketing application, only 1 subject in the clinical program has permanently discontinued treatment attributed to an AE, and no deaths have occurred. BioMarin has proposed risk minimization and pharmacovigilance activities to ensure the safe and effective long-term use of BMN 110 and to gain more knowledge about the safety of BMN 110 in the post-authorization setting. These activities will include not only routine pharmacovigilance practices and product labeling focusing on the risk-benefit balance of BMN 110 based on clinical trial experience, but also a voluntary disease registry to collect post-marketing safety experience and further evaluate identified and potential risks. This registry will follow patients for up to 10 years.

In summary, long- and short-term safety and efficacy data derived from the global BMN 110 clinical development program demonstrate clinical benefit and acceptable tolerability of BMN 110 infused at the proposed marketed dose of 2.0 mg/kg/week, and support an overall positive risk-benefit profile in the target patient population. Improvements across a variety of efficacy measures seen in the clinical trials of BMN 110 translate into clinically meaningful benefits to patients with Morquio A Syndrome, in particular when viewed in the context of the unrelenting progressive nature of the disease, the heterogeneity of disease manifestations, the broad age ranges of those affected, and the challenges in reversing the chronic effects caused by years of damage due to accumulated GAGs. Overall the patient populations studied in the BMN 110 clinical development program have disease manifestations

representative of the range of signs and symptoms reported in the literature and similar to characteristics of Morquio A Syndrome patients in a large natural history study representing approximately 10% of the overall patient population. Thus, results from the BMN 110 clinical studies are generalizable to the overall Morquio A Syndrome population.

1.1 MPS-IVA: An Unmet Medical Need

- Mucopolysaccharidosis IV Type A (Morquio A syndrome, MPS IVA) is a rare, severely debilitating, life-threatening inherited disorder caused by mutations of the gene that codes for N-acetylgalactosamine-6-sulfatase (GALNS) lysosomal enzyme.
- Insufficient GALNS activity causes GAGs to progressively accumulate in multiple organs and various tissues.
- Progressive accumulation of GAGs leads to significant morbidities and multisystemic clinical impairments resulting in diminished functional capacity, decreased endurance, impaired quality of life, and early mortality.
- MPS IVA is a heterogeneous disease, characterized most commonly by severe short stature due to a progressive skeletal dysplasia resulting in abnormalities of bones, including those of the hips, knees, chest, forearms, hands, and spine. In addition to extensive skeletal abnormalities, patients also suffer from pulmonary and cardiovascular disease.
- MPS IVA patients have a mean life expectancy of 40 years. Survival in patients with rapidly progressing phenotypes is limited to the second or third decade of life. Rarely, patients with slowly progressing forms of the disorder have been reported to survive beyond 60 years.
- The estimated prevalence of MPS IVA in the United States is approximately 520 to 800 patients.
- There is no approved treatment other than supportive care for MPS IVA. Typical treatments include extensive surgical procedures to mitigate orthopedic and soft tissue abnormalities.

1.2 BMN 110: recombinant human N-acetylgalactosamine-6-sulfatase (rhGALNS)

- rhGALNS is identical to the naturally occurring human lysosomal enzyme in terms of the amino acid sequence and N-linked glycosylation.
- BMN 110 provides exogenous GALNS that is taken up into the lysosomes and catabolizes GAGs.
- BMN 110 is administered intravenously at the proposed dose of 2.0 mg/kg/week.

1.3 Regulatory History

- BioMarin has received formal guidance, at all stages of development, from European and US regulatory health authorities within the context of meetings and written correspondence. BioMarin incorporated feedback from these regulatory agencies into the clinical development program for BMN 110.
- FDA agreed that the 6MWT could be used as a primary endpoint for the pivotal study but recommended that BioMarin define an MCID and analyze the primary endpoint utilizing a responder analysis.
- During development, the FDA commented on the importance of demonstrating the clinical meaningfulness of the treatment effect.
- During the pre-submission meeting, agreement was reached with the FDA regarding the structure and content of the marketing application.
- During review of the marketing application, the FDA has questioned the level of evidence to establish the effectiveness of BMN 110 in the target patient population.

1.4 Nonclinical Development

- The nonclinical pharmacology, pharmacokinetics, and toxicology of BMN 110 were evaluated in five *in vitro* and eleven *in vivo* studies.
- *In vitro* examination of BMN 110 in human Morquio fibroblasts demonstrated a calculated K_{uptake} of approximately 2.5 nM (138 ng/mL) and an intracellular $t_{1/2}$ of approximately 5-7 days. Co-incubation of human Morquio chondrocytes with BMN 110 led to the internalization of BMN 110 and the restoration of GALNS activity in the lysosomal compartment. Intracellular KS clearance after BMN 110 co-incubation was demonstrated using immunofluorescence and capillary electrophoresis.
- The BMN 110 toxicological profile was consistent with that observed in the nonclinical programs of other enzyme replacement therapies (ERTs) such as Naglazyme® and Aldurazyme®. The main findings were related to: 1) anaphylactoid-like reactions observed in the rat that were generally mitigated by the diphenhydramine pretreatment; and 2) the presence of anti-BMN 110 antibodies in all tested species. These reactions were expected since BMN 110 is a heterologous protein.
- The nonclinical data suggest that the above risks associated with the administration of BMN 110 to humans are low and expected to be manageable. The overall nonclinical data support the clinical use of BMN 110 at the proposed dose and interval of 2.0 mg/kg/week.

1.5 Overview of Clinical Development Program

- The BMN 110 clinical development program includes 7 multinational studies conducted in Europe, North America, South America, Asia, and other regions. The study population, which is representative of the global MPS IVA patient population, encompasses the spectrum of age and disease severity. In the placebo-controlled study (MOR-004), 18.6% (n=33) of subjects were enrolled in the US.
- A global longitudinal natural history study (MOR-001, or MorCAP) is being conducted to characterize symptoms and disease progression that are generalizable to all patients. MorCAP has enrolled over 350 patients to date, representing an estimated 10% of the global MPS IVA patient population, and will include 10 years of follow-up. Approximately 20% of the MorCAP patients are enrolled at sites in the United States.
- The clinical development program consists of 7 studies in patients with MPS IVA:

Study Identifier	Design and Brief Description	Dose	Number of Subjects	Status at time of marketing application
MOR-002	Phase 1/2 Open-Label, Dose-Escalation Study	36 week dose escalation (from 0.1 mg/kg/week to 2.0 mg/kg/week), followed by 1.0 mg/kg/week for an additional 36-48 weeks	20	Complete (February 2011)
MOR-100	Open-Label Extension Study	2.0 mg/kg/week	17	Ongoing
MOR-004	Phase 3 Double-Blind Placebo-Controlled Study in subjects with a 6MWT distance between 30m and 325m	Three arms: 2.0 mg/kg/week 2.0 mg/kg/every other week Placebo	177 randomized; 176 dosed	Complete (August 2012)
MOR-005	Phase 3 Extension, Double-Blind followed by Open-Label	Double blind: 2.0 mg/kg/week 2.0 mg/kg/every other week Open-label: 2.0 mg/kg/week	173	Ongoing
MOR-006*	Phase 2 Open-Label study in subjects with limited ambulation	2.0 mg/kg/week	2 enrolled as of 14 September 2012 (20 anticipated total)	Ongoing
MOR-007	Phase 2 Open-Label study in subjects < 5 years of age	2.0 mg/kg/week	15	Ongoing
MOR-008	Phase 2 Double-Blind study in subjects with at least 200m walk distance in the 6MWT	Double-Blind: 2.0 mg/kg/week 4.0 mg/kg/week	25	Ongoing

*As only 2 subjects were enrolled as of the data cutoff date (14 September 2012) no data from MOR-006 were included in the marketing application submission.

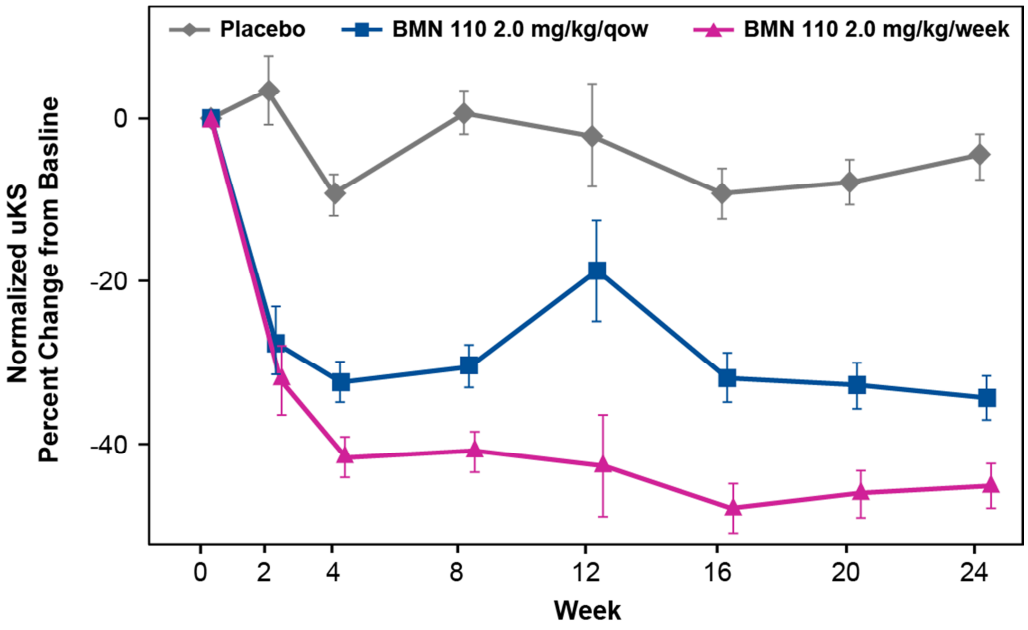
- In addition to the studies listed above:
    - BioMarin has planned a post-approval disease registry intended to track long-term clinical outcomes of patients with MPS IVA.
    - BioMarin has initiated an expanded access program to provide BMN 110 for patients in the US diagnosed with MPS IVA concurrent with the Biologics License Application review for BMN 110.

- As of the date of the marketing application submission, 235 subjects had been exposed to BMN 110, including 86 subjects exposed for at least 48 weeks and 52 subjects exposed at the proposed dose (2.0 mg/kg/week) for at least 48 weeks.
    - Study participation and subject retention was high in all clinical trials, with 98% of subjects either completing the studies or remaining enrolled in ongoing studies, as of the data cutoff date for each study. Of note, in the pivotal MOR-004 study, dosing compliance with infusions performed on schedule exceeded 98%, and very few data points for key efficacy variables, in particular 6MWT, were missing.
- The scope and breadth of this clinical development program exceeds those undertaken by previous ERTs prior to approval.

1.6 Clinical Pharmacology

- Pharmacokinetic (PK) data in subjects with MPS IVA are available for 2 clinical studies (MOR-002 and MOR-004) of BMN 110.
- The mean plasma half-life was approximately 35 minutes at steady state when subjects received IV infusions of BMN 110 2.0 mg/kg/week, and BMN 110 did not accumulate in plasma following weekly dosing. In human Morquio fibroblasts, BMN 110 uptake by cells into lysosomes is most likely mediated by binding to the CI-M6PR. The intracellular half-life was estimated to be 5 to 7 days in these cells.
- Both MOR-002 and MOR-004 showed dose-dependent and/or dose regimen-dependent improvements in PD endpoints (such as urine keratan sulfate (uKS) reduction).
- In MOR-002, mean urine KS concentration (normalized to urine creatinine) consistently declined in a dose-dependent manner during the study. An additional 72 to 84 weeks of treatment at 2.0 mg/kg/week in MOR-100 produced a similar level of reduction in normalized urine KS (mean percent decrease from MOR-002 Baseline to MOR-100 Week 72 was 35.1%).
- In MOR-004, treatment with BMN 110 led to a rapid and sustained reduction of uKS in both active treatment arms (2.0 mg/kg/week and 2.0 mg/kg/qow) when compared with placebo (Figure 1.6.1). The treatment effect on uKS was greater for the weekly regimen (40.7% improvement at Week 24, compared with 30.2% for the qow regimen).

Figure 1.6.1: Model-Based Repeated Measures ANCOVA Mean Percent Change in Normalized Urine Keratan Sulfate (ITT Population – MOR-004)



Placebo	58	58	58	58	57	59	59	56
BMN 110 2.0 mg/kg/week	58	55	56	54	55	55	53	54
BMN 110 2.0 mg/kg/qow	59	59	58	58	58	58	56	57

- There were no consistent trends with regards to subject demographics (gender, race, body weight, and age) on PK.

1.7 Clinical Efficacy

1.7.1 Phase 1/2 (MOR-002)

- **MOR-002** is a completed Phase 1/2, multicenter, open-label, dose-escalation study, designed to evaluate the safety, tolerability, and efficacy of BMN 110 in subjects with MPS IVA. The study enrolled 20 subjects aged 5 to 18 years. Subjects received BMN 110 over a 36-week Dose Escalation period of 12 weeks each of 0.1, 1.0, and 2.0 mg/kg/week, followed by 36-48 weeks of additional treatment at 1.0 mg/kg/week. After concluding the MOR-002 study, subjects were given the option to transition to a long-term extension study (**MOR-100**), during which they were dosed at 2.0 mg/kg/week.
- Seventeen of the 20 subjects enrolled in MOR-002 rolled over into the ongoing MOR-100 extension study. At the time of the marketing application submission, those subjects had completed between 74 and 87 weeks of additional treatment with BMN 110 2.0 mg/kg/week. All 17 subjects remained in the study and on treatment as of the cutoff date for the marketing application.

- In MOR-002, the 6MWT distance increased at Weeks 24 and 36 of the Dose-Escalation Period in conjunction with increasing dose of BMN 110, with the initial increase coming 12 weeks after the dose was changed from 0.1 mg/kg/week to 1.0 mg/kg/week and concomitant with the increase in dose to 2.0 mg/kg/week. The mean change from Baseline was 16.3 meters at Week 24 and 13.8 meters at Week 36. After decreasing the dose in the Continuation Period to 1.0 mg/kg/week, the mean change from Baseline at Week 72 in MOR-002 had decreased to 4.0 meters.
- After 72-84 weeks of treatment with BMN 110 in MOR-002, an additional 84 weeks of treatment in MOR-100 (at 2.0 mg/kg/week) led to sustained improvements in 6MWT distances at most study visits. Overall, the range of 6MWT increase during MOR-100 was consistent with increases seen during the MOR-002 Dose Escalation Period. The decline assessed in 6MWT at Week 72 of MOR-100 was driven primarily by 4 subjects who underwent orthopedic surgery within 4 weeks prior to their Week 72 assessment.
- In MOR-002, the 3-minute stair climb test (3MSCT) mean rate minimally improved from Baseline at end of Week 12, then increased by 6.1 stairs/min at the end of Week 24, and then by 7.8 stairs/min at the end of Week 36. After decreasing the dose in the Continuation Period, the mean change from Baseline at Week 72 was 9.7 stairs/min. These improvements were sustained in MOR-100, with an increase in the 3MSCT rate during the first 24 weeks of MOR-100 at a higher level than during the MOR-002 Dose Escalation Period.
- As the BMN 110 dose increased from 0.1 mg/kg/week to 1.0 mg/kg/week and then to 2.0 mg/kg/week, mean values for C_{max} and AUC_{0-t} increased far in excess of the increase in dose, indicating that the PK of BMN 110 was not linear over this dose range. Mean normalized urine KS consistently declined in a dose-dependent manner during the study.

1.7.2 Phase 3 (MOR-004)

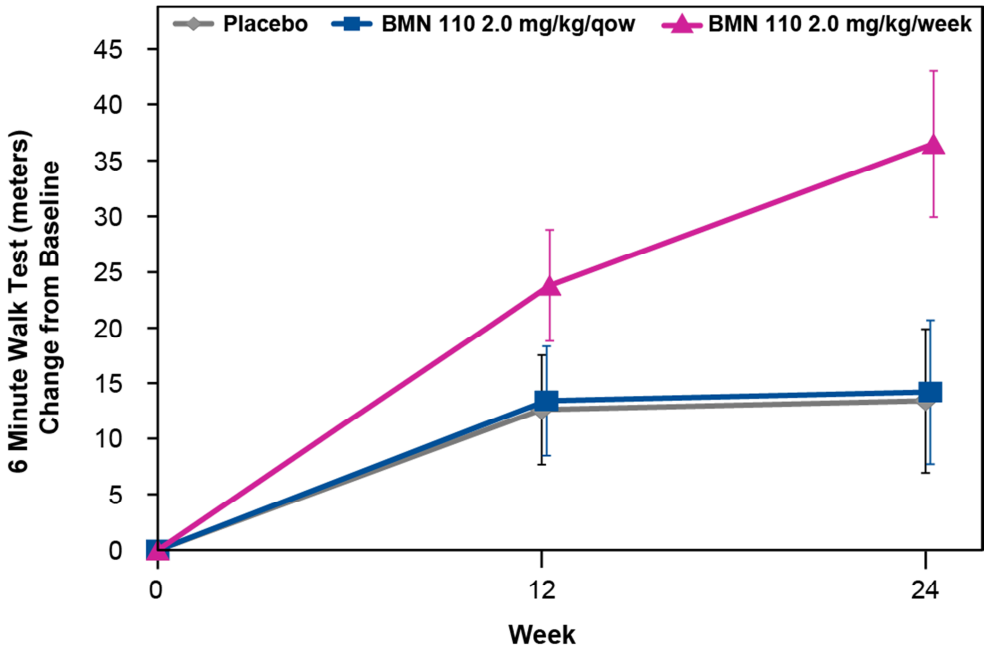
- **MOR-004** is a completed Phase 3, randomized, double-blind, placebo-controlled, multinational study in subjects with MPS IVA, designed to evaluate the efficacy and safety of BMN 110 in a subject population ≥ 5 years of age with a baseline 6MWT distance ≥ 30 and ≤ 325 meters. In MOR-004, subjects received 2.0 mg/kg/week BMN 110 (n=58), or 2.0 mg/kg/qow BMN 110 (n=59), or placebo (n=59), for a total of 24 weeks. The primary endpoint was the change at Week 24 from baseline in 6MWT distance compared to placebo. The secondary endpoints were the change from baseline in the 3 Minute Stair Climb Test (3MSCT) and urine KS levels at Week 24 compared to placebo.
- The study's broad inclusion criteria encompassed a wide spectrum of age and disease severity in the overall patient population, and therefore results are generalizable to patients anticipated to be treated in the post-approval setting.

- A total of 173/176 subjects subsequently enrolled in an extension trial (**MOR-005**), during which they received 2.0 mg/kg of BMN 110 every week or 2.0 mg/kg every other week. All subjects were switched to 2.0 mg/kg/week upon analysis of results from the pivotal study, as prespecified in the protocol.

Primary efficacy response (6MWT)

- MOR-004 met the primary endpoint of change from baseline in 6MWT distance at Week 24. BMN 110 2.0 mg/kg/week demonstrated a statistically significant improvement in 6MWT distance compared with placebo at Week 24. The modeled treatment effect was 22.5 m (CI_{95}, 4.0, 40.9; p=0.0174) for the 2.0 mg/kg/week regimen. The every other week regimen resulted in walk distances comparable to placebo. The repeated-measures ANCOVA analysis supported the Week 24 findings of the primary analysis (refer to Figure 1.7.2.1).

Figure 1.7.2.1: Repeated Measures ANCOVA Mean Change in 6-Minute Walk Test (Intent-To-Treat Population – MOR-004)



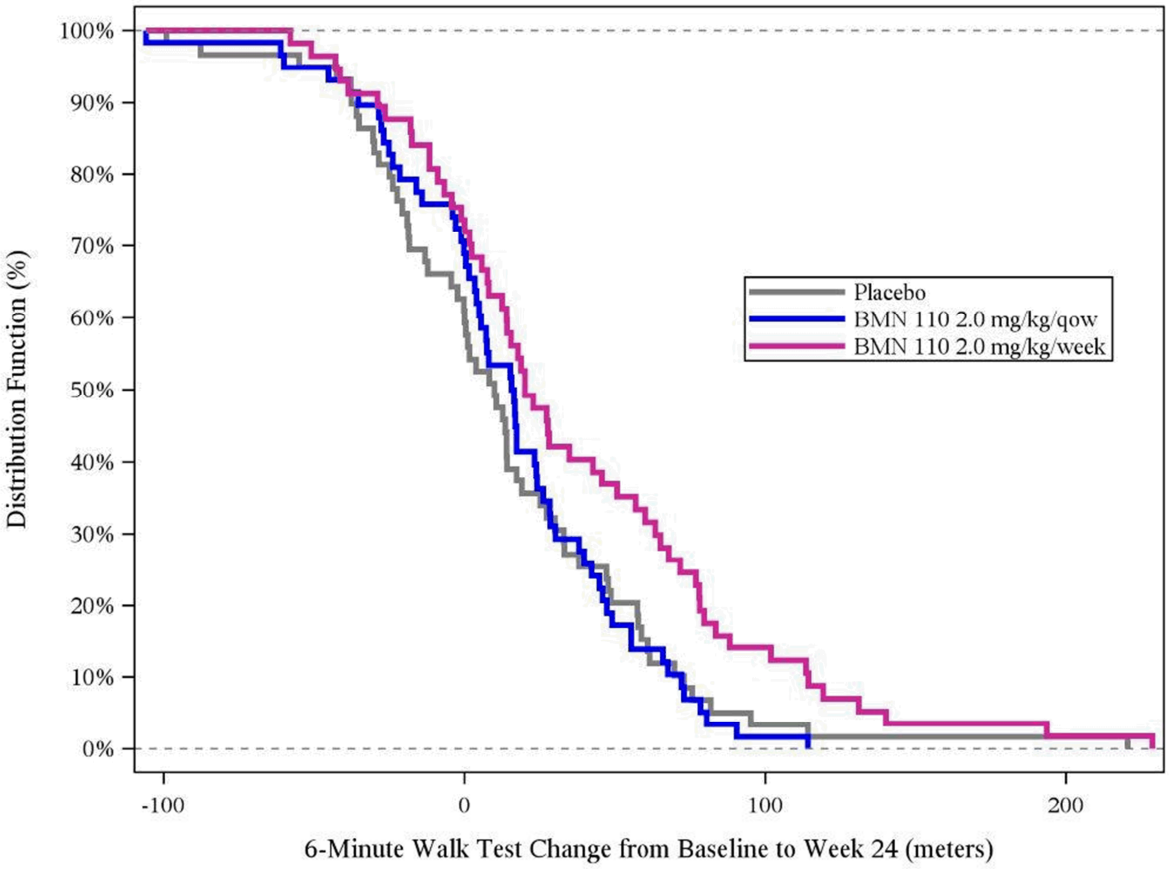
Placebo	59	59	59
BMN 110 2.0 mg/kg/week	58	58	57
BMN 110 2.0 mg/kg/qow	59	59	58

Error bars represent standard error of least squares mean change from Baseline.

qow: every other week

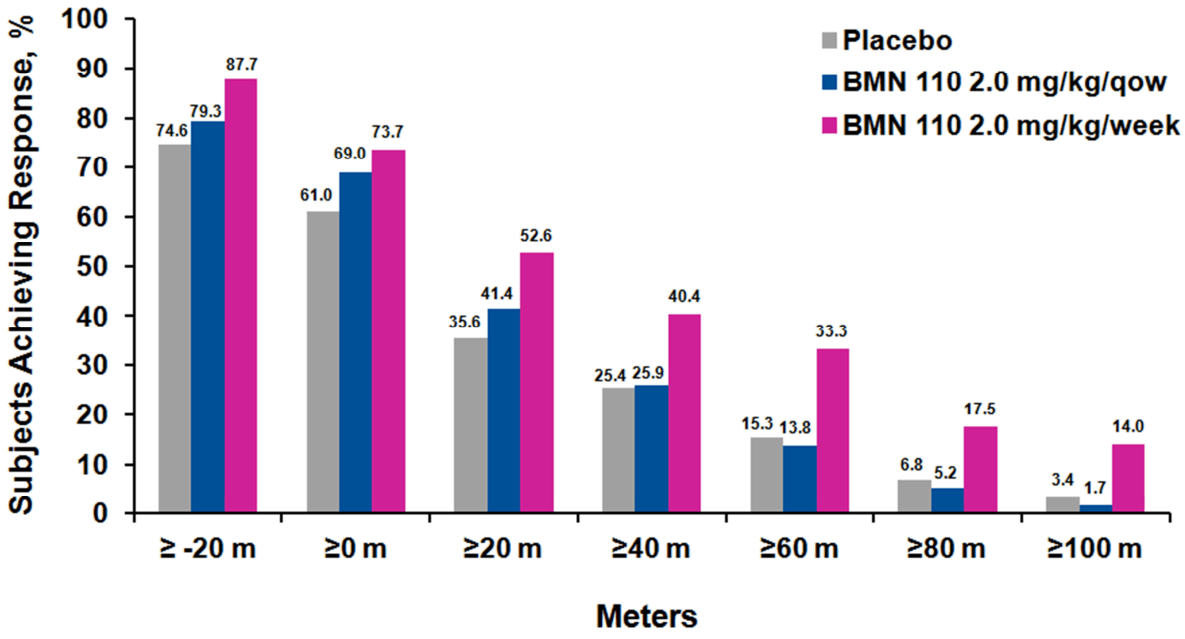
- A cumulative distribution function displays a continuous plot of the change from baseline (in 6MWT distance) on the horizontal axis, and the cumulative percent of subjects experiencing at least that level of change on the vertical axis. A responder analysis based on the cumulative distribution function in the placebo and BMN 110 2.0 mg/kg groups is shown in Figure 1.7.2.2. This analysis shows clear separation of the BMN 110 2.0 mg/kg/week treatment group from the placebo group across various levels of response. The curve for the BMN 110 2.0 mg/kg/qow treatment group is similar to the curve for placebo.

Figure 1.7.2.2: Responder Analysis of 6-Minute Walk Test Distance: Cumulative Distribution for Change from Baseline to Week 24 (Intent-To-Treat Population – MOR-004)



- A bar chart based on the cumulative distribution function and summarizing percentage of subjects achieving a response across baseline performance thresholds is provided in Figure 1.7.2.3. This analysis shows that, compared with placebo, a higher proportion of subjects who received BMN 110 2.0 mg/kg/week achieved greater improvement in 6MWT distance across various levels of response and that the BMN 110 2.0 mg/kg/qow treatment group results were similar to placebo.

Figure 1.7.2.3: Responder Analysis for 6-Minute Walk Test (Intent-To-Treat Population – MOR-004)



qow, every other week. Based on observed data at Week 24.

Change is calculated as Week 24 6MWT – Baseline 6MWT.

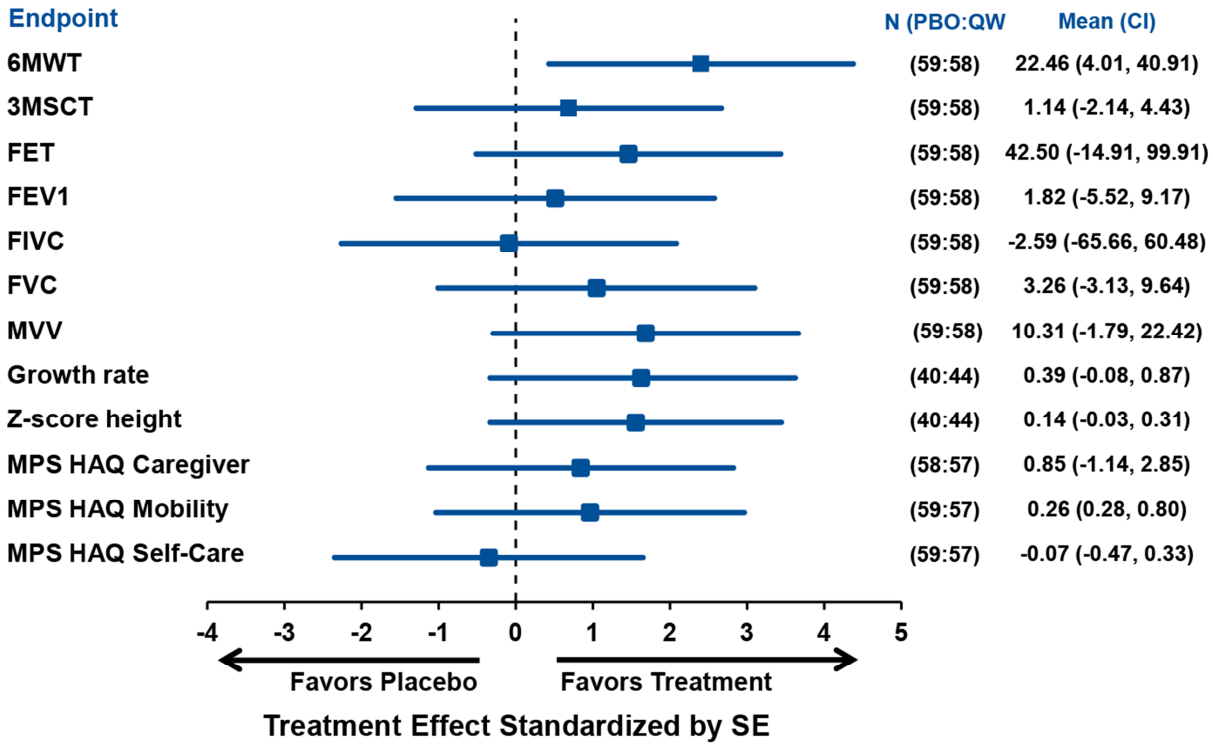
- Results of prespecified per protocol, supportive, sensitivity, and subgroup analyses were consistent with the primary analysis, confirming the robustness of the primary outcome. Treatment effects were similar to the overall group, regardless of Baseline 6MWT category, age, sex, race, or geographic region. Sensitivity analyses confirmed that duplicate 6MWTs performed on two separate days at each visit; missing data; presence of outliers; or the interactions of treatment and time point, age stratification, or Baseline 6MWT stratification did not affect efficacy conclusions.

Secondary Endpoints (3MSCT and uKS) and Other Measures of Efficacy

- The following analyses did not reach statistical significance according to the pre-specified multiplicity adjustments of the statistical analysis plan. Therefore, these analyses are considered exploratory in nature.

- The modeled treatment effect in stairs climbed per minute, compared to placebo, was 1.1 stairs/min (CI_{95}, -2.1, 4.4; p=0.4935) for the 2.0 mg/kg/week regimen. It is unknown why the 3MSCT did not parallel the statistically significant improvement in 6MWT distance. Notably, there is substantially less experience with this test from a clinical trial and regulatory standpoint, and due to severe skeletal impairments most Morquio A patients have difficulty climbing stairs.
- In MOR-004, treatment with BMN 110 led to a rapid and sustained reduction of urine KS in both treatment arms (Figure 1.6.1). The estimated treatment effect at Week 24, compared with placebo, was -40.7% (CI_{95}, -49.0, -32.4) for the BMN 110 2.0 mg/kg/week regimen and -30.2% (CI_{95}, -38.5, -22.0) for the 2.0 mg/kg/qow regimen.
- MVV and forced vital capacity (FVC) numerically improved in the active treatment cohorts of MOR-004 compared to placebo.
- Both BMN 110 dosing regimens showed a numerical improvement for normalized standing height and growth rate in subjects expected to have open bone growth plates (males ≤ 18 years and females ≤15 years).
- Treatment with BMN 110 2.0 mg/kg/week, compared with placebo, showed numeric improvements for almost all secondary and tertiary endpoints (Figure 1.7.2.4).

Figure 1.7.2.4: Summary of Treatment Effect of BMN 110 Weekly on Efficacy Endpoints (Analysis Population – Intent-to-Treat (MOR-004))



Efficacy in subpopulations

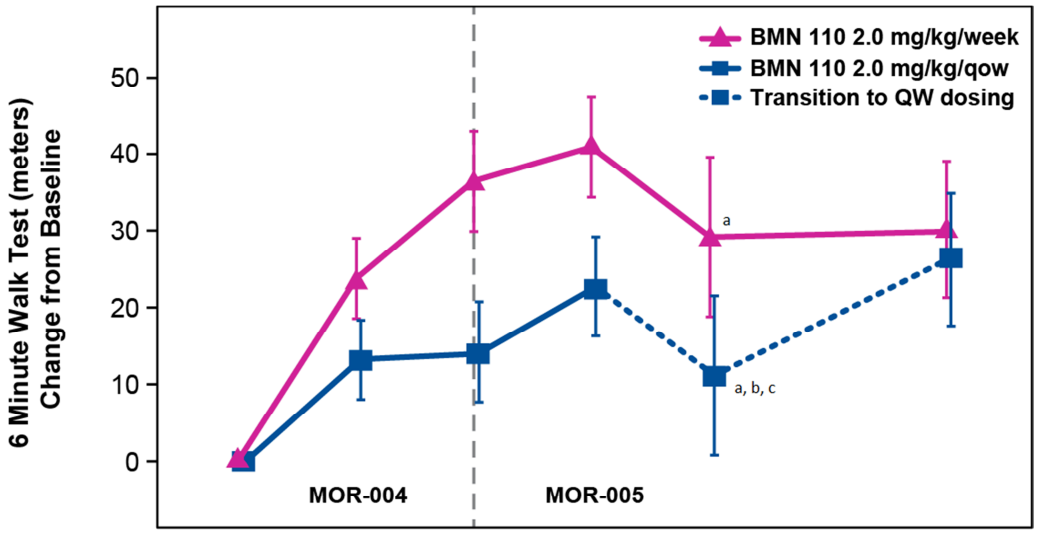
- In MOR-004, results were assessed in sub-populations based on screening 6MWT categories (≤ 200 meters and > 200 meters), age group at baseline (5-11, 12-18, ≥ 19 years), sex (female vs. male), race (White vs. non-white), and region (North America, Europe, other).
- Overall, the pre-specified subgroup analyses showed treatment effects similar to the overall group, regardless of age, sex, race, or geographic region, or Baseline 6MWT category, and consistently supported the 2.0 mg/kg/week dose regimen.

1.7.3 Efficacy with Extended Therapy (MOR-100 and MOR-005)

- Improvements in 6MWT observed with BMN 110 treatment at 2.0 mg/kg/week in MOR-002 and MOR-004 were generally sustained during the extension periods. This long-term improvement is clinically important, given that further declines in walking distance would be expected based on the natural history of MPS IVA (Montano, 2007, J Inherit Metab Dis), (Harmatz, 2013, Mol Genet Metab).
- In MOR-100, the extension study from subjects who completed the Phase 1/2 study MOR-002, treatment with BMN 110 for nearly 3 years resulted in sustained efficacy and in some cases further improvement in functional measures (such as the 6MWT) over time with no change in safety or tolerability, further supporting the proposed dose of 2.0 mg/kg/week.
- As of the most recent data cut-off date of 3 September 2013, continued treatment with BMN 110 in MOR-005, the extension study from subjects who completed the Phase 3 study MOR-004, showed a stable and sustained improvement in 6MWT distance in the continuously treated weekly (QW-QW) cohort in the ITT population at Week 72 from Baseline of MOR-004 (Figure 1.7.3.1). An examination of the 6MWT in the per protocol (PP) population (defined as the subset of the ITT population who were compliant with the requirements of the protocol) also demonstrates a sustained treatment effect in 6MWT at Week 72.
    - MOR-005 was designed in two parts. Part 1 (completed 30 November 2012) was a randomized double-blind study that continued until the primary analysis of MOR-004 was complete. Part 2 (initiated 1 December 2012) is an ongoing open-label study with a single dose regimen of BMN 110 (2.0 mg/kg weekly) that was selected on the basis of results from MOR-004 and the recommendation of the Data Monitoring Committee (DMC).

- As a result of the different assessment schedules in Part 1 and Part 2, not all subjects completed Week 48 endurance assessments. Upon the start of Part 2 of MOR-005,subjects in the PBO-QOW and QOW-QOW cohorts began receiving 2.0 mg/kg weekly; the specific timepoint of transition for each subject was different, depending on their date of study enrollment, but most subjects transitioned between Week 36 and Week 72. The Week 48 results include only subjects who reached Week 48 while still in Part 1 of the study (and thus includes only subjects still receiving QOW dosing); there was no Week 48 endurance assessment in Part 2.
- All subjects are included at the Week 72 timepoint; at the time of the Week 72 assessments, almost all (163/168) subjects in MOR-005 were receiving weekly dosing.

Figure 1.7.3.1: Analysis of 6MWT: Repeated Measures Model
Analysis Population: ITT Population (MOR-004/MOR-005)

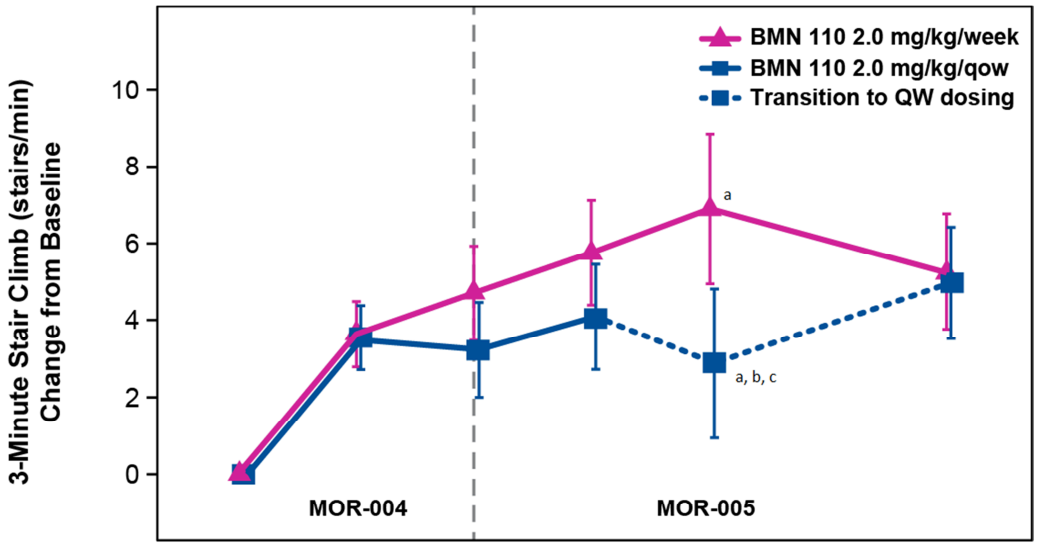


BMN 110 2.0 mg/kg/week	58	58	57	54	27	54
BMN 110 2.0 mg/kg/qow	59	59	58	58	26	56

Model based means (LSMEAN) and standard error bars displayed.
Model: Change from Baseline = age group + baseline walk category + treatment + visit + trt*visit, unstructured covariance matrix
[a]Due to different assessment schedule in Part 2, not all subjects have Week 48 endurance assessments available.
[b]With start of Part 2 of MOR-005 (01DEC2012), subjects in QOW-QOW cohort began receiving 2.0 mg/kg weekly; the specific time of transition for each subject depended on date of study enrollment, ranging from Week 36 to Week 72.
[c]Week 48 results for the QOW-QOW cohort include only subjects who reached Week 48 while still in Part 1 of the study as there was no Week 48 endurance assessment in Part 2. Thus for the QOW-QOW cohort, this time point includes data only from subjects still receiving QOW dosing.

- Continued treatment with BMN 110 in MOR-005 showed a stable and sustained improvement in 3MSCT in the continuous treated weekly (QW-QW) cohort in the ITT population at Week 72 from Baseline of MOR-004 (refer to Figure 1.7.3.2); this improvement was also maintained in the PP population at Week 72.

Figure 1.7.3.2: Analysis of 3MSCT: Repeated Measures Model
Analysis Population: ITT Population (MOR-004/MOR-005)

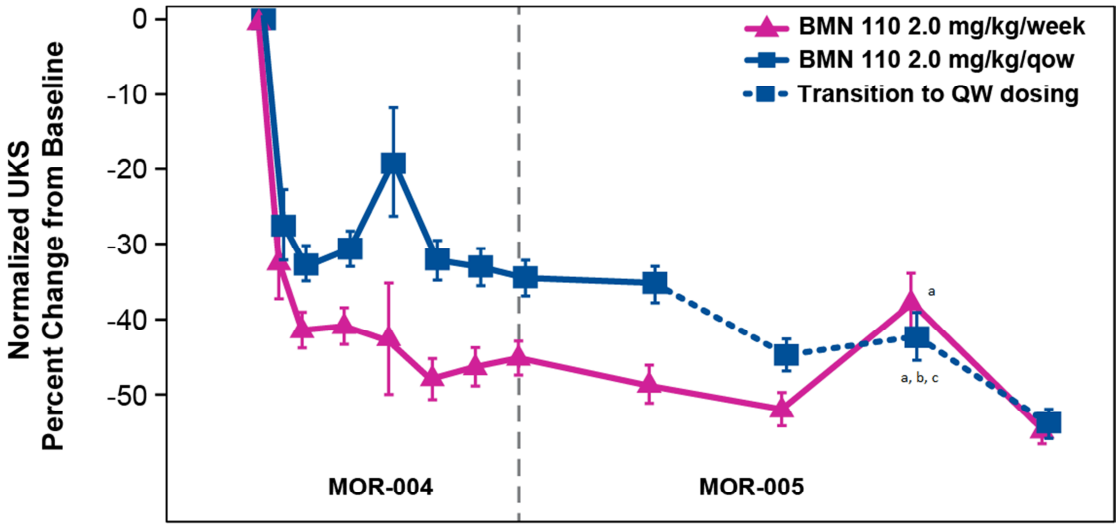


BMN 110 2.0 mg/kg/week	58	58	57	54	26	54
BMN 110 2.0 mg/kg/qow	59	59	58	58	26	56

Model based means (LSMEAN) and standard error bars displayed.
Model: Change from Baseline = age group + baseline walk category + treatment + visit + trt*visit + baseline 3msc, unstructured covariance matrix
[a]Due to different assessment schedule in Part 2, not all subjects have Week 48 endurance assessments available.
[b]With start of Part 2 of MOR-005 (01DEC2012), subjects in QOW-QOW cohort began receiving 2.0 mg/kg weekly; the specific time of transition for each subject depended on date of study enrollment, ranging from Week 36 to Week 72.
[c]Week 48 results for the QOW-QOW cohort include only subjects who reached Week 48 while still in Part 1 of the study as there was no Week 48 endurance assessment in Part 2. Thus for the QOW-QOW cohort, this time point includes data only from subjects still receiving QOW dosing.

- Continued treatment with BMN 110 in Study MOR-005 sustained the reduction in urine KS at Week 72 that had been achieved in MOR-004, with the greatest sustained reduction in the QW-QW cohort (Figure 1.7.3.3). As above, the transition of subjects into Part 2 of MOR-005 led to fewer assessments of urine KS at Week 60 than at other time points.

Figure 1.7.3.3: Analysis of Urine KS: Repeated Measures Model
Analysis Population: ITT Population (MOR-004/MOR-005)



BMN 110 2.0 mg/kg/week	58	55	56	54	55	55	53	54	49	51	11	46
BMN 110 2.0 mg/kg/qow	59	59	58	58	58	58	56	57	56	57	16	55

Model based means (LSMEAN) and standard error bars displayed.
Model: Change from Baseline = age group + baseline walk category + treatment + visit + trt*visit + baseline uks, unstructured covariance matrix
[a]Due to different assessment schedule in Part 2, not all subjects have Week 60 uKS assessments available.
[b]With start of Part 2 of MOR-005 (01DEC2012), subjects in QOW-QOW cohort began receiving 2.0 mg/kg weekly; the specific time of transition for each subject depended on date of study enrollment, ranging from Week 36 to Week 72.
[c]Week 60 results for the QOW-QOW cohort include only subjects who reached Week 60 while still in Part 1 of the study as there was no Week 60 uKS assessment in Part 2. Thus for the QOW-QOW cohort, this time point includes data only from subjects still receiving QOW dosing.

- Overall, sustained improvements across multiple efficacy measurements and across multiple studies provided evidence of continued benefit to patients with MPS IVA, a chronic, progressive disease in which clinical deterioration is the expected course.

1.8 Clinical Safety

- A total of 235 subjects were exposed to BMN 110 across 6 clinical studies at doses of 0.1, 1.0, 2.0, or 4.0 mg/kg/week or 2.0 mg/kg every other week for periods ranging from 1 week to 169.7 weeks (the *All Exposed Population)*; 86 of these subjects were exposed to BMN 110 for more than 48 weeks. A total of 222 subjects were exposed to BMN 110 at the proposed dose of 2.0 mg/kg/week, for periods ranging from 1 to 100.1 weeks (the *Proposed Dose Population*).
- To mitigate the risk for potential hypersensitivity reactions associated with the administration of BMN 110, an appropriate pretreatment dose of antihistamine was administered approximately 30 to 60 minutes before each study drug infusion.
- No deaths were reported in any BMN 110 treatment group during study drug treatment or during safety follow-up.
- Across all studies in the *Proposed Dose Population*, SAEs were reported for 17.6% of subjects. The most common SAEs, which were related to disease manifestations and study drug administration, included knee deformity and venous catheterization. Three subjects experienced hypersensitivity SAEs, and 12 subjects experienced infusion-associated reactions classified as SAEs. All subjects in the *Proposed Dose Population* who experienced SAEs received and tolerated subsequent infusions.
- One subject in MOR-002 experienced an infusion-associated SAE while on the dose of 0.1 mg/kg/week, prior to the inclusion of mandatory premedication for BMN 110 infusions, and discontinued from study drug as a result of this SAE.
- The most common adverse events overall were headache, vomiting, and pyrexia. The incidence of these events generally decreased with increasing duration of treatment.
- Most (71.2%) subjects in the *Proposed Dose Population* experienced at least one infusion-associated reaction (IAR), defined broadly in each protocol as all AEs (regardless of relationship to study drug) that occurred either after infusion onset and within 1 day after infusion end (MOR-004/005, MOR-002/100, MOR-008) or within 1 day after infusion onset (MOR-007). IARs tended to be mild or moderate in severity. Fewer than 1% of infusions were interrupted or discontinued and required medical intervention for an IAR. The mean annualized frequency of IARs decreased with increasing duration of treatment beyond 12 weeks. The Warnings and Precautions section of the proposed prescribing information includes language regarding the clinical study experience with IARs. A subset of IARs that meet the definition for an adverse drug reaction (ADR), as defined in the prescribing information, are deemed “Infusion Reactions”. The proposed prescribing information provides recommended management of and preventive measures for infusion reactions including administration of antihistamines with or without antipyretics prior to infusion.

- Potential Hypersensitivity AEs were identified by utilizing the broad Anaphylactic Reaction algorithmic Standardized MedDRA query (SMQ) and the broad Angioedema SMQ, which represent a broad range of terms to detect signals possibly indicative of hypersensitivity. Hypersensitivity AEs were reported in 16.2% of subjects in the *Proposed Dose Population*. No correlation was found between higher titers of anti-BMN 110 antibodies and increased incidence or severity of hypersensitivity AEs. The Warnings and Precautions section of the proposed prescribing information includes language regarding the clinical study experience with anaphylaxis and severe allergic reactions and provides recommended management of and preventive measures for severe allergic-type hypersensitivity reactions.
    - BioMarin reviewed all reported adverse events against the NIAID/FAAN 2006 criteria for anaphylaxis (Sampson H et al, 2006). Of the 235 subjects exposed to BMN 110 in the development program, the sponsor identified 16 (6.8%) cases consistent with NIAID/FAAN 2006 criteria for anaphylaxis. The reactions were successfully managed with infusion rate adjustments and/or medical intervention, and all but 2 subjects continue to receive subsequent BMN 110 infusions. This rate of anaphylaxis is comparable to other enzyme replacement therapies.
- Spinal/cervical cord compression (SCC), a known and serious complication of MPS IVA, may occur as part of the natural history of the disease. SCC was observed both in subjects receiving BMN 110 and subjects receiving placebo.
- There were no clinically meaningful changes in laboratory values, electrocardiograms (EKGs), or echocardiograms
- A comparison of safety profiles across all studies by study and dose regimens showed no evidence of a dose-dependent increase in incidence or annualized frequency (i.e., mean events/subject-year) of drug-related AEs, drug-related SAEs, Hypersensitivity AEs, and IARs.
- The overall safety profile of the drug is comparable to that seen with other ERTs including Aldurazyme and Naglazyme.
- BioMarin has the knowledge and expertise to ensure healthcare providers are adequately trained to administer ERTs and are informed of the associated risks. Specialists who administer these types of therapies do so in a controlled setting and are aware of the risks associated with ERT, and standard clinical practice involves informing patients of the risk-benefit profile of their treatment. A product monograph, infusion training video, and dosing and administration guide has been prepared to educate treating physicians and healthcare practitioners in the storage, preparation, and administration of BMN 110. These materials will be distributed, as appropriate, to healthcare providers, including infusion nurses and treating physicians.

- BioMarin has proposed risk minimization and pharmacovigilance activities to ensure the safe and effective long-term use of BMN 110 and to gain more knowledge about the safety and effectiveness of BMN 110 in the post-authorization setting. These activities will include, in addition to routine pharmacovigilance practices and product labeling focusing on the risk-benefit balance of BMN 110 based on clinical trial experience, a voluntary disease registry to collect post-marketing safety and effectiveness experience and further evaluate identified and potential risks. This registry will follow patients for up to 10 years.
- The safety profile of BMN 110 is acceptable and similar to that of other ERTs approved for clinical use.

1.9 Support for Clinical BMN 110 Dose

- BMN 110 at 2.0 mg/kg yielded plasma concentrations that were higher (mean C_{max}, 2023 ng/mL) than those seen with 1.0 mg/kg/week (mean C_{max}, 503 ng/mL) and were sustained above the K_{uptake} (2.8-4 nM or 154-220 ng/mL) of the CI-M6PR observed in vitro in human Morquio fibroblasts for longer durations (approximately 6 hours) than the lower dose of 1.0 mg/kg/week (approximately 5 hours). The intracellular $t_{1/2}$ is approximately 5-7 days, as measured in Morquio fibroblasts.
- In MOR-002, mean normalized uKS consistently declined in a dose-dependent manner during the study, with maximum reduction observed at the highest dose tested (2.0 mg/kg/week). MOR-002 also indicated that a dose of 2.0 mg/kg/week was a safe and efficacious dose for the pivotal trial. To explore a less frequent and more convenient dose regimen for subjects, 2.0 mg/kg/qow was also investigated in the Phase 3 study.
- In study MOR-004, BMN 110 at 2.0 mg/kg/week produced a statistically significant and clinically meaningful difference in 6MWT distance compared to placebo, a robust mean percent reduction in uKS compared to placebo, and an acceptable safety profile. The QOW regimen did not demonstrate significant clinical efficacy.

1.10 Immunogenicity

- All subjects treated with BMN 110 developed sustained anti-drug antibodies. Approximately 80% of subjects developed neutralizing antibodies capable of inhibiting the drug from binding to the cation-independent mannose-6-phosphate receptor *in vitro*. The universality of the anti-BMN 110 antibody responses suggests that antibody measurements cannot be used as a predictive indicator to determine which subjects are at greater risk for clinical consequences related to immunogenicity.
- There was no association between the total antibody titer and BMN 110 clearance in general. Subjects with positive NAb responses had decreased CL values and prolonged $t_{1/2}$ for weekly dosing.

- Despite the high incidence of anti-BMN 110 antibodies, decreases in urinary KS and improvements in efficacy measurements were sustained in BMN 110 treated subjects, and no correlation was found between higher NAb positivity rates and decreases in efficacy or PD measurements or increases in hypersensitivity AEs.
- IgE antibodies against BMN 110 were detected in ≤ 10% of treated subjects across studies and have not consistently been related to anaphylaxis, Hypersensitivity AEs, and/or treatment withdrawal.

1.11 Conclusions

- Long- and short-term safety and efficacy data derived from the global BMN 110 clinical development program demonstrate BMN 110 is an effective ERT for Morquio A Syndrome, providing clinical benefit and acceptable tolerability of the drug infused at the proposed marketed dose of 2.0 mg/kg/week.
- Improvements across a variety of efficacy measures in the clinical trials of BMN 110 translate into clinically meaningful benefits generalizable to all patients with MPS IVA, in the context of an unrelenting disease progression, heterogeneity of the patient population and the disease manifestations, and the challenges in reversing the chronic effects caused by years of damage due to accumulated GAGs.
- In subjects enrolled in the pivotal Phase 3 study who are still growing, BMN 110 had a positive effect of slowing the progressive negative deviation from normal growth rates and normal standing height experienced by MPS IVA patients. As with other ERTs in rare genetic diseases, initiating treatment as soon as possible after diagnosis is expected to provide maximal benefit to patients, both by improving existing symptoms and preventing further disease-related impairments.
- The primary risk associated with BMN 110 treatment is related to infusion reactions. These reactions can be effectively managed with appropriate medication prophylaxis and infusion rate adjustment.
- The totality of data from the completed Phase 1/2 and Phase 3 and the ongoing extension and subpopulation clinical trials included in the marketing application demonstrates that BMN 110, at the recommended dose of 2.0 mg/kg/week, has a favorable risk-benefit profile based on the evidence of clinical improvement along with an acceptable safety profile, and addresses the significant unmet medical need for patients with MPS IVA.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

BioMarin Pharmaceutical Inc. (BioMarin) is developing BMN 110 as an enzyme replacement therapy (ERT) for the treatment of mucopolysaccharidosis IV Type A (Morquio A syndrome, MPS IVA), a severely debilitating and progressive disease with an unmet medical need.

BioMarin has extensive experience developing and commercializing innovative biopharmaceuticals for serious diseases and medical conditions. The company's commercial portfolio includes two other products – Naglazyme® (galsulfase) and Aldurazyme® (laronidase) – indicated to treat MPS diseases (MPS VI and MPS I, respectively).

2.2 Mucopolysaccharidosis type IVA (MPS IVA; Morquio A Syndrome)

2.2.1 Mucopolysaccharidoses

Mucopolysaccharidoses (MPS) and related diseases are genetic lysosomal storage diseases (LSD) caused by the body's inability to produce specific enzymes. In individuals with MPS, the missing or insufficient enzyme activity prevents the proper intracellular recycling process of cellular materials, resulting in the abnormal storage of materials in most body cells. As a result, progressive damage may occur throughout the body, including the heart, bones, joints, respiratory system, and central nervous system. While the MPS diseases may not be apparent at birth, signs and symptoms develop with age as more cells become progressively damaged by the abnormal accumulation of cellular materials.

The group of MPS disorders includes over a dozen identified syndromes, which differ in the deficient enzyme, accumulated intracellular products, and clinical manifestations. The subtyping of MPS disorders is based largely on the deficient enzyme (eg, all MPS type I syndrome patients are missing the α-L-iduronidase enzyme) or accumulated products (eg, all MPS type III patients suffer from an accumulation of heparan sulfate, and each of the 4 subtypes of MPS III represents a different missing enzyme).

Mental retardation and developmental delay are features of some MPS syndromes (but not MPS IVA). Motor dysfunction, skeletal dysplasia, and short stature are common features of MPS IVA and also common to other MPS syndromes, including MPS VI (Maroteaux-Lamy syndrome) and MPS VII (Sly syndrome). Classic clinical abnormalities in the presentation of MPS IVA include short stature, short neck, pronounced pectus carinatum, pronounced genu valgum, and extreme hypermobility and hyperextension of the joints secondary to ligamentous laxity (Nyhan, 2011).

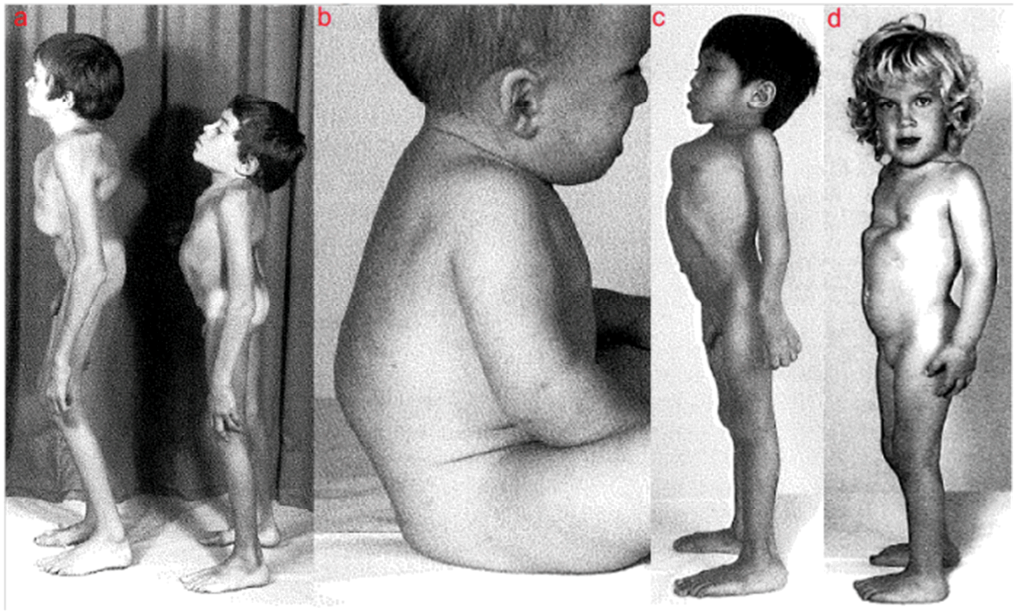
Only a few of the many MPS syndromes (MPS I, MPS II, and MPS VI) currently have approved enzyme replacement therapies (ERT) for treatment. There is currently no approved treatment for MPS IVA.

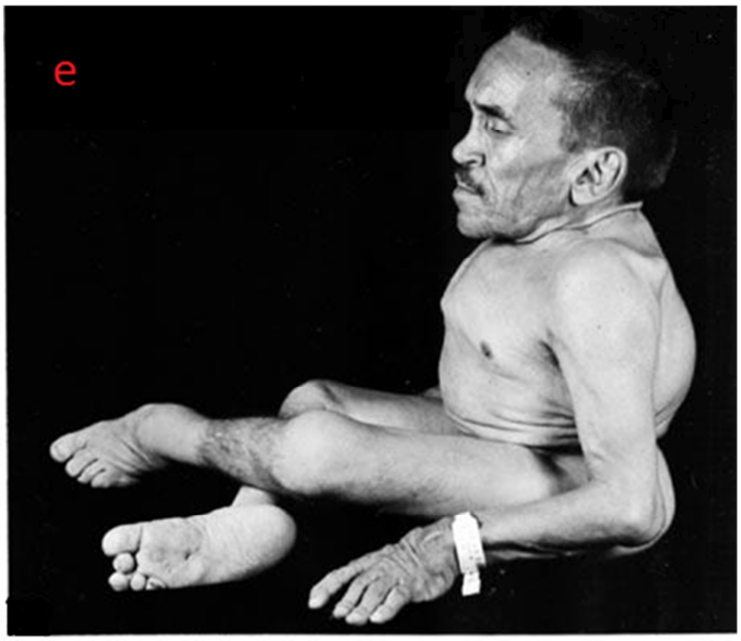
2.2.2 MPS IVA

MPS IVA is a rare, devastating, inherited disorder caused by mutations of the gene that codes for the lysosomal enzyme N‑acetylgalactosamine‑6‑sulfatase (GALNS), which degrades glycosaminoglycans (GAGs) including keratan sulfate (KS) and chondroitin-6-sulfate. GAGs are long chains of sugar carbohydrates present in most cells that help build bone, cartilage, cornea, skin, and other connective tissue. With insufficient GALNS, GAGs progressively accumulate in multiple organs and tissues. The pervasive and progressive accumulation of GAGs leads to significant morbidities and multisystemic clinical impairments resulting in diminished functional capacity, decreased endurance, impaired quality of life, and early mortality.

Most patients with MPS IVA begin to show symptoms in early childhood (between ages 1 and 3). The most common features of patients with MPS IVA are progressive skeletal dysplasia, motor dysfunction, short stature, frequent surgical procedures mostly related to musculoskeletal impairments, and a significant limitation in mobility, endurance, and respiratory function (Montano, 2007b, J.Inherit.Metab Dis.), (Harmatz P, 2013, Mol.Genet Metab). Many patients end up using scooters, wheelchairs or other mobility devices by their teen years. All patients have a profound skeletal dysplasia, which commonly results in severe short stature and malformations of the knees, chest, and spine (Figure 2.2.2.1). The skeletal dysplasia, short stature, and joint abnormalities all contribute to restriction in patient mobility. Patients may experience both restrictive lung disease due to thoracic deformity and obstructive disease due to laryngeal narrowing and tracheal and bronchial abnormalities. These mechanical impediments often result in dyspnea and recurrent respiratory infections, and potentially progress to respiratory failure. Additional symptoms may include hearing loss, cataracts, corneal clouding, and heart valve disease, among others. Intelligence is normal (Neufeld, 1995, McGraw-Hill), (Kakkis, 1996, McGraw-Hill), (Northover, 1996, J.Inherit.Metab Dis.).

Figure 2.2.2.1: Morquio A Syndrome





Source: (Kircher, 2007, International Medical Publishers), (McKusick VA, 1983, McGraw-Hill)
[a] Siblings, 17 and 13 years old, with flexion in hips and knees.
[b] 1-year old with gibbus deformity.
[c] 9-year old with overextension of head and sternal protrusion.
[d] 4-year old girl with extreme funnel breast.
[e] 55-year-old with pectus carinatum, bilateral genu valgum, diffuse corneal clouding, atlantoaxial subluxation, and bilateral sensorineural deafness.

Survival in patients with rapidly progressing phenotypes is limited to the second or third decade of life. Rarely, patients with slowly progressing forms of the disorder have been reported to survive beyond 60 years. Mortality is commonly due to cardiorespiratory or central nervous system complications (ie, spinal/cervical cord compression [SCC]). Obstructive and restrictive lung disease predisposes patients to developing fatal pneumonia and respiratory failure (Neufeld, 1995, McGraw-Hill), (Kakkis, 1996, McGraw-Hill) (Hendriksz, 2013, J.Inherit.Metab Dis.). Regardless of rate of disease progression, all patients have serious and debilitating morbidities.

MPS IVA is a rare disorder, with incidence estimated to range from 1 in 76,000 to 1 in 640,000 live births in different populations; the incidence in Northern Ireland is 1 in 76,000 live births (Nelson, 1997, Hum.Genet.); in Western Australia, it is 1 in 640,000 (Nelson, 2003, Am.J Med Genet.A) in the Netherlands incidence is 1 in 450,000 live births (Poorthuis, 1999, Hum Genet); and in Portugal incidence is 1 in 450,000 live births over a 20 year period (Pinto, 2004, Eur.J.Hum.Genet.).

Using available U.S. incidence figures (1 in 200,000 to 1 in 300,000 live births), and based on the U.S. birth rate of approximately 4 million live births per year, an estimate for the incidence of MPS IVA in the U.S. would be approximately 13-20 births each year. Based on an average lifespan of 40 years, the prevalence of MPS IVA in the U.S. would be approximately 520-800 patients (National MPS Society, 2008).

There is currently no standard treatment for MPS IVA. Supportive care includes both medications and surgical interventions. Nonsteroidal anti-inflammatory drugs have been administered for joint pain, antibiotics for pulmonary infection, and oxygen supplementation and CPAP/BiPAP for pulmonary compromise and obstructive sleep apnoea. Surgical interventions include cervical spine fusion and/or decompression, spinal stabilization, hip reconstruction and replacement, femoral osteotomies for straightening of the legs, corrective knee and ankle surgery for severe genu valgum deformity, umbilical and inguinal hernia repair, tonsillectomy/adenoidectomy, and cardiac valve replacement (Neufeld, 1995, McGraw-Hill) (Kakkis, 1996, McGraw-Hill). In MOR-002, the medical history included spinal fusion surgery in 30% of subjects and knee operation in 15% of subjects. In MOR-004, the medical history included spinal fusion surgery in 20.3% to 25.4% of subjects and knee operation in 15.5% to 18.6% of subjects.

Hematopoietic stem cell transplantation (HSCT) has been attempted in some patients with MPS IVA with some improvement reported (Tomatsu, 2011, Curr.Pharm.Biotechnol.); however, experience is limited and a clear benefit has not been established.

2.2.3 MPS IVA Natural History

The MPS disorders, including MPS IVA, are characterized by a clinical heterogeneity encompassing a range of symptoms and disease severity. To better understand the heterogeneity of MPS IVA, a multicenter, multinational, prospective natural history study (MorCAP) was initiated. MorCAP is the first longitudinal study involving direct assessments of MPS IVA patients, including assessment of growth, endurance, respiratory function, cardiac function, and medical and surgical history. MorCAP is estimated to represent approximately 10% of the global MPS IVA patient population based on an estimated average incidence of 1:250,000 births and world birth rates in developing countries The study provides the most comprehensive data about symptoms and disease progression in the overall MPS IVA patient population (Harmatz, 2013, Mol Genet Metab).

Baseline data collected from 325 subjects with MPS IVA enrolled in MorCAP in 10 countries showed that the majority (79%) of subjects were in the pediatric age group (18 years and younger); mean and median ages were 14.5 years and 11.6 years (range 1-66 years). The data indicated substantial impairment across multiple domains including growth, endurance and mobility, respiratory function, and the impact of burden of illness on quality of life. Musculoskeletal diagnoses were the most common category of medical event reported, with >90% of subjects reporting abnormal gait, genu valgum, short stature, and/or short neck. On average, the height of MPS IVA subjects was far below that predicted by the CDC normal pediatric growth charts, with mean ± SD height z-scores of -5.6 ± 3.1. Baseline height z-scores revealed increasing abnormality with age; mean z-scores were -2.09, -5.00 and -7.27 in the 0-4 years, 5-11 years and 12-18 years age groups, respectively, suggesting that in many patients growth slows or stops in early childhood. In their medical history, the majority of MPS IVA subjects (71%) reported surgical procedures; in subjects ≥5 years, >70% experienced at least one surgical procedure in each age group. Subjects also had frequent infections (11%) as compared to unaffected individuals. Vision and hearing impairments were also reported. The use of pain medications in all age categories was indicative of the pain associated with tasks of daily living for all individuals with MPS IVA. Almost 75% of subjects <12 years of age and more than 95% of subjects in the ≥12 years age groups required surgical or medical interventions, which carry a high risk for surgical and anesthetic complications. Spinal fusion and decompression surgeries were both reported in >10% of the MorCAP study subjects (Harmatz, 2013, Mol Genet Metab), reflecting the fragility of the vertebral column and spinal cord in these patients.

Functional endurance testing revealed limitations in walking and stair climbing ability, with mean ± SD of 212.6 ± 152.2 meters for the 6-minute-walk-test and 30.0 ± 24.0 stairs/minute

for the 3-minute-stair-climb test. The overall mean ± SD 6MWT distance of 212.6 ± 152.2 meters is substantially reduced when compared to the lower limit of normal, reported as ranging from 470 to 664 meters for healthy individuals aged 4 to 16 years (Li, 2007, Am J Respir Crit Care Med) (Lammers, 2008, Arch Dis Child) and approximately 500 to 580 meters for healthy adults. Although no normative data is available for the 3MSCT, the stair climb rate of 30.0 ± 24.0 stairs/minute reported in these MPS IVA subjects shows more substantial impairment when compared to the baseline stair climb rate of 50 ±29.5 in the MPS VI population (Harmatz, 2008, Mol Genet Metab). Respiratory function also showed limitations comparable to MPS VI subjects; mean ± SD was 1.2 ±0.9 liters based on forced vital capacity and 34.8 ± 25.5 liters/minute based on maximum voluntary ventilation in MorCAP.

Longitudinal data from patients who have been enrolled in and completed the assessments in MorCAP for at least 1 year demonstrates the progressive deterioration of patients with untreated MPS IVA. Data were analyzed using a repeated measure regression model and Visits 1, 2, and 3. The annualized estimate of change in 6MWT from Visit 1 across all subjects in MorCAP was -5.2 meters (CI_{95}, -11.5, 1.1). The annualized estimate of change in 6MWT from Visit 1 was -7.1 meters (CI_{95}, -17.6, 3.3) in the subset of patients selected to match the MOR-004 study population (age >= 5 years, 6WMT between 30 and 325 meters at Visit 1), using a repeated measure regression model and Visits 1, 2, and 3 (manuscript in preparation).

The MPS Health Assessment Questionnaire (HAQ) revealed impairments in mobility and activities of daily living; more than half of the MorCAP study population required a wheelchair or walking aid for mobility. Patient-reported outcome data in Morquio A patients show that the ability to ambulate and care for oneself in daily activities is directly correlated with a higher quality of life. A General Health-Related Quality of Life (HRQoL) questionnaire (EQ-5D-5L) used in a cross-sectional paper survey among 63 Morquio A patients including 27 adults and 36 children showed that less mobile patients report significantly lower HRQoL than patients with greater mobility. On a scale from 0 to 1.0 with 0 being death and 1 representing perfect health, MPS IVA patients who did not use a wheelchair at all had a relatively high average HRQoL score of 0.846 (Patient-reported outcomes (PRO) study: data on file). Adults with Morquio A syndrome who sometimes used a wheelchair had average HRQoL scores (0.582) similar to other serious chronic illnesses such as moderate-severe rheumatoid arthritis, non-insulin dependent diabetes and multiple sclerosis (Orme, 2007, Value Heath; Kobelt, 2005, Rheum; Kobelt, 2006, Eur Health Econ). Wheelchair-bound patients reported an average score of 0.057, only slightly better than death. Extremely poor HRQoL ratings were heavily driven by low scores for self-care,

mobility and pain. Other factors leading to decreased quality of life with disease progression included increasing difficulties in performing ADLs, frequent surgical/medical interventions, and increasing pain.

Because of the missing or decreased GALNS enzyme activity, MPS IVA patients experience progressive accumulation of GAGs, including KS; one consequence of this accumulation is that urinary excretion of KS is also increased. In the MorCAP population, mean urine KS was elevated for all ages, and negatively correlated with age; mean normalized urine KS was higher in patients ≤18 years when compared to patients >18 years. This difference in urine KS likely reflects to some degree the expected decrease in cartilage formation and bone growth as patients reach puberty and bone growth plates fuse. The rate of age related decline in urine KS is expected to be slower than that seen with BMN 110 treatment (a meaningful drop over the first 4 to 6 weeks of treatment as opposed to a more gradual decline with age) (Tomatsu, 2005, J Inherit Metab Dis).

In order to account for age-related decrease, urine KS cutoff levels were identified based on correlation between urine KS and 6MWT with locally weighted scatterplot smoothing. Low urine KS was defined as ≤20 μg/mg for subjects ≤18 years old and ≤10 μg/mg for subjects >18 years old. On average, subjects with high urine KS demonstrated greater clinical impairment, as measured by height and length z-scores, and endurance and respiratory function tests, than those with low urine KS levels. Pediatric patients with the lowest urine KS levels had the tallest average height, those with mid-range urine KS had mid-range height and those patients with the highest urine KS had the shortest or lowest heights. Both pediatric and adult subjects with low urine KS on average had closer to normal height, longer walk distance, greater stair climb result, and greater FVC and MVV volumes, while higher urine KS correlated with greater clinical impairment based on height z-scores, endurance and respiratory function tests (Harmatz, 2013, Mol Genet Metab).

Overall study findings suggest quality of life for MPS IVA patients is substantially impacted by disease progression and manifestations across all ages and phenotypes of MPS IVA. The initial results of the MorCAP study support the varied and multisystemic clinical presentation of MPS IVA, with all affected individuals experiencing substantial functional limitations and reduced quality of life. Direct clinical observation and testing in a large number of these subjects have demonstrated substantial impairment across multiple domains including endurance, mobility, respiratory function, stature, biochemical abnormalities and quality of life. Older patients have more severe exercise and respiratory capacity limitations illustrating the progressive nature of MPS IVA.

Baseline and longitudinal data from MorCAP provide insight into the clinical presentation and substantial burden of illness associated with MPS IVA in the overall population and into the progressive nature of the disease. As discussed below in Section 6.8.1**,** the range of baseline characteristics of MPS IVA subjects in MorCAP are similar to the range of baseline characteristics in the patient populations studied in the BMN 110 clinical development program.

2.3 Rationale for BMN 110 in the Treatment of MPS IVA

BMN 110 is a recombinant form of human N-acetylgalactosamine-6-sulfatase (rhGALNS), and is identical to the naturally occurring human lysosomal enzyme in terms of the amino acid sequence and N-linked glycosylation. BMN 110 provides exogenous GALNS that is taken up into the lysosomes and catabolyzes the GAGs keratan sulfate and chondroitin-6-sulfate (Harmatz, 2013, Mol.Genet.Metab.). BMN 110 uptake by cells into lysosomes is most likely mediated by the binding of mannose-6-phosphate-terminated oligosaccharide chains of BMN 110 to the cation-independent mannose-6-phosphate receptor (CI-M6PR).

BMN 110 cellular uptake, subsequent trafficking to the lysosomal compartment and PD activity in reducing KS storage was demonstrated in human primary Morquio chondrocytes (refer to Section 4).

3 OVERVIEW OF BMN 110 DEVELOPMENT PROGRAM IN MPS IVA

3.1 Clinical Studies

A comprehensive clinical development program was designed to examine outcomes across the full spectrum of age and disease severity to thoroughly assess the activity and safety of BMN 110 in the diverse MPS IVA patient population.

In addition to the longitudinal natural history study (MOR-001) discussed above (refer to Section 2.2.3), the clinical development program for BMN 110 included 7 studies (2 completed studies and 5 ongoing). Data from six of these studies were included in the marketing application submitted to FDA (MOR-006 was not included because of ongoing enrollment and very limited subject exposure at the data cutoff timepoint). A complete list of studies is provided below:

- **MOR-004** is a completed Phase 3, randomized, double-blind, placebo-controlled, multinational study of BMN 110 or placebo administered for a total of 24 weeks in 176 subjects with MPS IVA. The study compared BMN 110 infusions (2.0 mg/kg every other week [qow] or 2.0 mg/kg/week) with placebo in subjects ranging from 5 to 57 years of age.
- **MOR-005** is an ongoing Phase 3 extension study designed to evaluate the long-term effects of BMN 110 administered for up to 240 weeks in 173 subjects with MPS IVA who completed MOR-004. In Part 1 (completed), subjects who were initially randomized to BMN 110 in MOR-004 remained on their assigned dose regimen of 2.0 mg/kg/week or 2.0 mg/kg/qow, and subjects who were initially randomized to placebo in MOR-004 were re-randomized (1:1 ratio) to one of the two BMN 110 dose regimens (2.0 mg/kg/week or 2.0 mg/kg/qow). In Part 2 (ongoing), subjects were switched to 2.0 mg/kg/week based on the analysis of the final primary efficacy and safety results in MOR-004 and Data Monitoring Committee recommendation.
- **MOR-002** is a completed Phase 1/2, multicenter, open-label, dose-escalation study of BMN 110 in 20 subjects with MPS IVA who were 4 to 16 years of age at entry. Subjects who completed the 36-week Dose-Escalation Period (consisting of 3 consecutive 12 week dosing periods of 0.1, 1.0, and 2.0 mg/kg/week), had the option to continue BMN 110 treatment with weekly doses of 1.0 mg/kg for an additional 36 to 48 weeks. Eighteen of 20 subjects enrolled in the Continuation Period.
- **MOR-100** is an ongoing Phase 1/2 extension study designed to evaluate the long-term safety and efficacy of BMN 110 2.0 mg/kg/week administered for up to 240 weeks in 17 subjects with MPS IVA who completed MOR-002.

- **MOR-006** is an ongoing Phase 2, open-label, multinational study of BMN 110 2.0 mg/kg/week for an initial treatment period of 48 consecutive weeks in up to 20 subjects with *MPS IVA who have limited ambulation* (baseline 6MWT less than 30 meters). There will be an extension treatment phase of up to an additional 96 weeks.
- **MOR-007** is an ongoing Phase 2, open-label, multinational study of BMN 110 2.0 mg/kg/week for an initial treatment period of 52 consecutive weeks in 15 subjects with MPS IVA who are *<5 years of age* at the time of first study-drug infusion. There will be an extension treatment phase of up to an additional 157 weeks.
- **MOR-008** is an ongoing Phase 2, randomized, double-blind, multicenter 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 and able to walk ≥200 meters in the 6-minute walk test (6MWT)*. There will be an extension treatment phase of up to an additional 130 weeks.

Clinical data from 235 subjects exposed to BMN 110 (236 subjects total)[1] were provided in the marketing application, including 174 subjects exposed for at least 25 weeks, and 86 subjects exposed for at least 48 weeks. This submission represents the largest clinical data package in support of an initial marketing application for any previously approved ERT.

The BMN 110 clinical development program is multinational with subjects enrolled in Europe, North America, South America, Asia, and other regions. Based on the global nature of these studies and the broad inclusion criteria across studies, the study population is representative of the global MPS IVA patient population.

All clinical studies were designed to assess safety as well as efficacy of BMN 110. A summary of all BMN 110 clinical studies is provided in Table 6.1.1.

An expanded access program (EAP) has also been initiated to provide access to BMN 110 for patients in the US diagnosed with MPS IVA concurrent with the Biologics License Application review for BMN 110.

In addition, there are 2 studies planned for BMN 110: 1) a disease registry intended to track long-term clinical outcomes of patients with MPS IVA disease; and 2) a multicenter open-label, Phase 3B study of approximately 10 subjects in Australia to evaluate the efficacy and safety of BMN 110 in Australian patients with MPS IVA.

[1] One subject received placebo in MOR-004 and did not enroll in MOR-005; therefore, that subject was never exposed to BMN 110.

The design of the clinical studies for BMN 110 were conceived with input from specialists from the international academic community and reviewed and modified after consultation with European and US Regulatory Health Authorities.

Key inclusion criteria were broad and generally included 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. The combination of study populations in the BMN 110 clinical development program encompasses the spectrum of age and disease severity of the overall patient population, and therefore results are likely applicable to patients anticipated to be treated in the post-approval setting (Montano, 2007b, J.Inherit.Metab Dis.), (Neufeld, 1995, McGraw-Hill), (Kakkis, 1996, McGraw-Hill), (Northover, 1996, J.Inherit.Metab Dis.), (Hendriksz, 2013, J.Inherit.Metab Dis.), (Harmatz P, 2013, Mol.Genet Metab).

All clinical trials of BMN 110 were conducted according to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice requirements, and in compliance with local and national regulatory requirements.

3.2 Regulatory History

BioMarin has received formal guidance, at all stages of development, from European and US regulatory health authorities within the context of meetings and written correspondence. BioMarin incorporated feedback from these regulatory agencies into the clinical development program for BMN 110. During the Pre-BLA meeting held in December 2012, agreement was reached with the FDA regarding the structure and content of the marketing application.

During development, the FDA has commented on the importance of demonstrating the clinical meaningfulness of the treatment effect. With regard to the pivotal trial (MOR-004), FDA agreed that 6MWT could be used as a primary efficacy measure and recommended that BioMarin define a minimal clinically important difference (MCID) and analyze the primary endpoint utilizing a responder analysis. BioMarin explored multiple methodologies, including a literature review and a Delphi consensus panel of experts to define a MCID for 6MWT, 3MSCT, and MVV endpoints. Despite these efforts, uncertainty remains regarding these MCID thresholds in MPS IVA and the level of response required to define a "responder". In addition, substantial power is lost when a continuous measure is converted to a dichotomous measure. To address these issues in the pivotal trial in a prospective fashion, the entire distribution of responses for active treatment and placebo groups were evaluated using the cumulative distribution function (CDF). To aid in the interpretation of the

CDFs, bar charts using various thresholds for response were also provided. Additional post-hoc responder analyses were also conducted for selected efficacy measures.

During review of the BLA, the FDA Review Division has questioned the level of evidence to establish the effectiveness of BMN 110 in the target patient population. Without a longer controlled trial, the Division has stated that they cannot be sure that the trends toward improvement in the primary efficacy endpoint (6 minute walk test) and the secondary efficacy endpoint (3 minute stair climb test) seen in the extension study (MOR-005) are related to a BMN 110 treatment effect. In addition, the Division has stated that it is not clear whether the extent of improvement seen on the primary efficacy endpoint in the placebo-controlled trial (MOR-004) represents a clinically meaningful benefit to patients with Morquio A syndrome. It is for these reasons that the Division has indicated that an advisory committee meeting would be convened.

4 NONCLINICAL

The nonclinical pharmacology, pharmacokinetics, and toxicology of BMN 110 were evaluated in five *in vitro* and eleven *in vivo* studies. An overview of the nonclinical studies conducted with BMN 110 is presented in Appendix 11.1.

In vitro pharmacology studies investigated BMN 110 cellular uptake and intracellular half-life in a human Morquio fibroblast cell. In these cells, the calculated K_{uptake} was approximately 2.5 nM (138 ng/mL), and the intracellular $t_{1/2}$ was approximately 5-7 days.

In vitro BMN 110 cellular uptake and subsequent trafficking to the lysosomal compartment was shown in human Morquio primary chondrocytes. Co-incubation of human Morquio chondrocytes with BMN 110 led to the internalization of BMN 110 and the restoration of GALNS activity in the lysosomal compartment resulting in intracellular keratan sulfate clearance. Extracellular KS was not affected, thus confirming BMN 110 activity was limited to the lysosomal compartment with its acidic pH environment. In addition, a restoration of a normal chondrogenic gene expression profile was noted.

Based on the toxicokinetic (TK) analysis from single and repeat-dose IV toxicity and TK studies in rats and monkeys, $t_{1/2}$ generally increased after repeated doses and C_{max} and AUC_{0-t} increased after repeated doses in the animals given 20 mg/kg BMN 110.

Developmental and reproduction studies were conducted in rat and rabbit at doses up to 10 times the human dose and have revealed no evidence of impaired fertility, reproductive performance or toxicity to the fetus due to BMN 110. A peri- and postnatal development study in rats showed no evidence of any effects on pre- and postnatal development at doses up to 20 mg/kg. BMN 110 was detected in the plasma of rabbit fetuses and in the milk of lactating rats, confirming placental transfer and milk secretion, respectively. BMN 110 exposure via milk to pups is not anticipated, as intact BMN 110 is not expected to be absorbed after ingestion due to protein digestion in the stomach.

The BMN 110 nonclinical safety profile after chronic administration was similar to that of other ERTs and included species-specific anaphylactoid-type reactions in the rat that were managed with diphenhydramine pretreatment. Total and neutralizing (binding) anti-BMN 110 antibodies were detected in both rat and monkey and did not reduce exposure except in rats given 1 mg/kg/week BMN 110. The formation of antibodies had no toxicological impact. No target organ toxicity was observed in either species.

Exposure based safety factors (AUC_{0-t}), were 30-fold and 36-fold in rats and monkeys treated with 20 mg/kg, respectively, when compared to patients treated with 2.0 mg/kg.

Based on the nonclinical data, the risk associated with the administration of BMN 110 to humans is low and is expected to be manageable. The overall nonclinical data support the clinical use of BMN 110 at the proposed dose and interval of 2.0 mg/kg/week.

5 CLINICAL PHARMACOLOGY

5.1 Summary of Clinical Pharmacology Studies

The pharmacological activity of BMN 110 was assessed in 3 *in vitro* studies using 2 cell types, as described in Section 4. Of the 6 clinical studies in subjects with MPS IVA discussed in the marketing application, pharmacokinetic (PK) results are presented for 2 studies (MOR-004 and MOR-002), PD properties are presented for 5 studies (MOR-004, MOR-005, MOR-002, MOR-100, and MOR-007), and immunogenicity results are presented for all studies. All clinical studies with BMN 110 have been conducted in the MPS IVA patient population, and thus no data were obtained in healthy volunteers.

5.2 Pharmacokinetics

Pharmacokinetic data in subjects with MPS IVA are available for 2 clinical studies (MOR-002 and MOR-004) of BMN 110.

5.2.1 MOR-002

In MOR-002, as the BMN 110 dose increased from 0.1 mg/kg/week to 1.0 mg/kg/week and then to 2.0 mg/kg/week, the mean values for area under the plasma concentration time curve from time zero to the time of last measurable concentration (AUC_{0-t}) and maximum plasma concentration (C_{max}) increased far in excess of the increase in dose, indicating that the PK profile of BMN 110 is not linear over this dose range (refer to Appendix Table 11.3.1). This is supported by the analogous drop in CL, V_{dz}, and V_{dss}, and indicates that the clearance mechanism may be saturated at relatively low doses. These mechanisms could become saturated as the dose level increased due to a limited amount of receptors and/or proteases, or the presence of antibodies. The data also indicate a short half-life of <1 hr, which is comparable to other ERTs.

Results of the PK analyses from MOR-002 and results from in vitro studies in human Morquio fibroblasts supported use of the 2.0 mg/kg dose for the Phase 3 clinical trial. In MOR-002, the dose of 2.0 mg/kg/week yielded plasma BMN 110 concentrations that were higher (mean C_{max}, 2023 ng/mL) than those seen with 1.0 mg/kg/week (mean C_{max}, 503 ng/mL). Plasma BMN 110 concentration at the 2.0 mg/kg/week dose was sustained above the K_{uptake} (2.8-4 nM or 154-220 ng/mL) of the CI-M6PR in the in vitro studies in human Morquio fibroblasts for longer durations (approximately 6 hours) than the lower dose of 1.0 mg/kg/week (approximately 5 hours).

5.2.2 MOR-004

In MOR-004, PK was comparable between the 2.0 mg/kg/qow and 2.0 mg/kg/week dosing regimens at Week 0 (Table 5.2.2.1, Appendix Table 11.3.2). The AUC_{0-t}, observed C_{max}, and $t_{1/2}$ increased at Week 22 compared to Week 0 for the BMN 110 2.0 mg/kg groups. The increase in AUC_{0-t}, C_{max}, and $t_{1/2}$ at Week 22 may possibly be due to the formation of antibodies that interfere with cellular uptake. AUC_{0-t} and area under the plasma concentration time curve from time zero to infinity (AUC_{0-inf}) were highly correlated.

In MOR-004, mean AUC_{0-t} and C_{max} increased by 76 to 84% at Week 22 compared to Week 0 for the every other week dosing group, and 181% to 192% for the weekly dosing group (Figure 5.2.2.1). Mean $t_{1/2}$ was ~7 min at Week 0 for both dosage regimens, and 19 min and 36 min at Week 22 for the every other week and the weekly dosing groups, respectively. The increase in AUC_{0-t}, C_{max}, and $t_{1/2}$ at Week 22 may possibly be due to the formation of antibodies that interfere with cellular uptake. No accumulation of BMN 110 in plasma was evident following weekly or every other week dosing, as supported by the short half-life of BMN 110 (mean $t_{1/2}$ <1.5 hours) and pre-dose concentrations at Week 22 that were below the level of quantification (BLQ). These comparisons could not be performed for MOR-002 because of the design of that study (ie, MOR-002 was a dose-escalation study).

Table 5.2.2.1: Summary of Pharmacokinetic Parameters in Study MOR-004 (Pharmacokinetics Population)

Pharmacokinetic Parameter	Week 0 Mean (SD)	Week 22 Mean (SD)
AUC_{0-t}, min x µg/mL*	238 (100)	577 (416)
C_{max},µg/mL†	1.49 (0.534)	4.04 (3.24)
CL, mL/min/kg‡	10.0 (3.73)	7.08 (13.0)
V_{dss}, mL/kg§	396 (316)	650 (1842)
V_{dz}, mL/kg¶	124 (144)	300 (543)
$t_{1/2}$, min#	7.52 (5.48)	35.9 (21.5)
T_{max}, minÞ	172 (75.3)	202 (90.8)

* AUC_{0-t}, area under the plasma concentration-time curve from time zero to the time of last measurable concentration;

† C_{max}, observed maximum plasma concentration;

‡ CL, total clearance of drug after intravenous administration;

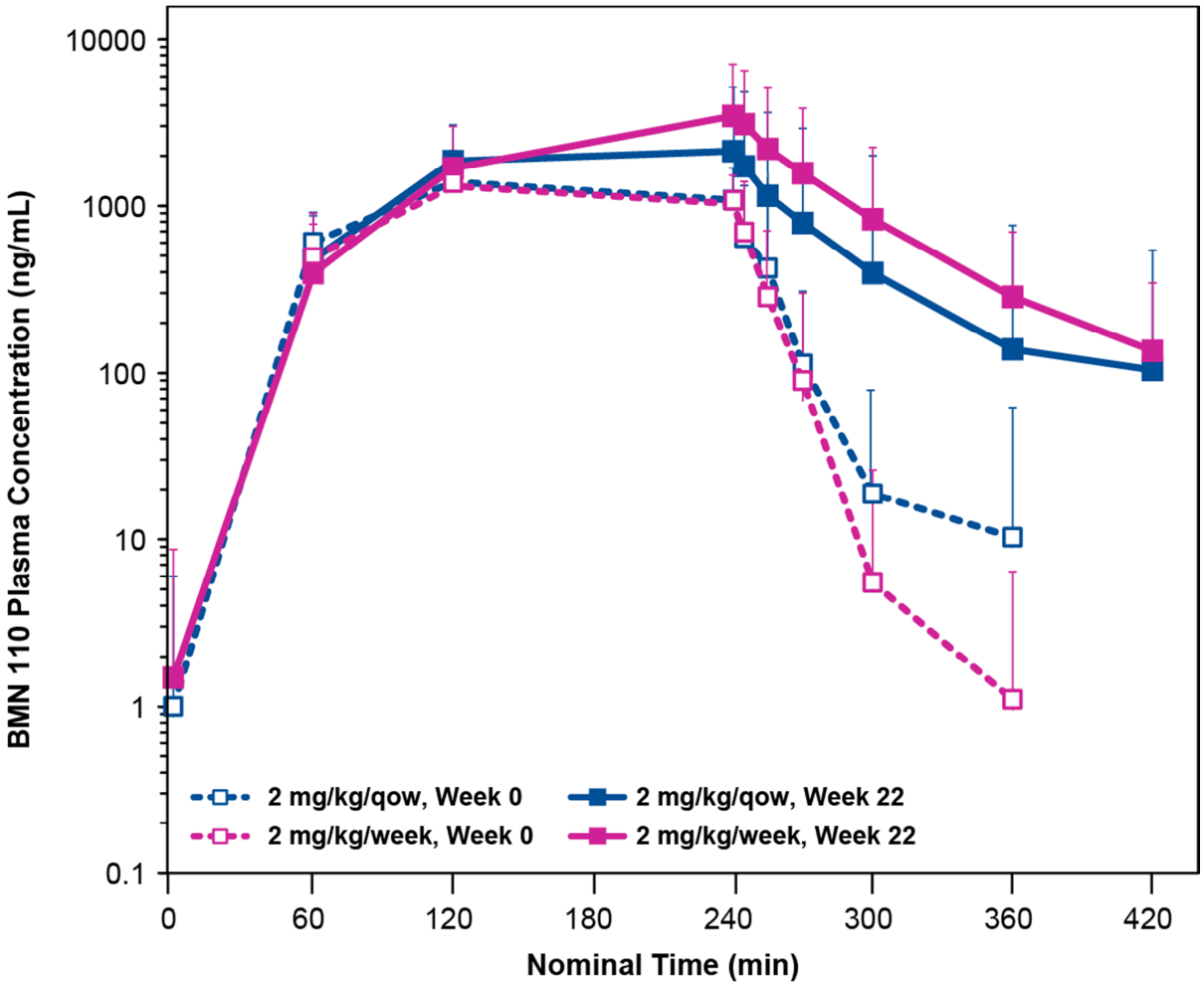
§ V_{dss}, apparent volume of distribution at steady-state;

¶ V_{dz}, apparent volume of distribution based upon the terminal phase;

$t_{1/2}$, elimination half-life;

Þ $T_{max,}$ time from zero to maximum plasma concentration

Figure 5.2.2.1: BMN 110 Mean Plasma Concentration Over Time (Pharmacokinetics Population – MOR-004)



In MOR-004, dosing regimen-dependent increases in efficacy (6MWT, 3-minute stair climb test [3MSCT], or maximum voluntary ventilation [MVV]) and PD (urine KS reduction) outcome measures were observed (refer to Section 6). The BMN 110 weekly treatment group exhibited better efficacy and PD outcomes than the BMN 110 every other week treatment group and the placebo group. Occurrence of AEs with incidences >10% in BMN 110 treatment group versus placebo was analyzed against BMN 110 exposure (AUC_{0-t} and C_{max}) indicating no substantial differences between subjects with and without adverse events (AEs). In addition, the increase in BMN 110 exposure (AUC_{0-t} and C_{max}) was not associated with increase in occurrence of AEs.

The potential impact of subject demographics (sex, race, body weight, and age) on BMN 110 clearance was evaluated at Week 0 and Week 22. Male and female subjects appeared to have

comparable BMN 110 clearance at both weeks. Due to a limited number of subjects in the PK sample size, only 2 categories of races were used in the pre-specified analysis: White and non-White. Comparison of BMN 110 clearance between races indicated a higher BMN 110 clearance in White subjects than non-White subjects at Week 0, but the trend was not observed at Week 22. BMN 110 clearance appeared to decrease with increase in body weight and age at Week 0, but the trend was not observed at Week 22. Results showed that BMN 110 exposure was not associated with 6MWT or 3MSCT results, urine KS reduction, or increased occurrence of AEs. These results, along with the lack of trends at Week 22, suggest that the apparent differences observed in BMN 110 clearance with race, body weight, or age at Week 0 are not clinically significant. There were no consistent trends on other BMN 110 PK parameters ($AUC_{0-\infty}$, AUC_{0-t}, C_{max} V_{dss}, and $t_{1/2}$) based on subject demographics.

There was no consistent relationship between PK and demographics (sex, race, body weight, and age) and no clear correlation between individual PK exposure (AUC_{0-t} and C_{max}) and PD (urine KS) or efficacy (6MWT, 3MSCT, and MVV) in MOR-004. It appeared that subjects ≤18 years old (n=23) had higher BMN 110 clearance than subjects >18 years old (n=6) at Week 0. However, that trend disappeared at Week 22. BMN 110 clearance, available from 74% of White and Asian PK subjects, appeared to be higher in White than in Asian subjects. However, a comparison of the total drug exposure (AUC_{0-t}), which was available from all subjects, demonstrated comparable BMN 110 exposure between White and Asian subjects at Weeks 0 and 22 after receiving BMN 110 at 2.0 mg/kg/qow or 2.0 mg/kg/week.

5.3 Pharmacodynamics

BMN 110 is administered to MPS IVA patients by intravenous infusion, allowing cellular uptake by the CI-M6PR and localization to the lysosomes. GALNS hydrolyzes the sulfate ester bonds from N-acetyl-galactosamine-6-sulfate or galactose-6-sulfate on the non-reducing ends of KS. GALNS does not cleave sulfate groups internal to GAG chains and thus cannot further degrade GAGs without the participation of all enzymes in the degradation pathway (Neufeld, 2001, McGraw-Hill). GALNS has a narrow pH optimum for enzyme activity of between 4.8 and 5.3 (Tomatsu, 2007, Hum.Mol.Genet.), and therefore shows no enzymatic activity at neutral pH (Masue, 1991, J.Biochem.(Tokyo)). BMN 110 is not anticipated to degrade other GAGs or KS outside of the lysosomal compartment due to the lack of activity of BMN 110 at neutral pH, its CI-M6PR-targeted delivery to the lysosomal compartment, and its substrate specificity.

In the absence of a relevant disease model for MPS IVA, the pharmacological activity of BMN 110 was evaluated in vitro in primary human Morquio chondrocytes and a Morquio

fibroblast cell line (Section 4). BMN 110 cellular uptake, trafficking to the lysosomal compartment, and pharmacological activity (clearance of intracellular KS storage) were confirmed in primary human Morquio chondrocytes. Internalization of BMN 110 was confirmed within in vitro studies in human Morquio fibroblasts. A K_{uptake} value of ~2.5 nM (138 ng/mL) was measured in human Morquio fibroblasts and the intracellular $t_{1/2}$ was estimated to be 5-7 days in these same cells. The intracellular $t_{1/2}$ data from these in vitro studies in human cells support the every other week and weekly dosing regimens used in the Phase 3 studies. Incubation of the Morquio chondrocytes with 1 nM (55 ng/mL) BMN 110 resulted in internalization of the enzyme and clearance of stored lysosomal KS. Additionally, treatment with 10 nM (555 ng/mL) BMN 110 induced clearance of KS lysosomal storage and restored a normal expression profile for some chondrogenic genes such as Sox9, a master transcription factor for the chondrogenic lineage. Extracellular KS was not affected by BMN 110 treatment, verifying that BMN 110 activity was restricted to the lysosome.

The distribution of BMN 110 to MPS IVA target tissues (growth plate, liver, and heart valves) and its subsequent trafficking to the lysosomal compartment was demonstrated in BALB/c wild-type mice after single or repeat dose bolus IV injections of BMN 110 via the tail vein. Treatment with BMN 110 results in a rapid and sustained reduction in urine KS, a marker of biologic effect, demonstrating that BMN 110 is capable of breaking down accumulated body and tissue storage of KS (refer to Section 6.5.5). The relationship of urinary KS to other measures of clinical response has not been established.

6 CLINICAL EFFICACY

6.1 Overview of BMN 110 Clinical Efficacy Studies

As discussed above (refer to Section 3), the clinical development program for BMN 110 includes the longitudinal natural history study (MOR-001, or MorCAP), plus 7 clinical studies:

- The initial Phase 1/2 study (MOR-002), plus its extension (MOR-100)
- The pivotal placebo-controlled Phase 3 study (MOR-004), plus its extension (MOR-005)
- Three ongoing Phase 2 studies (MOR-006, MOR-007, MOR-008)

The marketing application includes efficacy data from 5 of the 7 clinical studies in the BMN 110 clinical development program: MOR-002/MOR-100, MOR-004/MOR-005, and MOR-007. Efficacy data from MOR-006 and MOR-008 was not presented due to insufficient data at the data cutoff timepoint.

Summaries of all completed and ongoing studies in the BMN 110 clinical development program are shown in Table 6.1.1.

Table 6.1.1: Overview of Clinical Studies

Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Study Population	Duration of Treatment	Status at time of marketing application submission; Anticipated Date of Last Subject Visit
MOR-001 (MorCAP)[a]	To quantify endurance and respiratory function in subjects with MPS IVA and to better characterize the spectrum of symptoms and biochemical abnormalities in MPS IVA over time.	Natural History Study	Not applicable[b]	325	MPS IVA subjects	Duration of participation[b]: up to 10 years	Ongoing; Oct 2018
MOR-002	Primary objective: • To evaluate the safety of weekly infusions of BMN 110 administered in escalating doses to subjects with MPS IVA.	Phase 1/2, Multicenter, Open-Label, Dose-Escalation Study	BMN 110; Dose-Escalation Period: • Weeks 1-12: 0.1 mg/kg/week • Weeks 13-24: 1.0 mg/kg/week • Weeks 25-36: 2.0 mg/kg/week Optional continuation period: 1.0 mg/kg/week for an additional 36-48 weeks. Weekly 4 to 5 hour intravenous (IV) infusions	20 (actual)	MPS IVA subjects age 5-18 years	Dose-escalation period: 36 weeks Optional continuation period: 36-48 weeks Total duration: 72-84 weeks	Complete; Feb 2011 (actual)

Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Study Population	Duration of Treatment	Status at time of marketing application submission; Anticipated Date of Last Subject Visit
MOR-100	Primary objective: • To evaluate the long-term safety and efficacy of weekly infusions of 2.0 mg/kg of BMN 110 administered in subjects with MPS IVA who participated in MOR-002	Multicenter, Open-Label, Extension Study	BMN 110: 2.0 mg/kg/week 4 hour intravenous (IV) infusions	17 (actual)	MPS IVA subjects who completed MOR-002	Up to 240 weeks	Ongoing; Nov 2015
MOR-004	Primary objective: • To evaluate the ability of 2.0 mg/kg/week BMN 110 and 2.0 mg/kg/qow BMN 110 compared with placebo to enhance endurance in subjects with MPS IVA, as measured by an increase in the number of meters walked in the 6 minute walk test (6MWT) from Baseline to Week 24.	Phase 3, Multinational, Multicenter, Double-blind, Placebo-controlled Study	BMN 110: 2.0 mg/kg/week and 2.0 mg/kg/every other week Placebo 4 hour intravenous (IV) infusions	177 randomized; 176 dosed (actual)	MPS IVA subjects age 5 years and older who are able to walk ≥ 30 and ≤ 325 meters in the 6MWT	24 weeks	Complete; Aug 2012 (actual)

Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Study Population	Duration of Treatment	Status at time of marketing application submission; Anticipated Date of Last Subject Visit
MOR-005	Primary objective: • To evaluate the long-term safety and efficacy of BMN 110 administration at 2.0 mg/kg/week and 2.0 mg/kg/qow in subjects with MPS IVA.	Phase 3 Extension, Multinational, Multicenter, Double-Blind followed by Open-Label Study	BMN 110: Double Blind: 2.0 mg/kg/week and 2.0 mg/kg/every other week Open-Label: 2.0 mg/kg/week as determined after analysis of the final primary efficacy and safety results in MOR-004 4 hour intravenous (IV) infusions	173 (actual)	MPS IVA subjects who completed MOR-004	Up to Week 240	Ongoing; Mar 2017
MOR-006	Primary objective: • To evaluate the efficacy and safety of weekly intravenous (IV) infusions of 2.0 mg/kg BMN 110 in an MPS IVA subject population with limited ambulation (efficacy as defined by the domains of upper extremity function and dexterity, mobility, pain and self-care functional abilities).	Phase 2, Multinational, Open-Label Study	BMN 110: 2.0 mg/kg/week 4 hour intravenous (IV) infusions	Approx. 20 (planned) 2 enrolled as of 14 Sep 2012	MPS IVA subjects age 5 years and older who have severely limited ambulation, defined as an inability to walk $\geq$ 30 meters in the 6MWT	48 weeks	Ongoing; May 2014

Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Study Population	Duration of Treatment	Status at time of marketing application submission; Anticipated Date of Last Subject Visit
MOR-007	Primary objective of the primary treatment phase: • To evaluate safety and tolerability of infusions of BMN 110 at a dose of 2.0 mg/kg/week over a 52-week period in MPS IVA subjects less than 5 years of age Primary objective of the extension phase: • To evaluate the long-term safety of BMN 110 at a dose of 2.0 mg/kg/week in subjects with MPS IVA less than 5 years of age at enrollment	Phase 2, Multinational, Open-Label Study	BMN 110: 2.0 mg/kg/week 4 hour intravenous (IV) infusions	15 with 8 subjects <5 (but ≥3 years of age) (actual)	MPS IVA subjects less than 5 years of age	Primary treatment phase: 52 weeks Total study duration including extension treatment phase: Up to 209 weeks	Ongoing; Jun 2016
MOR-008	Primary objective of the primary treatment phase: • To evaluate the safety of 2.0 and 4.0 mg/kg/week BMN 110 administered for 27 weeks Primary objective of the extension phase: • To evaluate the long-term safety of 2.0 and 4.0 mg/kg/week BMN 110 in subjects with MPS IVA	Phase 2, Randomized, Double-Blind, Multicenter study	BMN 110 2.0 mg/kg/week and 4.0 mg/kg/week 4 hour intravenous (IV) infusions	25 (actual)	MPS IVA subjects age 7 years and older who are able to walk at least 200 meters in the 6MWT	Primary treatment phase: 27 weeks Extension phase: up to 130 weeks Total study duration: Up to 157 weeks	Ongoing; Sep 2015

[a] Morquio Clinical Assessment Program (MorCAP)

[b] No test product is administered in this study.

6.2 Key Design Aspects

Inclusion criteria across the different studies were broad to ensure evaluation of the heterogeneity within the MPS IVA patient population. These criteria included documented clinical diagnosis of MPS IVA based on clinical signs and symptoms and documented reduced GALNS enzyme activity or genetic confirmation.

Opinion-leading clinicians were consulted in regard to optimal Phase 3 study design, and because of the patients' need for frequent surgeries to correct bone and joint deformities, it was imperative to design a study of limited duration to minimize the confounding effects of these procedures. The advanced skeletal damage that exist in these patients make it difficult to show large improvements in measures of mobility. Nonetheless, the 6MWT was selected because it is a relevant, standardized, functional measure that is reasonably easy to conduct and can be performed by many patients with Morquio A Syndrome. The heterogeneous course of Morquio A Syndrome with involvement of multiple organs and tissues makes it difficult to decide on the best primary endpoint, but no other single endpoint more relevant than 6MWT could be identified. 6MWT as a primary endpoint has formed the basis for approval of other treatments for lysosomal storage disorders including Aldurazyme (laronidase), Elaprase (idursulfase) and Myozyme (alglucosidase alfa).

Secondary and tertiary endpoints were selected because they either were used in prior studies of other MPS disorders or were anticipated to provide insight into potential benefits of enzyme replacement therapy for patients with Morquio A Syndrome, based on promising data from the Phase 1/2 study (MOR-002). Consideration was given to primary evaluation of other disease morbidities, but their rate of occurrence was sufficiently low that these could not be considered feasible given the rarity of the disease. Nonetheless, relevant data were collected to facilitate understanding of the overall treatment benefit and to serve as the basis for longer-term registry studies following approval.

The use of these submaximal evaluations of endurance (6MWT and 3MSCT) took into account the physical limitations of the subjects while still providing a measure of clinical benefit. A decline in urine KS excretion, a key biochemical measure of reduction of storage material in these subjects, provided objective evidence of biologic effect (Tomatsu, 2004, Pediatr.Res.), (Tomatsu, 2008, Hum.Mol.Genet.). Results from the MPS Health Assessment Questionnaire (HAQ) were also used to evaluate functional capabilities and performance. In addition, exploratory measures of baseline cardiac, respiratory, and anthropometric measurements allow documentation of long-term impacts of BMN 110 on these clinical disease markers.

The safety assessments from these trials included examinations of treatment-emergent adverse events (AEs); infusion-associated reactions (IARs); Hypersensitivity AEs; clinical laboratory results; vital signs, and physical examination findings; concomitant medications; immunogenicity; and electrocardiogram (ECG) and echocardiogram (ECHO) data.

For MOR-004 and MOR-005 specifically, study site personnel were trained and certified in order to minimize variability in the conduct of 6MWT and 3MSCT endurance tests. In addition to initial training during an Investigator Meeting, an Endurance Testing Quality Assurance Program involved on-site visits to review test procedures, observe, and certify study staff who administered endurance tests. For most sites, these on-site visits occurred prior to enrollment of the first study subject and again after enrollment of approximately two or three study subjects. On-site retraining and recertification occurred in the event of staff changes or investigator requests. A strong effort was made to optimize data quality during the pivotal Phase 3 study by implementing stringent quality measures, thoroughly training sites, and investigators, and vigorously tracking completeness of data throughout the study. This effort resulted in high quality data supporting the validity of the outcomes.

The statistical methods employed in each clinical study are detailed in the prospectively defined statistical analysis plan (SAP) for each study. Statistical analysis plans were prepared for each clinical study prior to database lock and unblinding of the study. The MOR-004 SAP (dated 24AUG2012) and an addendum to the SAP (dated 3OCT2012), which defined the per-protocol population, were finalized prior to data unblinding on 19OCT2012.

MOR-004 inclusion criteria were broad, and subjects enrolled were generally representative of the overall patient population. A total of 204 patients were screened and 177 were randomized. Of the 27 individuals who failed screening, 22 had a Screening 6MWT distance that exceeded the allowable maximum of 325 meters, 3 withdrew consent, and 2 were not randomized for other unspecified reasons.

Several efficacy variables were common across clinical studies and the same instrument and/or protocol was used to collect these data. These variables were endurance measures (6MWT and 3MSCT, for study populations in which these endpoints were appropriate), respiratory function tests, and anthropometry.

6.3 Phase 1/2 Study MOR-002

MOR-002 is a completed Phase 1/2, multicenter, open-label, dose-escalation study, designed to evaluate the safety, tolerability, and efficacy of BMN 110 in subjects with MPS IVA. This study enrolled 20 subjects aged 5 to 18 years. No minimum or maximum performance in the 6MWT was required as a condition of enrollment. Subjects who completed the 36-week

Dose-Escalation Period (consisting of 3 consecutive 12 week dosing periods of 0.1, 1.0, and 2.0 mg/kg/week), had the option to continue BMN 110 treatment with weekly doses of 1.0 mg/kg for an additional 36 to 48 weeks. During this Continuation Period, an interim analysis of data from the Dose-Escalation Period was conducted to determine the highest dose level that was well tolerated and that provided maximal improvement in plasma and/or urine KS levels. Efficacy assessments included endurance tests, respiratory function tests (RFT), plasma KS concentration, urine KS normalized to creatinine, anthropometric measurements, and an MPS Health Assessment Questionnaire (HAQ). After concluding the MOR-002 study, subjects were given the option to transition to a separate long-term, open-label treatment protocol, MOR-100, in which they would be treated at the optimal dose determined from the interim analysis of data from the Dose Escalation Period.

6.3.1 MOR-002 Demographics and Baseline Characteristics

Baseline demographics data for the 20 patients who enrolled in Study MOR-002 are provided in Table 6.3.1.1 and their Baseline characteristics are provided in Table 6.3.1.2.

Table 6.3.1.1: Demographics at Baseline All Enrolled Patients (MOR-002)

Characteristic	Dose-Escalation Period (n = 20)
Age at enrollment, years	
n	20
Mean (SD)	8.0 (2.89)
Median	7.5
Min , Max	4 , 16
Age category	
≥ 4 to < 8	10 (50.0%)
≥ 8 to < 10	6 (30.0%)
≥ 10 to ≤ 18	4 (20.0%)
Sex	
Male	12 (60.0%)
Female	8 (40.0%)
Race	
Asian	9 (45.0%)
White	9 (45.0%)
Other	2 (10.0%)
Ethnicity	
Not Hispanic Or Latino	20 (100.0%)

f, frequency; SD, standard deviation.

As shown in Table 6.3.1.2, the mean ± SD weight and height at Baseline were 22.4 ± 14.7 kg and 102.3 ± 19.8 cm, respectively. The heights of 15 patients (75.0%) were below the 3rd percentile of normal height for their age (one patient's height was missing). Sixteen patients (80.0%) used a wheelchair and two patients (10.0%) used walking aids at Baseline. "Wheelchair use" could include both patients who were wheelchair bound and those who used wheelchairs only on an as-needed basis.

Table 6.3.1.2: Baseline Characteristics All Enrolled Patients (MOR-002)

Characteristic	**Dose-Escalation Period (n = 20)**
Weight, kg	
n	20
Mean (SD)	22.4 (14.74)
Median	17.90
Min , Max	11.4 , 67.3
Standing height, cm	
n	19
Mean (SD)	102.3 (19.79)
Median	98.80
Min , Max	74.3 , 154.9
Body Mass Index, kg/m^2	
n	19
Mean (SD)	19.7 (3.57)
Median	18.90
Min , Max	15.2 , 28.0
< 30th Percentile	19 (95.0%)
Missing	1 (5.0%)
Height percentile groups	
< 3rd percentile	15 (75.0%)
≥ 3rd to < 10th percentile	1 (5.0%)
≥ 10th to < 25th percentile	1 (5.0%)
≥ 25th to < 50th percentile	1 (5.0%)
≥ 75th percentile	1 (5.0%)
Missing	1 (5.0%)
Use of Wheelchairs	16 (80.0%)
Use of Walking Aids	2 (10.0%)

SD, standard deviation.

Note: Walking aids include braces, AFOs, splints, crutches, cane, and walker.

Baseline values from the 6MWT and 3MSC test are presented in Table 6.3.1.3.

Table 6.3.1.3: Baseline Observed Values from the 6MWT and 3MSC Test (MOR-002)

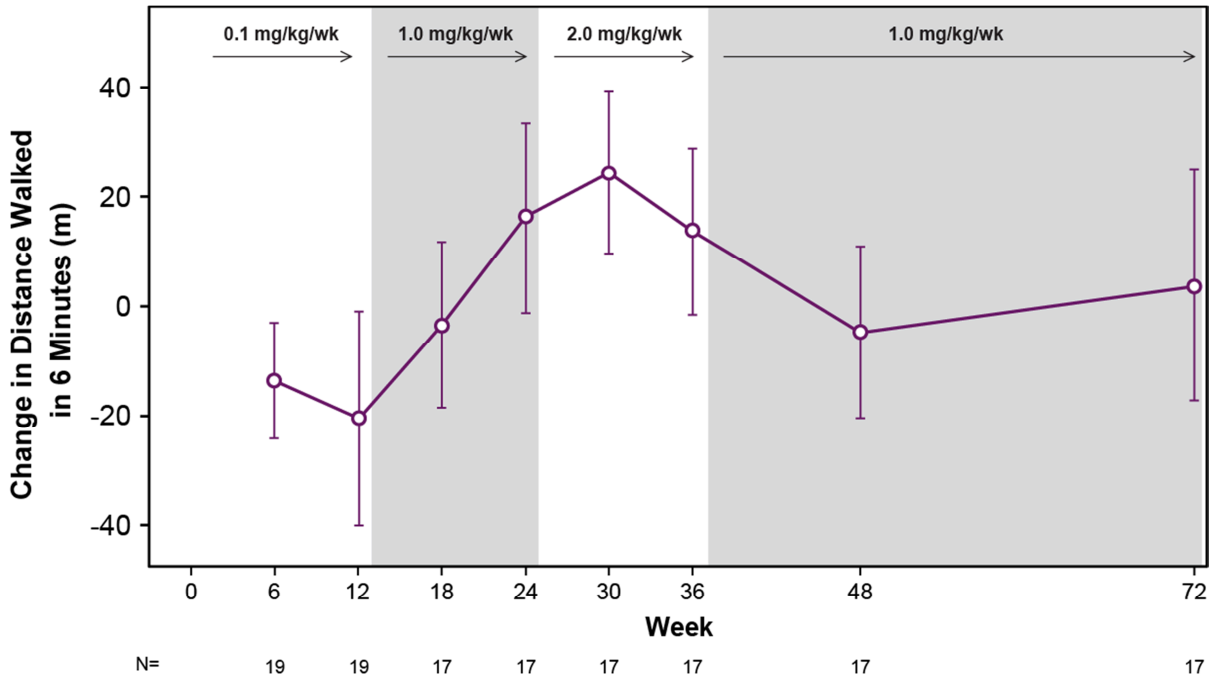
Baseline Test Results	Observed Value
6MWT	Meters
n	20
Mean (SD)	266.9 (137.39)
Median	257.7
Min , Max	0.0 , 511.0
3MSC Test	Stairs Per Minute
n	20
Mean (SD)	38.9 (25.39)
Median	32.6
Min , Max	0.0 , 115.0

6.3.2 MOR-002 Efficacy Results

6MWT:

In MOR-002, the 6MWT distance increased at Weeks 24 and 36 of the Dose-Escalation Period in conjunction with increasing dose of BMN 110, with the initial increase coming 12 weeks after the dose was changed from 0.1 mg/kg/week to 1 mg/kg/week and concomitant with the increase in dose to 2.0 mg/kg/week. The mean change from Baseline was 16.3 meters at Week 24 and 13.8 meters at Week 36. After decreasing the dose in the Continuation Period, the mean change from Baseline at Week 72 was 4.0 meters (refer to Figure 6.3.2.1).

Figure 6.3.2.1: Mean Change from Baseline in Total Distance Walked During 6-Minute Walk Test versus Study Week (MOR-002 ITT Population)



Note: Error bar refers to standard error.

3MSCT:

The 3MSCT mean stair climb rate minimally changed from Baseline at end of Week 12, then increased by 6.1 stairs/min at the end of Week 24, and then by 7.8 stairs/min at the end of Week 36. After decreasing the dose in the Continuation Period, the mean change from Baseline at Week 72 was 9.7 stairs/min.

Normalized Urine KS:

Mean-normalized urine KS consistently declined in a dose-dependent manner during the study, with mean percent decreases from Baseline of 23.2% at Week 12 (0.1 mg/kg/week), 27.9% at Week 24 (1.0 mg/kg/week), and 40.6% at Week 36 (2.0 mg/kg/week). After the BMN 110 dose was reduced to 1.0 mg/kg/week in the Continuation Period, mean urine KS values trended upwards, to a mean percent decrease from Baseline of 32.2% at Week 72.

Respiratory Function:

Most RFT means increased from Baseline during the 36-week Dose-Escalation Period, with continued increase through the Continuation Period (Week 72). Mean percent increases from Baseline at Week 72 were 8.4% for forced expiratory volume in 1 second (FEV_1), 10.1% for total lung capacity (TLC), 12.5% for forced vital capacity (FVC), 18.4% for maximum

voluntary ventilation (MVV), 18.7% for forced inspiratory vital capacity (FIVC), and 61.7% for forced expiratory time (FET).

Anthropometric Measurements:

After 72 weeks of treatment, mean anthropometric measurements all increased from Baseline: length by 5.3 cm; sitting and standing height by 2.3 cm; right knee mean height by 1.5 cm and left knee mean height by 1.7 cm; and weight by 2.6 kg.

Health Assessment Questionnaire:

Baseline capability was moderately impaired as reflected by Self-Care Domain and Mobility Proficiency Domain mean scores, which were mid-range at Baseline (5.0 ± 2.96 and 4.9 ± 2.69, respectively). The mean Caregiver Assistance score was mid-range at Baseline, 31.3 (± 8.86) (12 to 48, with 48=complete assistance required). There was minimal change of unclear significance in the mean HAQ category scores during the course of the study.

6.4 Phase 1/2 Extension Study MOR-100

MOR-100 is an ongoing multicenter, multinational, open-label extension study designed to assess long-term safety and efficacy of BMN 110 infusions of 2.0 mg/kg weekly in subjects with MPS IVA who were enrolled in any BioMarin-sponsored BMN 110 clinical study, except MOR-004. As of this date, only the 17 subjects from MOR-002 have enrolled in this study, and results are presented from the baseline values of MOR-002 to the data cutoff date of 19JUL2012 for MOR-100.

Of the 17 subjects enrolled in MOR-100, 17 subjects have completed 74 to 87 weeks of treatment, no subjects have discontinued study participation early, and no subjects have permanently discontinued study drug.

6.4.1 MOR-100 Demographics and Baseline Characteristics

Baseline demographics data for the 17 patients who enrolled in Study MOR-100 are provided in Table 6.4.1.1 and their Baseline characteristics are provided in Table 6.4.1.2. Both sets of data are presented along with the overall MOR-002 population for comparison.

Table 6.4.1.1: Demographics at MOR-002 Baseline (Intent-to-Treat Population – MOR-100)

Demographics	MOR-002 (n = 20)	MOR-100 (n = 17)
Age at Enrollment (years)		
n	20	17
Mean (SD)	8.4 (2.90)	8.1 (2.78)
Median	7.9	7.5
Min , Max	4.9, 16.1	4.9, 16.1
Age Group		
≥ 4 to < 8	10 (50.0%)	9 (52.9%)
≥ 8 to < 10	5 (25.0%)	5 (29.4%)
≥ 10 to ≤18	5 (25.0%)	3 (17.6%)
Sex		
Female	8 (40.0%)	8 (47.1%)
Male	12 (60.0%)	9 (52.9%)
Race		
American Indian or Alaska Native	0	0
Asian	9 (45.0%)	8 (47.1%)
Black or African American	0	0
Native Hawaiian or Pacific Islander	0	0
White	9 (45.0%)	9 (52.9%)
Other	2 (10.0%)	0
Ethnicity		
Hispanic or Latino	0	0
Not Hispanic or Latino	20 (100.0%)	17 (100.0%)

SD, standard deviation.

Demographics evaluated at the time of enrollment to MOR-002

In the group including all subjects enrolled into MOR-100, the mean (±SD) weight at Baseline was 22.6 (± 14.73) kg and the mean subject standing height was 102.3 (±19.79) cm. The majority of subjects (75% of those enrolled in MOR-002 and 82.4% of those

continuing in MOR-100) had short stature at MOR-002 baseline, categorized in the < 3rd percentile for age per Center for Disease Control (CDC) pediatric normal growth curves.

The mean (±SD) Baseline 6MWT distance was 266.9 (± 137.39) meters, mean (±SD) Baseline 3MSCT performance was 38.9 (± 25.39) stairs/minute, and mean (±SD) Baseline urine KS (normalized to creatinine) was 26.9 (±12.72) µg/mg. In MOR-002, 16 (80%) subjects used wheelchairs and 2 (10%) subjects used a walker; in MOR-100 13 (76.5%) subjects used wheelchairs and 1 (5.9%) subject used a walker (Table 6.4.1.2). Due to the heterogeneity of the disease, subjects had a wide variation in their functional impairment and organ system involvement.

Table 6.4.1.2: Baseline Characteristics at MOR-002 Baseline (Intent-to-Treat Population – MOR-100)

	MOR-002 (n = 20)	MOR-100 (n = 17)
6-minute Walk Test (meters)		
n	20	17
Mean (SD)	266.9 (137.39)	251.2 (116.86)
Median	257.7	256.0
25th , 75th Percentile	186 , 375	192 , 305
Min , Max	0 , 511	0 , 435
≤ 325 m	14 (70.0%)	13 (76.5%)
> 325 m	6 (30.0%)	4 (23.5%)
Walking Aids Used[a]		
Braces, Afos, Splints	1 (5.0%)	1 (5.9%)
Walker	2 (10.0%)	1 (5.9%)
None	18 (90.0%)	16 (94.1%)
Wheelchair Use[a]		
No	4 (20.0%)	4 (23.5%)
Yes	16 (80.0%)	13 (76.5%)

SD, standard deviation

Baseline Characteristics evaluated at the time of enrollment to MOR-002.

[a] Walking aids and wheelchair use defined per MPS-HAQ. Subjects may have used more than one type of walking aid.

6.4.2 MOR-100 Efficacy Results

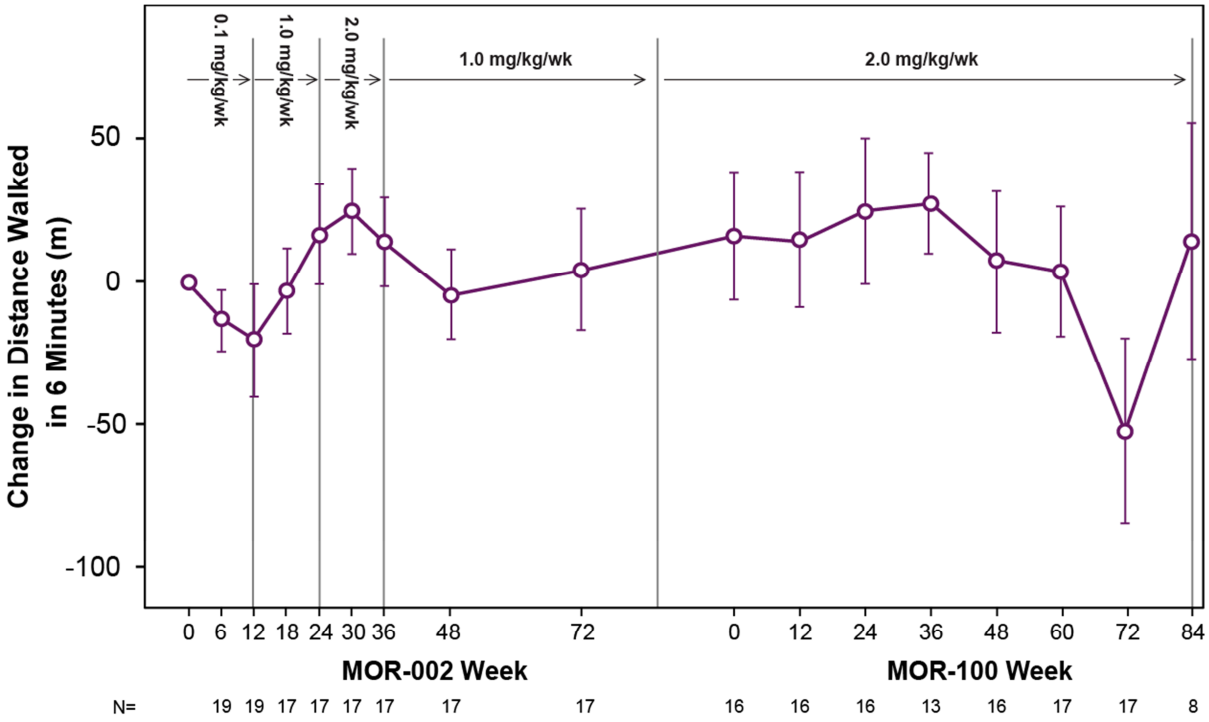
Based on the results of the MOR-002 study, the dose was increased from 1.0 mg/kg/week to 2.0 mg/kg/week at the Baseline visit of MOR-100.

6MWT:

After subjects were treated with BMN 110 for 72 to 84 weeks in MOR-002, an additional 84 weeks of treatment in MOR-100 led to sustained improvement in 6MWT distances at the majority of study visits. The mean (±SD) increase in 6MWT distance in the Intent-to-Treat (ITT) population from MOR-002 Baseline to MOR-100 Baseline was 15.6 (± 88.84) meters; the mean increase from MOR-002 Baseline to MOR-100 Week 12 was 14.5 (± 94.69) meters, to MOR-100 Week 24 was 24.5 (±101.23) meters; to MOR-100 Week 36 was 27.2 (±62.51) meters; to MOR-100 Week 48 was 6.8 (±98.66) meters; to MOR-100 Week 60 was 3.4 meters (±93.24) meters to MOR-100 Week 72 was -52.7 (±133.78) meters; and to MOR-100 Week 84 was 13.9 (±116.44) meters (only 8 subjects had evaluable data at Week 84 as of the data cutoff for this report).

The decline assessed in 6MWT at Week 72 was primarily driven by 4 subjects with orthopedic surgery within 4 weeks prior to the Week 72 assessment. Overall, the range of 6MWT increase during MOR-100 was consistent with increases seen during the MOR-002 Dose Escalation Period (Figure 6.4.2.1).

Figure 6.4.2.1: Mean Change From Baseline in Total Distance Walked During 6-Minute Walk Test versus Study Week
Analysis Population: Intent-to-Treat (MOR-002/MOR-100)



N = number of subjects at each time point
Note: Error bar refers to standard error.

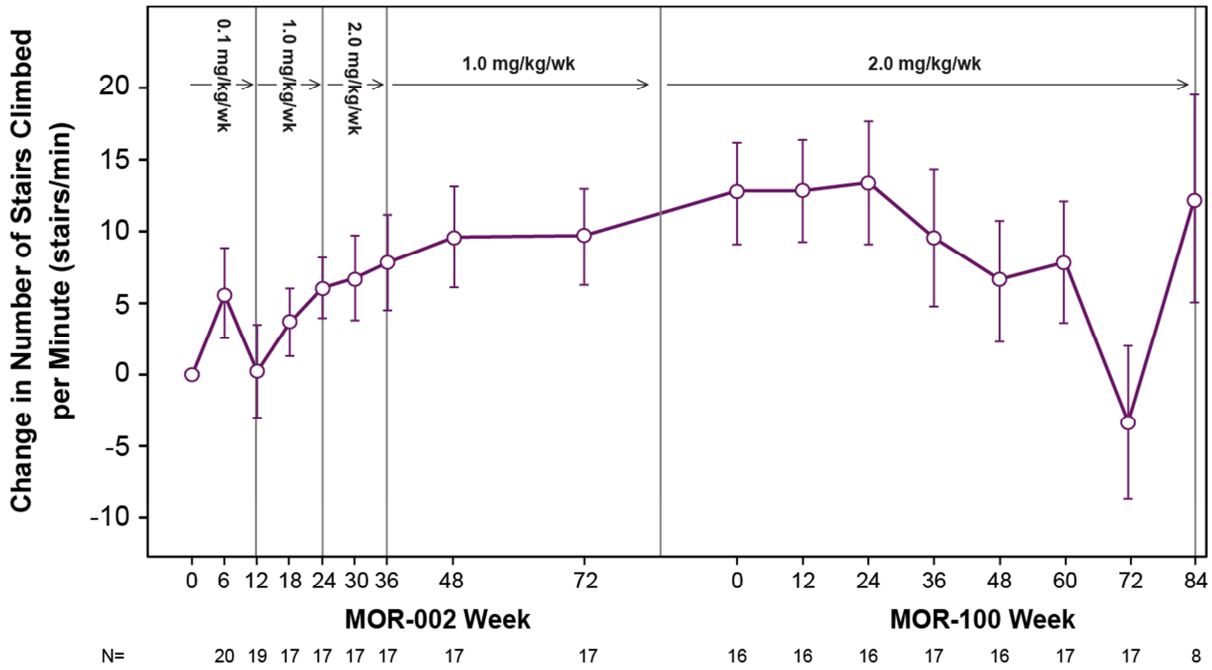
3MSCT:

After subjects were treated with BMN 110 for 72 to 84 weeks in MOR-002, an additional 84 weeks of treatment led to sustained improvements in 3MSCT at the majority of study visits. The mean (±SD) increase in 3MSCT in the ITT population from MOR-002 Baseline to MOR-100 Baseline was 12.7 (±13.96) stairs/min; to MOR-100 Week 12 was 12.9 (±14.51) stairs/min; to MOR-100 Week 24 was 13.4 (±17.07) stairs/min; to MOR-100 Week 36 was 9.6 (±19.63) stairs/min; to MOR-100 Week 48 was 6.6 (±16.87) stairs/min; to MOR-100 Week 60 was 7.9 (±17.30) stairs/min; to MOR-100 Week 72 was -3.3 (±21.97) stairs/min; and to MOR-100 Week 84 was 12.3 (±20.59) stairs/min (only 8 subjects had available data at Week 84 as of the data cutoff for this marketing application).

The large decline assessed in 3MSCT at Week 72 was primarily driven by 4 subjects with orthopedic surgery within 4 weeks prior to the Week 72 assessment. The increase in 3MSCT

rate during the first 24 weeks of the MOR-100 study was sustained at a higher level than during the MOR-002 Dose Escalation Period (Figure 6.4.2.2).

Figure 6.4.2.2: Mean Change from Baseline in Number of Stairs Climbed Per Minute During 3 Minute Stair Climb Test Vs Study Week
Analysis Population: Intent-to-Treat (MOR-002/MOR-100)



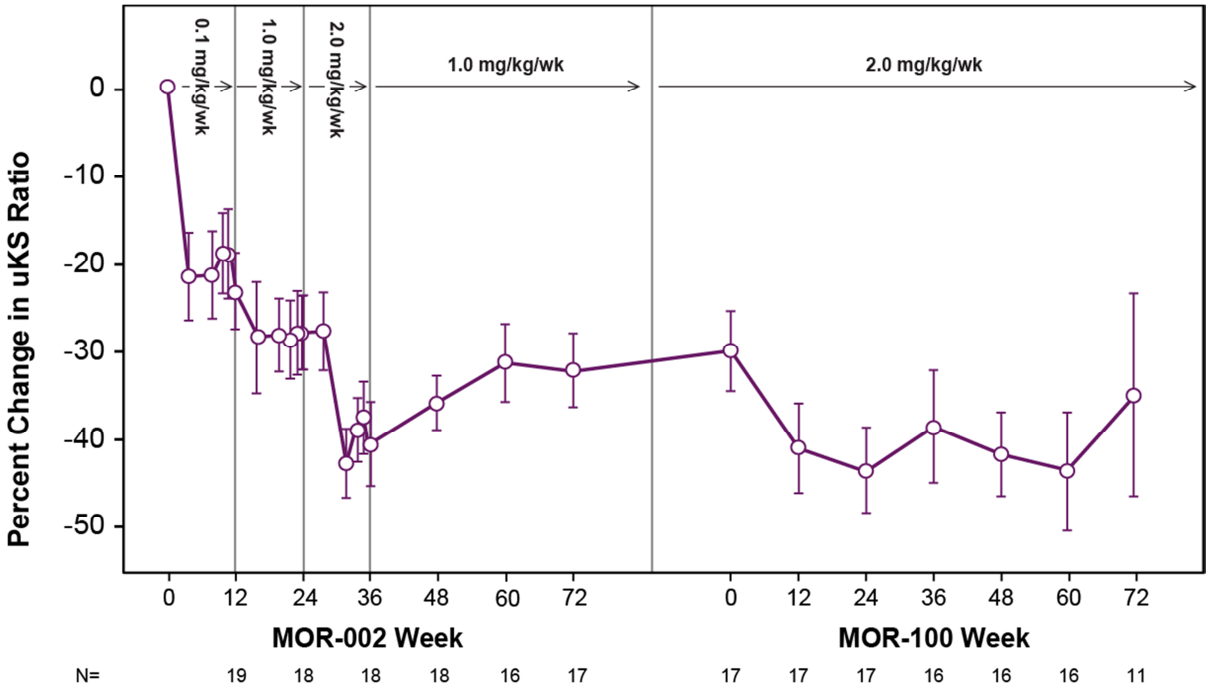
N = number of subjects at each time point
Note: Error bar refers to standard error.

Normalized Urine KS:

After subjects were treated with BMN 110 for 72 to 84 weeks in MOR-002, an additional 72 to 84 weeks of treatment produced a similar level of reduction in normalized urine KS comparable to that seen during dosing in MOR-002 at 2.0 mg/kg/week. (Data was not available for urine KS at Week 84 at the time of the data cutoff). Based on the results of the MOR-002 study, the dose was increased from 1.0 mg/kg/week to 2.0 mg/kg/week at the Baseline visit of MOR-100. The mean (±SD) percent decrease in urine KS in the ITT population from MOR-002 Baseline to MOR-100 Baseline was 30.0 (± 19.23)%; the mean percent decrease from MOR-002 Baseline to MOR-100 Week 12 was 41.1 (± 20.72)%; to MOR-100 Week 24 was 43.6 (±19.56)%; to MOR-100 Week 36 was 38.7 (± 25.73)%; to MOR-100 Week 48 was 41.9 (±19.29)%; to MOR-100 Week 60 was 43.7 (± 26.92)%; and to MOR-100 Week 72 was 35.1 (±38.19)%.

The increase in urine KS observed from Week 60 to Week 72 may have been spurious because of the smaller number of samples available. Urine KS values were consistently lower during dosing at 2.0 mg/kg/week during both studies MOR-002 and MOR-100 (Figure 6.4.2.3).

Figure 6.4.2.3: Mean Percent Change from Baseline in Urine Keratan Sulfate Creatinine Ratio vs Study Week
Analysis Population: Intent-to-Treat (MOR-002/MOR-100)



N = number of subjects at each time point
Note: Error bar refers to standard error.

Respiratory Function Tests:

After subjects were treated with BMN 110 for 72 to 84 weeks in MOR-002, an additional 72 weeks of treatment led to sustained improvements in respiratory function at the majority of study visits. (RFT assessments are not performed at Week 84). The mean (± SD) percent increases in MVV and FVC in the ITT population from MOR-002 Baseline to MOR-100 Baseline were 11.1 (± 16.44)% and 11.8 (± 14.97)%, respectively; mean percent increases in MVV and FVC from MOR-002 Baseline to MOR-100 Week 24 were 9.8 (± 22.25)% and 15.3 (± 16.31)%, respectively; to MOR-100 Week 48 were 3.5 (± 17.78)% and 15.8 (± 16.56)%, respectively; and to MOR-100 Week 72 were 10.1(± 27.83)% and 16.1 (± 21.96)%, respectively. MVV improvement at MOR-002 Week 24 was sustained

through MOR-100 Week 72. FVC continued to improve through MOR-100 Week 24. This improvement was maintained through Week 72.

6.5 Phase 3 Study MOR-004

MOR-004 is a completed Phase 3, randomized, double-blind, placebo-controlled, multinational study in subjects with MPS IVA, designed to evaluate the efficacy and safety of BMN 110 at 2.0 mg/kg/week and 2.0 mg/kg/every other week (qow) in a subject population ≥ 5 years of age with an average baseline 6MWT distance ≥ 30 and ≤ 325 meters. The study compared BMN 110 infusions with placebo in 176 subjects in pre-adolescent (5 to 11 years), adolescent (12 to 18 years), and adult (≥ 19 years old) age groups, which enabled evaluation of safety, efficacy, and immunogenicity between each active-dose group and the placebo group over 24 weeks.

A duration of 24 weeks was chosen to determine the effects of BMN 110 on measures of endurance in subjects with MPS IVA. This study duration was informed by data from Study MOR-002 showing median improvements from Baseline in 6MWT of 42 meters (of subjects with a Baseline walk <325 meters) and 3MSCT of 7.3 stairs/minute at Week 24. This is also supported by the duration of Phase 3 pivotal trials for other ERTs; Naglazyme (24 weeks) and Aldurazyme (26 weeks).

The feasibility of collecting endurance data over longer durations in subjects with MPS IVA is limited by the frequent need for MPS IVA patients to undergo orthopedic surgeries; it would be inappropriate to prohibit these procedures for more than 6 months, particularly in growing children. In addition, based upon the time course of antibody development and PD markers observed in MOR-002 and other ERT trials, it was expected that 24 weeks would be sufficient to evaluate the effect of antibody development and detect decreases in urine of the lysosomal storage marker KS.

In MOR-004, randomization was stratified by 2 factors: screening 6MWT categories (≤200 meters and >200 meters) and age group. The 3 age stratifications (5-11, 12-18, and ≥19 years old) represent pre-adolescent, adolescent, and adult age groups. Because MPS IVA patients have a shortened lifespan, with many not surviving beyond the second decade, it was expected that the mean age of subjects enrolled would be heavily skewed toward patients 18 years of age and younger, and this could result in imbalance between treatment arms if just a few adults were randomized to a single arm. These specific age strata are supported by the balanced mean age distribution between treatment arms in a Phase 3 study using a similar design in patients with a similar disease, MPS II, also known as Hunter syndrome (Muenzer, 2006, Genet.Med). In addition, patients with lysosomal storage disorders experience growth abnormalities and progressive deterioration in multiple body systems; treatment initiation at

an older age, after growth plates are fused and after development of severe, irreversible manifestations of disease may result in less measurable improvement. Therefore, presence of both pre-adolescent and adolescent subjects was required for each treatment arm.

Subjects were required to have an average 6MWT distance ≥30 and ≤325 meters at Screening to be included in the study. The minimum enrollment distance of 30 meters was chosen because, according to key opinion leaders in MPS IV disease management, patients with a greater severity of walk limitation are likely to have limited potential for improvement in the walk test, although improvements in other functional domains might be feasible. The upper limit of 325 meters represented approximately the 75th percentile of 6MWT distance results in an ongoing observational clinical assessment program of MPS IVA patients (MOR-001, MorCAP). There was no inclusion criterion based on a patient's baseline ability in the 3MSCT. MOR-004 inclusion criteria were broad, and subjects enrolled were generally representative of the overall patient population.

All subjects received weekly double-blind infusions of 2.0 mg/kg of study drug. The 2.0 mg/kg/week group received active drug every week, the 2.0 mg/kg/qow group received BMN 110 and placebo infusions on alternating weeks for a total of 24 consecutive weeks. As subjects may experience hypersensitivity reactions associated with the administration of BMN 110, antihistamine was administered prior to infusions for all patients as specified in the protocol. Pretreatment with an antipyretic or other medications (eg, steroids, H2 blockers, etc.) may have been given at the Investigator's discretion. Premedication was administered across the program as specified in each clinical protocol. Vital signs were measured just before, during, and immediately following the infusion. Adverse events and concomitant medications were recorded throughout the study.

Clinical laboratory tests were performed at Screening, Baseline, and every 6 weeks. At Screening and/or Baseline and every 12 weeks duplicate endurance testing (6MWT and 3MSCT) and physical examinations were performed, MPS Health Assessment Questionnaire were completed, and blood samples for evaluating exploratory biomarkers were collected. Blood samples for immunogenicity testing and urine samples for urine KS and urine creatinine were collected at Baseline, Week 2, Week 4, and every 4 weeks thereafter. Respiratory function testing and anthropometric measurements were performed at Baseline and Week 24. At selected sites, audiometry examinations were performed at Baseline and Week 24. Echocardiograms and ECGs were performed at Screening and at Week 24. Cervical spine radiographs were performed at Screening. Radiographs of the lumbar spine were performed at Baseline. Patients ≤ 20 years old underwent radiographs of the lower extremity at Baseline and Week 24.

Blood samples for PK analysis were obtained at Weeks 0 and 22 at selected sites from approximately 65 subjects (17 placebo, 24 BMN 110 2.0 mg/kg/week, 24 BMN 110 2.0 mg/kg/qow).

An independent Data Monitoring Committee (DMC) appointed by BioMarin acted in an advisory capacity to BioMarin to monitor subject safety and efficacy of BMN 110. In addition, an independent Allergic Reaction Review Board (ARRB), appointed by BioMarin, served as consultants for severe or serious infusion associated reactions (IARs) during the study. The ARRB was also available to provide recommendations regarding the appropriate prevention and management of IARs.

All subjects who completed MOR-004 were eligible to receive BMN 110 in the extension study, MOR-005.

6.5.1 Statistical Methods for Efficacy Analysis in MOR-004

In MOR-004, the Week 24 change from Baseline in the 6MWT distance was the primary efficacy endpoint. In all analyses of this endpoint, the treatment effect of each active treatment group was compared with the treatment effect of the placebo group. The Hochberg method (Hochberg, 1988, Biometrika) was used for the multiplicity adjustment to maintain the overall Type I error rate of 0.05. The result was considered positive if the two comparisons of active drug regimens to placebo both result in $P<0.05$ or comparison of either drug regimen to placebo results in $P<0.025$.

The primary analysis of the primary endpoint was the analysis of covariance (ANCOVA) of the Week 24 change from Baseline in the 6MWT measurement using a model with treatment, age stratification (5–11, 12–18, ≥ 19 years), and Baseline 6MWT stratification (≤ 200 meters and > 200 meters) as factors. Each active treatment group was compared to the placebo group using contrasts and P values calculated using the t test. Least squares (LS) means and confidence interval (CI) for the two treatment effects were also provided. There were only 2 missing assessments of 6MWT and the two values were imputed using multiple imputation. A number of additional prespecified supportive, sensitivity, and subgroup analyses were also performed on the primary endpoint.

The secondary efficacy endpoints were: Week 24 change from Baseline in 3MSCT compared to placebo and Week 24 percent change from Baseline in urine KS compared to placebo. The number of stairs climbed per minute in the 3MSCT and normalized urine KS were analyzed similarly to the 6MWT. Additional tertiary efficacy endpoints were also analyzed similarly to the 6MWT.

6.5.1.1 Responder Analysis

Responder analyses were performed to look across all levels of change as represented by a cumulative distribution function (CDF). The CDF shows a continuous plot of the proportion of subjects at each point along the continuum of change in the measure (McLeod, 2011, Expert Rev Pharmacoecon.Outcomes.Res), an approach that offers the benefit of visually comparing the separation between groups across all levels of change so that a variety of responder definitions can be considered simultaneously. In a rare disease setting such as MPS IVA, this approach is preferred over applying a categorical responder definition due to the limitations in sample size and the potential loss of statistical power to detect a treatment effect.

In addition, prior to initiation of the pivotal MOR-004 study, efforts were made to define a MCID for key efficacy variables through a literature review and through consultation with leading experts in the treatment of MPS IVA using a Delphi panel. Given the lack of published human data and the highly variable, multi-systemic nature of the disease, it was difficult to reach consensus on a discrete numerical threshold of improvement that would be clinically meaningful for all patients. Research on MCID in 6MWT reveals that at lower levels of baseline function, smaller improvements can result in clinically meaningful changes, while at higher levels of baseline function, larger increases may be necessary to achieve the same degree of clinical benefit (Henricson, 2013, PLoS Curr). This principle makes defining a MCID by an absolute threshold difficult in a heterogeneous disease such as Morquio A Syndrome, which presents with a wide spectrum of symptoms and disease severity.

Nonetheless, values were established prior to database lock in MOR-004 for clinically meaningful responses in three key efficacy measures (6MWT, 3MSCT, and MVV). Consensus recommendations for the responder definition threshold, expressed as the percent change improvement from Baseline after 24 weeks of treatment, were as follows:

- A 15% change for the 6MWT
- A 20% change for the 3MSCT
- A 20% change for MVV

Responder analyses, based on these thresholds for 6MWT, 3MSCT, and MVV were performed.

6.5.2 MOR-004 Demographics and Baseline Characteristics

A total of 204 patients were screened and 177 were randomized. One randomized subject was not dosed because the diagnosis of MPS IVA was not confirmed and, in accordance with the prespecified SAP, this subject was excluded from all analyses.

Of the 176 subjects in the ITT population, 59 were randomized to placebo, 59 to BMN 110 2.0 mg/kg/qow, and 58 to BMN 110 2.0 mg/kg/week. Of the 176 subjects in the ITT population, 175 (99.4%) completed the study, 1 (0.6%) discontinued from the study (Subject 0050-4090, BMN 110 2.0 mg/kg/week), and no subjects permanently discontinued study drug. All study drug infusions were administered at a clinical site. Subjects in each treatment group received a similar mean number of infusions, had a similar mean number of incomplete infusions, and all treatment groups achieved similar and high mean dosing compliance (range 96.8% to 99.2%). Although variability in some demographic and baseline characteristics was evident, there were no meaningful imbalances between treatment groups in the ITT Population at Baseline in demographic and other Baseline parameters, notably including disease state characteristics.

Age of study subjects at enrollment ranged from 5 to 57 years and, as expected in this subject population, the most frequently represented age group was 5 to 11 years (Table 6.5.2.1). Distribution of age groups was generally similar across treatment groups. The proportion of males and females was approximately equal across treatment groups.

Table 6.5.2.1: Baseline Demographics (Intent-to-Treat Population – MOR-004)

	Placebo (n = 59)	BMN 110 2.0 mg/kg/qow[a] (n = 59)	BMN 110 2.0 mg/kg/week (n = 58)
Age at Enrollment (years)			
n	59	59	58
Mean (SD)	15.0 (11.30)	15.3 (10.79)	13.1 (8.10)
Median	11.9	12.0	11.1
Min , Max	5 , 57	5 , 49	5 , 42
Age Group (years)[b]			
5 - 11	30 (50.8%)	31 (52.5%)	32 (55.2%)
12 - 18	15 (25.4%)	16 (27.1%)	16 (27.6%)
≥ 19	14 (23.7%)	12 (20.3%)	10 (17.2%)
Sex			
Female	32 (54.2%)	25 (42.4%)	32 (55.2%)
Male	27 (45.8%)	34 (57.6%)	26 (44.8%)
Race			
Asian	11 (18.6%)	15 (25.4%)	14 (24.1%)
Black or African American	0	2 (3.4%)	2 (3.4%)
White	44 (74.6%)	35 (59.3%)	36 (62.1%)
Other	4 (6.8%)	7 (11.9%)	6 (10.3%)
Ethnicity			
Hispanic or Latino	13 (22.0%)	16 (27.1%)	9 (15.5%)
Not Hispanic or Latino	46 (78.0%)	43 (72.9%)	49 (84.5%)
Region			
North America	16 (27.1%)	16 (27.1%)	15 (25.9%)
Europe	27 (45.8%)	21 (35.6%)	25 (43.1%)
Other	16 (27.1%)	22 (37.3%)	18 (31.0%)

[a]qow, every other week; SD, standard deviation; [b]Stratification Factor.

Baseline disease characteristics were similarly distributed across treatment groups (Table 6.5.2.2). With respect to the primary efficacy measurement, Baseline 6MWT distance ranged from 36 to 322 meters. Subjects in the placebo group walked further at baseline in the 6MWT (211.9 meters) compared to the BMN 110 2.0 mg/kg/qow (205.7 meters) or BMN 110 2.0 mg/kg/week (203.9 meters) groups. The proportion of subjects with walk categories ≤200 meters and >200 meters, which was a stratification factor, was balanced

between groups. With respect to secondary efficacy measurements, Baseline 3MSCT performance and urine KS levels were similar across treatment groups. Baseline 3MSCT performance ranged from 0 to 72 stairs/min and Baseline urine KS ranged from 2 to 117 µg/mg. The proportion of subjects who used walking aids at Baseline was higher in the BMN 110 2.0 mg/kg/qow group (27.1%) compared to the placebo (18.6%) or BMN 110 2.0 mg/kg/week (15.5%) groups.

In the placebo, BMN 110 2.0 mg/kg/qow, and BMN 110 2.0 mg/kg/week groups, respectively, mean standing height (105.5, 104.6, 101.3 cm) and mean weight (25.4, 26.5, 22.9 kg) of study subjects was similar across treatment groups. Most subjects were in the $<3^{rd}$ percentile height category in the placebo (91.5%), BMN 110 2.0 mg/kg/qow (88.1%), and BMN 110 2.0 mg/kg/week (96.6%) treatment groups.

Due to the heterogeneity of the disease, subjects had a wide variation in their functional impairment and organ system involvement.

Table 6.5.2.2: Baseline Characteristics (Intent-to-Treat Population – MOR-004)

	Placebo (n = 59)	BMN 110 2.0 mg/kg/qow[a] (n = 59)	BMN 110 2.0 mg/kg/week (n = 58)
6-Minute Walk Test (meters)			
n	59	59	58
Mean (SD)	211.9 (69.88)	205.7 (81.19)	203.9 (76.32)
Median	228.9	218.0	216.5
Min , Max	36 , 312	47 , 320	42 , 322
Walk Category[b]			
<= 200m	23 (39.0%)	24 (40.7%)	23 (39.7%)
> 200m	36 (61.0%)	35 (59.3%)	35 (60.3%)
Walking Aids Used during 6MWT[c]			
Any	11 (18.6%)	16 (27.1%)	9 (15.5%)
Crutches	4 (6.8%)	3 (5.1%)	1 (1.7%)
Walker/Walking Frame	6 (10.2%)	12 (20.3%)	7 (12.1%)
Cane/Walking Stick	1 (1.7%)	1 (1.7%)	1 (1.7%)
None	48 (81.4%)	43 (72.9%)	49 (84.5%)
3-Minute Stair Climb Test (stairs/minute)			
n	59	59	58
Mean (SD)	30.0 (14.05)	27.1 (15.80)	29.6 (16.44)
Median	30.8	25.5	30.5
Min , Max	0 , 59	0 , 67	0 , 72
Normalized Urine KS[d] (ug/mg)			
n	58	59	58
Mean (SD)	25.7 (15.09)	28.6 (21.17)	26.9 (14.11)
Median	26.7	27.4	24.1
Min , Max	2 , 53	2 , 117	2 , 59

[a]qow, every other week; SD, standard deviation

[b]Stratification Factor.

[c] walking aids used in 6MWT include crutches, walker/walking frame and cane/walking stick.

[d] normalized urine KS (keratan sulfate) is calculated as urine keratan sulfate divided by urine creatinine.

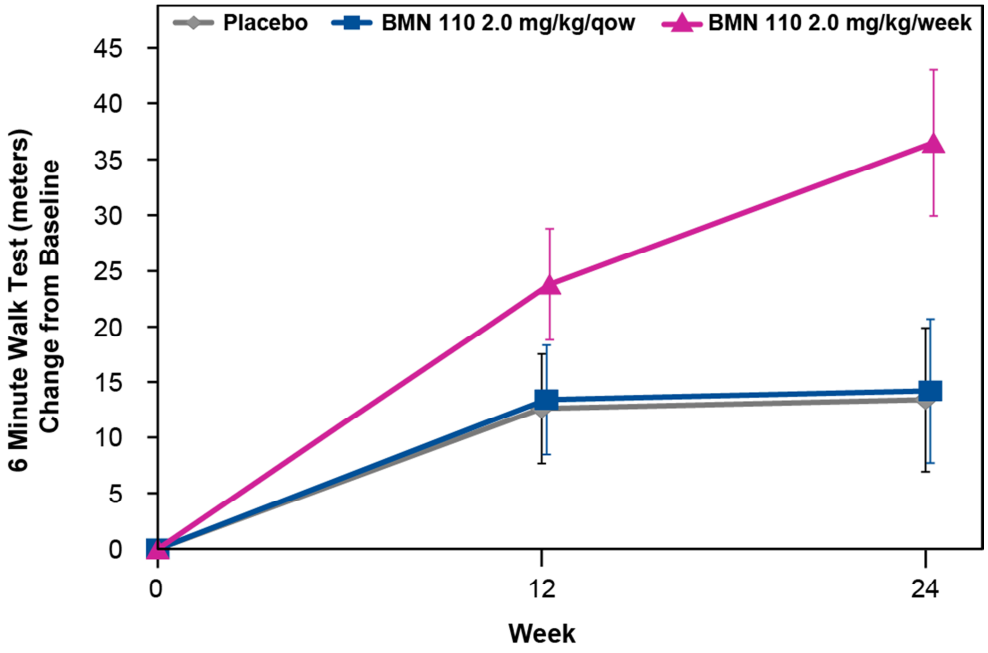
6.5.3 6MWT (Primary Endpoint)

The pivotal Phase 3 study (MOR-004) met the primary endpoint of change from baseline in 6MWT distance at Week 24.

BMN 110 2.0 mg/kg/week demonstrated a statistically significant improvement in 6MWT distance compared with placebo at Week 24. The estimated treatment effect at Week 24, compared with placebo, was 22.5 meters (CI_{95}, 4.0, 40.9; P=0.0174) for the 2.0 mg/kg/week regimen (Table 6.5.5.1). The every other week regimen resulted in walk distances comparable to placebo. The estimated treatment effect at Week 24 compared with placebo was 0.5 m (CI_{95}, -17.8, 18.9; P=0.9542) for the 2.0 mg/kg/qow regimen.

The repeated-measures ANCOVA analysis supported the Week 24 findings of the primary analysis (Figure 6.5.3.1). Improvement over placebo in 6MWT distance was observed as early as Week 12, the time of the first post-Baseline walk assessment, with further improvement at Week 24, suggesting a continuing upward trajectory in 6MWT improvement.

Figure 6.5.3.1: Model-Based Repeated Measures ANCOVA Mean Change in 6-Minute Walk Test in MOR-004 (Intent-To-Treat Population)



Placebo	59	59	59
BMN 110 2.0 mg/kg/week	58	58	57
BMN 110 2.0 mg/kg/qow	59	59	58

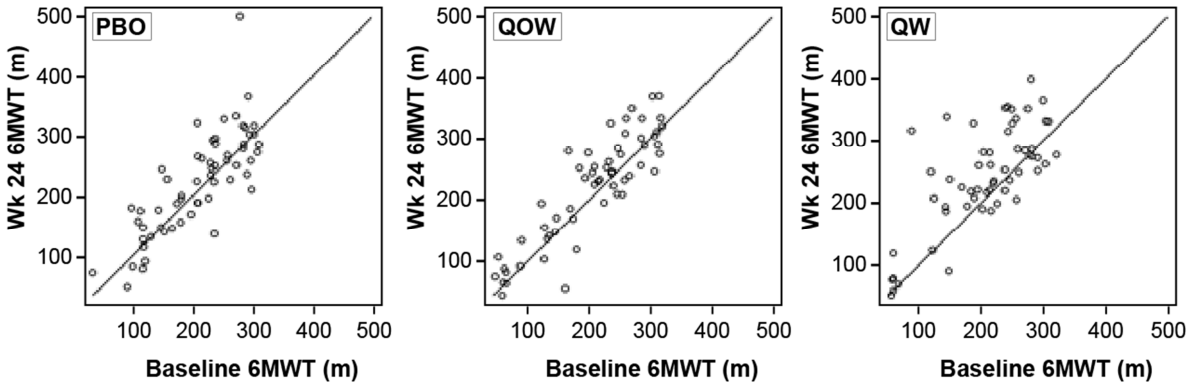
qow, every other week.
Error bars represent standard error of least squared mean change from Baseline.

Improvement in walking distance is clinically relevant in the setting of this chronic disease that is characterized by progressive debilitation, frequently leading to immobility and loss of functional capacity (Montano, 2007a, J.Inherit.Metab Dis.), (Harmatz, 2013, Mol Gen Metab). All subjects in MOR-004 had substantial impairment in mobility at study entry, and improved walking ability is expected to have an important impact on independence and activities of daily living.

A scatter plot demonstrating the relationship between Baseline 6MWT and Week 24 6MWT for subjects in each of the three treatment groups is presented in Figure 6.5.3.2. The diagonal line running from bottom left to top right in each plot would represent a subject showing no change from Baseline to Week 24 (eg, a subject with a Baseline walk of 300m and a Week 24 walk of 300m would fall directly on the line). Data points falling above the line represent subjects whose Week 24 walk distance was greater than the Baseline walk distance; points below the line represent a Week 24 walk distance less than the Baseline distance.

The plot shows that the improvement seen in the 2.0 mg/kg/week group is driven by a large proportion of subjects showing improvement, rather than by a few outliers.

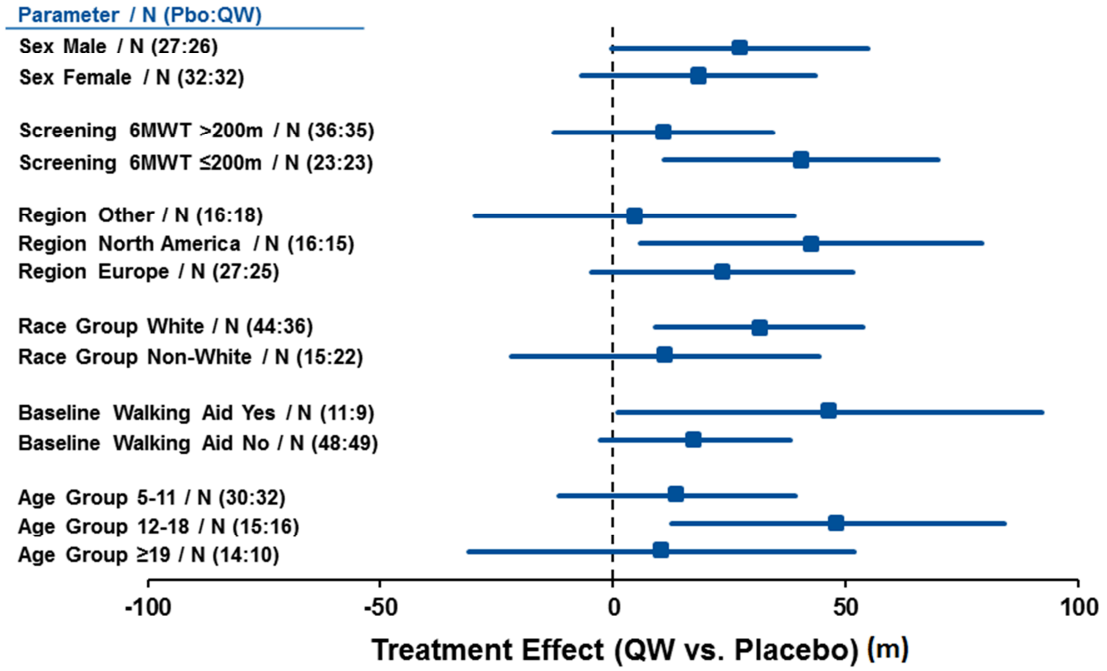
Figure 6.5.3.2: Baseline Score vs Week 24 Score for 6MWT
(MOR-004 Analysis Population: ITT Population)



A number of additional analyses were undertaken to investigate the robustness of the primary analysis results, and to explore the uniformity of the overall treatment effect. To explore

uniformity of treatment effect in MOR-004, analyses were performed to determine the possible interaction of subgroups with treatment using the ANCOVA model of the primary analysis with an additional interaction-by-subgroup covariate term. In MOR-004, 6MWT results were assessed in sub-populations based on screening 6MWT categories (≤ 200 meters and > 200 meters), age group at baseline (5-11, 12-18, ≥ 19 years), sex (female vs. male), race (White vs. non-white), and region (North America, Europe, other). Overall, the subgroup analyses demonstrated that treatment effects were similar to the overall group, regardless of age, sex, race, or geographic region, or Baseline 6MWT category, and consistently supported the 2.0 mg/kg/week dose regimen (Figure 6.5.3.3). P values for the test for interaction ranged from 0.1132 to 0.8271 for BMN 110 2.0 mg/kg/qow versus placebo and from 0.1224 to 0.8921 for BMN 110 2.0 mg/kg/week versus placebo.

Figure 6.5.3.3: Treatment Effect in Subgroups (MOR-004 6MWT)

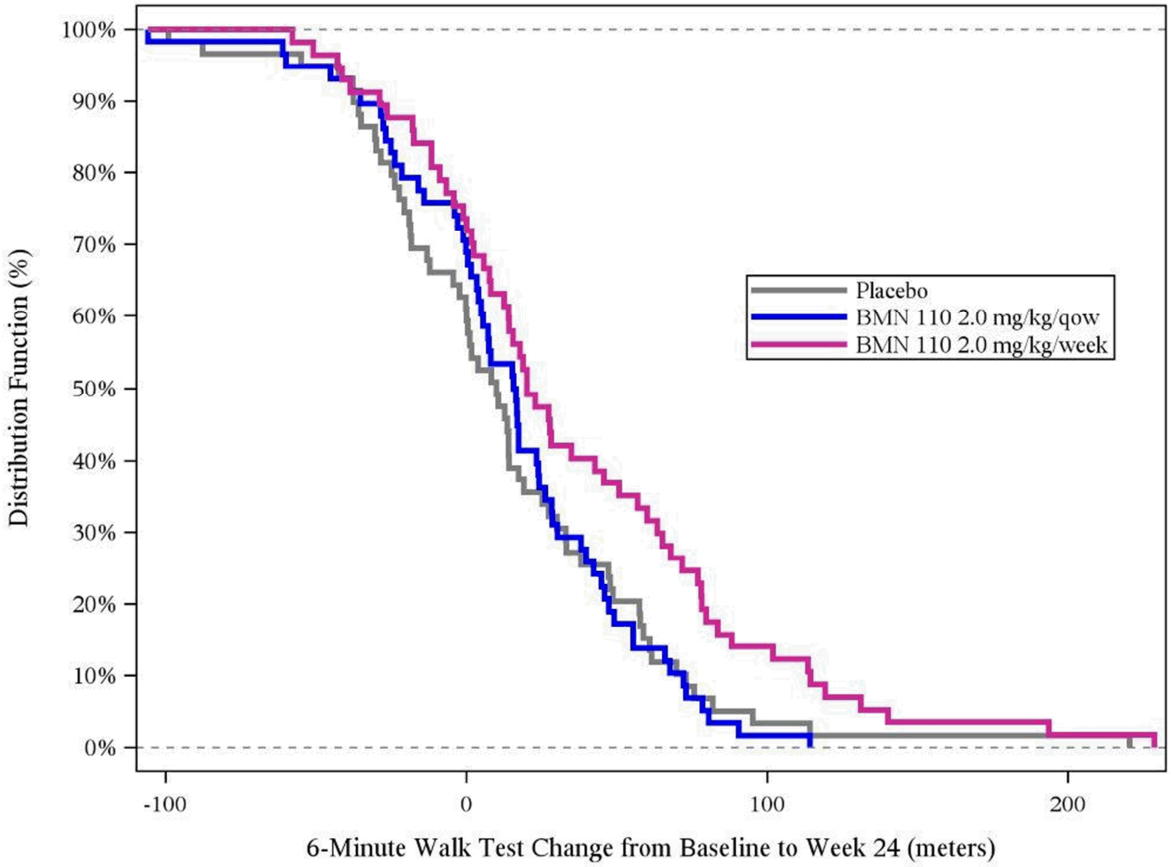


A cumulative distribution function displays a continuous plot of the change from Baseline (in 6MWT distance) on the horizontal axis, and the cumulative percent of subjects experiencing at least that level of change on the vertical axis. For any point on the curve, the y-axis value represents the proportion of subjects whose 6MWT distance change from Baseline to Week 24 is greater than or equal to the corresponding value on the x-axis at that point.

A responder analysis based on the estimated cumulative distribution function in the placebo and BMN 110 2.0 mg/kg groups is shown in Figure 6.5.3.4. The figure demonstrates a clear

separation of the response curve for the 2.0 mg/kg/week treatment group from the 2.0 mg/kg/qow and placebo groups.

Figure 6.5.3.4: Responder Analysis of 6-Minute Walk Test Distance: Cumulative Distribution for Change from Baseline to Week 24 (Intent-To-Treat Population – MOR-004)



qow, every other week.

Sensitivity analyses confirmed that duplicate 6MWTs performed on two separate days at each visit; missing data; presence of outliers; or the interactions of treatment and time point, did not affect efficacy conclusions. There were very few missing data points for key efficacy variables, in particular 6MWT, and over 99% of subjects completed the study.

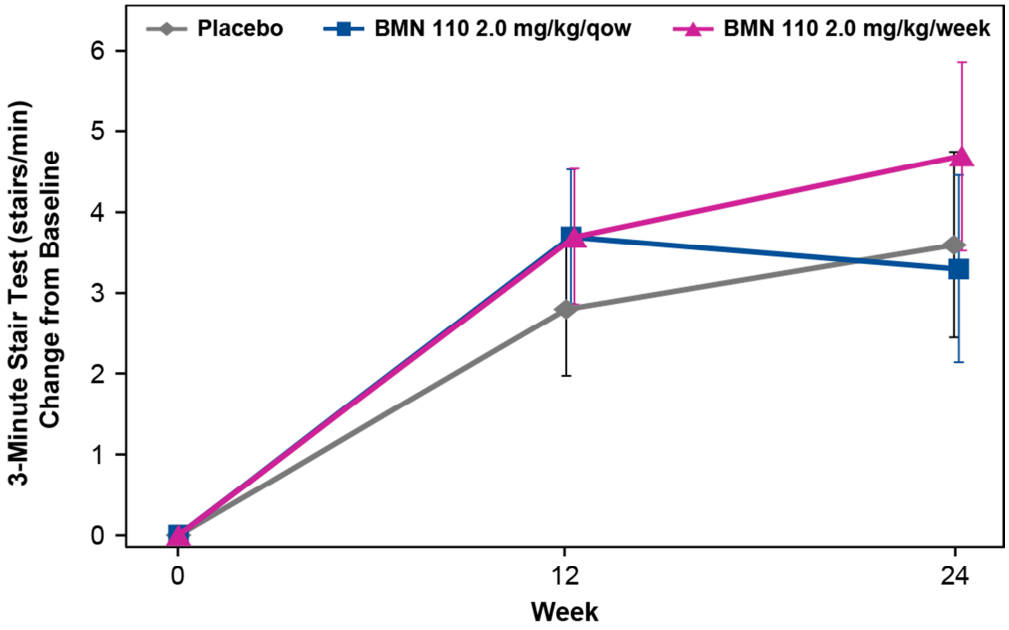
6.5.4 3MSCT (Secondary Endpoint)

In the pivotal Phase 3 study MOR-004, BMN 110 showed a small numerical increase in 3MSCT performance (in stairs/minute) compared with placebo at Week 24 for BMN 110 2.0 mg/kg/week treatment group, but statistical significance was not reached. The estimated

treatment effect in the ITT population at Week 24, compared with placebo, was 1.1 stairs/min (CI95, -2.1, 4.4; P=0.4935) for the BMN 110 2.0 mg/kg/week regimen and -0.5 stairs/min (CI95, -3.7, 2.8; P=0.7783) for the BMN 110 2.0 mg/kg/qow regimen (Table 6.5.5.1).

The repeated-measures ANCOVA analysis supported the Week 24 findings of the primary analysis (Figure 6.5.4.1).

Figure 6.5.4.1: Model-Based Repeated Measures ANCOVA Mean Change in 3-Minute Stair-Climb Test in MOR-004 (Intent-To-Treat Population)



qow, every other week
Error bars represent standard error of least-square mean change from Baseline.

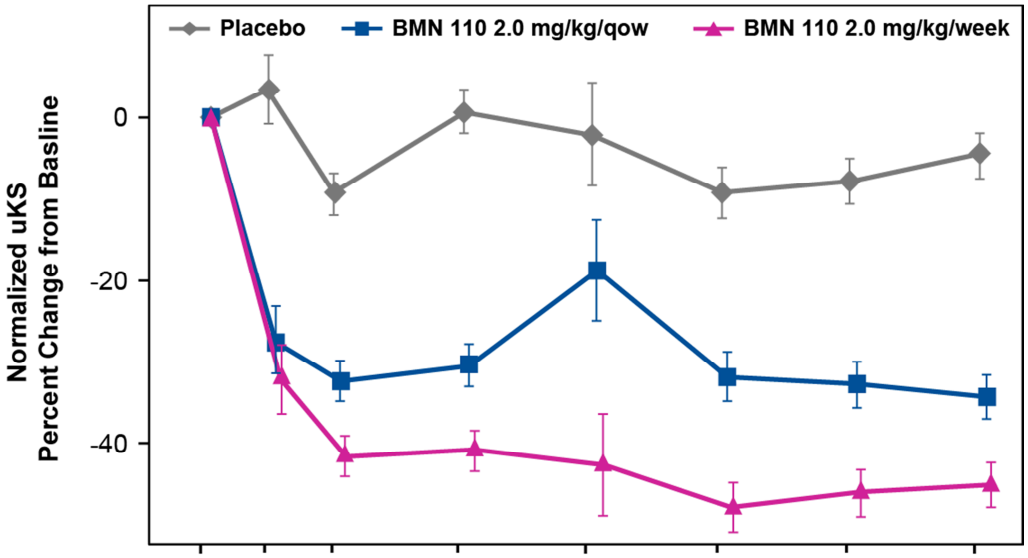
It is unknown why the 3MSCT did not parallel the statistically significant improvement in 6MWT distance. Notably, there is substantially less experience with this test from a clinical trial and regulatory standpoint, and due to severe skeletal impairments most Morquio A patients have difficulty climbing stairs.

6.5.5 Urine KS (Secondary Endpoint)

In MOR-004, treatment with BMN 110 led to a rapid and sustained reduction of urine KS in both treatment arms. The estimated treatment effect at Week 24, compared with placebo, was -40.7% (CI_{95}, -49.0, -32.4) for the BMN 110 2.0 mg/kg/week regimen and -30.2% (CI_{95}, -38.5, -22.0) for the 2.0 mg/kg/qow regimen (Table 6.5.5.1).

The repeated-measures ANCOVA analysis supported the Week 24 primary analysis findings; there was a rapid and sustained reduction in urine KS (Figure 6.5.5.1).

Figure 6.5.5.1: Model-Based Repeated Measures ANCOVA Mean Percent Change in Normalized Urine Keratan Sulfate in MOR-004 (Intent-To-Treat Population)



Placebo	58	58	58	58	57	59	59	56
BMN 110 2.0 mg/kg/week	58	55	56	54	55	55	53	54
BMN 110 2.0 mg/kg/qow	59	59	58	58	58	58	56	57

qow, every other week; uKS, urine keratan sulfate
Error bars represent standard error of least squared mean change from Baseline.

Reduction in urinary KS demonstrates biological activity of the replacement of the missing enzyme, and in that way it is more appropriately thought of as a pharmacodynamic measure than an efficacy endpoint. Urine KS showed a rapid and sustained reduction in both the 2.0 mg/kg/week and 2.0 mg/kg/qow treatment groups in MOR-004, demonstrating that BMN 110 is capable of breaking down accumulated body and tissue storage of KS. However, this reduction in urine KS is not a biomarker that is predictive of efficacy (ie, there

was no dose-regimen dependent difference as was seen in 6MWT). The relationship of urinary KS to other measures of clinical response has not been established.

A summary of the results of MOR-004 for the primary efficacy variable (6MWT), and primary secondary variables (3MSCT and urine KS), is presented in Table 6.5.5.1.

Table 6.5.5.1: Results from Placebo-Controlled Clinical Study at 2 mg/kg/week

	BMN 110			Placebo			BMN 110 vs. Placebo
	Baseline	Week 24	Change	Baseline	Week 24	Change	Difference in Changes
N	58	57*	57	59	59	59	57
6-Minute Walk Test (Meters)							
Mean ± SD	203.9 ± 76.32	243.3 ± 83.53	36.5 ± 58.49	211.9 ± 69.88	225.4 ± 83.22	13.5 ± 50.63	23.0† (CI95, 2.9, 43.1)
Median Min, Max	216.5 42.4, 321.5	251.0 52.0, 399.9	20.0 -57.8, 228.7	228.9 36.2, 312.2	229.4 50.6, 501.0	9.9 -99.2, 220.5	22.5‡ (CI95, 4.0, 40.9) (p = 0.0174)‡,§
3-Minute Stair Climb Test (Stairs/Minute)							
Mean ± SD	29.6 ± 16.44	34.9 ± 18.39	4.8 ± 8.06	30.0 ± 14.05	33.6 ± 18.36	3.6 ± 8.51	1.1† (CI_{95}, -1.9, 4.2)
Median Min, Max	30.5 0.0, 71.9	34.7 0.0, 82.3	4.3 -12.4, 20.5	30.8 0.0, 59.0	32.0 0.0, 79.3	0.9 -13.0, 32.4	1.1‡ (CI_{95}, -2.1, 4.4) (p = 0.4935)‡,§
Urine Keratan Sulfate							
N¶	58	54	54	58	56	55	54
	µg/mg		% Change	µg/mg		% Change	% Change
Mean ± SD	26.9 ± 14.11	14.2 ± 8.38	-45.1 ± 19.89	25.7 ± 15.09	24.3 ± 13.45	-4.4 ± 27.03	-40.7† (CI_{95}, -49.7, -31.6)
Median Min, Max	24.1 2.1, 59.0	13.6 0.7, 37.6	-50.8 -79.4, 5.3	26.7 2.5, 52.8	25.5 2.2, 49.9	-12.3 -50.0, 73.6	-40.7‡ (CI_{95}, -49.0, -32.4) (p<0.0001)‡,§

* One subject in the BMN 110 group dropped out after 1 infusion

† Observed mean of BMN 110 - Placebo

‡ Model-based mean of BMN 110 - Placebo, adjusted for baseline

§ p-value based on the model-based mean difference

¶ Results not available for all subjects enrolled

6.5.6 Respiratory Function Tests (Tertiary Endpoint)

Several respiratory function tests were analyzed in MOR-004:

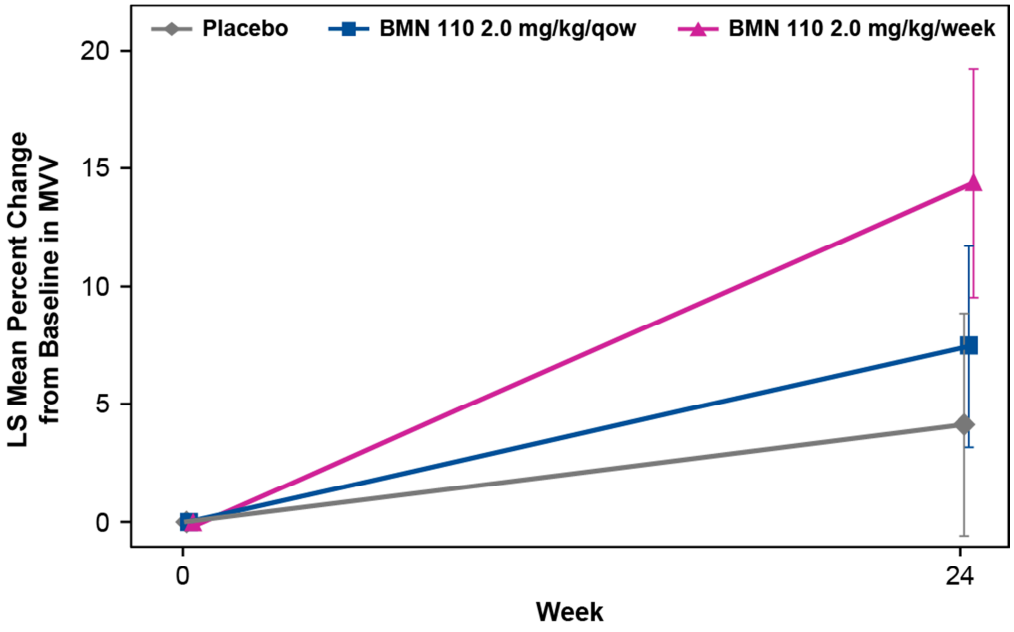
- MVV (maximum voluntary ventilation) – maximum amount of air that can be inhaled and exhaled within one minute, measured in liters/minute
- FVC (forced vital capacity) – volume of air that can be forcibly blown out after full inspiration, measured in liters
- FEV_1 (forced expiratory volume in 1 second) – volume of air that can be blown out in 1 second, after full inspiration, measured in liters
- FIVC (forced inspiratory vital capacity) – the volume change of the lung between a maximal expiration and a maximum inspiration, measured in liters
- FET (forced expiratory time) – the time it takes to perform a maximal exhalation, measured in seconds

A summary of the treatment effect of BMN 110 on these respiratory endpoints can be found in Figure 6.5.9.1.

In MOR-004, treatment with BMN 110 led to an improvement in the MVV percent change from Baseline compared with placebo at Week 24, with a trend toward statistical significance for BMN 110 2.0 mg/kg/week. The estimated treatment effect at Week 24, compared with placebo, was 10.3% (CI_{95}, -1.8, 22.4; P=0.0943) for the 2.0 mg/kg/week regimen and 3.4% (CI_{95}, -9.9, 16.6; P=0.6111) for the 2.0 mg/kg/qow regimen.

A plot of the least-square mean percent change in MVV at each visit is provided in Figure 6.5.6.1. The wide and overlapping standard error bars further demonstrate the considerable between-subject variation in MVV results that is consistent across treatment groups.

Figure 6.5.6.1: Least Squares Mean Percent Change from Baseline in Maximum Voluntary Ventilation (Intent-To-Treat Population – MOR-004)



Placebo	59	59
BMN 110 2.0 mg/kg/week	58	58
BMN 110 2.0 mg/kg/qow	59	59

MVV, maximum voluntary ventilation; qow, every other week
Error bars represent standard error of least square mean change from Baseline. Figure uses imputed values.

Although the treatment effect at Week 24 for both BMN 110 treatment groups, compared with placebo, was generally positive on the basis of percent change from Baseline for FVC, FEV_1, FIVC, and FET, the magnitude of absolute change was small. A longer duration of exposure may be necessary to identify appreciable change in respiratory function.

6.5.7 Effects on Anthropometric Measurements (Tertiary Endpoint)

Profound skeletal dysplasia and severe short stature are hallmarks of MPS IVA. Typically, until 2 years of age, the 50th percentile of length and height of boys and girls with MPS IVA is similar to those of a normal population. However, at 4 years of age the mean height of MPS IVA patients starts to fall markedly below 2 standard deviations lower than normal (Montano, 2008, Am.J.Med.Genet.A). Baseline data from MorCAP (MOR-001) showed that the average height of MPS IVA subjects was more than 5 standard deviations below that predicted by the CDC normal pediatric growth charts (Harmatz, 2013, Mol Genet Metab).

Normalized standing height (z-score) was computed using CDC normals (CDC 2000) and analysis was restricted to males with age ≤ 18 years and females with age ≤ 15 years (ie, subjects within age ranges of normal growth). A z-score (also known as z-value, standard score, or normal score) is a measure of the divergence of an individual experimental result from the most probable result, the mean for the set of data points. Z is expressed in terms of the number of standard deviations (SDs) from the mean value; a z-score value of 0 is equal to the group mean, +1 is 1 SD above the group mean, -1 is 1 SD below the group mean. The z-score metric for standing height was chosen because it removes variation due to age, resulting in an analysis that is potentially more sensitive to treatment effect. In addition, the z-score can more easily be interpreted as a measure of disease progression; a z-score rate of zero is what is expected of a normal population and a high target for efficacy.

Growth rate on study was compared with growth rate prior to study entry (for subjects who have growth measurements within 2 years prior to study entry). For each subject, the pre-study growth rate was estimated as follows:

> [(standing height z-score measured at Baseline) – (standing height z-score closest to but not greater than, 2 years prior to study entry)] / time (in years) between measurements].

In MOR-004, the treatment effect at Week 24 compared to placebo for both BMN 110 dosing regimens trended toward improvement in normalized standing height and growth rate z-scores in males ≤18 years and females ≤15 years. At Week 24, the least-square mean (±SE) change from Baseline in the normalized standing height z-score was -0.2 (±0.06) for the placebo group, -0.1 (±0.06) for the BMN 110 2.0 mg/kg/qow group, and 0.0 (±0.06) for the BMN 110 2.0 mg/kg/week group. The estimated treatment effect on normalized standing height z-score at Week 24, compared with placebo, was 0.1 (CI_{95}, 0.0, 0.3; P=0.1149) for the BMN 110 2.0 mg/kg/week group, and 0.1 (CI_{95}, -0.1, 0.3; P=0.2218) for the BMN 110 2.0 mg/kg/qow group.

Similarly, the Baseline least-square mean (± SE) normalized growth rate z-scores in the age-restricted population were -0.7 (±0.14) for the placebo group, -0.3 (±0.14) for the BMN 110 2.0 mg/kg/qow group, and -0.6 (±0.13) for the BMN 110 2.0 mg/kg/week group, indicating that all treatment groups were within 1 standard deviation below normal age-adjusted growth rate values. The least-square mean change in the normalized growth rate z-score from Baseline to Week 24 was 0.2 (±0.18) for the placebo group, 0.5 (±0.18) for the BMN 110 2.0 mg/kg/qow group, and 0.5 (±0.16) for the BMN 110 2.0 mg/kg/week group. The estimated treatment effect on growth rate z-score at Week 24, compared with placebo,

was 0.4 (CI_{95}, -0.1, 0.9; P=0.1032) for the BMN 110 2.0 mg/kg/week group and 0.4 (CI_{95}, -0.1, 0.9; P=0.1384) for the BMN 110 2.0 mg/kg/qow group.

These findings suggest that BMN 110 may slow the progressive negative deviation from normal growth rates and normal standing height in patients with MPS IVA who are still growing. However, the relatively short duration of the study (24 weeks) made it difficult to see statistically significant changes in anthropometric measurements such as height.

6.5.8 Effects on MPS HAQ (Tertiary Endpoint)

The MPS health assessment questionnaire (HAQ) assessed self-care (eating/drinking, dressing, bathing, grooming, tooth brushing, and toileting), mobility skills (dexterity, mobility, walking, stair climbing, and gross motor skills), and the extent of required caregiver assistance in the performance of these activities. In MOR-004, HAQ results numerically improved in the Caregiver Assistance and Mobility Domains, but not in the Self-Care Domain. While numeric improvement in some HAQ domain scores was observed with BMN 110 treatment, this tool may not be sensitive enough to detect overall changes in the lives of subjects with this multifaceted disease. For purposes of these scales, a negative value at Week 24 represents an improvement in the domain.

Mean change in the Self-Care Domain score from Baseline at Week 24 was -0.4 (±1.19) in the placebo group, -0.5 (±1.29) in the BMN 110 2.0 mg/kg/qow group, and -0.3 (±0.90) in the BMN 110 2.0 mg/kg/week group. The estimated treatment effect for the Self-Care Domain score in the ITT Population at Week 24, compared with placebo, was 0.1 (CI_{95}, -0.3, 0.5; P=0.7367) in the BMN 110 2.0 mg/kg/week group and -0.1 (CI_{95}, -0.5, 0.3; P=0.7242) in the BMN 110 2.0 mg/kg/qow group.

Mean change in the Caregiver Assistance Domain score from Baseline at Week 24 was -1.1 (±5.79) in the placebo group, -2.4 (±5.84) in the BMN 110 2.0 mg/kg/qow group, and -2.3 (±7.02) in the BMN 110 2.0 mg/kg/week group. The estimated treatment effect for the Caregiver Assistance Domain score in the ITT Population at Week 24, compared with placebo, was -0.9 (CI_{95}, -2.8, 1.1; P=0.3990) in the BMN 110 2.0 mg/kg/week group and -0.4 (CI_{95}, -2.4, 1.6; P=0.6794) in the BMN 110 2.0 mg/kg/qow group.

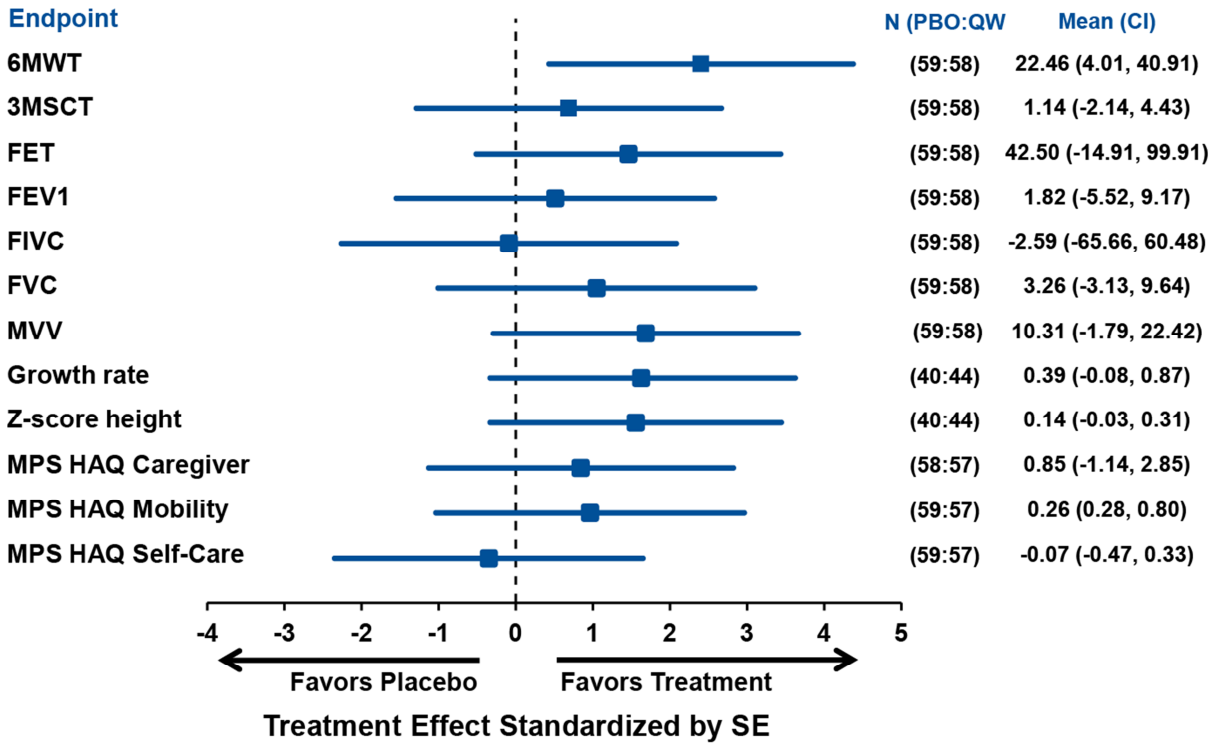
Mean change in the Mobility Domain score from Baseline at Week 24 was -0.5 (±1.80) in the placebo group, -1.0 (±1.37) in the BMN 110 2.0 mg/kg/qow group, and -0.7 (±1.59) in the BMN 110 2.0 mg/kg/week group. The estimated treatment effect for the Mobility Domain score in the ITT Population at Week 24, compared with placebo, was -0.3 (CI_{95}, -0.8, 0.3; P=0.3355) in the BMN 110 2.0 mg/kg/week group and -0.3 (CI_{95}, -0.8, 0.2; P=0.2611) in the BMN 110 2.0 mg/kg/qow group.

Because it is of primary importance to patients, clinicians, and certain Health Authorities to understand the potential influence of treatment on wheelchair use and walking aid use, post-hoc analyses were performed to more closely examine results from this objective individual question that is not included in the Mobility Domain score. In MOR-004, no wheelchair was required at Baseline by 35 subjects (59.3%) in the placebo group, 23 subjects (39.0%) in the BMN 110 2.0 mg/kg/qow group, and 27 subjects (46.6%) in the BMN 110 2.0 mg/kg/week group. The number of subjects using a wheelchair at Week 24 increased by 5 (8.8%) in the placebo group, 0 (0%) in the BMN 110 2.0 mg/kg/qow group, and 0 (0%) in the BMN 110 2.0 mg/kg/week group, as compared to Baseline. The increase in wheelchair use in subjects on placebo is expected, given the natural history of progressive decline in these patients. The lack of a similar increase in wheelchair use amongst subjects on active treatment is notable and may be clinically relevant in light of the progressive nature of MPS IVA.

6.5.9 Additional Tertiary Endpoints

Figure 6.5.9.1 displays efficacy for results for primary (6MWT), secondary (3MSCT), and tertiary endpoints (respiratory, anthropometric, MPS-HAQ) for the QW group versus placebo group. These endpoints use different scales and units of measurement, so in order to display the efficacy of these endpoints together, the estimates are standardized to a common scale of measurement by dividing the estimate and confidence interval bounds for each endpoint by the standard error of that estimate. The figure demonstrates that, for most of the tertiary endpoints, subjects in the weekly dosing group showed a more positive response than subjects receiving placebo.

Figure 6.5.9.1: Summary of Treatment Effect of BMN 110 Weekly on Efficacy Endpoints (Analysis Population – Intent-to-Treat (MOR-004))



6.5.10 Additional Responder Analyses Based on Delphi Consensus

In addition to the pre-specified responder analyses reported above using a cumulative distribution function (CDF), additional responder analyses were performed on 6MWT, 3MSCT, and MVV, using Delphi consensus recommendations defining a responder threshold (as described in Section 6.5.1.1).

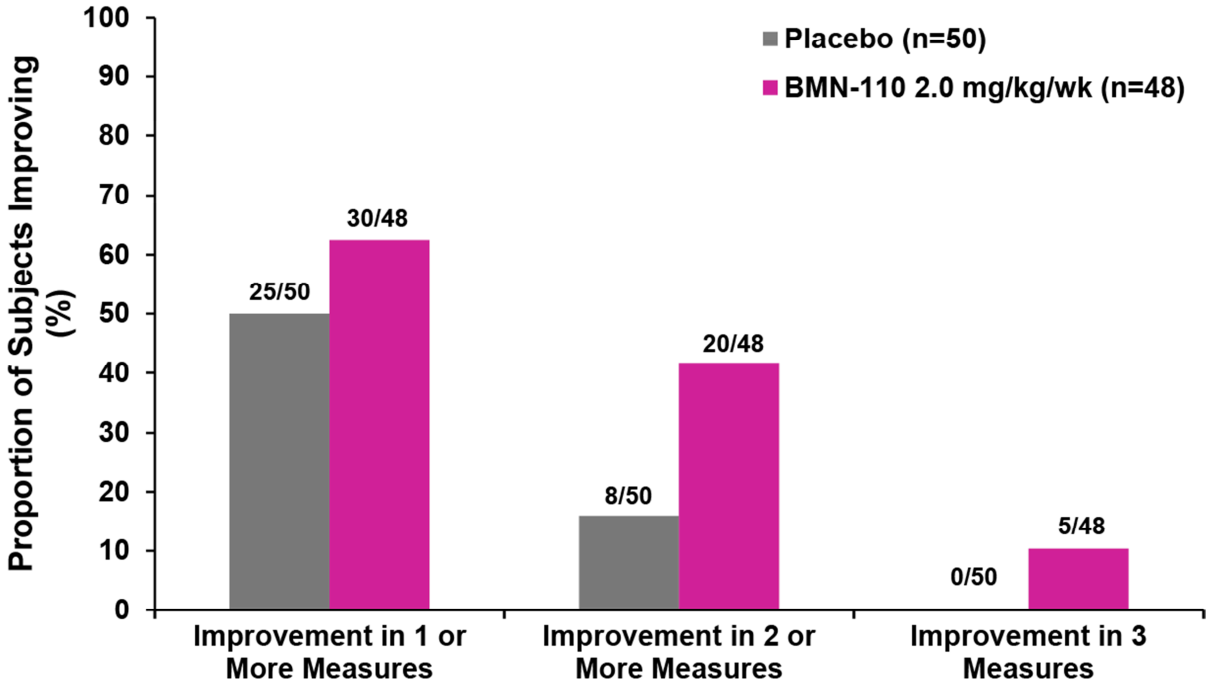
Results using these thresholds for 6MWT, 3MSCT, and MVV showed a higher proportion of responders in the weekly group compared with the placebo group for all three measures:

- 6MWT (weekly vs. Placebo): 45.6% vs. 30.5%; P=0.0603
- 3MSCT (weekly vs. Placebo): 45.6% vs. 25.4%; P=0.0228
- MVV (weekly vs. Placebo): 28.6% vs. 12.0%; P=0.0576

Additional responder analyses using these Delphi thresholds showed that the proportion of subjects with improvement in 1 or more of these measures (6MWT, 3MSCT, or MVV) was 62.5% vs. 50.0% (weekly vs. placebo). The proportion of subjects with improvement in 2 or more measures was 41.7% vs. 16.0% (weekly vs. placebo), and the proportion of subjects with improvement in all 3 measures was 10.4% vs. 0% (weekly vs. placebo). These results

support the conclusion that the effects observed in the Phase 3 study are clinically meaningful. meaningful (Figure 6.5.10.1).

Figure 6.5.10.1: Delphi Threshold Responder Analysis for 6MWT/3MSCT/MVV (MOR-004)



6.6 Phase 3 Extension Study MOR-005

In response to a FDA request, a post-BLA data cut, using a data cut-off date of 3 September 2013, has been performed to examine long-term efficacy data from Study MOR-005. This data cut captures efficacy results for all subjects up to Week 72 (MOR-004 and MOR-005 combined).

The purpose of the MOR-005 extension study is to evaluate the long-term efficacy and safety of BMN 110 in subjects with Mucopolysaccharidosis (MPS) IV type A (Morquio A syndrome, MPS IVA) who completed the parent study (MOR-004). MOR-005 was designed in two parts. Part 1, which was completed on 30NOV2012, was a randomized double-blind study that continued until the primary analysis of MOR-004 was complete. Part 2, which was initiated on 01DEC2012, is an ongoing open-label study with a single dose regimen of BMN 110 (2.0 mg/kg weekly) that was selected based upon results from MOR-004 and the Data Monitoring Committee (DMC) recommendation.

In Part 1, subjects initially randomized to BMN 110 (MOR-004) remained on their assigned dose regimen of 2.0 mg/kg/week or 2.0 mg/kg/qow (MOR-005). Subjects initially randomized to placebo (MOR-004) were re-randomized without stratification (1:1 ratio) to 1 of the 2 BMN 110 dose regimens used in MOR-004 (2.0 mg/kg/week or 2.0 mg/kg/qow). After analysis of the final primary efficacy and safety results in MOR-004 and DMC recommendation, the dose for Part 2 of MOR-005 (2.0 mg/kg/week) was determined.

Cohorts in Part 1 were:

- Cohort QW-QW: Subjects received BMN 110 dose regimens of 2.0 mg/kg/week in MOR-004 and MOR-005 (Part 1)
- Cohort QOW-QOW: Subjects received BMN 110 dose regimens of 2.0 mg/kg/qow in MOR-004 and MOR-005 (Part 1)
- Cohort PBO-QW: Subjects received placebo in MOR-004 and a BMN 110 dose regimen of 2.0 mg/kg/week in MOR-005 (Part 1)
- Cohort PBO-QOW: Subjects received placebo in MOR-004 and a BMN 110 dose regimen of 2.0 mg/kg/qow in MOR-005 (Part 1)

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

6.6.1 Disposition of Subjects and Baseline Characteristics

Of the 175 subjects who completed MOR-004, 173 continued into MOR-005. In Part 1, a total of 59 and 56 subjects who received BMN 110 at 2.0 mg/kg/qow and 2.0 mg/kg/week, respectively, throughout the entire study duration of MOR-004 enrolled in MOR-005. Fifty-eight subjects who received placebo throughout the entire study duration of MOR-004 enrolled in MOR-005 and were randomized (1:1) to the BMN 110 2.0 mg/kg/qow (cohort PBO-QOW; n = 29) and BMN 110 at 2.0 mg/kg/week (cohort PBO-QW; n = 29) treatment groups.

In Part 1 of MOR-005, one subject in the QW-QW cohort withdrew consent after completing Week 0. All other subjects (172 total) remained on Part 1 of MOR-005 until 01DEC2012, when Part 2 of the study was started.

As of the 03SEP2013 data cut, 168 subjects are receiving treatment in Part 2 of MOR-005. One subject withdrew during Part 2 of MOR-005 due to difficulty with travel to the infusion site. The remaining 3 subjects have not yet been treated in Part 2 because they are waiting for an infusion center to open nearby. Refer to Table 6.6.1.1 for an overview of subject disposition in MOR-005.

Table 6.6.1.1: Subject Disposition in MOR-005
Analysis Population: Randomized Subjects

	PBO-QOW (N=29)	PBO-QW (N=29)	QOW-QOW (N=59)	QW-QW (N=56)
Subjects Enrolled in MOR-005[a]	29	29	59	56
Subjects Treated in MOR-005	29 (100.0%)	29 (100.0%)	59 (100.0%)	56 (100.0%)
Subjects with follow-up ongoing	29 (100.0%)	29 (100.0%)	59 (100.0%)	54 (96.4%)
Subjects who Completed Week 72 (MOR-005 Week 48) in Part 1	2 (6.9%)	2 (6.9%)	2 (3.4%)	5 (8.9%)
Subjects who Completed Week 72 (MOR-005 Week 48) in Part 2	27 (93.1%)	26 (89.7%)	56 (94.9%)	48 (85.7%)
Subjects waiting for entry to MOR-005 Part 2[b]	0	1 (3.4%)	1 (1.7%)	1 (1.8%)
Subjects who Discontinued in MOR-005 Part 1	0	0	0	1 (1.8%)
Subjects who Discontinued in MOR-005 Part 2	0	0	0	1 (1.8%)
Subjects still on treatment	29 (100.0%)	28 (96.6%)	58 (98.3%)	53 (94.6%)
Subjects waiting for entry to MOR-005 Part 2[b]	0	1 (3.4%)	1 (1.7%)	1 (1.8%)
Subjects who Permanently Discontinued Study Drug in MOR-005	0	0	0	0
Subjects Evaluable for Per-Protocol Analysis	27 (93.1%)	27 (93.1%)	54 (91.5%)	48 (85.7%)

[a] Three MOR-004 subjects did not enroll to MOR-005: MOR004-0024-4151 (Placebo) completed MOR-004, MOR004-0050-4090 (QW) withdrew consent during MOR-004, MOR004-1235-4021 (QW) completed MOR-004

[b] Waiting for infusion center to open in their home town: MOR004-0018-4065, MOR004-0018-4071, MOR004-0018-4072

Includes MOR-005 Part 1 and Part 2 data

While the overall objective of the MOR-005 extension study was to evaluate long-term efficacy and safety in subjects who received active treatment in the pivotal MOR-004 trial, the intent was also to provide BMN 110 treatment to subjects previously randomized to placebo until marketing authorization allowed access to commercial product. Thus, stratification was not performed for placebo subjects transitioning from MOR-004 into MOR-005 (the PBO-QOW and PBO-QW groups described above); and a chance imbalance in MOR-005 Baseline characteristics resulted, with the PBO-QOW cohort performing better

on 6MWT and 3MSC than the PBO-QW cohort (refer to Section 6.6.3.1.2). In addition, each of the placebo-switch cohorts is approximately 50% of the size of the continuous dose cohorts, since the two placebo-switch cohorts were constructed out of the single PBO cohort in MOR-004. Along with the randomization imbalance, the small sample size makes the placebo-switch data difficult to interpret.

6.6.2 Extent of Exposure

Study drug exposure for MOR-005 (Parts 1 and 2), including exposure in MOR-004, as of the 03SEP2013 data cut-off date is presented in Table 6.6.2.1. All 173 subjects (100%) received at least one dose of study drug in MOR-005. Mean weekly study drug dose/subject was approximately 2.0 mg/kg in all cohorts.

As of the data cut-off date, the mean (±SD) total study drug exposure in MOR-004 and MOR-005 combined was 72.79 (±2.361) weeks in cohort PBO-QOW, 71.92 (±7.147) weeks in cohort PBO-QW, 72.53 (±5.032) weeks in cohort QOW-QOW, and 71.19 (±8.159) weeks in cohort QW-QW.

Table 6.6.2.1: Study Drug Exposure for Subject Entered to MOR-005
Analysis Population: Safety – MOR-004 & MOR-005

Dosing Category	PBO-QOW (n = 29)	PBO-QW (n = 29)	QOW-QOW (n = 59)	QW-QW (n = 56)
Total Study Drug Exposure[a] (weeks)				
n	29	29	59	56
Mean (SD)	72.79 (2.361)	71.92 (7.147)	72.53 (5.032)	71.19 (8.159)
Median	73.00	73.14	73.14	73.14
25th , 75th Percentile	73.00 , 73.29	73.00 , 73.29	73.00 , 73.29	72.93 , 73.29
Min , Max	60.86 , 76.00	34.86 , 75.29	34.86 , 75.29	25.00 , 75.29
Mean Weekly Dose/Subject (mg/kg)				
n	29	29	59	56
Mean (SD)	1.92 (0.111)	1.88 (0.227)	1.92 (0.155)	1.88 (0.176)
Median	1.95	1.94	1.95	1.94
25th , 75th Percentile	1.92 , 1.99	1.89 , 2.00	1.92 , 1.98	1.86 , 1.97
Min , Max	1.44 , 2.00	0.92 , 2.00	0.92 , 2.00	1.26 , 2.00
Total Dose/Subject (mg/kg)				
n	29	29	59	56
Mean (SD)	140.31 (8.085)	137.49 (16.713)	139.85 (11.436)	135.62 (17.411)
Median	142.01	141.95	142.24	141.94
25th , 75th Percentile	139.88 , 145.55	137.98 , 145.92	139.87 , 144.37	135.44 , 144.14
Min , Max	105.42 , 146.18	65.98 , 146.21	66.11 , 146.12	49.09 , 146.11

SD, standard deviation

[a] Study drug exposure (in week) is defined (last infusion date - first infusion date + 7)/7.

Includes MOR-004 and MOR-005 data.

6.6.3 Efficacy Results

Efficacy results up to Week 72 are summarized below for 6MWT, 3MSCT, and uKS. Two aspects of the study design of MOR-005 are important to note to aid in interpretation of these results:

1) As a result of the different assessment schedules in Part 1 and Part 2, not all subjects completed Week 48 endurance assessments
2) Upon the start of Part 2 of MOR-005, subjects in the PBO-QOW and QOW-QOW cohorts began receiving 2.0 mg/kg weekly; the specific timepoint of transition for

each subject was different, depending on their date of study enrollment, but most subjects transitioned between Week 36 and Week 72.

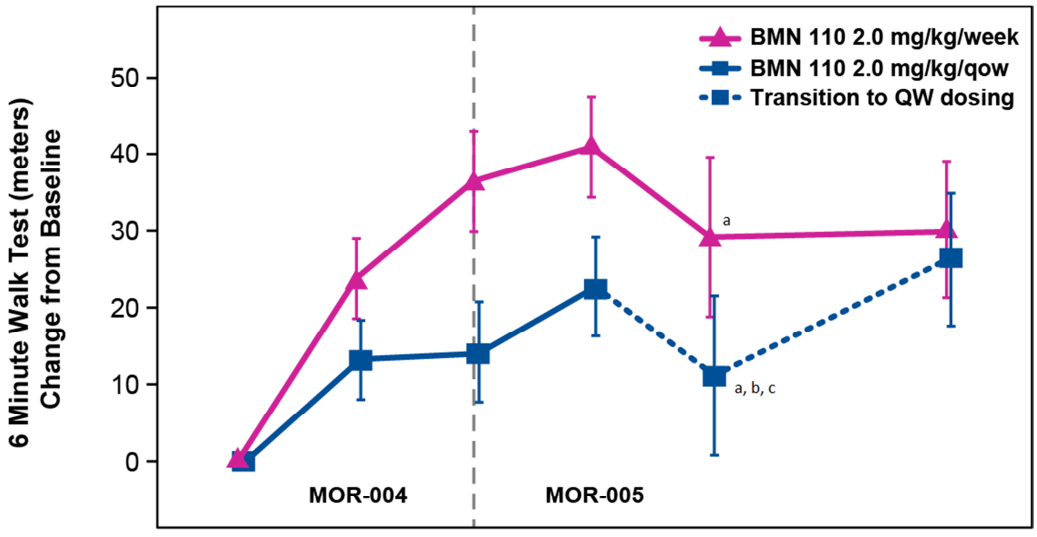
Also, the Week 48 results include only subjects who reached Week 48 while still in Part 1 of the study (and thus, for the PBO-QOW and QOW-QOW arms, include only subjects still receiving QOW dosing); there was no Week 48 endurance assessment in Part 2. However, all subjects are included at the Week 72 timepoint; at the time of the Week 72 assessments, almost all (163/168) subjects in MOR-005 were receiving weekly dosing.

6.6.3.1 6MWT

6.6.3.1.1 QOW-QOW and QW-QW Cohorts

Continued treatment with BMN 110 in MOR-005 showed a stable and sustained improvement in 6MWT distance in the QW-QW cohort at Week 72 from Baseline of MOR-004 (Figure 6.6.3.1.1.1); this improvement was also maintained in the per protocol (PP) population at Week 72. (Figure 6.6.3.1.1.2).

Figure 6.6.3.1.1.1: Analysis of 6MWT: Repeated Measures Model
Analysis Population: ITT Population (MOR-004/MOR-005)



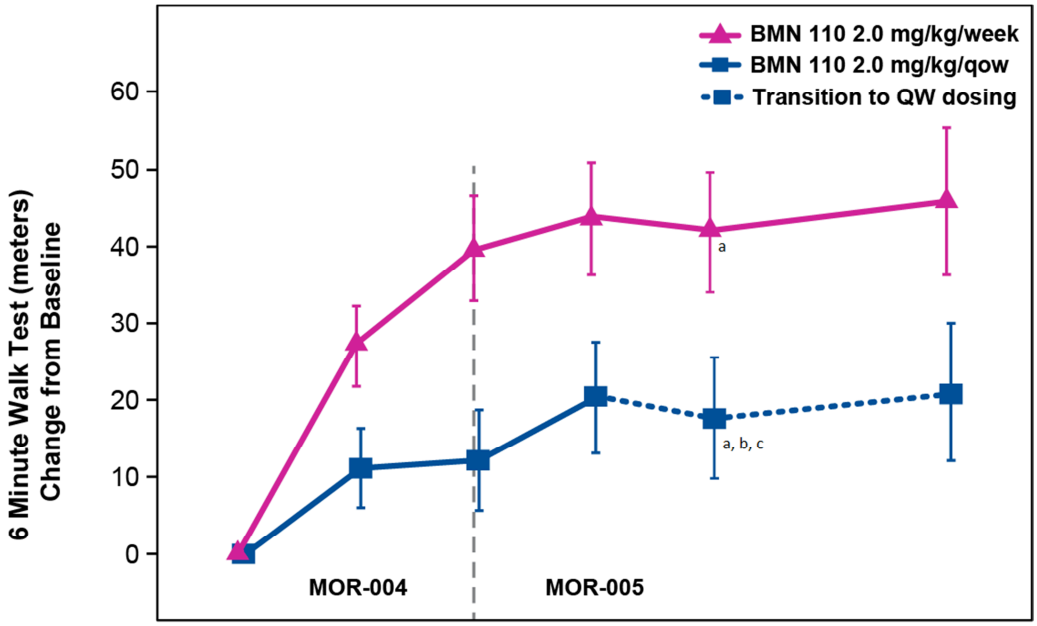
Model based means (LSMEAN) and standard error bars displayed.
Model: Change from Baseline = agegroup + baseline walk category + treatment + visit + trt*visit, unstructured covariance matrix
[a]Due to different assessment schedule in Part 2, not all subjects have Week 48 endurance assessments available.
[b]With start of Part 2 of MOR-005 (01DEC2012), subjects in QOW-QOW cohort began receiving 2.0 mg/kg weekly; the specific time of transition for each subject depended on date of study enrollment, ranging from Week 36 to Week 72.
[c]Week 48 results for the QOW-QOW cohort include only subjects who reached Week 48 while still in Part 1 of the study as there was no Week 48 endurance assessment in Part 2. Thus for the QOW-QOW cohort, this time point includes data only from subjects still receiving QOW dosing.

Using the primary analysis repeated measures ANCOVA model in the ITT population, the least square mean changes from MOR-004 Baseline for the QOW-QOW and QW-QW cohorts, respectively, at Week 36 were 22.7 (CI_{95}, 9.8, 35.5) and 40.9 (CI_{95}, 27.8, 54.0) meters, at Week 48 were 11.0 (CI_{95}, -9.6, 31.7) and 29.1 (CI_{95}, 8.5, 49.7) meters, and at Week 72 were 26.3 (CI_{95}, 9.1, 43.5) and 30.1 (CI_{95}, 12.6, 47.6) meters.

Sensitivity analyses performed on the PP population yielded results at Week 36 consistent with those of the ITT population (Figure 6.6.3.1.1.2). However, there were differences between the ITT and PP population results at Week 48 and Week 72 which could not be attributed to any single factor. Instead, the differences were a cumulative effect of subject data excluded from the PP population for various reasons (including orthopedic surgeries and

multiple missed doses of study treatment). While orthopedic surgeries were not permitted during MOR-004, they were allowed during MOR-005; some surgeries which occurred during MOR-005 had already been planned prior to subject entry in MOR-004 but had to be delayed until the double-blind placebo-control period in MOR-004 was complete. The relatively smaller number of subjects in the PP population for the QW-QW cohort at Week 72, compared with the QOW-QOW cohort (35 subjects in QW-QW, 42 subjects in QOW-QOW) is a result of more missed dosing in the QW-QW cohort.

Figure 6.6.3.1.1.2: Analysis of 6MWT: Repeated Measures Model
Analysis Population: Per Protocol Population (MOR-004/MOR-005)



BMN 110 2.0 mg/kg/week	52	52	52	47	22	35
BMN 110 2.0 mg/kg/qow	55	55	55	49	19	42

Model based means (LSMEAN) and standard error bars displayed.
Model: Change from Baseline = agegroup + baseline walk category + treatment + visit + trt*visit, unstructured covariance matrix
[a]Due to different assessment schedule in Part 2, not all subjects have Week 48 endurance assessments available.
[b]With start of Part 2 of MOR-005 (01DEC2012), subjects in QOW-QOW cohort began receiving 2.0 mg/kg weekly; the specific time of transition for each subject depended on date of study enrollment, ranging from Week 36 to Week 72.
[c]Week 48 results for the QOW-QOW cohort include only subjects who reached Week 48 while still in Part 1 of the study as there was no Week 48 endurance assessment in Part 2. Thus for the QOW-QOW cohort, this time point includes data only from subjects still receiving QOW dosing.

Using the primary analysis repeated measures ANCOVA model in the per protocol population, the least square mean changes from MOR-004 Baseline in 6MWT for the QOW-QOW and QW-QW cohorts, respectively, at Week 36 were 19.9 (CI_{95}, 6.1, 33.6) and 43.7 (CI_{95}, 29.6, 57.7) meters, and at Week 72 were 20.7 (CI_{95}, 3.0, 38.3) and 46.0 (CI_{95}, 27.4, 64.6) meters.

6.6.3.1.2 PBO-QOW and PBO-QW Cohorts

In the PBO-QOW cohort of the ITT population, the mean ± standard deviation (±SD) change in 6MWT distance from MOR-004 Baseline at Week 36 was 31.2 (±55.36) meters, at Week 48 was 15.8 (±119.49) meters, and at Week 72 was 40.1 (±90.57) meters. In the PBO-QW cohort of the ITT population, the mean change in 6MWT distance from MOR-004 Baseline at Week 36 was 4.0 (±68.48) meters, at Week 48 was -4.2 (±105.85) meters, and at Week 72 was -2.5 (±112.33) meters.

In the PBO-QOW cohort of the per protocol population, the mean ± standard deviation (±SD) change in 6MWT distance from MOR-004 Baseline at Week 36 was 34.0 (±56.62) meters, at Week 48 was 38.1 (±79.84) meters, and at Week 72 was 49.2 (±86.54) meters. In the PBO-QW cohort of the per protocol population, the mean change in 6MWT distance from MOR-004 Baseline at Week 36 was 10.8 (±59.03) meters, at Week 48 was 46.3 (±54.17) meters, and at Week 72 was 37.6 (±71.77) meters.

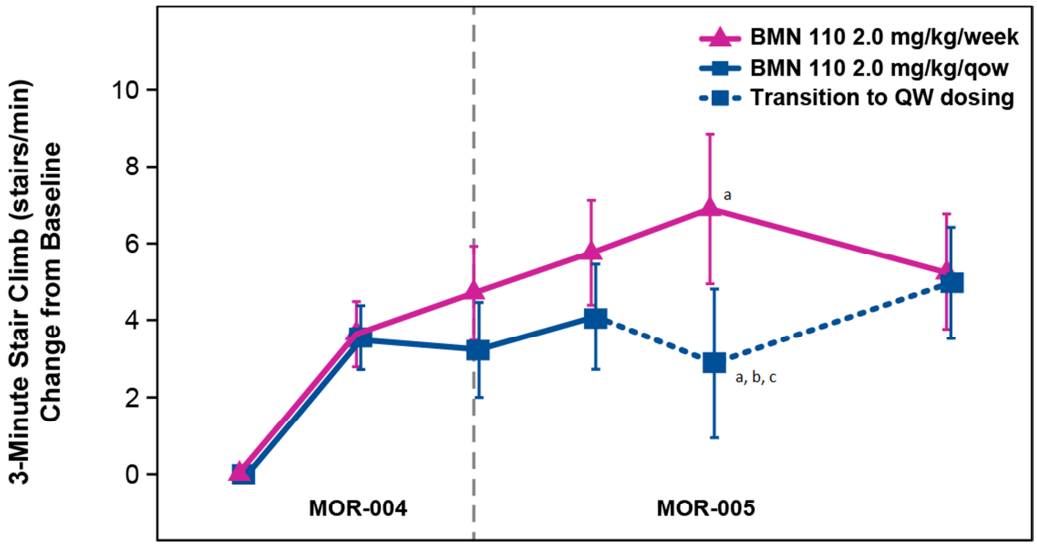
It is difficult to compare the results obtained with treatment after PBO in MOR-005 with results obtained from patients treated initially with BMN-110 in MOR-004, for several reasons. Subjects who had received placebo in MOR-004 were randomized without stratification to BMN 110 for Part 1 of MOR-005, resulting in a substantial between-cohort imbalance in age and endurance measures at Week 24 (MOR-005 Baseline). The numbers of subjects in the placebo-switch cohorts at Week 72 were only half the size of the continuous-treatment cohorts, resulting in large standard errors and overlapping confidence intervals.

6.6.3.2 3MSCT

6.6.3.2.1 QOW-QOW and QW-QW Cohorts

Continued treatment with BMN 110 in MOR-005 showed a stable and sustained improvement in 3MSCT in the QW-QW cohort at Week 72 (Figure 6.6.3.2.1.1); this improvement was also maintained in the per protocol (PP) population at Week 72. (Figure 6.6.3.2.1.2).

Figure 6.6.3.2.1.1: Analysis of 3MSCT: Repeated Measures Model
Analysis Population: ITT Population (MOR-004/MOR-005)



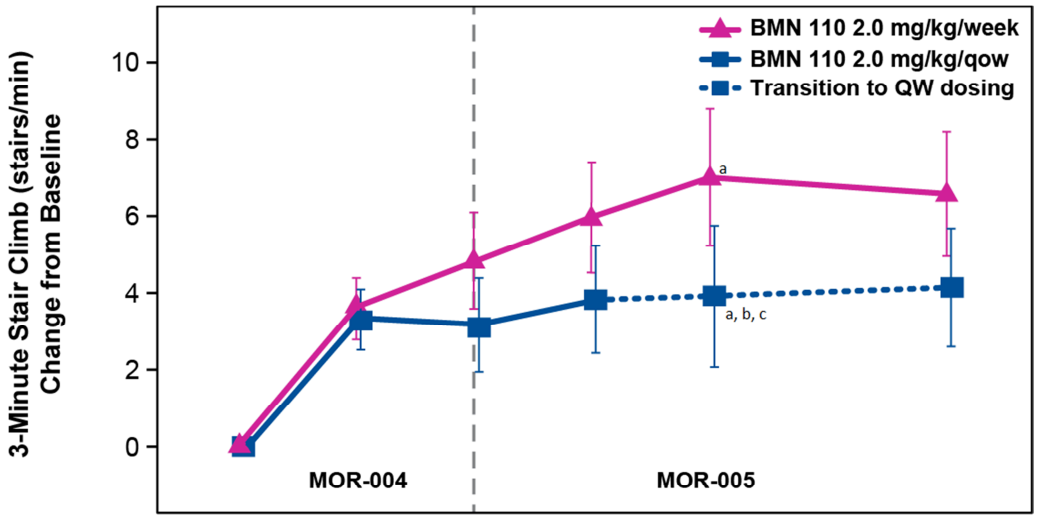
BMN 110 2.0 mg/kg/week	58	58	57	54	26	54
BMN 110 2.0 mg/kg/qow	59	59	58	58	26	56

Model based means (LSMEAN) and standard error bars displayed.
Model: Change from Baseline = agegroup + baseline walk category + treatment + visit + trt*visit + baseline 3msc, unstructured covariance matrix
[a]Due to different assessment schedule in Part 2, not all subjects have Week 48 endurance assessments available.
[b]With start of Part 2 of MOR-005 (01DEC2012), subjects in QOW-QOW cohort began receiving 2.0 mg/kg weekly; the specific time of transition for each subject depended on date of study enrollment, ranging from Week 36 to Week 72.
[c]Week 48 results for the QOW-QOW cohort include only subjects who reached Week 48 while still in Part 1 of the study as there was no Week 48 endurance assessment in Part 2. Thus for the QOW-QOW cohort, this time point includes data only from subjects still receiving QOW dosing.

Using the primary analysis repeated measures ANCOVA model in the ITT population, the least square mean change from MOR-004 Baseline in 3MSCT results for the QOW-QOW and QW-QW cohorts, respectively, at Week 36 were 4.1 stairs/min (CI_{95}, 1.4, 6.8) and 5.8 stairs/min (CI_{95}, 3.0, 8.5), at Week 48 were 2.9 stairs/min (CI_{95}, -0.9, 6.8) and 6.9 stairs/min (CI_{95}, 3.0, 10.8), and at Week 72 were 5.0 stairs/min (CI_{95}, 2.1, 7.9) and 5.3 stairs/min (CI_{95}, 2.3, 8.2).

Similar analysis in the PP population yielded results at Week 72 consistent with those of the ITT population (Figure 6.6.3.2.1.2).

Figure 6.6.3.2.1.2: Analysis of 3MSCT: Repeated Measures Model
Analysis Population: Per Protocol (MOR-004/MOR-005)



BMN 110 2.0 mg/kg/week	52	52	52	48	23	35
BMN 110 2.0 mg/kg/qow	55	55	55	50	19	42

Model based means (LSMEAN) and standard error bars displayed.
Model: Change from Baseline = agegroup + baseline walk category + treatment + visit + trt*visit + baseline 3msc, unstructured covariance matrix
[a]Due to different assessment schedule in Part 2, not all subjects have Week 48 endurance assessments available.
[b]With start of Part 2 of MOR-005 (01DEC2012), subjects in QOW-QOW cohort began receiving 2.0 mg/kg weekly; the specific time of transition for each subject depended on date of study enrollment, ranging from Week 36 to Week 72.
[c]Week 48 results for the QOW-QOW cohort include only subjects who reached Week 48 while still in Part 1 of the study as there was no Week 48 endurance assessment in Part 2. Thus for the QOW-QOW cohort, this time point includes data only from subjects still receiving QOW dosing.

Using the primary analysis repeated measures ANCOVA model in the PP population, the least square mean change from MOR-004 Baseline in 3MSCT results for the QOW-QOW and QW-QW cohorts, respectively, at Week 36 were 3.8 stairs/min (CI_{95}, 1.1, 6.6) and 6.0 stairs/min (CI_{95}, 3.1, 8.8), at Week 48 were 3.9 stairs/min (CI_{95}, 0.3, 7.5) and 7.0 stairs/min (CI_{95}, 3.5, 10.5), and at Week 72 were 4.2 stairs/min (CI_{95}, 1.1, 7.2) and 6.6 stairs/min (CI_{95}, 3.3, 9.8).

6.6.3.2.2 PBO-QOW and PBO-QW Cohorts

In the PBO-QOW cohort of the ITT population, the mean (±SD) change from MOR-004 Baseline at Week 36 was 6.8 (±10.81) stairs/min, at Week 48 was 2.9 (±21.75) stairs/min, and at Week 72 was 8.9 (±15.44) stairs/min. In the PBO-QW cohort of the ITT population,

the mean (±SD) change from MOR-004 Baseline at Week 36 was 2.3 (±10.57) stairs/min, at Week 48 was 3.2 (±14.70) stairs/min, and at Week 72 was 1.2 (±14.95) stairs/min.

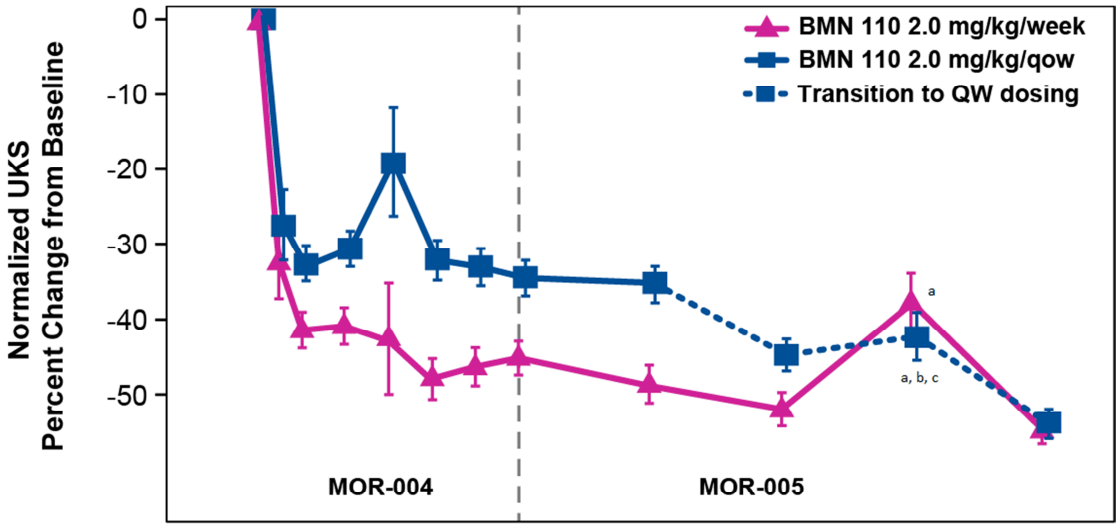
In the PBO-QOW cohort of the PP population, the mean (±SD) change from MOR-004 Baseline at Week 36 was 7.4 (±11.22) stairs/min, at Week 48 was 8.0 (±14.77) stairs/min, and at Week 72 was 9.7 (±13.83) stairs/min. In the PBO-QW cohort of the PP population, the mean (±SD) change from MOR-004 Baseline at Week 36 was 3.5 (±10.67) stairs/min, at Week 48 was 7.9 (±13.13) stairs/min, and at Week 72 was 5.2 (±11.72) stairs/min.

As described for 6MWT, results in subjects previously treated with placebo in MOR-004 are difficult to interpret.

6.6.3.3 Urine KS

Continued treatment with BMN 110 in Study MOR-005 sustained the reduction in urine KS at Week 72 that had been achieved in MOR-004, with the greatest sustained reduction in the QW-QW cohort. At Week 24, mean percent changes from MOR-004 Baseline for cohorts QOW-QOW and QW-QW in the ITT population were -34.6% and -45.5%, respectively. Using the primary analysis repeated measures ANCOVA model in the ITT population, the least square mean percent changes in urine KS levels from MOR-004 Baseline at Week 48 were -45.0% (CI_{95}, -49.0, -41.1) and -51.5% (CI_{95}, -55.7, -47.3) for the QOW-QOW and QW-QW cohorts, respectively. At Week 72, when most subjects were receiving the same weekly regimen (2.0 mg/kg/week), the least square mean percent changes from MOR-004 Baseline were -53.8% (CI_{95}, -57.4, -50.1) and -54.3% (CI_{95}, -58.3, -50.3) for the QOW-QOW and QW-QW cohorts, respectively (Figure 6.6.3.3.1).

Figure 6.6.3.3.1: Analysis of Urine KS: Repeated Measures Model
Analysis Population: ITT Population (MOR-004/MOR-005)



BMN 110 2.0 mg/kg/week	58	55	56	54	55	55	53	54	49	51	11	46
BMN 110 2.0 mg/kg/qow	59	59	58	58	58	58	56	57	56	57	16	55

Model based means (LSMEAN) and standard error bars displayed.
Model: Change from Baseline = agegroup + baseline walk category + treatment + visit + trt*visit + baseline uks, unstructured covariance matrix
[a]Due to different assessment schedule in Part 2, not all subjects have Week 60 uKS assessments available.
[b]With start of Part 2 of MOR-005 (01DEC2012), subjects in QOW-QOW cohort began receiving 2.0 mg/kg weekly; the specific time of transition for each subject depended on date of study enrollment, ranging from Week 36 to Week 72.
[c]Week 60 results for the QOW-QOW cohort include only subjects who reached Week 60 while still in Part 1 of the study as there was no Week 60 uKS assessment in Part 2. Thus for the QOW-QOW cohort, this time point includes data only from subjects still receiving QOW dosing.

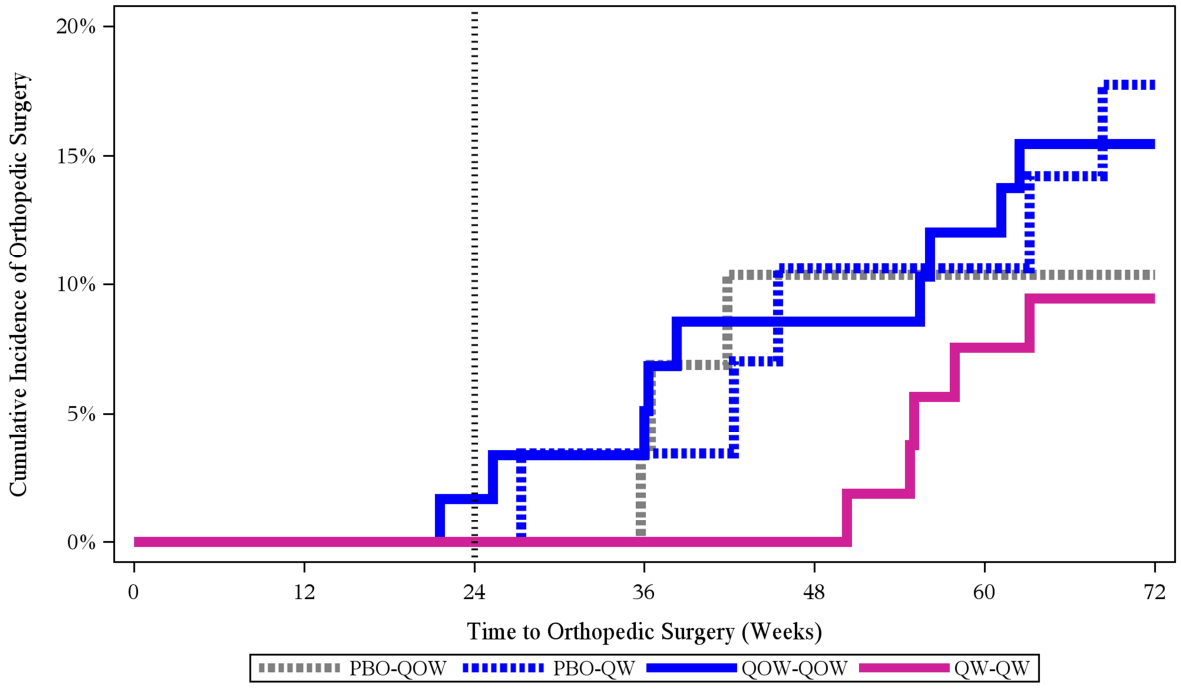
The greater decline in urine KS in the QOW-QOW cohort (relative to the QW-QW cohort) likely reflects the switch in dosing regimen to 2.0 mg/kg/week in this cohort as they entered Part 2 of MOR-005, consistent with dose-dependent decreases in urine KS that have been previously observed in MOR-002/MOR-100.

Sensitivity analyses performed on the PP population up to Week 72 yielded results consistent with those described for the ITT population. In the placebo-switch cohorts in the ITT population, urine KS levels dropped rapidly at Week 36 (-34.1% PBO-QOW and -48.2% PBO-QW) and this reduction was sustained at Week 72 (-53.2% PBO-QOW and -56.8% PBO-QW).

6.6.3.4 Orthopedic Surgeries

During Study MOR-005, when surgical procedures were allowed, there have been fewer orthopedic surgeries in subjects receiving continuous weekly infusions of BMN 110 from the beginning of study MOR-004 compared to subjects randomized to qow or placebo groups in MOR-004 (Figure 6.6.3.4.1). Additionally, subjects in the qow and placebo groups had surgeries earlier in the course of MOR-005 than the weekly dosed subjects, including some procedures that occurred during MOR-004, indicating possible urgency for some interventions (planned major surgery during the 24-week treatment period was an exclusion criterion for MOR-004). Although preliminary, these data suggest that BMN 110 treatment may reduce or delay the need for orthopedic surgeries in patients with MPS IVA. Long-term treatment results from the patient registry will more fully inform this early observation.

Figure 6.6.3.4.1: Time to Orthopedic Surgery in MOR-004/005



6.7 Phase 2 Study MOR-007

MOR-007 is an ongoing Phase 2, open-label, multinational study to evaluate the safety and efficacy of BMN 110 in pediatric subjects less than 5 years of age with MPS IVA. In addition to safety and tolerability, normalized urine KS, anthropometric measurements, and other characteristics of MPS IVA are evaluated in this young population.

A total of 15 subjects were enrolled in MOR-007. As of the data cutoff date of 28SEP2012, subjects received 8 to 44 weeks of treatment with BMN 110. No subjects have completed the 52-week primary treatment phase. All 15 subjects are continuing treatment in the primary treatment phase of the study as of the data cutoff date. Following the primary treatment phase, subjects will continue into the extension treatment phase for an additional 156 weeks of dosing plus 1 week of final assessments (up to a total of 209 weeks in the study).

The marketing application included available efficacy data from all 15 subjects collected up to the data cutoff date of 28SEP2012 for this study. Efficacy results presented in this marketing application included urine KS and anthropometric measurements.

6.7.1 MOR-007 Demographics and Baseline Characteristics

The mean (±SD) age at the time of MPS IVA diagnosis was 2.1 (±1.1) years and the mean (±SD) time since MPS IVA diagnosis was 1.4±0.66. The mean weight at Baseline was 13.1 ± 3.17 kg, the mean subject length was 90.7 ± 9.37 cm, and the mean standing height was 88.9 ± 8.95 cm. Baseline body length ranged from 76 to 113 cm and Baseline standing height ranged from 72 to 109 cm. Baseline normalized urine KS ranged from 18.8 to 56.5µg/mg.

6.7.2 Urine KS

As in other studies, in subjects who completed Week 26 (n=8), treatment with BMN 110 led to sustained reductions in urine KS. The mean percent change (±SD) in these 8 subjects was -39.8% (±18.70) at Week 13 and -35.2% (±15.57) at Week 26.

6.7.3 Anthropometric Measurements

Anthropometric increases were also seen in children under 5 years old in MOR-007. Treatment with BMN 110 over 26 weeks resulted in an increase in mean (±SD) standing height from Baseline to Week 26 by 2.5 (±2.17) cm and an increase in mean (±SD) body length from Baseline to Week 26 by 1.4 (±4.16) cm. In the 8 subjects evaluated, the mean normalized standing height (z-score) was 1.8 SD below normal at Baseline and remained below normal at Week 26. Other anthropometric measures, such as knee height and weight showed mean increases from Baseline to Week 26.

Although there is no control group for comparison, data from the literature suggest that these children experience growth failure in early childhood; thus it is possible these subjects would have fallen even further below normal without intervention (Harmatz P, 2013, Mol.Genet Metab), (Montano, 2007b, J.Inherit.Metab Dis.). Earlier intervention is anticipated to provide

greater benefit. Future assessments in all 15 subjects over a longer treatment period will provide more comprehensive data on growth effects in this young population.

6.8 Efficacy: Discussion and Conclusions

6.8.1 Characteristics of Disease and Differences Between Populations Included in Efficacy Analyses

MPS IVA is characterized by clinical heterogeneity and substantial impairment across multiple domains including growth, stature, endurance and mobility, respiratory function, biochemical abnormalities and quality of life. The most common features of patients with MPS IVA are progressive skeletal dysplasia, marked joint laxity, pulmonary complications, frequent surgical procedures (mostly related to musculoskeletal deformities), and a substantial limitation in walking distance (Montano, 2007a, J Inherit Metab Dis), (Hendriksz, 2013, J.Inherit.Metab Dis.), (Harmatz, 2013, Mol Genet Metab).

Skeletal dysplasia commonly results in severe short stature and malformations of the knees, chest, and spine. A high proportion of subjects in BMN 110 clinical studies had a Baseline height below the 10th percentile (95.5% in MOR-004/005, 80.0% in MOR-002/100, 66.7% in MOR-007, and 88.0% in MOR-008). Percentiles were determined from CDC height charts. Subjects over 19 years of age had percentiles calculated using the norms for 19 year olds. In MOR-004, mean baseline normalized standing height z-scores were 5 or more standard deviations below that predicted by the CDC normal pediatric growth charts. This is consistent with MorCAP data, with mean ± SD height z-scores of –5.6 ±3.1. Normalized growth rates in MOR-004 were also below normal at baseline. Knee deformity was one of the most common medical history findings, reported in 75.0% of subjects in MOR-002, 51.7% in MOR-004, and 20.0% of subjects in MOR-008.

The skeletal dysplasia, short stature, and joint abnormalities all contribute to a substantial restriction in patient mobility, and collectively diminish the functional capacity and endurance of MPS IVA patients. The MorCAP study demonstrated a mean ± SD 6MWT of 212.6±152.2 meters, revealing limitations in functional endurance testing. Specifically the MorCAP data demonstrate endurance limitations as measured by 6MWT that are at least 2-3 fold below the age-specific normal range in healthy populations of similar ages: one study in the U.K. found the mean 6MWT distance to be 470 ± 59 meters in healthy children (boys and girls) aged 4 to 11 years; the distance ranged from 383 ± 41 meters at 4 years of age to 512 ± 41 meters at 11 years (Lammers, 2008, Arch.Dis Child) while another study in Hong Kong found the mean 6MWT distance to be 680.9 ± 65.3 and 642.7 ± 58.9 in healthy boys and girls, respectively, aged 7 to 16 years (Li, 2007, Am J Resp Crit Care Med). The endurance limitations observed in MorCAP are reflected in the interventional studies as well:

in MOR-002/100 the mean baseline 6MWT was 266.9 meters (range 0.0-511.0 meters), which was higher than the mean value for subjects in MOR-004/005 (overall mean of 203.9-211.9 meters, range 36-322 meters) because subjects in MOR-004/005 were required to have an average screening 6MWT distance of ≥ 30 and ≤ 325 meters at study entry. MOR-002 did not have any entry criteria related to walk distance. MOR-008 required an average screening 6MWT distance of ≥ 200 meters, and as a result, mean Baseline 6MWT values were higher (mean of 370-376, range 256-596 meters) than the other studies (Harmatz, 2013, Mol Genet Metab).

The practical importance of the 6MWT can be seen when considering crossing a street. Since street widths and traffic conditions vary, the Federal Highway Administration identified a normal walking speed as 1.22 meters/second, which is the equivalent of 439 meters in 6 minutes. (Federal Highway Administration Website: http://www.fhwa.dot.gov/ environment/bicycle_pedestrian/ publications/sidewalk2/sidewalks208.cfm; accessed 2/3/13) Their Manual on Uniform Traffic Control Devices has recommended that the crossing time allowed in the operation of traffic signals be calculated based on a walking speed of 1.065 meters/second, which equates to 384 meters in 6 minutes. All of the subjects in MOR-004/005 and a majority of the subjects in MOR-002/100 would likely have difficulty safely crossing the street at a standard signalized intersection prior to the light turning red. Consequently, increasing a subject's walking speed as measured by a 6MWT may improve their ability to safely cross the street, move between classrooms in a timely manner, and perform other normal daily activities that require ambulation.

The restriction in patient mobility is further exemplified by the use of a wheelchair in 37.3% to 57.6% of subjects in MOR-004 and 80.0% of subjects in MOR-002 at Baseline. In addition, walking aids were used by 29.3 to 37.3% of subjects in MOR-004 and 10% of subjects in MOR-002 at Baseline. These data are consistent with results of MorCAP, in which wheelchairs were used in 45% of subjects and walking aids in 24%. Note that use of a wheelchair could include both subjects who are wheelchair-bound (ie, very limited or no mobility without a wheelchair) and wheelchair-assisted (ie, subjects with some mobility but who may use a wheelchair as needed). As these are multinational studies, there may also be some variability in how wheelchairs are used/prescribed between countries.

Stair climbing has historically been used as part of preoperative assessment to assess lung function in subjects scheduled for lung resection (Harmatz, 2005, Pediatrics) and has been shown to cause more prolonged lung hyperinflation, higher blood lactate production, and more dyspnea than walking (Dreher, 2008, Respir.Med). Therefore, stair climbing may provide incremental information about disease burden and functional status compared to flat

walking alone. The degree of strain put on the cardiopulmonary system during the 3MSCT is greater than during the 6MWT. Baseline 3MSCT values followed a similar pattern across studies to 6MWT values. Mean Baseline 3MSCT was 27.1 to 30.0 (range 0-71.9) stairs/minute in MOR-004/005, 38.9 (range 0-115) stairs/minute in MOR-002, and 64.2-65.5 (range 27.7-118.7) stairs/minute in MOR-008. These data are consistent with results from MorCAP, which also revealed limitations in stair climbing ability, with a mean ±SD of 30.0 ± 24.0 (range 0.0 to 115.0) stairs/minute for the 3MSCT. These mobility restrictions combined with respiratory dysfunction lead to a dependence on devices as well as caregivers.

Respiratory dysfunction with MPS IVA consists of both restrictive lung disease due to thoracic deformity and obstructive disease due to laryngeal narrowing and tracheal and bronchial abnormalities. These mechanical impediments often result in dyspnea and recurrent respiratory infections, and potentially progress to respiratory failure. A survey of MPS IVA patients showed that patients commonly experience upper airway obstruction, leading to frequent respiratory infections, sleep apnea and breathing difficulty (Montano, 2007b, J Inherit Metab Dis). MorCAP also showed limitations in respiratory function with a mean ± SD FVC of 1.2 ± 0.9 liters and MVV of 34.8 ± 25.5 liters/minute. In MOR-004, mean ±SD FVC was 0.9 ± 0.5 to 1.2 ± 0.9, and MVV was 28.3 ± 16.6 to 34.8 ± 27.3 at Baseline, which is consistent with MorCAP.

Overall the patient populations studied in the BMN 110 clinical development program and in particular the Phase 3 studies have disease characteristics representative of the range of disease manifestations of MPS IVA, and thus results from the BMN 110 clinical studies are anticipated to be generalizable to the overall MPS IVA population.

6.8.2 6MWT in Other Diseases

To provide additional context regarding the observed treatment effect on 6MWT in the Phase 3 study, published data on the use of 6MWT in other disease settings including Duchenne Muscular Dystrophy (DMD), other MPS disorders, pulmonary arterial hypertension, and chronic obstructive pulmonary disease (COPD) were examined. A literature review conducted prior to submission of the BLA revealed that studies that investigated percent change from baseline yielded results in the 10-14% range for 6MWT. In a recent study of patients with DMD, a disease with similar mobility impairments as Morquio A Syndrome, changes in 6MWT distances were correlated with MCID based on patient reported outcome instruments (PROs) at different levels of baseline ability (Henricson, 2013). The authors report that at lower levels of function, smaller increases in 6MWT distance result in meaningful change in quality of life (QoL) instrument scores. At higher levels of function, larger increases may be necessary to achieve the same QoL change score. Specifically, this

analysis showed that a clinically meaningful change in a QoL score for DMD patients aged 4 to 12 years with a baseline walk distance between 150-156 meters corresponded to an increase in 6MWT distance of 5.6 meters. At the other end of the spectrum, for patients with nearly normal baseline walk distances of 431 to 477 meters, clinically meaningful QoL scores correlated with a 6MWT change of 46 meters.

The 6MWT has also been used to support approval of ERTs for other MPS disorders and highlights that an approximate 10% improvement is clinically meaningful. In the pivotal clinical trial for Elaprase (Muenzer, 2006, Genet Med), an improvement of 37 m compared to placebo was observed in the weekly dose group who had a mean baseline 6MWT distance of 392 m. For Aldurazyme (Wraith, 2004, J Pediatr), in a patient population with a baseline 6MWT of 319 m, a treatment improvement of 38 m was demonstrated. These treatment responses as a percent-change-from-baseline are comparable to the treatment effect seen with BMN 110 2 mg/kg/week dosing relative to placebo, further supporting the clinical relevance of the improvement in MPS IVA patients.

Although reference is made to a higher mean improvement in 6MWT being clinically relevant in studies of COPD and pulmonary arterial hypertension (PAH), it is BioMarin's position that DMD is a more relevant comparison to MPS IVA on the basis of disease manifestations. COPD and PAH are disorders of the cardiopulmonary system without musculoskeletal involvement. Improvements in cardiac or pulmonary function in these conditions result in increased oxygen uptake and improved exercise capacity that directly translate into improvements in functional endurance, as measured by the 6MWT (Redelmeier, 1997, Amer J Resp Critical Care Med 1997, Groepenhoff, 2013, PLoS ONE). In contrast, patients with Morquio A Syndrome have numerous morbidities that limit exercise capacity including deformities in their ankles, knees and hips that require surgical correction, and thus a ceiling effect exists for anticipated improvements in 6MWT with ERT alone.

Thus, based on this literature review, a mean treatment effect of 22.5 meters observed after 24 weeks of BMN 110 treatment at 2.0 mg/kg/week represents a clinically relevant benefit for Morquio A patients with an average baseline 6MWT distance of approximately 200 meters.

6.8.3 BMN 110 and Clinical Meaningfulness

Given the natural history and rarity of MPS IVA, there are challenges to demonstrate clinically meaningful benefits in long-term disease outcomes in the limited study period of a clinical trial. Despite these study challenges, a number of relevant and clinically meaningful improvements of patient' lives were detected and documented in the clinical program.

The totality of BMN 110 data translates into clinically meaningful benefits for patients with Morquio A syndrome. In MOR-004, a pre-specified responder analysis shows improvement with 2.0 mg/kg/week BMN 110 over placebo in 6MWT at various levels of response, including those proposed by the Delphi panel. Based on published data on 6MWT in other diseases, the mean change in 6MWT distance is clinically meaningful for the population of patients with Morquio A Syndrome where progressive decline in endurance and overall function is expected as part of the natural history of the disease. In addition to 6MWT, nearly all efficacy endpoints were directionally favorable for the weekly dosing regimen. Finally, additional data from MOR-005 shows long-term durability of benefit with up to 72 weeks of continuous treatment, with a longitudinal data cut from the ongoing natural history study (MOR-001) showing a decline in walk distance in a comparable patient population of approximately 7 m per year.

While there is potential for enzyme replacement therapy to reduce or prevent clinical deterioration consistent with the disease, extended treatment, ideally started prior to the development of substantial and potentially irreversible skeletal deformities, will be required to affect long-term disease outcomes. As an example, deafness is a recognized complication of MPS IVA and occurred in 14.2% of subjects in MOR-004 at Baseline. However, hearing loss is expected to progress slowly, and one would anticipate improvement to be slow and subtle over time and require long-term therapy. Therefore, BioMarin commits to set up a registry to evaluate long-term patient benefits including wheelchair/walking aid dependence, mechanical ventilation, hospitalizations, hearing loss, visual acuity, bone marrow/stem cell transplant, growth, ECG/ECHO, skeletal surveys, and assessments of pain and quality of life. This registry will follow patients for up to 10 years to enable evaluation of events changing at relatively lower rates than can be practically studied in controlled trials.

6.8.4 Efficacy Conclusions

The pivotal Phase 3 Study MOR-004 met the primary endpoint, demonstrating a statistically significant improvement from baseline in 6MWT distance at Week 24 for BMN 110 2.0 mg/kg/week compared to placebo.

- Treatment with BMN 110 was shown to be effective in improving performance in endurance tests (statistically significant for 6MWT) and in reducing urinary KS.
- The magnitude of this observed effect on 6MWT is clinically important in the context of a disease characterized by progressive decline in mobility and endurance, resulting ultimately in physical incapacity and the need for life-long assistance with activities of daily living.

- Results of pre-specified per protocol, supportive, sensitivity, and subgroup analyses were consistent with the primary analysis, confirming the robustness of BMN 110 efficacy as demonstrated by improvement in 6MWT.
- Responder analyses show clear and consistent benefit for the BMN 110 2.0 mg/kg/week treatment group compared to the placebo group across various levels of response.
- In addition, smaller but directionally favorable results occurred for most secondary and tertiary endpoints, including 3MSCT, respiratory function tests, and anthropometric measurements. These results provide supportive evidence for improvement in a wide range of disease-related manifestations.
- BMN 110 was efficacious across a full spectrum of age, disease severity, and baseline clinical manifestations of MPS IVA in this diverse patient population which faces an unrelenting disease progression, as documented in the longitudinal MorCAP data.

A clinical dose of 2.0 mg/kg/week of BMN 110 in patients with MPS IVA is supported by the statistically significant and clinically meaningful difference in 6MWT distance compared to placebo, compared with no discernible treatment effect with the BMN 110 2.0 mg/kg/qow dosing regimen. The BMN 110 efficacy data provide evidence of benefit of BMN 110 2.0 mg/kg/week as an ERT and treatment in multiple domains of function, including growth, mobility, respiratory, and endurance. Such improvements are clinically meaningful benefits to patients with MPS IVA, a disease characterized by a heterogeneous population with progressive decline in mobility and endurance.

7 CLINICAL SAFETY

The marketing application included safety data from 6 clinical studies, including 2 completed studies and 4 ongoing studies: the completed, randomized, double-blind, placebo-controlled pivotal Phase 3 study (MOR-004), plus its long-term extension (MOR-005); the completed Phase 1/2 study (MOR-002), plus its long-term extension (MOR-100); and two ongoing ancillary Phase 2 studies (MOR-007 and MOR-008). Safety data from the ongoing Phase 2 study (MOR-006) was not presented due to incomplete enrollment and very limited exposure at the data cutoff timepoint. Safety data collected from each study included data up to the respective cutoff date for each study. Refer to Table 6.1.1 for an overview of key aspects of these individual clinical studies.

The safety assessments from these trials included examinations of AEs, infusion associated reactions (IARs), clinical laboratory results, vital signs, and physical examination findings; concomitant medications; immunogenicity; and ECG and ECHO data. Adverse events that occurred during infusion were distinguished from other AEs to account for potential IARs due to study drug infusion. In the BMN 110 program, IARs were defined broadly as any AE occurring after the onset of the infusion and within 1 day following the end of the infusion, regardless of the Investigator's assessment of relatedness to study drug administration. Immunogenicity assessments included measurement of anti-BMN 110 total antibody (TAb), neutralizing antibodies that inhibit binding to the CI-M6PR (NAb), and IgE antibody.

In the BMN 110 program, potential Hypersensitivity AEs were identified by utilizing the broad Anaphylactic Reaction algorithmic Standardized MedDRA query (SMQ) and the broad Angioedema SMQ (refer to Appendix 11.2).

To mitigate potential hypersensitivity reactions associated with the administration of BMN 110, an appropriate pretreatment dose of antihistamine (preferably nonsedating, such as cetirizine or loratadine) was administered approximately 30 to 60 minutes following pre-infusion efficacy assessments and before each study drug infusion. Antipyretic premedications were also administered at the discretion of the Investigator. For subjects who had a history of IARs or other risk factors (eg, history of allergies), a sedating antihistamine, such as diphenhydramine or chlorpheniramine, and consideration of premedication with additional agents, such as H2 blockers, montelukast sodium, or steroids was recommended to Investigators.

Immunogenicity monitoring was performed throughout the studies. Investigators were instructed to collect blood samples to characterize immune response on a regular periodic basis throughout the conduct of the study protocols. Tests were performed using validated

immunogenicity assays. Blood samples for immunogenicity tests were collected at selected time points for all subjects.

Immunogenicity tests included:

- Total antibody (TAb)
- Neutralizing antibody (NAb; capable of inhibiting binding to the CI-M6PR); note that when TAb was negative, NAb was not assessed.
- Immunoglobulin E (IgE)

Spinal/cervical cord compression is a known and serious complication of MPS IVA and may occur as part of the natural history of the disease. In BioMarin-sponsored clinical trials in subjects with MPS IVA, SCC was observed in both subjects receiving BMN 110 and subjects receiving placebo.

7.1 Safety Populations

A summary of safety results are presented for the pivotal Phase 3 study (MOR-004) followed by integrated safety analyses for 2 distinct analysis populations:

- The *All Exposed Population*, defined as all subjects from any of the 6 clinical studies included in the marketing application who received any dose of BMN 110 on any dosing regimen.
- The *Proposed Dose Population*, defined as subjects from any of the 6 clinical studies included in the marketing application treated with BMN 110 at the proposed dose of 2.0 mg/kg/week.

For integrated safety results by treatment duration, 5 treatment duration intervals were examined: four 12 week intervals (1 to 12, 13 to 24, 25 to 36, and 37 to 48 weeks) and a greater than 48 week interval.

7.2 Duration of Exposure

In the *All Exposed Population*, a total of 235 subjects were treated with BMN 110 at doses of 0.1, 1.0, 2.0, or 4.0 mg/kg/week or 2.0 mg/kg every other week for periods ranging from 1 week to 169.7 weeks; 86 of these subjects were exposed to BMN 110 for more than 48 weeks. The overall mean (±SD) duration of exposure was 50.2 (±37.03) weeks. Table 7.2.1 presents exposure separately for each study.

Table 7.2.1: BMN 110 Exposure
All Exposed Population by Study

	Phase 3						Phase 1/2		Ancillary Phase 2			
	MOR-004 2.0 mg/kg		MOR-005 2.0 mg/kg				MOR-002 <= 2.0 mg/kg	MOR-100 2.0 mg/kg	MOR-007 2.0 mg/kg	MOR-008		
	QOW (n=59)	QW (n=58)	PBO-QOW (n=29)	PBO-QW (n=29)	QOW-QOW (n=59)	QW-QW (n=56)	/QW (n=20)	/QW (n=17)	/QW (n=15)	2.0 mg/kg/QW (n=15)	4.0 mg/kg/QW (n=10)	Total (n=235)
Total Study Drug Exposure (weeks)												
n	59	58	29	29	59	56	20	17	15	15	10	235
Mean (SD)	24.0 (0.19)	23.6 (3.03)	32.9 (13.17)	31.7 (14.27)	31.6 (13.53)	32.4 (14.95)	69.5 (22.05)	82.9 (3.46)	24.8 (9.12)	11.6 (4.59)	10.0 (3.51)	50.2 (37.03)
Median	24.0	24.0	29.1	29.0	24.0	26.0	78.4	84.0	26.9	10.3	9.3	44.6
Min, Max	23.3, 24.4	1.0, 25.0	19.9, 66.0	11.0, 75.6	11.0, 76.6	1.0, 76.1	9.1, 84.0	74.0, 87.0	8.0, 44.0	6.4, 20.0	6.4, 15.9	1.0, 169.7
Mean Weekly Dose/Subject (mg/kg)												
n	59	58	29	29	59	56	20	17	15	15	10	235
Mean (SD)	0.99 (0.030)	1.96 (0.073)	1.99 (0.015)	2.00 (0.004)	1.99 (0.034)	1.99 (0.033)	0.91 (0.280)	1.99 (0.067)	1.91 (0.146)	1.95 (0.079)	3.96 (0.167)	1.64 (0.686)
Median	1.00	1.99	2.00	2.00	2.00	2.00	1.00	2.00	1.96	1.99	4.02	1.90
Min, Max	0.88, 1.03	1.68, 2.05	1.93, 2.00	1.98, 2.01	1.75, 2.01	1.83, 2.01	0.09, 1.06	1.87, 2.20	1.50, 2.04	1.73, 2.04	3.72, 4.22	0.09, 4.22

	Phase 3						**Phase 1/2**		**Ancillary Phase 2**			
	MOR-004 2.0 mg/kg		**MOR-005 2.0 mg/kg**				**MOR-002 <= 2.0 mg/kg**	**MOR-100 2.0 mg/kg**	**MOR-007 2.0 mg/kg**	**MOR-008**		
	QOW (n=59)	**QW (n=58)**	**PBO-QOW (n=29)**	**PBO-QW (n=29)**	**QOW-QOW (n=59)**	**QW-QW (n=56)**	**/QW (n=20)**	**/QW (n=17)**	**/QW (n=15)**	**2.0 mg/kg/QW (n=15)**	**4.0 mg/kg/QW (n=10)**	**Total (n=235)**
Total Dose/Subject (mg/kg)												
n	59	58	29	29	59	56	20	17	15	15	10	235
Mean (SD)	23.7 (0.70)	46.2 (6.18)	62.2 (25.11)	60.9 (27.60)	60.2 (25.94)	61.0 (27.66)	65.6 (23.74)	147.3 (22.09)	48.0 (18.88)	22.8 (9.29)	39.7 (14.64)	73.2 (54.37)
Median	24.0	48.0	51.9	54.1	44.0	49.1	72.0	152.1	49.9	20.1	36.5	55.0
Min, Max	21.0, 24.3	1.8, 48.1	36.0, 125.3	20.0, 143.9	20.0, 145.2	2.0, 136.0	0.8, 83.9	91.7, 171.4	12.0, 88.1	12.0, 40.1	23.9, 64.4	0.8, 251.7

Study drug exposure (in week) is defined (last infusion date - first infusion date + 7)/7 ; SD, standard deviation

PBO: placebo ; QOW: every other week ; QW: every week

Table 7.2.2 presents the overall exposure to BMN 110 in the *All Exposed Population* by treatment duration. In the table, each column represents exposure occurring during a particular range of weeks in a study (or studies):

- Weeks 1-12 (n=235) – all 235 subjects in the *All Exposed Population* received at least 1-12 weeks of BMN 110 treatment (at any dose – 0.1, 1.0, 2.0, or 4.0 mg/kg/week, or 2.0 mg/kg/every other week)
- Weeks 13-24 (n=211) – 211 of the 235 subjects in the *All Exposed Population* received at least 13-24 weeks of BMN 110 treatment at any dose
- Weeks 25-36 (n=174) – 174 of the 235 subjects in the *All Exposed Population* received at least 25-36 weeks of BMN 110 treatment at any dose
- Weeks 37-48 (n=150) – 150 of the 235 subjects in the *All Exposed Population* received at least 37-48 weeks of BMN 110 treatment at any dose
- Weeks >48 (n=86) – 86 of the 235 subjects in the *All Exposed Population* received more than 48 weeks of BMN 110 treatment at any dose

Note that this table includes only the time period during which a subject was receiving BMN 110; patients who receive placebo were not included while they were on the placebo arm. For example, a subject who received 24 weeks of placebo in MOR-004 and then 8 weeks of BMN 110 in MOR-005 would be considered to have only 8 weeks of exposure.

Table 7.2.2: BMN 110 Exposure
All Exposed Population by Treatment Duration Interval

	Duration of Dosing, Weeks					
	1-12 (n=235)	**13-24 (n=211)**	**25-36 (n=174)**	**37-48 (n=150)**	**>48 (n=86)**	**Total (n=235)**
Total Study Drug Exposure (weeks)						
n	235	211	174	150	86	235
Mean (SD)	50.2 (37.03)	55.0 (36.13)	62.4 (35.68)	67.4 (35.87)	84.4 (39.68)	50.2 (37.03)
Median	44.6	45.3	48.1	52.5	67.1	44.6
Min, Max	1.0, 169.7	15.0, 169.7	25.0, 169.7	37.6, 169.7	49.0, 169.7	1.0, 169.7
Mean Weekly Dose/Subject (mg/kg)						
n	235	211	174	150	86	235
Mean (SD)	1.64 (0.686)	1.55 (0.534)	1.51 (0.474)	1.48 (0.471)	1.50 (0.449)	1.64 (0.686)
Median	1.90	1.64	1.52	1.50	1.51	1.90
Min, Max	0.09, 4.22	0.94, 4.06	0.94, 2.02	0.94, 2.00	0.96, 2.00	0.09, 4.22
Total Dose/Subject (mg/kg)						
n	235	211	174	150	86	235
Mean (SD)	73.2 (54.37)	79.2 (54.05)	88.9 (54.59)	95.4 (55.87)	119.1 (61.57)	73.2 (54.37)
Median	55.0	63.0	72.3	84.4	104.0	55.0
Min, Max	0.8, 251.7	18.0, 251.7	25.0, 251.7	37.1, 251.7	42.8, 251.7	0.8, 251.7

Study drug exposure (in week) is defined (last infusion date-first infusion date + 7)/7 ; SD, standard deviation
Data in the >48 week column contains data from weeks 49 to 170

In the *Proposed Dose Population* (Table 7.2.3), a total of 222 subjects were treated with BMN 110 at the dose of 2.0 mg/kg/week for periods ranging from 1 week to 100.1 weeks. The overall mean (± SD) duration of exposure was 30.2 (± 29.57) weeks. The mean (± SD) weekly BMN 110 dose per subject was 2.0 (± 0.11) mg/kg. Total BMN 110 dose per subject ranged from 1.8 mg/kg to 193.5 mg/kg. The mean (± SD) total BMN 110 dose per subject was 56.8 (± 54.89) mg/kg. For the *Proposed Dose Population*, exposure results are summarized only for the period of time that a subject is receiving BMN 110 2.0 mg/kg/week.

Table 7.2.3: BMN 110 Exposure
Proposed Dose Population by Treatment Duration Interval

	Duration of Dosing, Weeks					
	1 - 12 (n=222)	**13-24 (n=121)**	**25-36 (n=98)**	**37-48 (n=82)**	**>48 (n=52)**	**Total (n=222)**
Total Study Drug Exposure (weeks)						
n	222	121	98	82	52	222
Mean (SD)	30.2 (29.57)	51.1 (25.45)	58.4 (22.70)	64.0 (20.40)	75.3 (17.49)	30.2 (29.57)
Median	20.0	45.4	50.2	58.5	74.6	20.0
Min, Max	1.0, 100.1	13.0, 100.1	25.0, 100.1	37.6, 100.1	49.0, 100.1	1.0, 100.1
Mean Weekly Dose/Subject (mg/kg)						
n	222	121	98	82	52	222
Mean (SD)	2.0 (0.11)	2.0 (0.04)	2.0 (0.04)	2.0 (0.03)	2.0 (0.04)	2.0 (0.11)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Min, Max	0.8, 2.2	1.8, 2.2	1.8, 2.2	1.9, 2.2	1.9, 2.2	0.8, 2.2
Total Dose/Subject (mg/kg)						
n	222	121	98	82	52	222
Mean (SD)	56.8 (54.89)	96.0 (46.12)	109.6 (40.59)	119.9 (36.20)	139.1 (32.20)	56.8 (54.89)
Median	38.0	88.1	94.0	108.0	137.4	38.0
Min, Max	1.8, 193.5	24.0, 193.5	47.9, 193.5	72.6, 193.5	84.6, 193.5	1.8, 193.5

Study drug exposure (in week) is defined (last infusion date-first infusion date + 7)/7 ; SD, standard deviation
Data in the >48 week column contains data from weeks 49 to 100

Exposure to study drug has been nearly maximal in the 6 studies, with > 98% of the infusions performed on schedule.

7.3 Adverse Events

7.3.1 Adverse Events – MOR-004

In MOR-004, nearly all subjects reported at least 1 treatment-emergent AE (Table 7.3.1.1). Infusion associated reactions were common in all treatment arms during this trial. Most AEs were graded mild to moderate in severity. SAEs were reported for 2 (3.4%) subjects in the

placebo group, 4 (6.8%) subjects in the BMN 110 2.0 mg/kg/qow group, and 9 (15.5%) subjects in the BMN 110 2.0 mg/kg/week group; SAEs were either infusion or procedure-related or consistent with underlying disease comorbidities. Study drug-related SAEs occurred infrequently, and were reported in 0 subjects in the placebo group, 1 (1.7%) subject in the BMN 110 2.0 mg/kg/qow group, and 2 (3.4%) subjects in the BMN 110 2.0 mg/kg/week group. No deaths were reported during the trial.

The most common AEs in the study overall were also the most common IARs, and were vomiting (35.6% placebo, 35.6% BMN 110 2.0 mg/kg/qow, 44.8% BMN 110 2.0 mg/kg/week); pyrexia (28.8%, 37.3%, 43.1%), headache (35.6%, 40.7%, 41.4%); and nausea (20.3%, 23.7%, 31.0%) (Table 7.3.1.2). In the placebo group, the most common AEs (incidence ≥ 10%) were cough (35.6%), vomiting (35.6%), headache (35.6%), arthralgia (28.8%) and pyrexia (28.8%). In the BMN 110 2.0 mg/kg/qow group, the most common AEs were headache (40.7%), pyrexia (37.3%), and vomiting (35.6%). In the BMN 110 2.0 mg/kg/week group, the most common AEs were vomiting (44.8%), pyrexia (43.1%), and headache (41.4%). In general, BMN 110 2.0 mg/kg/week subjects had at least 10% greater incidence of pyrexia, nausea, and abdominal pain than placebo subjects. Placebo subjects had at least 10% higher incidences than BMN 110-treated subjects for arthralgia (28.8% placebo, 15.3% BMN 110 2.0 mg/kg/qow, 17.2% BMN 110 2.0 mg/kg/week) and fatigue (25.4%, 13.6%, 15.5%).

Table 7.3.1.1: Overall Summary of Adverse Events, MOR-004 Safety Population

	Placebo (n=59)	BMN 110 2.0 mg/kg/qow[b] (n=59)	BMN 110 2.0 mg/kg/week (n=58)
Any AE	57 (96.6%)	59 (100.0%)	56 (96.6%)
Mild	36 (61.0%)	33 (55.9%)	28 (48.3%)
Moderate	20 (33.9%)	23 (39.0%)	26 (44.8%)
Severe	1 (1.7%)	3 (5.1%)	2 (3.4%)
Number of AEs per subject Mean/Median	10.4/10.0	13.0/12.0	14.3/12.0
Any Study Drug-Related AE [a]	36 (61.0%)	42 (71.2%)	42 (72.4%)
Mild	32 (54.2%)	27 (45.8%)	24 (41.4%)
Moderate	4 (6.8%)	14 (23.7%)	16 (27.6%)
Severe	0 (0.0%)	1 (1.7%)	2 (3.4%)
Any SAE	2 (3.4%)	4 (6.8%)	9 (15.5%)
Mild	0 (0.0%)	2 (3.4%)	2 (3.4%)
Moderate	1 (1.7%)	1 (1.7%)	6 (10.3%)
Severe	1 (1.7%)	1 (1.7%)	1 (1.7%)
Number of SAEs per subject Mean/Median	0.0/0.0	0.1/0.0	0.2/0.0
Any Study Drug-Related SAE [a]	0 (0.0%)	1 (1.7%)	2 (3.4%)
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	1 (1.7%)
Severe	0 (0.0%)	1 (1.7%)	1 (1.7%)
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%)

[a] A drug related AE was classified by investigator as possibly or probably related to study drug.

AEs coded by MedDRA version 15.0; maximum severity is summarized by subject.

[b] qow, every other week;

Severity categories: Mild, no limitation of usual activities; Moderate, some limitation of usual activities; Severe, inability to carry out usual activities.

All AEs are treatment emergent; subjects with more than one AE within a category were counted once at the highest severity level

Table 7.3.1.2: Adverse Events By Treatment Group: Incidence in ≥10% in BMN 110 2.0 mg/kg/week Subjects by Preferred Term (Safety Population)

Preferred Term	Placebo (n = 59)	BMN 110 2.0 mg/kg/qow[a] (n = 59)	BMN 110 2.0 mg/kg/week (n = 58)
Subjects with at Least 1 Reported AE	57 (96.6%)	59 (100.0%)	56 (96.6%)
Vomiting	21 (35.6%)	21 (35.6%)	26 (44.8%)
Pyrexia	17 (28.8%)	22 (37.3%)	25 (43.1%)
Headache	21 (35.6%)	24 (40.7%)	24 (41.4%)
Nausea	12 (20.3%)	14 (23.7%)	18 (31.0%)
Cough	21 (35.6%)	17 (28.8%)	16 (27.6%)
Abdominal pain	5 (8.5%)	8 (13.6%)	14 (24.1%)
Diarrhoea	7 (11.9%)	12 (20.3%)	12 (20.7%)
Oropharyngeal pain	7 (11.9%)	9 (15.3%)	12 (20.7%)
Arthralgia	17 (28.8%)	9 (15.3%)	10 (17.2%)
Nasopharyngitis	9 (15.3%)	12 (20.3%)	10 (17.2%)
Upper respiratory tract infection	9 (15.3%)	10 (16.9%)	10 (17.2%)
Abdominal pain upper	5 (8.5%)	4 (6.8%)	9 (15.5%)
Fatigue	15 (25.4%)	8 (13.6%)	9 (15.5%)
Otitis media	4 (6.8%)	5 (8.5%)	9 (15.5%)
Pain in extremity	9 (15.3%)	14 (23.7%)	9 (15.5%)
Back pain	6 (10.2%)	10 (16.9%)	7 (12.1%)
Dizziness	3 (5.1%)	4 (6.8%)	7 (12.1%)
Dyspnoea	3 (5.1%)	6 (10.2%)	7 (12.1%)
Gastroenteritis	4 (6.8%)	8 (13.6%)	7 (12.1%)
Chills	1 (1.7%)	6 (10.2%)	6 (10.3%)
Oxygen saturation decreased	6 (10.2%)	7 (11.9%)	6 (10.3%)
Rash	5 (8.5%)	6 (10.2%)	6 (10.3%)

[a] qow, every other week;

AEs coded by MedDRA version 15.0;

Subjects who experienced more than one AE within a category were counted once within that category.

7.3.2 Adverse Events – All Exposed Population

Table 7.3.2.1 represents the overall safety summary for the *All Exposed Population*, broken out by treatment duration interval. As with the exposure numbers above (refer to Section 7.2), the data are presented by duration of exposure to BMN 110 – events are recorded in the table according to when they occurred relative to a patient's exposure to

BMN 110. For example, a subject who experienced a headache in Week 8 of MOR-002 would have that event counted in the Weeks 1-12 column (because the subject had between 1-12 weeks of BMN 110 exposure at the time of the event). If the subject then had another headache at Week 20, that event would be counted in the Weeks 13-24 column (because the event occurred at a time when the subject had between 13-24 weeks of BMN 110 exposure). Presenting the data in this way provides an opportunity to examine whether AEs or other safety-related issues occur more or less frequently with increasing cumulative exposure to BMN 110.

In the *All Exposed Population*, AEs were reported for 96.2% of subjects. The mean annualized frequency was 24.99 AEs per subject-year. There is a steady decrease in the mean subject-year frequencies of AEs with duration of treatment from a peak mean of 31.80 AEs per subject-year during the 1 to 12-week treatment duration interval to a low mean of 11.58 AEs per subject-year during the more than 48-week interval. Incidences of study drug-related AEs decreased after the 1 to 12-week interval. Mean SAE subject-year frequencies in the 5 treatment duration intervals were low overall and relatively constant over time. Study drug-related SAEs occurred at low incidences of approximately 1% to 2% during most treatment duration intervals. There were no deaths (Table 7.3.2.1). A single subject (Subject 0119-2007) in MOR-002 experienced an AE during the 1 to 12-week interval that resulted in permanent study discontinuation.

In subjects in the *All Exposed Population*, the subject-year incidence of the most common AEs of headache, vomiting, and pyrexia generally decreased with duration of treatment (Table 7.3.2.2).

Table 7.3.2.1: Overall Safety Summary
All Exposed Population by Treatment Duration Interval

Incidence: n (%)	Duration of BMN 110 Dosing, Weeks					
	1-12 (n=235)	**13-24 (n=211)**	**25-36 (n=174)**	**37-48 (n=150)**	**>48 (n=86)**	**Total (n=235)**
Any AE	222 (94.5%)	185 (87.7%)	144 (82.8%)	113 (75.3%)	66 (76.7%)	226 (96.2%)
AEs per subject-year, mean	31.80	24.39	21.81	19.42	11.58	24.99
Any Related AE	142 (60.4%)	79 (37.4%)	58 (33.3%)	45 (30.0%)	36 (41.9%)	175 (74.5%)
Any SAEs	24 (10.2%)	15 (7.1%)	18 (10.3%)	9 (6.0%)	21 (24.4%)	69 (29.4%)
SAEs per subject-year, mean	0.54	0.38	0.52	0.53	0.52	0.45
Any Serious Related SAEs	5 (2.1%)	3 (1.4%)	2 (1.1%)	1 (0.7%)	5 (5.8%)	13 (5.5%)
Deaths	0	0	0	0	0	0
Any AE leading to permanent study discontinuation	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)

Each dosing weeks column only contains events starting within that duration interval; Data in the >48 week column contains data from weeks 49 to 170

Mapping was based on MedDRA version 15.0

Table 7.3.2.2: Incidence (≥10%) and Frequency of Adverse Events by Preferred Term: All Exposed Population by Treatment Duration Interval

Incidence: n (%) Annualized Frequency: mean events/subject year	Duration of BMN 110 Dosing, Weeks					
Preferred Term	**1-12 (n=235)**	**13-24 (n=211)**	**25-36 (n=174)**	**37-48 (n=150)**	**>48 (n=86)**	**Total (n=235)**
Subjects with at least 1 reported AE	222 (94.5%) 31.80	185 (87.7%) 24.39	144 (82.8%) 21.81	113 (75.3%) 19.42	66 (76.7%) 11.58	226 (96.2%) 24.99
Headache	68 (28.9%) 2.71	46 (21.8%) 1.94	35 (20.1%) 1.74	27 (18.0%) 1.75	24 (27.9%) 1.15	118 (50.2%) 2.41
Vomiting	67 (28.5%) 2.10	53 (25.1%) 1.68	26 (14.9%) 1.06	22 (14.7%) 1.32	27 (31.4%) 0.85	117 (49.8%) 1.51
Pyrexia	67 (28.5%) 1.76	51 (24.2%) 1.53	33 (19.0%) 1.08	22 (14.7%) 0.95	23 (26.7%) 0.78	116 (49.4%) 1.34
Cough	37 (15.7%) 0.85	33 (15.6%) 0.81	15 (8.6%) 0.50	17 (11.3%) 0.72	20 (23.3%) 0.32	88 (37.4%) 0.66
Arthralgia	36 (15.3%) 0.89	20 (9.5%) 0.59	16 (9.2%) 0.66	13 (8.7%) 0.53	12 (14.0%) 0.34	66 (28.1%) 0.77
Nausea	45 (19.1%) 1.24	20 (9.5%) 0.71	14 (8.0%) 0.60	17 (11.3%) 0.69	6 (7.0%) 0.15	66 (28.1%) 0.87
Pain in extremity	32 (13.6%) 0.83	18 (8.5%) 0.58	12 (6.9%) 0.37	17 (11.3%) 0.76	13 (15.1%) 0.24	66 (28.1%) 0.69
Diarrhoea	27 (11.5%) 0.69	17 (8.1%) 0.36	17 (9.8%) 0.60	5 (3.3%) 0.17	13 (15.1%) 0.38	61 (26.0%) 0.53
Nasopharyngitis	23 (9.8%) 0.44	19 (9.0%) 0.47	12 (6.9%) 0.32	11 (7.3%) 0.50	15 (17.4%) 0.26	60 (25.5%) 0.39
Abdominal pain	34 (14.5%) 1.08	14 (6.6%) 0.45	12 (6.9%) 0.41	6 (4.0%) 0.31	5 (5.8%) 0.07	56 (23.8%) 0.77
Upper respiratory tract infection	23 (9.8%) 0.53	18 (8.5%) 0.43	19 (10.9%) 0.55	10 (6.7%) 0.45	9 (10.5%) 0.32	54 (23.0%) 0.48
Oropharyngeal pain	18 (7.7%) 0.38	14 (6.6%) 0.34	11 (6.3%) 0.36	10 (6.7%) 0.44	12 (14.0%) 0.20	51 (21.7%) 0.34
Fatigue	25 (10.6%) 0.67	12 (5.7%) 0.35	8 (4.6%) 0.37	6 (4.0%) 0.26	10 (11.6%) 0.23	49 (20.9%) 0.54
Abdominal pain upper	22 (9.4%) 0.77	10 (4.7%) 0.27	13 (7.5%) 0.55	3 (2.0%) 0.20	8 (9.3%) 0.18	42 (17.9%) 0.41
Back pain	18 (7.7%) 0.44	12 (5.7%) 0.33	8 (4.6%) 0.25	4 (2.7%) 0.13	5 (5.8%) 0.10	37 (15.7%) 0.32
Rash	12 (5.1%) 0.26	12 (5.7%) 0.27	8 (4.6%) 0.23	6 (4.0%) 0.25	12 (14.0%) 0.28	37 (15.7%) 0.26

Incidence: n (%) Annualized Frequency: mean events/subject year	Duration of BMN 110 Dosing, Weeks					
Preferred Term	**1-12 (n=235)**	**13-24 (n=211)**	**25-36 (n=174)**	**37-48 (n=150)**	**>48 (n=86)**	**Total (n=235)**
Nasal congestion	14 (6.0%) 0.26	10 (4.7%) 0.24	14 (8.0%) 0.38	5 (3.3%) 0.18	5 (5.8%) 0.22	34 (14.5%) 0.25
Ear pain	11 (4.7%) 0.20	8 (3.8%) 0.21	3 (1.7%) 0.12	11 (7.3%) 0.38	9 (10.5%) 0.13	33 (14.0%) 0.18
Gastroenteritis	11 (4.7%) 0.22	17 (8.1%) 0.39	5 (2.9%) 0.12	2 (1.3%) 0.07	1 (1.2%) 0.02	32 (13.6%) 0.23
Otitis media	16 (6.8%) 0.31	5 (2.4%) 0.11	9 (5.2%) 0.30	0 (0.0%) 0.00	4 (4.7%) 0.06	29 (12.3%) 0.17
Dyspnoea	12 (5.1%) 0.30	13 (6.2%) 0.29	5 (2.9%) 0.15	4 (2.7%) 0.23	1 (1.2%) 0.01	27 (11.5%) 0.24
Pruritus	10 (4.3%) 0.20	4 (1.9%) 0.08	7 (4.0%) 0.25	4 (2.7%) 0.16	3 (3.5%) 0.04	26 (11.1%) 0.17
Rhinitis	16 (6.8%) 0.37	6 (2.8%) 0.20	6 (3.4%) 0.28	6 (4.0%) 0.20	5 (5.8%) 0.09	26 (11.1%) 0.25

Each dosing weeks column only contains events starting within that duration interval; Data in the >48 week column contains data from weeks 49 to 170

Mapping was based on MedDRA version 15.0

7.3.3 Adverse Events – Proposed Dose Population

In the *Proposed Dose Population*, AEs were reported for 77.0% of subjects. The mean annualized frequency was 23.03 AEs per subject-year. There is a decrease in the mean subject-year frequencies of AEs with duration of treatment from a peak mean of 27.50 AEs per subject-year during the 1 to 12-week interval to a low mean of 11.68 AEs per subject-year during the more than 48-week interval. Incidences of study drug-related AEs decreased after the 1 to 12-week interval. Mean SAE subject-year frequencies in the 5 treatment duration intervals were low overall and relatively constant over time. Study drug-related SAEs occurred at low incidences (1% to 4%) during the 5 treatment duration intervals. There were no deaths or AEs that resulted in permanent study discontinuation (Table 7.3.3.1).

In subjects in the *Proposed Dose Population*, the subject-year incidence of the most common AEs of vomiting, pyrexia, and headache, as in the *All Exposed Population*, generally decreased with duration of treatment (Table 7.3.3.2).

Table 7.3.3.1: Overall Safety Summary
Proposed Dose Population by Treatment Duration Interval

Incidence: n (%) Annualized Frequency: mean events/subject year	Duration of BMN 110 Dosing, Weeks					
	1-12 (n=222)	**13-24 (n=121)**	**25-36 (n=98)**	**37-48 (n=82)**	**>48 (n=52)**	**Total (n=222)**
Any AE	170 (76.6%)	97 (80.2%)	73 (74.5%)	66 (80.5%)	42 (80.8%)	171 (77.0%)
AEs per subject-year, mean	27.50	22.10	17.27	19.74	11.68	23.03
Any Related AE	97 (43.7%)	43 (35.5%)	29 (29.6%)	28 (34.1%)	19 (36.5%)	116 52.3%)
Any SAEs	20 (9.0%)	9 (7.4%)	5 (5.1%)	4 (4.9%)	11 (21.2%)	39 (17.6%)
SAEs per subject-year, mean	0.52	0.39	0.35	0.39	0.44	0.31
Any Serious Related SAEs	4 (1.8%)	2 (1.7%)	2 (2.0%)	1 (1.2%)	2 (3.8%)	9 4.1%)
Deaths	0	0	0	0	0	0
Any AE leading to permanent study discontinuation	0	0	0	0	0	0

Each dosing weeks column only contains events starting within that duration interval; Data in the >48 week column contains data from weeks 49 to 100

Mapping was based on MedDRA version 15.0

Table 7.3.3.2: Incidence (≥10%) and Frequency of Adverse Events by Preferred Term: Proposed Dose Population

Incidence: n (%) Annualized Frequency: mean events/ subject year	Duration of BMN 110 Dosing, Weeks					
Preferred Term	**1-12 (n=222)**	**13-24 (n=121)**	**25-36 (n=98)**	**37-48 (n=82)**	**>48 (n=52)**	**Total (n=222)**
Subjects with at least 1 reported AE	170 (76.6%) 27.50	97 (80.2%) 22.10	73 (74.5%) 17.27	66 (80.5%) 19.74	42 (80.8%) 11.68	171 (77.0%) 23.03
Vomiting	55 (24.8%) 2.22	23 (19.0%) 1.31	13 (13.3%) 0.96	14 (17.1%) 1.35	15 (28.8%) 0.98	77 (34.7%) 1.64
Pyrexia	46 (20.7%) 1.41	28 (23.1%) 1.64	20 (20.4%) 1.16	13 (15.9%) 1.12	14 (26.9%) 0.82	76 (34.2%) 1.14
Headache	52 (23.4%) 2.92	24 (19.8%) 2.10	14 (14.3%) 1.11	14 (17.1%) 1.60	13 (25.0%) 0.96	75 (33.8%) 2.56
Cough	29 (13.1%) 0.85	14 (11.6%) 0.62	7 (7.1%) 0.45	5 (6.1%) 0.35	9 (17.3%) 0.22	52 (23.4%) 0.68
Nausea	32 (14.4%) 1.16	12 (9.9%) 0.90	6 (6.1%) 0.35	10 (12.2%) 0.65	4 (7.7%) 0.21	43 (19.4%) 0.98
Diarrhoea	22 (9.9%) 0.65	7 (5.8%) 0.26	4 (4.1%) 0.22	4 (4.9%) 0.25	9 (17.3%) 0.43	37 (16.7%) 0.47
Pain in extremity	19 (8.6%) 0.62	5 (4.1%) 0.25	8 (8.2%) 0.49	9 (11.0%) 0.77	5 (9.6%) 0.23	36 (16.2%) 0.59
Arthralgia	18 (8.1%) 0.72	11 (9.1%) 0.45	9 (9.2%) 0.49	5 (6.1%) 0.28	5 (9.6%) 0.28	35 (15.8%) 0.71
Abdominal pain	21 (9.5%) 0.72	7 (5.8%) 0.43	5 (5.1%) 0.23	4 (4.9%) 0.30	2 (3.8%) 0.06	33 (14.9%) 0.46
Nasopharyngitis	11 (5.0%) 0.29	13 (10.7%) 0.53	6 (6.1%) 0.30	5 (6.1%) 0.34	7 (13.5%) 0.27	33 (14.9%) 0.34
Fatigue	15 (6.8%) 0.44	8 (6.6%) 0.45	5 (5.1%) 0.48	8 (9.8%) 0.58	5 (9.6%) 0.33	31 (14.0%) 0.41
Oropharyngeal pain	17 (7.7%) 0.51	9 (7.4%) 0.34	6 (6.1%) 0.33	7 (8.5%) 0.55	3 (5.8%) 0.16	31 (14.0%) 0.44
Upper respiratory tract infection	11 (5.0%) 0.26	13 (10.7%) 0.54	11 (11.2%) 0.62	6 (7.3%) 0.50	3 (5.8%) 0.14	30 (13.5%) 0.32
Abdominal pain upper	15 (6.8%) 0.59	5 (4.1%) 0.29	6 (6.1%) 0.49	3 (3.7%) 0.37	6 (11.5%) 0.31	25 (11.3%) 0.32
Rash	7 (3.2%) 0.22	10 (8.3%) 0.40	5 (5.1%) 0.24	5 (6.1%) 0.27	6 (11.5%) 0.22	23 (10.4%) 0.27

Each dosing weeks column only contains events starting within that duration interval; Data in the >48 week column contains data from weeks 49 to 100

Mapping was based on MedDRA version 15.0

7.4 Deaths and Serious Adverse Events

No deaths were reported in any treatment group during study drug treatment or during follow-up in any of the BioMarin-sponsored MPS IVA clinical trials.

7.4.1 Serious Adverse Events – MOR-004

In MOR-004, treatment-emergent SAEs were reported for 2 (3.4%) subjects in the placebo group, 4 (6.8%) subjects in the BMN 110 2.0 mg/kg/qow group, and 9 (15.5%) subjects in the BMN 110 2.0 mg/kg/week group. The overall incidence of SAEs was greater in the BMN 110 groups (4 subjects, 6.8% BMN 110 2.0 mg/kg/qow, 9 subjects, 15.5% BMN 110 2.0 mg/kg/week) than placebo (2 subjects, 3.4%) (Table 7.4.1.1). All SAEs appeared to be associated with infusions, or with surgical or venous access procedures, or are recognized complications of MPS IVA. No SAE by PT, other than pneumonia and otitis media (all unrelated to study drug as assessed by the investigator), occurred in more than 1 subject, and no subject experienced more than 1 SAE.

All subjects who experienced an SAE continued in the study and continued to receive study drug.

Table 7.4.1.1: Serious Adverse Events, MOR-004
Safety Population

Preferred Term	Placebo (n = 59)	BMN 110 2.0 mg/kg/qow[a] (n = 59)	BMN 110 2.0 mg/kg/week (n = 58)
Subjects with at Least 1 Reported SAE	2 (3.4%)	4 (6.8%)	9 (15.5%)
Pneumonia	0	0	2 (3.4%)
Hypersensitivity	0	0	1 (1.7%)
Infusion site pain	0	0	1 (1.7%)
Lower respiratory tract infection	0	0	1 (1.7%)
Otitis media	0	1 (1.7%)	1 (1.7%)
Urticaria	0	0	1 (1.7%)
Viral upper respiratory tract infection	0	0	1 (1.7%)
Vomiting	0	0	1 (1.7%)
Anaphylactic reaction	0	1 (1.7%)	0
Cervical cord compression	1 (1.7%)	0	0
Deafness	1 (1.7%)	0	0
Dengue fever	0	1 (1.7%)	0
Suture removal	0	1 (1.7%)	0

[a] qow, every other week;

SAEs coded by MedDRA version 15.0.

Subjects with more than one SAE within a MedDRA PT were counted once.

Includes only Treatment Emergent Serious Adverse Events.

7.4.2 Serious Adverse Events – All Exposed/Proposed Dose Populations

In the *All Exposed Population*, SAEs were reported for 29.4% of subjects. The mean annualized frequency was 0.45 SAEs per subject-year. Mean SAE subject-year frequencies in the 5 treatment duration intervals were low overall and relatively constant over time. Overall, the most common SAEs were related to disease manifestations and included knee deformity, poor venous access, otitis media, and lower respiratory tract infection. All of these events were assessed as unrelated to study drug. Of the 69 subjects who had at least 1 SAE, 49 subjects had single SAEs; the other 20 subjects had more than 1 SAE. Subject 0121-2003 had 5 SAEs of infusion related reactions on different days and Subject 0121-2012 had 3 episodes of flushing or infusion site reactions on 3 different days, but there were no other

subjects with repeated similar SAEs. There were 7 subjects who had Hypersensitivity AEs (identified by utilizing the broad Anaphylactic Reaction algorithmic SMQ and the broad Angioedema SMQ) that were also SAEs. There were 20 subjects who had IAR SAEs during infusion. With the exception of 1 subject (Subject 0119-2007) in MOR-002 who experienced a grade 4 AE of Type I hypersensitivity and discontinued study participation after Week 11, all subjects who experienced SAEs received and tolerated subsequent infusions.

In the *Proposed Dose Population*, SAEs were reported for 17.6% of subjects. The mean annualized frequency was 0.31 SAEs per subject-year. Mean SAE subject-year frequencies in the 5 treatment duration intervals were low overall and relatively constant over time. Overall, the most common SAEs were related to disease manifestations and included knee deformity (as in the *All Exposed Population*) and catheterization venous. Both of these events were assessed as unrelated to study drug. There were 3 subjects who had Hypersensitivity SAEs (identified by utilizing the broad Anaphylactic Reaction algorithmic SMQ and the broad Angioedema SMQ). There were 12 subjects who had IAR SAEs during infusion. In the *Proposed Dose Population*, all subjects who experienced SAEs received and tolerated subsequent infusions.

7.5 Discontinuations From Study Drug

Study participation was high, with 98% (231/236) of subjects either completing the studies or remaining on for ongoing studies, as of the data cutoff date for each study.

One subject in MOR-002 during the 0.1 mg/kg/week dose interval withdrew from the study due to a study drug-related grade 4 SAE of type I hypersensitivity that occurred in the first 12 weeks of treatment. His symptoms included generalized urticaria, edema, and difficulty breathing with stridor and wheezing. The infusion was stopped, and treatment for the event included oxygen, hydrocortisone, epinephrine, and chlorpheniramine. The event resolved later that day after treatment, but the subject received no further infusions of BMN 110. Note that this IAR occurred before mandatory premedication was required, and that after this event, mandatory antihistamine premedication was added to this and all subsequent protocols.

No other subject in any study discontinued from study drug or withdrew from the study due to an AE.

A total of 4 additional subjects discontinued study drug or withdrew from a study for reasons other than an AE (3 subjects withdrew voluntarily, 1 by Investigator's decision).

7.6 Hypersensitivity Reactions

Potential Hypersensitivity AEs were identified by utilizing the broad Anaphylactic Reaction algorithmic standardized MedDRA query (SMQ) and the broad Angioedema SMQ, which represent a broad range of terms to detect signals possibly indicative of hypersensitivity. To minimize the risk of hypersensitivity reactions associated with the administration of BMN 110, premedication with antihistamines was employed before each study drug infusion (refer to Section 7).

In MOR-004, 7 (11.9%) subjects in the placebo group, 16 (27.1%) subjects in the BMN 110 every other week group, and 12 (20.7%) subjects in the BMN 110 weekly group reported at least one Hypersensitivity AE (Table 7.6.1). The most common preferred terms in either SMQ were urticaria and hypersensitivity. No events of angioedema were reported during the study; one event of anaphylactic reaction was reported in a subject (Subject 1075-4007) in the BMN 110 2.0 mg/kg/qow group. This subject experienced an additional event of anaphylactic reaction in MOR-005. He continues to receive treatment and has consistently tested negative for anti-BMN 110 IgE antibodies. The most Hypersensitivity AEs occurred in the BMN 110 2.0 mg/kg/qow group, suggesting that the incidence was not a function of increased dose frequency. In addition, 100% of treated subjects developed anti-drug antibodies in both dose cohorts, and no correlation was found between higher titers and increased incidence or severity of Hypersensitivity AEs.

Table 7.6.1: Hypersensitivity Adverse Events using Standardized MedDRA Queries, MOR-004 (Safety Population)

	Placebo (n=59) Incidence	BMN110 2.0 mg/kg/qow[a] (n=59) Incidence	BMN110 2.0 mg/kg/week (n=58) Incidence
Subjects with at least 1 Hypersensitivity AE[b]	7(11.9%)	16(27.1%)	12(20.7%)
Anaphylactic Reaction SMQ[b]	1(1.7%)	2(3.4%)	3(5.2%)
Flushing	0	1(1.7%)	2(3.4%)
Cough	1(1.7%)	0	1(1.7%)
Dyspnoea	0	1(1.7%)	1(1.7%)
Hypotension	0	0	1(1.7%)
Urticaria	0	0	1(1.7%)
Anaphylactic reaction	0	1(1.7%)	0
Lip swelling	1(1.7%)	0	0
Angioedema SMQ[b]	7(11.9%)	14(23.7%)	10(17.2%)
Urticaria	0	4(6.8%)	4(6.9%)
Hypersensitivity	1(1.7%)	4(6.8%)	3(5.2%)
Eyelid oedema	0	0	1(1.7%)
Obstructive airways disorder	0	0	1(1.7%)
Oedema peripheral	2(3.4%)	4(6.8%)	1(1.7%)
Throat tightness	0	0	1(1.7%)
Wheezing	1(1.7%)	0	1(1.7%)
Auricular swelling	1(1.7%)	0	0
Lip swelling	1(1.7%)	1(1.7%)	0
Nasal obstruction	2(3.4%)	1(1.7%)	0
Oedema	1(1.7%)	0	0
Stridor	0	1(1.7%)	0

[a]qow, every other week. Preferred Terms coded by MedDRA version 15.0

[b]SMQ, standardized MedDRA query; Hypersensitivity adverse events were identified by utilizing the broad Anaphylactic Reaction algorithmic Standardized MedDRA query and the broad Angioedema Standardized MedDRA query. Subjects with more than one AE within a MedDRA PT were counted once.

In the *All Exposed Population*, Hypersensitivity AEs were reported for 27.2% of subjects (Table 7.6.2). The mean annualized frequency was 0.92 Hypersensitivity AEs per subject-year. Mean AE subject year frequencies in the 5 treatment duration intervals were low overall and relatively constant over time.

Table 7.6.2: Hypersensitivity Adverse Events Using Standardized MedDRA Queries by Duration of BMN 110 (All Exposed Population by Treatment Duration Interval)

Incidence: n (%) Annualized Frequency: mean events/subject year		Duration of BMN 110 Dosing, Weeks					
Hypersensitivity	**Preferred Term**	**1-12 (n=235)**	**13-24 (n=211)**	**25-36 (n=174)**	**37-48 (n=150)**	**>48 (n=86)**	**Total (n=235)**
Subjects with at least 1 reported Hypersensitivity AE[a]		27 (11.5%) 0.88	27 (12.8%) 0.92	13 (7.5%) 0.97	14 (9.3%) 0.80	10 (11.6%) 0.32	64 (27.2%) 0.92
Angioedema SMQ	At least 1 reported Angioedema AE	24 (10.2%) 0.67	25 (11.8%) 0.78	10 (5.7%) 0.80	12 (8.0%) 0.58	9 (10.5%) 0.26	59 (25.1%) 0.68
	Urticaria	7 (3.0%) 0.18	11 (5.2%) 0.36	5 (2.9%) 0.61	6 (4.0%) 0.36	4 (4.7%) 0.14	22 (9.4%) 0.33
	Hypersensitivity	6 (2.6%) 0.17	5 (2.4%) 0.11	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	11 (4.7%) 0.08
	Oedema peripheral	3 (1.3%) 0.10	4 (1.9%) 0.14	1 (0.6%) 0.06	1 (0.7%) 0.03	4 (4.7%) 0.10	11 (4.7%) 0.10
	Wheezing	3 (1.3%) 0.06	3 (1.4%) 0.08	1 (0.6%) 0.02	3 (2.0%) 0.09	1 (1.2%) 0.01	10 (4.3%) 0.07
	Nasal obstruction	2 (0.9%) 0.07	0 (0.0%) 0.00	1 (0.6%) 0.02	1 (0.7%) 0.04	0 (0.0%) 0.00	4 (1.7%) 0.02
	Throat tightness	0 (0.0%) 0.00	1 (0.5%) 0.02	1 (0.6%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	2 (0.9%) 0.01
	Drug hypersensitivity	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.6%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.4%) 0.00
	Eye swelling	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (1.2%) 0.01	1 (0.4%) 0.00
	Eyelid oedema	0 (0.0%) 0.00	1 (0.5%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.4%) 0.01
	Laryngeal oedema	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.6%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.4%) 0.00
	Lip swelling	0 (0.0%) 0.00	1 (0.5%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.4%) 0.00
	Obstructive airways disorder	1 (0.4%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.4%) 0.00

Incidence: n (%) Annualized Frequency: mean events/subject year		Duration of BMN 110 Dosing, Weeks					
Hypersensitivity	**Preferred Term**	**1-12 (n=235)**	**13-24 (n=211)**	**25-36 (n=174)**	**37-48 (n=150)**	**>48 (n=86)**	**Total (n=235)**
	Oedema	0 (0.0%) 0.00	1 (0.5%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.4%) 0.01
	Palatal oedema	1 (0.4%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.4%) 0.00
	Pharyngeal oedema	1 (0.4%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.4%) 0.00
	Stridor	1 (0.4%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.4%) 0.00
	Swollen tongue	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (1.2%) 0.01	1 (0.4%) 0.00
	Tracheal obstruction	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.7%) 0.03	0 (0.0%) 0.00	1 (0.4%) 0.00
	Tracheostomy	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.7%) 0.03	0 (0.0%) 0.00	1 (0.4%) 0.00
	Type I hypersensitivity	1 (0.4%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.4%) 0.02
Anaphylactic Reaction SMQ	At least 1 reported Anaphylactic Reaction AE	7 (3.0%) 0.27	4 (1.9%) 0.16	3 (1.7%) 0.17	4 (2.7%) 0.30	1 (1.2%) 0.06	15 (6.4%) 0.25
	Cough	3 (1.3%) 0.07	0 (0.0%) 0.00	1 (0.6%) 0.02	1 (0.7%) 0.04	0 (0.0%) 0.00	5 (2.1%) 0.05
	Flushing	2 (0.9%) 0.04	2 (0.9%) 0.04	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	4 (1.7%) 0.01
	Anaphylactic reaction	1 (0.4%) 0.02	2 (0.9%) 0.04	0 (0.0%) 0.00	1 (0.7%) 0.03	0 (0.0%) 0.00	3 (1.3%) 0.02
	Dyspnoea	0 (0.0%) 0.00	2 (0.9%) 0.04	0 (0.0%) 0.00	2 (1.3%) 0.07	0 (0.0%) 0.00	3 (1.3%) 0.01
	Urticaria	1 (0.4%) 0.02	1 (0.5%) 0.02	0 (0.0%) 0.00	1 (0.7%) 0.04	0 (0.0%) 0.00	3 (1.3%) 0.02
	Erythema	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.6%) 0.02	1 (0.7%) 0.03	0 (0.0%) 0.00	2 (0.9%) 0.01

Incidence: n (%) Annualized Frequency: mean events/subject year		Duration of BMN 110 Dosing, Weeks					
Hypersensitivity	**Preferred Term**	**1-12 (n=235)**	**13-24 (n=211)**	**25-36 (n=174)**	**37-48 (n=150)**	**>48 (n=86)**	**Total (n=235)**
	Hypotension	0 (0.0%) 0.00	1 (0.5%) 0.02	1 (0.6%) 0.02	1 (0.7%) 0.03	0 (0.0%) 0.00	2 (0.9%) 0.01
	Nasal obstruction	1 (0.4%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.7%) 0.04	0 (0.0%) 0.00	2 (0.9%) 0.01
	Pruritus	1 (0.4%) 0.02	0 (0.0%) 0.00	1 (0.6%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	2 (0.9%) 0.01
	Rash	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.6%) 0.02	1 (0.7%) 0.04	0 (0.0%) 0.00	2 (0.9%) 0.01
	Rash erythematous	2 (0.9%) 0.05	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	2 (0.9%) 0.04
	Asthma	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (1.2%) 0.03	1 (0.4%) 0.00
	Cardio-respiratory arrest	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (1.2%) 0.03	1 (0.4%) 0.00
	Chest discomfort	1 (0.4%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.4%) 0.01
	Cyanosis	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.6%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.4%) 0.00
	Sneezing	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.6%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.4%) 0.01
	Type I hypersensitivity	1 (0.4%) 0.02	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	0 (0.0%) 0.00	1 (0.4%) 0.02

[a]Hypersensitivity adverse events were identified by utilizing the broad Anaphylactic Reaction algorithmic Standardized MedDRA query and the broad Angioedema Standardized MedDRA query

Each dosing weeks column only contains events starting within that duration interval; Data in the >48 week column contains data from weeks 49 to 170

Mapping was based on MedDRA version 15.0; Sorted by descending incidence in Total column

In the *Proposed Dose Population*, Hypersensitivity AEs were reported for 16.2% of subjects. The mean annualized frequency was 1.06 Hypersensitivity AEs per subject-year. Mean Hypersensitivity AEs subject-year frequencies in the 5 treatment duration intervals were low overall and relatively constant over time.

7.6.1 Anaphylaxis

In response to a request from the FDA, BioMarin performed a retrospective review of the reported AEs identified by these SMQ searches, as well as of the full AE database and global safety database, to identify cases with temporal component signs and/or symptoms that potentially met the NIAID/FAAN 2006 criteria for anaphylaxis (Sampson H et al, 2006). Available data from 73 subjects who experienced 152 distinct events were reviewed.

Out of 235 subjects exposed to BMN 110 in the development program at the time of the data cutoffs for the marketing application, 16 subjects may have experienced signs and/or symptoms consistent with the NIAID/FAAN anaphylaxis criteria (corresponding to an incidence rate of 6.8%). These reactions were successfully managed with BMN 110 infusion rate adjustments and/or medical intervention, and all but two subjects continued to receive subsequent BMN 110 infusions. The remainder of the cases reviewed (128 AEs in 57 subjects) did not meet the NIAID/FAAN criteria; most of these subjects experienced single AEs of local reactions such as mild rashes or urticaria.

Descriptive narratives for the 16 subjects identified by the search are provided in Appendix 11.4.

The Warnings and Precautions section of the proposed prescribing information includes language regarding the clinical study experience with anaphylaxis and severe allergic reactions and provides recommended management of and preventive measures for severe allergic-type hypersensitivity reactions.

7.7 Infusion-related Reactions

Infusion associated reactions were defined broadly in each protocol as all AEs (regardless of relationship to study drug) that occurred either after infusion onset and within 1 day after infusion end (MOR-004/005, MOR-002/100, MOR-008) or within 1 day after infusion onset (MOR-007). For this summary, IAR is defined as any AE that occurred after the onset of the infusion and within 1 day following the end of the infusion. Medical intervention is defined as at least one of the following: IV antihistamine, IV steroids, IV fluids, or oxygen, as determined from World Health Organization (WHO) Drug coding.

In MOR-004, the number of subjects with at least 1 reported IAR and number of events reported was 54 (91.5%) subjects and 291 events in the placebo group, 56 (94.9%) subjects and 393 events in the BMN 110 2.0 mg/kg/qow group, and 52 (89.7%) subjects and 511 events in the BMN 110 2.0 mg/kg/week group. High incidence of IARs across treatment groups was not unexpected, given the broad definition of IARs, number of infusions for each subject, duration of infusions, number of children in the study population, and comorbidities

in this population. Higher frequency of IARs was also expected for the groups which received active study drug. Over 80% of subjects experienced IARs during one or more infusions. These IARs occurred in 48 subjects (81.4%) in the placebo group, 53 subjects (89.8%) in the BMN 110 2.0 mg/kg/qow group, and 52 subjects (89.7%) in the BMN 110 2.0 mg/kg/week group. These IARs more commonly led to infusion interruption in the BMN 110 groups (35.6% BMN 110 2.0 mg/kg/qow, 31.0% BMN 110 2.0 mg/kg/week) than in placebo (13.6%). These IARs infrequently led to infusion discontinuation at the study visit day (1.7% placebo, 6.8% BMN 110 2.0 mg/kg/qow, 10.3% BMN 110 2.0 mg/kg/week). No IARs resulted in permanent study drug discontinuation for any subject.

In MOR-004, the proportion of individual infusions that were interrupted or discontinued because the subject experienced an AE during infusion that also required medical intervention was 0% in placebo; 0.64% in BMN 110 weekly group and 1.26% in BMN 110 qow group. The frequency and type of medical intervention used to manage the AEs was similar between BMN 110 treatment groups. The most commonly used medical interventions were IV antihistamines and IV steroids.

The most common AEs during the IAR period were also the most common AEs in the study overall: vomiting (15.3% placebo, 23.7% BMN 110 2.0 mg/kg/qow, 37.9% BMN 110 2.0 mg/kg/week), pyrexia (18.6%, 22.0%, 36.2%), and headache (20.3%, 32.2%, 32.8%) (Table 7.7.1).

Table 7.7.1: Incidence (≥10% Subjects in BMN 110 2.0 mg/kg/week Subjects) of IARs by Preferred Term [MOR-004 (Safety Population)]

	Placebo (n=59)	BMN110 2.0 mg/kg/qow (n=59)	BMN110 2.0 mg/kg/week (n=58)
Subjects with at Least 1 Reported IAR	54 (91.5%)	56 (94.9%)	52 (89.7%)
Vomiting	9 (15.3%)	14 (23.7%)	22 (37.9%)
Pyrexia	11 (18.6%)	13 (22.0%)	21 (36.2%)
Headache	12 (20.3%)	19 (32.2%)	19 (32.8%)
Nausea	8 (13.6%)	10 (16.9%)	16 (27.6%)
Abdominal pain upper	5 (8.5%)	1 (1.7%)	8 (13.8%)
Cough	5 (8.5%)	9 (15.3%)	8 (13.8%)
Fatigue	7 (11.9%)	2 (3.4%)	8 (13.8%)
Abdominal pain	2 (3.4%)	6 (10.2%)	7 (12.1%)
Oropharyngeal pain	3 (5.1%)	3 (5.1%)	7 (12.1%)
Chills	1 (1.7%)	5 (8.5%)	6 (10.3%)
Diarrhoea	7 (11.9%)	6 (10.2%)	6 (10.3%)

qow, every other week. Preferred Terms coded by MedDRA version 15.0

Subjects with more than one AE within a MedDRA PT were counted once. Table is sorted in decreasing frequency of the BMN 110 2.0 mg/kg/week column by PATIENT. IARs are considered associated with the administration of study drug if they occur after the onset of the infusion or within one day following the end of the infusion.

In the *All Exposed Population*, IARs were reported for 92.8% of subjects. The mean annualized frequency was 12.92 IARs per subject-year. There was a consistent decline in the mean subject-year frequencies of IARs and IARs during infusion with duration of treatment. Mean annualized frequencies of IARs leading to infusion interruption and of IARs requiring medical intervention decreased after the 1 to 12-week treatment duration interval. Mean annualized frequencies of IAR SAEs in the 5 treatment duration intervals were low overall and relatively constant over time. In the *All Exposed Population*, only 0.80% (90/11239) of individual infusions were interrupted or discontinued because the subject experienced an AE during infusion that also required medical intervention.

The most common IARs by incidences (and annualized frequencies) in the *All Exposed Population* were headache, 36.6% (1.21 IAR events/subject year); vomiting 35.7% (1.01), and pyrexia, 34.5% (0.84). The frequencies of most IARs were higher during the first 12

weeks of treatment than during subsequent treatment duration intervals, and the IARs tended to occur less frequently with time (Table 7.7.2).

Table 7.7.2: Incidence (≥10% Subjects) and Frequency of Infusion Associated Reactions by Preferred Term
All Exposed Population

Incidence: n (%) Annualized Frequency: mean events/subject year	Duration of BMN 110 Dosing, Weeks					
Preferred Term	1-12 (n=235)	13-24 (n=211)	25-36 (n=174)	37-48 (n=150)	>48 (n=86)	Total (n=235)
Subjects with at least 1 reported AE	198 (84.3%) 18.18	142 (67.3%) 11.97	117 (67.2%) 10.97	86 (57.3%) 9.40	56 (65.1%) 5.18	218 (92.8%) 12.92
Headache	48 (20.4%) 1.51	26 (12.3%) 0.96	21 (12.1%) 1.01	15 (10.0%) 0.87	16 (18.6%) 0.49	86 (36.6%) 1.21
Vomiting	52 (22.1%) 1.60	32 (15.2%) 0.92	17 (9.8%) 0.72	11 (7.3%) 0.67	15 (17.4%) 0.36	84 (35.7%) 1.01
Pyrexia	46 (19.6%) 1.24	28 (13.3%) 0.81	17 (9.8%) 0.61	11 (7.3%) 0.39	15 (17.4%) 0.50	81 (34.5%) 0.84
Nausea	34 (14.5%) 0.96	18 (8.5%) 0.54	11 (6.3%) 0.52	12 (8.0%) 0.45	4 (4.7%) 0.14	55 (23.4%) 0.68
Cough	19 (8.1%) 0.38	12 (5.7%) 0.27	3 (1.7%) 0.13	5 (3.3%) 0.16	4 (4.7%) 0.08	39 (16.6%) 0.24
Diarrhoea	14 (6.0%) 0.30	10 (4.7%) 0.21	12 (6.9%) 0.37	4 (2.7%) 0.13	9 (10.5%) 0.28	39 (16.6%) 0.26
Fatigue	19 (8.1%) 0.46	8 (3.8%) 0.22	7 (4.0%) 0.30	4 (2.7%) 0.14	6 (7.0%) 0.12	36 (15.3%) 0.38
Abdominal pain	22 (9.4%) 0.59	10 (4.7%) 0.35	5 (2.9%) 0.17	2 (1.3%) 0.10	1 (1.2%) 0.01	33 (14.0%) 0.39
Pain in extremity	11 (4.7%) 0.23	6 (2.8%) 0.14	6 (3.4%) 0.15	6 (4.0%) 0.24	4 (4.7%) 0.08	31 (13.2%) 0.18
Abdominal pain upper	17 (7.2%) 0.60	6 (2.8%) 0.14	9 (5.2%) 0.35	2 (1.3%) 0.14	3 (3.5%) 0.07	29 (12.3%) 0.30
Arthralgia	13 (5.5%) 0.26	6 (2.8%) 0.12	2 (1.1%) 0.05	5 (3.3%) 0.17	4 (4.7%) 0.06	26 (11.1%) 0.19
Rash	7 (3.0%) 0.15	6 (2.8%) 0.15	4 (2.3%) 0.13	4 (2.7%) 0.16	8 (9.3%) 0.15	24 (10.2%) 0.15

Each dosing weeks column only contains events starting within that duration interval; Data in the >48 week column contains data from weeks 49 to 170

Mapping was based on MedDRA version 15.0

Infusion Associated Reaction (IAR) are considered associated with the administration of study drug if they occur after the onset of the infusion or within one day following end of the infusion.

In the *Proposed Dose Population*, IARs were reported for 71.2% subjects. The mean annualized frequency was 12.76 IARs per subject-year. There were decreases with duration of treatment in the mean subject-year frequencies of IARs and IARs during infusion. Mean annualized frequencies of IARs leading to infusion interruption and of IARs requiring medical intervention decreased after the 1 to 12-week treatment duration interval. Mean annualized frequencies of IAR SAEs in the 5 treatment duration intervals were low overall and decreased during the more than 48 week interval.

In the *Proposed Dose Population*, only 0.82% of individual infusions were interrupted or discontinued because the subject experienced an AE during infusion that also required medical intervention.

The Warnings and Precautions section of the proposed prescribing information includes language regarding the clinical study experience with IARs. A subset of IARs that meet the definition for an adverse drug reaction (ADR), as defined in the prescribing information, are deemed "Infusion Reactions". The prescribing information provides recommended management of and preventive measures for infusion reactions including administration of antihistamines with or without antipyretics prior to infusion.

7.8 Spinal Cord Compression

Spinal cord compression is a well-known and potentially severe complication in patients with MPS IVA. Spinal cord compression has been identified as a potential risk for treatment with BMN 110. In order to better monitor potential events of spinal cord compression, BioMarin has searched the cumulative database using the following MedDRA preferred terms:

- Atlantoaxial instability, cervical cord compression, cervical myelopathy, cervical spinal stenosis, foramen magnum stenosis, quadriparesis, scoliosis, spinal column injury, spinal column stenosis, spinal cord compression, spinal decompression, spinal disorder, spinal laminectomy, joint instability, spinal cord oedema, quadriplegia, and spinal operation

As of the marketing application data cutoff dates, a total of 13 events identified by this search have been reported in 10 subjects in the BMN 110 development program. The most commonly reported preferred terms were joint instability (3), cervical cord compression (2), and spinal cord compression (2).

Of the 10 subjects with reported SCC events, 1 subject (with 2 events) was enrolled in MOR-002/MOR-100, 1 subject (with 1 event) was enrolled in MOR-007[2], and the remaining 8 subjects (with 10 events) were enrolled in MOR-004/MOR-005. No events meeting the definition of spinal cord compression have been reported at the time of data cut in MOR-006 or MOR-008.

Two events occurred during the pivotal MOR-004 study; both events occurred in subjects receiving placebo. Six of the 13 events overall were reported as SAEs, and 7/13 were reported as severe in grade. No subjects discontinued treatment with BMN 110 as a result of an event of SCC.

BioMarin will continue to closely monitor for events of spinal cord compression.

7.9 Laboratory Findings, ECG Data, and Echocardiography

No evidence of treatment-emergent increases in hematology abnormalities was apparent in subjects treated with BMN 110 across all studies. There were few reported hematology abnormalities in any treatment group, and incidences of clinically significant hematologic results and clinically significant changes from Baseline were uncommon.

Incidences of clinically significant serum chemistry results or changes from Baseline were uncommon, and BMN 110 treatment was not associated with a clinically meaningful increase in abnormalities of serum chemistry values. Across all studies, no evidence of treatment-emergent increases in urinalysis abnormalities was apparent in subjects treated with BMN 110.

In studies for which echocardiography (MOR-002, MOR-004, MOR-100) and ECG (MOR-002, MOR-004, MOR-100, MOR-007) data were available at the time of this submission, there were no treatment-emergent, clinically-significant abnormalities during the study in any subject**.**

7.10 Safety in Extended Use

Long-term safety was evaluated in the MOR-005 and MOR-100 extension studies.
The evaluation of the various safety parameters monitored during the study, including AEs, physical examination, vital signs, standard laboratory tests, and immunogenicity testing indicates that long-term administration of BMN 110 was well tolerated.

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[2] The subject from study MOR-007 had been admitted to the study on a waiver despite having concurrent symptoms of SCC at Baseline.

Serious adverse events (SAEs) and Hypersensitivity AEs occurred infrequently and did not increase with time. Infusion associated reactions tended to occur less frequently with duration of treatment. Most AEs reported in MOR-005 and MOR-100 were grade 1 or grade 2. No subject discontinued the study due to an AE and there were no deaths on study. Despite drug exposure (ie, overall mg/subject) in MOR-100 being more than twice that in MOR-002, there was no apparent dose-related increase in AEs and there were no new safety signals identified with longer duration of therapy.

Anti-drug antibody development was universal in BMN 110 treated subjects. There was no apparent change in the immunogenicity profile with long-term treatment. No relationship was observed between higher anti-BMN 110 TAb titers or increased NAb positivity and higher incidence or severity of Hypersensitivity AE. Sustained improvements in efficacy measures and reductions in urine KS were observed across studies, despite the development of anti-drug antibodies. Anti-BMN 110 IgE antibody was detected in ≤ 10% of subjects across studies and was not consistently associated with Hypersensitivity AEs or drug interruptions or withdrawal. Refer to Section 8 for a more detailed immunogenicity discussion.

7.11 Adverse Drug Reactions

Regional regulatory guidance was used to identify suspected ADRs for purposes of regional prescribing information. A suspected ADR means any AE for which there is a reasonable possibility that BMN 110 caused the AE based on evidence to suggest a causal relationship. AEs were identified using a 5% greater incidence in the subjects receiving weekly active-drug compared to placebo and having a plausible and clinically meaningful relationship to drug.

Based on these criteria, the following events were defined as ADRs:

- Vomiting
- Pyrexia
- Headache
- Nausea
- Abdominal pain
- Diarrhea
- Oropharyngeal pain
- Chills
- Abdominal pain upper
- Dizziness
- Dyspnea
- Myalgia

In addition to the adverse reactions listed above, less commonly reported adverse reactions observed in clinical trials include anaphylaxis and hypersensitivity reactions.

7.12 Proposed Risk Management Plan

Based on available data, the safety profile of BMN 110 is consistent with that observed with other approved ERTs, including the occurrence of hypersensitivity reactions. BioMarin has the knowledge and expertise to ensure healthcare providers are adequately trained to

administer ERTs and are informed of the associated risks. Specialists who administer these types of therapies are aware of the risks associated with ERT, and standard clinical practice involves informing patients of the risk-benefit balance of their treatment.

The following safety concerns have been identified during the BMN 110 development program and will be further evaluated in the post-marketing setting:

Important Identified Risks

- Infusion Reactions (including anaphylaxis and severe allergic reactions)

Important Potential Risks

- Immunogenicity
- Spinal/Cervical Cord Compression (SCC)
    - *Note*: This known serious complication of MPS IVA is being monitored as a precautionary measure to assess any influence of enzyme replacement therapy (positive or negative) on the natural history of SCC.
- Medication Errors

Important Missing Information

- Size of Safety Database
    - *Note*: The size of the BMN 110 safety database is larger than that established for any other ERT at the time of initial marketing authorization. However, the patient population for this orphan drug is relatively small, and the safety database will be made more robust through the capture of post-marketing and registry information.
- Subgroup Safety Experience (pregnancy & lactation, renal, cardiac, or hepatic impairment)

BioMarin proposes the following risk minimization and pharmacovigilance activities to ensure safe and effective use of BMN 110, and to gain more knowledge about the safety of BMN 110 in the post-authorization setting.

- Evidence-based product labeling to characterize the risk-benefit balance of BMN 110 from pivotal clinical trial experience
- Routine pharmacovigilance (eg, robust collection and follow-up of all reports of suspected adverse reactions and special situation events; submission of expedited safety reports and periodic benefit risk evaluations reports in accordance with applicable regulations; continuous monitoring of the safety profile of BMN 110 including signal management, updating of labeling, and liaison with applicable regulatory authorities)

- A voluntary disease registry using observational methods to collect uniform data on specified effectiveness outcomes and post-marketing safety experience in MPS IVA patients. Additional safety data collected through the BMN 110 registry for identified and potential risks will also be reported accordingly.

BioMarin's Pharmacovigilance department (BPV) performs the following routine pharmacovigilance (PV) activities for all BioMarin products: collection and collation of all suspected adverse drug reactions that are reported to personnel of the company; reporting to regulatory authorities; continuous monitoring of the safety profiles of BioMarin products; submission of aggregate reports as required (e.g., periodic adverse experience reports, periodic safety update reports, or periodic risk-benefit evaluation reports); continuous monitoring of the safety profiles of BioMarin products including signal detection, updating labeling and risk management planning; and meeting other local regulatory agency requirements.

An independent BioMarin Good Pharmacovigilance Practices (GPvP) Compliance group schedules and performs periodic audits of pharmacovigilance systems and processes, effectiveness verification of corrective and preventive action plans, and tracking of all regulatory commitments to closure.

BioMarin has the knowledge and expertise to ensure healthcare providers are adequately trained to administer ERTs and are informed of the associated risks. Specialists who administer these types of therapies do so in a controlled setting and are aware of the risks associated with ERT, and standard clinical practice involves informing patients of the risk-benefit profile of their treatment. A product monograph, infusion training video, and dosing and administration guide has been prepared to educate treating physicians and healthcare practitioners in the storage, preparation, and administration of BMN 110. These materials will be distributed, as appropriate, to healthcare providers, including infusion nurses and treating physicians.

At this stage of BMN 110's life cycle, the primary proposed risk minimization activities are labeling to educate healthcare practitioners and patients about potential risks of BMN 110, and provision of educational material to guide safe and effective use of BMN 110 for the treatment of MPS IVA. The goal of these activities is to minimize the occurrence and severity of identified and potential risks.

7.13 Clinical Safety Conclusions

The clinical safety database includes safety results from 235 subjects with MPS IVA exposed to BMN 110 across 6 clinical trials. The combination of study populations in the BMN 110 clinical development program encompasses the spectrum of age and disease severity of the

overall patient population. Included were subjects between the ages of 0.8 and 57.4 years. Subjects were exposed for up to 169.7 weeks of continuous treatment (overall mean [SD] duration of exposure was 50.2 [±37.03] weeks).

- Across all studies, only 1 subject (from MOR-002) permanently discontinued study drug due to an AE. There were no deaths.
- The most common AEs were associated with infusions and included vomiting, pyrexia, and headache.
- Most subjects experienced at least 1 IAR. Although some AEs during infusion required slowing or stopping of the infusion and, less often, medical intervention, all subjects except for one (the MOR-002 subject referred to above) received and tolerated subsequent infusions. IARs tended to occur less frequently with duration of treatment.
- SAEs and Hypersensitivity AEs occurred infrequently. Most SAEs were related to the underlying disease or to catheterization or venous access issues.
- Analyses of the data show that BMN 110 continues to be well tolerated with longer-term exposure. The mean annualized frequencies of AEs including related AEs and IARs decreased over time. In addition, the mean annualized frequencies of SAEs and Hypersensitivity AEs did not increase over time.
- There were no clinically meaningful changes in laboratory values, ECGs, or ECHOs.

The clinical dose of 2.0 mg/kg/week of BMN 110 in patients with MPS IVA is supported by an acceptable safety profile in the MOR-004 study. Analysis of data from both individual studies and integrated data from multiple studies indicates that the safety profile of BMN 110 is acceptable and similar to that of other ERTs approved for clinical use (Naglazyme Package Insert [BioMarin], 2012), (Aldurazyme (Laronidase) Package Insert, 2011), (Elaprase Package Insert [Shire], 2013) (Elelyso Package Insert, 2012) (Myozyme Package Insert, 2012), (VPRIV Package Insert [Shire], 2013).

8 OVERVIEW OF IMMUNOGENICITY

Immunogenicity testing included BMN 110-specific TAb, NAb, and IgE. The TAb assay measures multiple anti-drug antibody isotypes in one assay, eliminating the need for multiple isotype-specific assays to assess the anti-BMN 110 antibody response. TAb positive samples were tested for NAb capable of inhibiting BMN 110 from binding to the CI-M6PR *in vitro*. A NAb assay to detect antibodies that inhibit enzymatic activity of BMN 110 was not developed, because the drug is not active at neutral pH in the blood (Masue, 1991, J.Biochem.(Tokyo)). BMN 110 is activated within the low pH environment of the lysosome, where antibody binding is an unlikely factor. TAb and NAb testing was performed in each study, except for MOR-007 where TAb alone was measured due to blood volume restrictions in pediatric subjects. BMN 110-specific IgE testing was conducted in all studies following a severe IAR or an IAR requiring infusion cessation. BMN 110-specific IgE was also assessed at routine study visits in MOR-002, MOR-100, MOR-004, and MOR 005, as well as during the primary treatment phases of MOR-007 and MOR-008.

All subjects treated with BMN 110 developed sustained anti-drug antibodies across studies. Antibody incidence reached 100% by Week 4 in the 2.0 mg/kg/week cohort in the pivotal study. Approximately 80% of subjects developed NAb capable of inhibiting the drug from binding to the CI-M6PR by Week 24. Sustained improvements in efficacy measures and reductions in urine KS were observed, despite the development of anti-drug antibodies. No associations were found between higher antibody titers or NAb positivity rates and reductions in efficacy measurements or the occurrence of Hypersensitivity AEs. Anti-BMN 110 IgE antibodies were detected in ≤10% of treated subjects across studies and have not consistently been related to anaphylaxis or other hypersensitivity reactions, and/or treatment withdrawal.

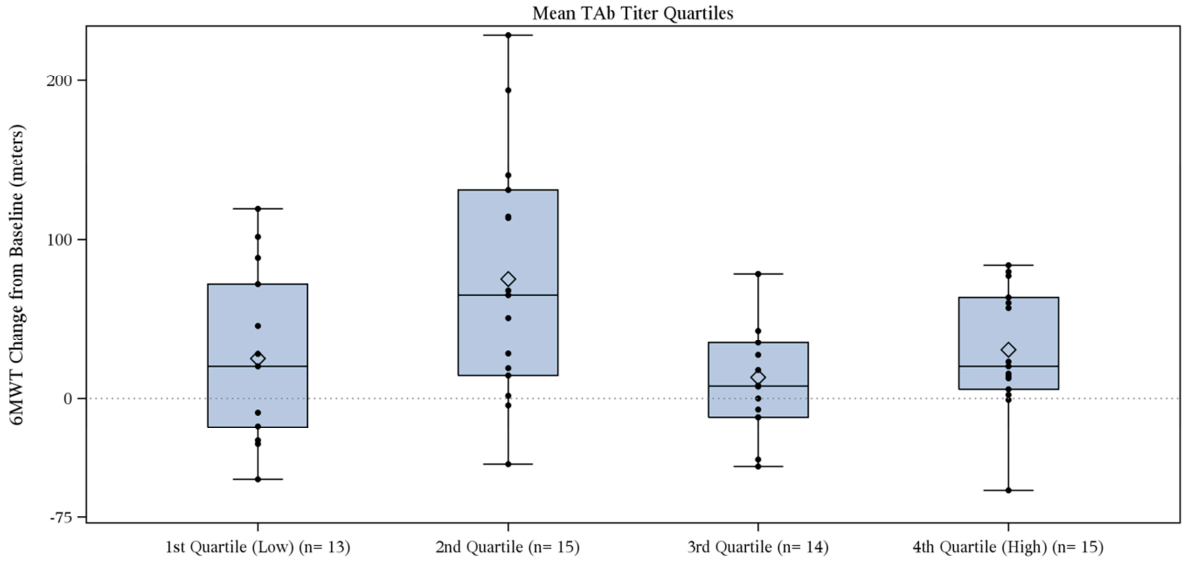
8.1 Effects on Efficacy

No correlations were evident between TAb titer or NAb positivity and 6MWT, 3MSCT, or MVV measurements in studies MOR-004, MOR-005, MOR-002, and MOR-100.

In MOR-004, efficacy measurements did not follow a pattern with TAb titer or NAb positivity. Higher TAb titers and NAb positivity rates were not associated with lower 6MWT measurements (Figure 8.1.1 and Figure 8.1.2; results shown for the QW treatment cohort in MOR-004). Preservation of efficacy, despite a high incidence of anti-enzyme antibodies has been demonstrated in other lysosomal storage diseases treated with ERT (Harmatz, 2008, Mol Genet Metab), (Germain, 2007, J.Am.Soc.Nephrol.), (Brooks, 2003, Trends Mol.Med.), (Desnick, 2012, Annu.Rev.Genomics Hum.Genet.). While it is encouraging that NAb have

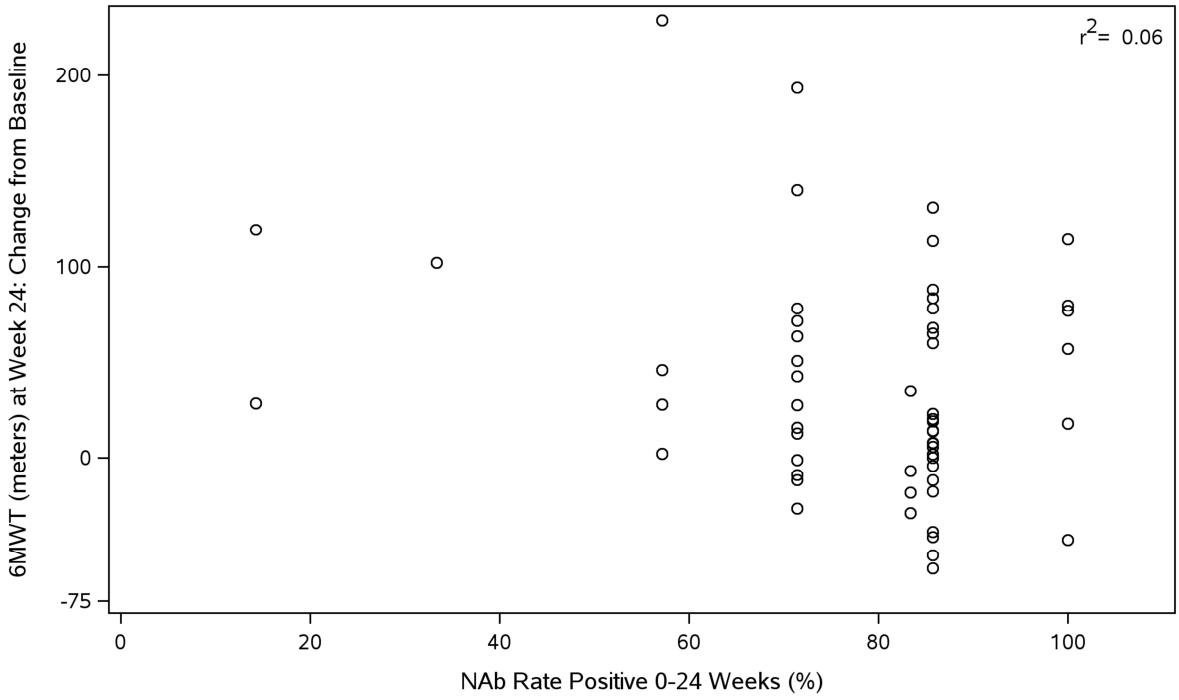
not been associated with a reduction in BMN 110 efficacy thus far, NAb will continue to be monitored in the extension study and evaluated for impact on long-term efficacy.

Figure 8.1.1: Weekly (QW) Treatment Change in 6MWT at 24 Weeks by TAb Quartile Groups (Analysis Population: Safety [MOR-004])



Mean TAb Titer Quartile Ranges: 1st Quartile (Low)=0 to <26080, 2nd Quartile=26080 to <43820, 3rd Quartile=43820 to <75000, 4th Quartile (High)=75000 to 789971.

Figure 8.1.2: Week 24 Antibody Responses and 6MWT – QW Cohort
Analysis Population: Safety (MOR-004)



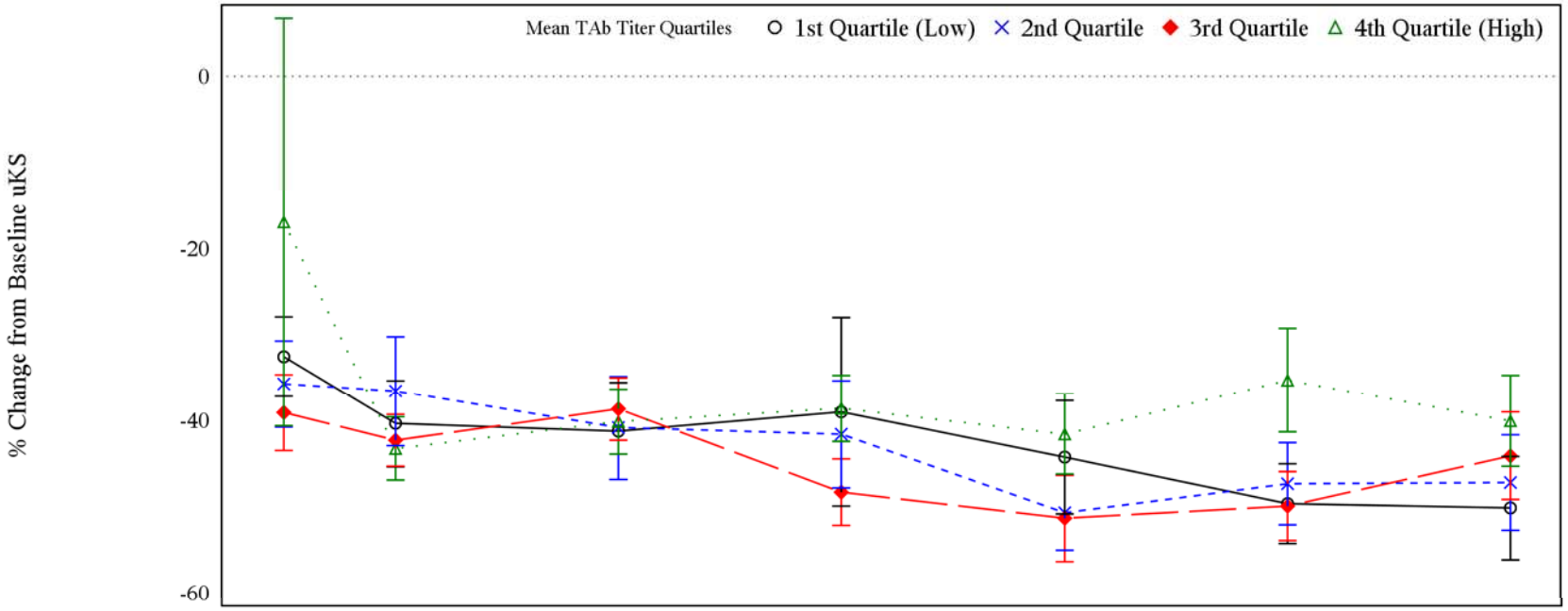
In MOR-005, as of the 03SEP2013 data cut-off, additional exposure up to 72 weeks of treatment showed no apparent associations between TAb titers or NAb positivity and efficacy, based on 6MWT and 3MSCT.

8.2 Effects on Pharmacodynamics

Sustained reductions in urine KS were detected across studies and treatment cohorts, despite the development of anti-BMN 110 antibodies.

In MOR-004, no association was detected between TAb titer or NAb positivity rate and the percent change in normalized urine KS from baseline. Higher TAb titers and NAb positivity rates were not associated with diminished uKS reduction (Figure 8.2.1 and Figure 8.2.2; results shown for the QW treatment cohort in MOR-004).

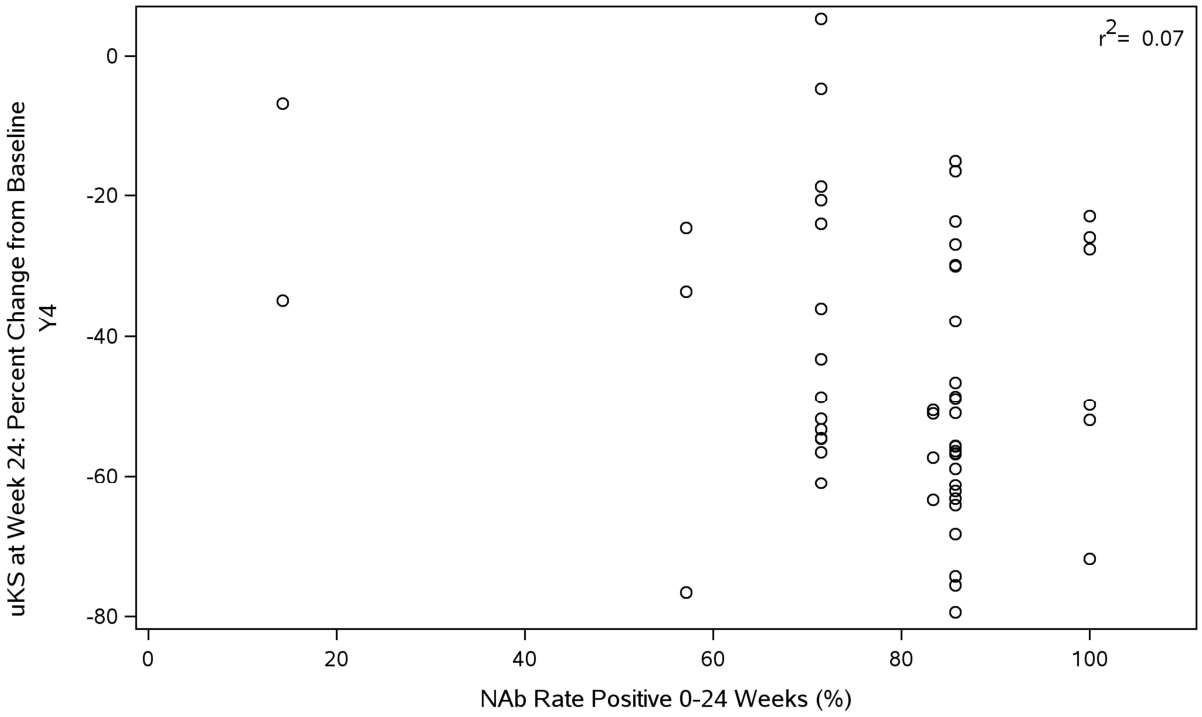
Figure 8.2.1: Weekly (QW) Treatment: Mean Percent Change in uKS by TAb Quartile Groups
Analysis Population: Safety (MOR-004)



1st Quartile (Low)	14	13	11	12	13	12	12
2nd Quartile	13	14	15	15	15	14	14
3rd Quartile	14	14	14	13	12	12	13
4th Quartile (High)	14	15	14	15	15	15	15

TAb titers for each subject in the QW treatment cohort were categorized into titer quartile groups: 1st Quartile (low) 0 to <26,080; 2nd quartile 26,080 to <43,820; 3rd Quartile 43,820 to <75,000; 4th Quartile (High) 75,000 to 789,971.
The percent change in uKS from Baseline for each quartile group is plotted over the course of the Study.
The number of subjects within each titer quartile group at each treatment week is listed below the graph.

Figure 8.2.2: Weekly (QW) Treatment: Mean Percent Change in uKS by NAb Response Groups
Analysis Population: Safety (MOR-004)



In MOR-005, continued reduction in urine KS occurred in the QOW-QOW and QW-QW cohorts, despite sustained levels of anti-BMN 110 TAb and NAb. No correlation was detected between TAb titers or NAb positivity and the percent change in urine KS from Baseline.

Despite the high incidence of NAb, decreases in urinary KS and improvements in efficacy measurements were sustained at the proposed treatment dose (2.0 mg/kg/week). No associations were found between higher NAb positivity rates or higher total anti-drug antibody titers and reduced efficacy or pharmacodynamic effect, providing evidence that a sufficient amount of drug is taken up by the cells and transported to the lysosomes, in the presence of antibody, to mediate a sustained treatment effect. This may be explained by the stoichiometric ratio of antibody to drug during the infusion, when the concentration of drug in the blood likely greatly exceeds the concentration of serum antibody. Furthermore, the rapid plasma clearance rate of the drug via the CI-M6PR, limits the time that the drug is exposed to antibodies in systemic circulation ($t_{1/2}$ ~35 min). Once the drug reaches the intracellular compartment, where it is relatively protected from the immune response, the

half-life of the drug is on average between 5-7 days. NAb will continue to be monitored and evaluated for impact on long-term efficacy in treated subjects.

8.3 Effects on Safety

Higher TAb titers and/or NAb positivity have not been associated with increased incidence or severity of Hypersensitivity AEs. Anti-BMN 110 specific IgE positivity has not consistently been associated with Hypersensitivity AEs and/or drug interruption across studies. In MOR-004, a total of 6.8% (4/59) and 8.6% (5/58) of subjects tested positive for BMN 110-specific IgE in the every other week and weekly treatment groups, respectively. In each case, drug-specific IgE was transient and not associated with severe Hypersensitivity AEs or treatment cessation. In MOR-002, one subject that tested positive for anti-BMN 110 IgE developed infusion reactions primarily characterized by urticaria and vomiting. This subject subsequently stopped receiving treatment as a result of these reactions. The reason for the increased clinical impact of IgE in MOR-002 is not clear, but may have been related to the unique intra-patient dose escalation in this study and/or the lack of antihistamine pre-treatment in that study.

8.4 Effects on Pharmacokinetics

The effect of antibodies on BMN 110 PK was evaluated in subjects in MOR-004 and MOR-002. In MOR-004, the mean plasma half-life was ~7 minutes at Week 0 and ~ 35 minutes at Week 22 in the weekly dosed cohort. The increased half-life at Week 22 may be associated with the formation of anti-drug antibodies. Although no association was detected between TAb titer and BMN 110 clearance, NAb positive subjects in the weekly dosed cohort had lower plasma clearance and prolonged plasma half-life compared to NAb negative subjects. This difference was not detected in the every other week dosing cohort. Despite the alteration of the PK profile in the weekly-dosed cohort, the presence of NAb did not affect PD, efficacy, or safety of treated subjects, suggesting that enough BMN 110 reached the lysosomal compartment to mediate a sustained treatment effect.

In MOR-002, the relationship between PK and immunogenicity was evaluated at Week 24 and Week 36, when subjects received 1.0 and 2.0 mg/kg/week of BMN 110 respectively. Subjects with positive NAb appear to have a prolonged $t_{1/2}$ and decreased clearance of BMN 110. The prolonged $t_{1/2}$ and decreased clearance led to increased $AUC_{0\text{-inf}}$ and C_{max} in subjects with positive NAb results compared with subjects without detectable NAbs at both Week 24 and Week 36.

8.5 Summary

The universality of the anti-BMN 110 antibody responses suggests that antibody measurements cannot be used as a predictive indicator to determine which subjects are at greater risk for clinical consequences related to immunogenicity. Despite the high incidence of anti-BMN 110 antibodies, decreases in urinary KS and improvements in efficacy measurements were sustained in BMN 110 treated subjects, and no correlations were found between higher NAb positivity rates and decreases in efficacy or PD measurements or increases in hypersensitivity AEs. This phenomenon may be explained by the relatively short-lived plasma half-life of BMN 110 (~ 35 minutes). The rapid cellular uptake of BMN 110 *in vivo* via the CI-M6PR limits the time the drug is exposed to antibodies in circulation. This likely restricts immune complex formation and reduces the potential negative impact of anti-drug antibodies on efficacy and overall immunogenicity-related clinical consequences. NAb will continue to be monitored in the extension study and evaluated for impact on long-term efficacy and safety.

9 RISK-BENEFIT PROFILE

MPS IVA is a rare, debilitating and progressive disorder with an onset of symptoms in early childhood and an average life span of only 40 years. The most common features of patients with MPS IVA are progressive skeletal dysplasia, short stature, and joint abnormalities, all of which contribute to restriction in patient mobility. Patients may experience both restrictive lung disease due to thoracic deformity and obstructive disease due to laryngeal narrowing and tracheal and bronchial abnormalities. These mechanical impediments often result in dyspnea and recurrent respiratory infections, and potentially progress to respiratory failure.

The MPS disorders, including MPS IVA, are characterized by a clinical heterogeneity encompassing a range of disease symptoms and severities. To better understand the heterogeneity of MPS IVA, a longitudinal natural history study (MorCAP) is being conducted. Baseline data in over 325 subjects in 10 countries demonstrate substantial impairment across multiple functional areas, including growth, mobility, respiratory function, endurance, and the impact of burden of illness on quality of life. Subjects had frequent infections as compared to unaffected individuals. Vision and hearing impairments were also reported. The use of pain medications in all age categories was indicative of the pain associated with tasks of daily living for all individuals with MPS IVA.

Functional endurance testing revealed limitations in walking and stair climbing ability, with the overall mean 6MWT distance less than half of the reported average for healthy individuals of the same age. More than half of the MorCAP study population required a wheelchair or walking aid for mobility.

Overall study findings suggest quality of life for MPS IVA patients is favorably impacted by disease progression and manifestations across all ages and phenotypes of MPS IVA.
The initial results of the MorCAP study support the varied and multisystemic clinical presentation of MPS IVA, with all affected individuals experiencing substantial functional limitations and reduced quality of life. Direct clinical observation and testing in a large number of these subjects have demonstrated substantial impairment across multiple domains including biochemical abnormalities, stature, mobility, respiratory function, endurance , and quality of life. Older patients have more severe exercise and respiratory capacity limitations illustrating the progressive nature of MPS IVA.

There is currently no approved, effective treatment for MPS IVA other than supportive care to manage pain and infections and frequent corrective surgeries with varying degrees of success.

9.1 Benefits

- The pivotal Phase 3 Study MOR-004 met the primary endpoint, demonstrating a statistically significant improvement (p=0.0174) from baseline in 6MWT distance at Week 24 for BMN 110 2.0 mg/kg/week compared to placebo. The estimated treatment effect at Week 24, compared with placebo, was 22.5 meters for the 2.0 mg/kg/week regimen.
- Treatment with BMN 110 was shown to be effective in improving performance in endurance tests (statistically significant for 6MWT) and in reducing urinary KS.
- The magnitude of this observed effect is clinically important in the context of a disease characterized by progressive decline in mobility and endurance, resulting ultimately in physical incapacity and the need for life-long assistance with activities of daily living.
- Analysis of a cumulative distribution function in MOR-004 shows that a higher proportion of subjects who received BMN 110 2.0 mg/kg/week achieved numerically higher improvement in 6MWT distance across various levels of response.
- Results of pre-specified per protocol, supportive, sensitivity, and subgroup analyses were consistent with the primary analysis, confirming the robustness of BMN 110 efficacy as demonstrated by improvement in 6MWT.
- In addition, smaller but directionally favorable results occurred for most secondary and tertiary endpoints, including 3MSCT, respiratory function tests, and anthropometric measurements. These results provide supportive evidence for improvement in a wide range of disease-related manifestations.
- BMN 110 was efficacious across a full spectrum of age, disease severity, and baseline clinical manifestations of MPS IVA in this diverse patient population.
- In long-term extension studies, continuous treatment with 2.0 mg/kg/week BMN 110 generally maintained or improved efficacy measures.

The BMN 110 efficacy data provide evidence of benefit of BMN 110 2.0 mg/kg/week as ERT treatment in multiple domains of function, including growth, mobility, respiration, and endurance. Such improvements are clinically meaningful benefits to patients with MPS IVA, a disease characterized by a progressive decline in mobility and endurance.

9.2 Risks

- The clinical safety database includes safety results from 235 subjects with MPS IVA exposed to BMN 110 across 6 clinical trials. The combination of study populations in the BMN 110 clinical development program encompasses the spectrum of age and disease severity of the overall patient population.
- Across all studies, only 1 subject (from MOR-002) permanently discontinued study drug due to an AE. There were no deaths.

- The most common AEs were associated with infusions and included vomiting, pyrexia, and headache.
- While most subjects experienced at least 1 IAR, IARs related to BMN 110 were generally mild to moderate in severity and manageable with symptomatic treatment and/or infusion rate modification. Less than 1% of infusions in the *All Exposed Population* were interrupted or discontinued and also required medical intervention.
- Although some AEs during infusion required slowing or stopping of the infusion and, less often, medical intervention, all subjects except for one (the MOR-002 subject referred to above) received and tolerated subsequent infusions.
- IARs tended to occur less frequently with duration of treatment.
- SAEs and Hypersensitivity AEs occurred infrequently. Most SAEs were related to the underlying disease or to catheterization or venous access issues.
- There were no clinically meaningful changes in laboratory values, ECGs, or ECHOs.
- Increasing BMN 110 dose or treatment duration was not associated with an increased incidence of AEs, study drug related AEs, or SAEs.
- All BMN 110-treated subjects developed a persistent antibody response. However, antibody formation was not associated with decreased efficacy or increased safety risk.
- Hypersensitivity AEs did not increase in incidence or severity with time of treatment or with development of anti-drug antibodies.

In summary, the data shows that short-term and long-term treatment with BMN 110 is well tolerated with a favorable safety profile. Based on available data, the safety profile of BMN 110 is consistent with that observed with other approved ERTs, including the occurrence of hypersensitivity reactions. BioMarin has the knowledge and expertise to ensure healthcare providers are adequately trained to administer ERTs and are informed of the associated risks. Specialists who administer these types of therapies are aware of the risks associated with ERT, and standard clinical practice involves informing patients of the risk-benefit balance of their treatment. A product monograph, infusion training video, and dosing and administration guide will be prepared to educate treating physicians and healthcare practitioners in the storage, preparation, and administration of BMN 110. These materials will be distributed, as appropriate, to healthcare providers, including infusion nurses and treating physicians.

9.3 Conclusions

- MPS IVA is a rare, debilitating disease that can progressively lead to a wide spectrum of functional deficits. Weakness and mobility problems, respiratory issues, frequent

infections, and other problems highlight the heterogeneity of the issues faced by MPS IVA patients and the difficulty of assessing the success of an MPS IVA treatment by looking at a single endpoint.

- Long- and short-term safety and efficacy data derived from the global BMN 110 clinical development program demonstrate clinical benefit and acceptable tolerability of the drug infused at the proposed marketed dose of 2.0 mg/kg/week.
- Improvements across a variety of efficacy measures seen in the clinical trials of BMN 110 translate into clinically meaningful benefits generalizable to all patients with MPS IVA, in the context of an unrelenting disease progression, heterogeneity of the patient population and the disease manifestations, and the challenges in reversing the chronic effects caused by years of damage due to accumulated GAGs.
- In subjects enrolled in the pivotal Phase 3 study who are still growing, BMN 110 had a positive effect of slowing the progressive negative deviation from normal growth rates and normal standing height experienced by MPS IVA patients.
- The primary risk associated with BMN 110 treatment is related to infusion reactions. These reactions can be effectively managed with appropriate medication prophylaxis and infusion rate adjustment. Health care providers will be closely trained and monitored for the potential risks associated with BMN 110.
- Replacement of the deficient GALNS enzyme with BMN 110 leads to improvement in walk distance and other parameters of endurance, respiratory function, growth, and quality of life. As with other ERTs in rare genetic diseases, initiating treatment as soon as possible after diagnosis is expected to provide maximal benefit to patients, both by improving existing symptoms and preventing further disease-related impairments.

The totality of data from the completed Phase 1/2 and Phase 3 and the ongoing extension and Phase 2 clinical trials demonstrates that BMN 110, at the recommended dose of 2.0 mg/kg/week, has a favorable risk-benefit profile based on the evidence of clinical improvement along with an acceptable safety profile, and is an ERT that addresses the significant unmet medical need for patients with MPS IVA.

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11 APPENDICES

11.1 Table of Non-Clinical Studies

Study Type	Species	Method of Administration	Duration and Administration Schedule	Doses (mg/kg)	GLP
PHARMACODYNAMICS					
In vitro primary Pharmacodynamics					
GALNS cDNA sequence 0110-10-062	Rabbit	n/a	n/a	n/a	No
GALNS cDNA sequence 0110-08-043	Cynomolgus monkey	n/a	n/a	n/a	No
BMN 110 cellular uptake GNS-TR-AC-006	Human Morquio fibroblasts	in vitro	n/a	0.78 to 25 nM	No
Determination of BMN 110 intracellular half-life. GNS-TR-AC-010	Human Morquio fibroblasts	in vitro	n/a	25 to 100 nM	No
BMN 110 pharmacological activity 0110-08-042	Human Morquio chondrocytes	in vitro	n/a	1 and 10 nM	No
Safety Pharmacology					
Central Nervous System (CNS) [a] 0110-08-021	Rat	IV, bolus	Single dose	0, 1, 6, 20	Yes
Respiratory 0110-08-022	Rat	IV, bolus	Single dose	0, 1, 6, 20	Yes
Cardiovascular (CV) 0110-08-025	Cynomolgus monkey	IV, 4 hour infusion	Latin square design:8 days (Days 1, 3, 5 and 8)	0, 1, 6, 20	Yes

Study Type	Species	Method of Administration	Duration and Administration Schedule	Doses (mg/kg)	GLP
PHARMACOKINETICS[b]					
Distribution					
Distribution 0110-08-041	Mouse	IV, bolus	- Single dose - Every other day for a total duration of 8 days (5 injections)	10[c]	No
TOXICOLOGY					
Single and Repeat-Dose Studies					
Single-dose toxicity and toxicokinetic study[a] 0110-08-021	Rat	IV, bolus	Single dose 2-week recovery	0, 1, 6, 20	Yes
Repeat-dose toxicity and toxicokinetic study 0110-08-020	Rat	IV, bolus	26 weeks, weekly 4-week recovery	0 0[d], 1[e], 6[e], 20[e]	Yes
Repeat-dose toxicity and toxicokinetic study[f] BMN110-10-100	Cynomolgus Monkey	IV, 4 hour infusion	Weekly, 28 days	0, 20, 20, 20	Yes
Repeat-dose toxicity and toxicokinetic study 0110-08-018	Cynomolgus Monkey	IV, 4 hour infusion	52 weeks, weekly 4-week recovery	0, 1, 6, 20	Yes
Reproductive Toxicity Studies					

Study Type	Species	Method of Administration	Duration and Administration Schedule	Doses (mg/kg)	GLP
Combined fertility and embryo-fetal development toxicity study BMN110-10-007	Rat	IV bolus	Daily dosing Males: during premating and mating Females: from premating to GD 20	0 0[g], 1[g], 6[g], 20[g]	Yes
Developmental and peri/postnatal reproduction study BMN 110-12-013	Rat	IV bolus	Daily from GD7 to Postpartum Day 21	0 0[g], 1[g], 6[g], 20[g]	Yes
Dose-range embryo-fetal development toxicity study BMN110-10-008	Rabbit	IV, 4 hour infusion	Daily dosing from GD 7 to GD 20	0, 0[h], 1, 6, 20	No
Embryo-fetal development toxicity study BMN110-10-061	Rabbit	IV, 4 hour infusion	Daily dosing from GD 7 to GD 20	0, 0[h], 1, 3 and 10	Yes

TK, toxicokinetics; IV, intravenous, GD, gestational day; DPH, diphenhydramine; n/a, not applicable

[a] The single-dose toxicity and TK study in rat was conducted in combination with the CNS safety pharmacology assessment in rat.

[b] The nonclinical pharmacokinetic assessment was conducted in conjunction with the toxicity studies.

[c] rhGALNS conjugated to the fluorochrome alexa-488.

[d] Vehicle-treated animals that received DPH to control for the administration of DPH to BMN 110-treated animals. The DPH control animals received an oral pretreatment of DPH (2 mg/kg) at least 30 minutes prior to dosing on Week 4 and at least 1 to 2 hours prior to dosing on Week 5 through the end of the dosing phase. The animals were euthanized during Week 28 and thereby received an extra dose of vehicle/DPH. This was done to match the number of DPH doses that BMN 110-treated animals received.

[e] DPH was administered IV or subcutaneously (4 mg/kg) following Week 3 dose administration to animals given 1, 6 and 20 mg/kg that exhibited the clinical signs of anaphylactoid-type reactions. BMN 110-treated animals (both male and female toxicity and toxicokinetic animals) received an oral pretreatment of DPH (2 mg/kg) prior to dosing on Week 4 through the end of the dosing phase.

[f] The purpose of this study was to evaluate the toxicity of BMN 110 at 20 mg/kg from differing production processes (one lot of Phase 1/2 material and two lots of Phase 3 material).

[g] BMN 110-treated animals received 10 mg/kg DPH, IP, 10 to 20 minutes prior to BMN 110 administration from the first dose onward to mitigate an expected anaphylactoid-type reaction. An additional vehicle-treated group was given 10 mg/kg DPH, IP, 10 to 20 minutes prior to BMN 110 administration to control for potential DPH-related effects.

[h] An additional group was added to control for DPH administration if warranted. No anaphylactoid-type reactions were observed and therefore this group was not treated with DPH. Two groups of rabbits were consequently treated with vehicle only. In the GLP embryo-fetal development toxicity study, these two groups were combined for reporting purposes.

11.2 Hypersensitivity SMQ information

Table 11.2.1: Query Terms for Anaphylactic Reaction and Angioedema

Anaphylactic Reaction Standardized MedDRA[a] Query

Narrow Search Preferred Terms	Anaphylactic reaction; Anaphylactic shock; Anaphylactic transfusion reaction; Anaphylactoid reaction; Anaphylactoid shock; Circulatory collapse; First use syndrome; Kounis syndrome; Shock; Type I hypersensitivity
Broad Search Preferred Terms	Acute respiratory failure; Asthma; Bronchial oedema; Bronchospasm; Cardio-respiratory distress; Chest discomfort; Choking; Choking sensation; Circumoral oedema; Cough; Cyanosis; Dyspnoea; Hyperventilation; Laryngeal dyspnoea; Laryngeal oedema; Laryngospasm; Laryngotracheal oedema; Nasal obstruction; Oedema mouth; Oropharyngeal spasm; Oropharyngeal swelling; Respiratory arrest; Respiratory distress; Respiratory failure; Reversible airways obstruction; Sensation of foreign body; Sneezing; Stridor; Swollen tongue; Tachypnoea; Throat tightness; Tongue oedema; Tracheal obstruction; Tracheal oedema; Upper airway obstruction; Wheezing; Allergic oedema; Angioedema; Erythema; Eye oedema; Eye pruritus; Eye swelling; Eyelid oedema; Face oedema; Fixed eruption; Flushing; Generalised erythema; Injection site urticaria; Lip oedema; Lip swelling; Ocular hyperaemia; Oedema; Periorbital oedema; Pruritus; Pruritus allergic; Pruritus generalized; Rash; Rash erythematous; Rash generalized; Rash pruritic; Skin swelling; Swelling; Swelling face; Urticaria; Urticaria papular; Blood pressure decreased; Blood pressure diastolic decreased; Blood pressure systolic decreased; Cardiac arrest; Cardio-respiratory arrest; Cardiovascular insufficiency; Diastolic hypotension; Hypotension

[a] MedDRA, Medical Dictionary for Regulatory Activities (version 15.0).

Angioedema Standardized MedDRA[a] Query

Narrow Search Preferred Terms	Allergic oedema; Angioedema; Circumoral oedema; Conjunctival oedema; Corneal oedema; Epiglottic oedema; Eye oedema; Eye swelling; Eyelid oedema; Face oedema; Gingival oedema; Gingival swelling; Gleich's syndrome; Hereditary angioedema; Idiopathic urticaria; Laryngeal oedema; Laryngotracheal oedema; Limbal swelling; Lip oedema; Lip swelling; Oculorespiratory syndrome; Oedema mouth; Oropharyngeal swelling; Palatal oedema; Periorbital oedema; Pharyngeal oedema; Scleral oedema; Small bowel angioedema; Swelling face; Swollen tongue; Tongue oedema; Tracheal oedema; Urticaria; Urticaria cholinergic; Urticaria chronic; Urticaria popular
Broad Search Preferred Terms	Auricular swelling; Breast oedema; Breast swelling; Choking; Choking sensation; Drug hypersensitivity; Endotracheal intubation; Gastrointestinal oedema; Generalised oedema; Genital swelling; Hypersensitivity; Laryngeal dyspnoea; Laryngeal obstruction; Local swelling; Localised oedema; Nasal obstruction; Nasal oedema; Nipple oedema; Nipple swelling; Obstructive airways disorder; Oedema; Oedema genital; Oedema mucosal; Oedema neonatal; Oedema peripheral; Orbital oedema; Penile oedema; Penile swelling; Peripheral oedema neonatal; Reversible airways obstruction; Scrotal oedema; Scrotal swelling; Skin oedema; Skin swelling; Stridor; Suffocation feeling; Swelling; Throat tightness; Tracheal obstruction; Tracheostomy; Type I hypersensitivity; Upper airway obstruction; Vaginal oedema; Vulval oedema; Visceral oedema; Vulvovaginal swelling; Wheezing

[a] MedDRA, Medical Dictionary for Regulatory Activities (version 15.0).

SMQ Detail

Name: Anaphylactic reaction (SMQ)

Code: 20000021

Level: 1

Description:
Anaphylaxis is an acute systemic reaction characterized by pruritus, generalized flush, urticaria, respiratory distress and vascular collapse. It occurs in a previously sensitized person upon re-exposure to the sensitizing antigen. Other signs and symptoms include agitation, palpitation, paresthesias, wheezing, angioedema, coughing, sneezing and difficulty breathing due to laryngeal spasm or bronchospasm. Less frequent clinical presentations may include seizures, vomiting, abdominal cramps and incontinence.[1]

Source:
[1]The Merck Manual. 15th edition. Merck, Sharp & Dohme Research Laboratories. (1987): 306-7

Note:
The following algorithm is used: All narrow search terms as well as: If one term from category B and one term from category C is present, or If one term from (category B or category C) plus one term from category D.

MedDRA Dictionary Version: 15.1

Status: Active

Algorithm: A or (B and C) or (D and (B or C))

11.3 Pharmacokinetic Parameters in MOR-002 and MOR-004

Table 11.3.1: Descriptive Statistics for Pharmacokinetic Parameters of BMN 110 by Dose Level in Study MOR-002

Para-meter	Unit	N*	Mean	SD	Geometric Mean	Min	Median	Max
			Dose Level 0.1 mg/kg/week Week 1					
AUC_{0-t}	min*ng/mL	10	5634.81	2237.81	5299.14	2850.00	5212.88	11140.50
C_{max}	ng/mL	17	34.28	14.70	31.76	16.90	30.30	65.60
T_{max}	Min	17	158.82	71.66	147.62	113.00	120.00	343.00
			Dose Level 0.1 mg/kg/week Week 12					
AUC_{0-t}	min*ng/mL	7	3606.23	839.80	3509.55	2227.35	3834.00	4418.75
C_{max}	ng/mL	8	25.49	7.92	24.24	12.90	25.75	36.20
T_{max}	min	8	137.38	44.34	132.96	120.00	121.50	247.00
			Dose Level 1.0 mg/kg/week Week 24					
AUC_{inf}	min*ng/mL	7	119127.38	51722.14	109010.21	46105.77	118226.54	213666.63
AUC_{0-t}	min*ng/mL	17	89427.57	42581.99	80268.38	31189.00	80521.50	199888.50
C_{max}	ng/mL	17	503.18	207.52	462.44	228.00	456.00	863.00
T_{max}	min	17	175.35	68.95	163.47	120.00	120.00	292.00
$t_{1/2}$	min	7	43.66	21.76	35.75	7.43	52.02	64.91
CL	mL/min/kg	7	10.18	5.55	9.17	4.68	8.46	21.69
V_{dz}	mL/kg	7	562.85	265.30	473.18	95.32	598.64	919.38
V_{dss}	mL/kg	7	1047.27	874.69	784.06	203.45	827.37	2824.35
			Dose Level 2.0 mg/kg/week Week 36					
AUC_{inf}	min*ng/mL	11	409351.69	267503.02	332742.35	95395.24	280500.56	852069.73
AUC_{0-t}	min*ng/mL	16	335814.36	233133.20	275827.05	94936.75	241244.63	838256.00
C_{max}	ng/mL	18	2022.61	2056.22	1441.26	419.00	1190.00	7930.00
T_{max}	min	18	196.28	82.98	180.68	118.00	186.00	355.00
$t_{1/2}$	min	11	35.07	25.01	25.11	6.25	28.75	75.72
CL	mL/min/kg	11	7.46	5.36	6.01	2.35	7.13	20.97
V_{dz}	mL/kg	11	281.25	209.76	217.76	77.54	247.48	695.93
V_{dss}	mL/kg	11	642.76	852.73	373.71	44.48	333.11	2945.62

* N: number of subjects.

Table 11.3.2: Summary of Pharmacokinetic Parameters in Study MOR-004 (Pharmacokinetics Population)

Study Visit	BMN 110 2.0 mg/kg/qow Mean (n, SD)	BMN 110 2.0 mg/kg/week Mean (n, SD)	[a]Ratio of BMN 110 qow/week (%)
Week 0			
n	24	22	
AUC $_{0-\infty}$, min*ng/mL	287597 (14, 96432.1)	231074 (15, 103207.4)	124.5
AUC_{0-t}, min*ng/mL	248720 (24, 97063.7)	237884 (22, 100328.6)	104.6
C_{max}, ng/mL	1438 (24, 435.3)	1494 (22, 534.1)	96.2
CL, mL/min/kg	7.54 (14, 2.002)	10.04 (15, 3.733)	75.1
V_{dss}, mL/kg	219.42 (12, 95.483)	395.74 (14, 315.636)	55.4
V_{dz}, mL/kg	68.79 (14, 34.008)	123.66 (15, 144.115)	55.6
$T_{1/2}$, min	6.57 (14, 3.110)	7.52 (15, 5.484)	87.4
T_{max}, min	150 (24, 58.1)	172 (22, 75.3)	87.2
Week 22			
n	23	22	
AUC $_{0-\infty}$, min*ng/mL	463460 (19, 491418.9)	619080 (20, 422048.3)	74.9
AUC_{0-t}, min*ng/mL	411687 (23, 420279.7)	577371 (22, 416316.6)	71.3
C_{max}, ng/mL	2616 (23, 2702.1)	4036 (22, 3237.1)	64.8
CL, mL/min/kg	6.50 (19, 2.942)	7.08 (20, 12.997)	91.8
V_{dss}, mL/kg	245.19 (17, 273.145)	649.67 (20, 1841.703)	37.7
V_{dz}, mL/kg	120.11 (19, 71.076)	299.52 (20, 543.309)	40.1
$T_{1/2}$, min	19.25 (19, 19.217)	35.86 (20, 21.485)	53.7
T_{max}, min	159 (23, 60.6)	202 (22, 90.8)	78.5
Week 22/Week 0[b] (%)			
n	23	21	
AUC $_{0-\infty}$, min*ng/mL	179.2	328.6	
AUC_{0-t}, min*ng/mL	176.3	280.6	
C_{max}, ng/mL	183.6	291.6	
CL, mL/min/kg	87.0	46.4	
V_{dss}, mL/kg	127.0	188.9	
V_{dz}, mL/kg	147.0	246.0	
$T_{1/2}$, min	280.0	696.0	
T_{max}, min	119.8	145.7	

[a] Ratio is ratio of means.

[b] Only subjects with PK data available for both visits are included.
$AUC_{0-\infty}$, area under the plasma concentration-time curve from time zero to infinity; AUC_{0-t}, area under the plasma concentration-time curve from time zero to the time of last measurable concentration; C_{max}, observed maximum plasma concentration; CL, total clearance of drug after intravenous administration; qow, every other week; SD, standard deviation V_{dss}, apparent volume of distribution at steady-state; V_{dz}, apparent volume of distribution based upon the terminal phase; $t_{1/2}$, elimination half-life;

For subjects who have missing values of $AUC_{0-\infty}$, $t_{1/2}$, CL, V_{dz} and V_{dss}, the parameters could not be estimated due to insufficient data in the terminal phase of the plasma profile. For subjects who have missing values of V_{dss} only, their V_{dss} was not reported due to a negative value. Adjusting for infusion caused a negative MRTinf value. The V_{dss} value was also negative because of the relationship: Vdss=MRTinf*CL

11.4 Narratives for Subjects with Events Assessed by the Sponsor as Meeting the NIAID/FAAN 2006 Criteria for Anaphylaxis

Subject No: MOR002-0119-2007 (13-year-old mixed race male)

Treatment Arm: BMN 110 0.1 mg/kg/week
Premedication(s): None
Timing: During 10th infusion (65 minutes following start of infusion)
Adverse Event(s) and grade: Life-threatening type I hypersensitivity
Serious AE(s): Yes

This subject started treatment in MOR-002 (0.1 mg/kg/week) on 5 June 2009. The first 9 weekly infusions were all completed without any infusion interruptions as a result of an adverse event. On 14 August 2009, the subject was scheduled for his 10th infusion at 0.1 mg/kg/week. No premedications were given. His pre-infusion vital signs taken at 10:05 AM included pulse 85 beats per minute (bpm), blood pressure 96/57 mmHg, temperature 36.5°C, and respiratory rate 22/minute. The infusion was started at 10:30 AM at 1.4 ml/hr, increased to 18.5 ml/hr at 11:30 AM.

At 11:35 AM, the subject experienced a serious, life-threatening type I hypersensitivity reaction. His symptoms included generalized urticaria, edema, and difficulty breathing with stridor and wheezing. The infusion was stopped, and treatment for the event included oxygen, hydrocortisone, adrenaline, and chlorpheniramine. His vital signs for the next several hours were as follows:

Time	Pulse (bpm)	BP (mmHg)	Temperature (°C)	Respiratory rate (/minute)
12:45 PM	103	116/59	36.4	16
1:30 PM	102	107/55	36.4	21
14:30 PM	103	115/51	37	24

The type I hypersensitivity reaction was considered resolved as of 4:00 PM that day. The subject received no further BMN 110 infusions and later withdrew from the study.

The investigator considered the event of type I hypersensitivity to be probably related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Subject No: MOR002-0121-2003 (7-year-old Asian male)

Event #1:
Treatment Arm: BMN 110 1.0 mg/kg/week (Continuation Period)
Premedication(s): Cetirizine, acetaminophen
Timing: During 39th infusion (100 minutes following start of infusion)
Adverse Event(s) and grade: Moderate generalized rash
Serious AE(s): Yes

This subject started treatment in MOR-002 (0.1 mg/kg/week) on 19 May 2009, and completed the Dose Escalation portion of the study on 19 January 2010. During several infusions in the Dose Escalation period, the subject experienced non-serious infusion-related reactions, with symptoms including flushing, pallor, decreased oxygen saturation, and rash. All infusions were completed following symptomatic treatment with medications such as oxygen, acetaminophen, and chlorphenamine, as well as decreases in the infusion rate.

He was enrolled in the Continuation Period (1.0 mg/kg/week) starting on 26 January 2010 (Week 37). On (b) (6) the subject received 1.0 mg/kg/week BMN 110, following premedication with acetaminophen and cetirizine. His pre-infusion vital signs taken at 10:35 AM included pulse 118 bpm, blood pressure 107/69 mmHg, temperature 35.7°C, and respiratory rate 28/minute. The infusion was started at 10:40 AM at 3 ml/hr and gradually increased to 36 ml/hr by 12:10 PM.

At 12:20 PM, the subject developed a serious moderate rash (described as "urticarial") on his face, stomach, fingers, and back. The infusion rate was decreased to 18 ml/hr at that time. Treatment for the event included chlorphenamine, and the rash improved. The infusion rate was gradually increased again, but at 2:45 PM the rash worsened again. The infusion rate was decreased again, and then the infusion was discontinued at 3:05 PM. Additional treatment for the rash included IV hydrocortisone and acetaminophen. Vital signs remained stable throughout the infusion.

The subject was observed in the hospital for several hours, and the rash was considered resolved as of 5:15 PM. The investigator considered the event of generalized rash to be probably related to study treatment.

Premedication for the next infusion (16 February 2010) was changed to include prednisolone. During that infusion, the subject developed a serious generalized maculopapular rash on the face, arms, legs, and abdomen. The rash resolved following treatment with chlorphenamine and IV hydrocortisone, and the infusion was completed at a lower rate (15 ml/hr for 8 hours following onset of the rash).

The subject developed a non-serious rash during his next infusion (23 February 2010). Treatment with chlorphenamine and IV hydrocortisone was again employed, and the rash resolved after about 1 hour. The infusion was completed, with a maximum rate of 18 ml/hr.

Premedications for the next scheduled infusion (2 March 2010) were changed to hydroxyzine, hydrocortisone, and acetaminophen.

Company comment: The Sponsor has reviewed this event (9 February 2010) and determined that it meets the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #2:
Treatment Arm: BMN 110 1.0 mg/kg/week (Continuation Period)
Premedication(s): Hydroxyzine, hydrocortisone, acetaminophen
Timing: During 42nd infusion (80 minutes following start of infusion)
Adverse Event(s) and grade: Moderate infusion related reaction
Serious AE(s): Yes

On 2 March 2010, the subject received 1.0 mg/kg/week BMN 110, following premedication with hydroxyzine, hydrocortisone, and acetaminophen. His pre-infusion vital signs taken at 9:25 AM included pulse 121 bpm, blood pressure 119/76 mmHg, temperature 36.7°C, and respiratory rate 30/minute. The infusion was started at 9:25 AM at 3 ml/hr and gradually increased to 15 ml/hr by 10:30 AM. Vital signs at 10:25 AM included a blood pressure of 88/47 mmHg.

At 10:45 AM, the subject experienced a serious, moderate infusion related reaction. Symptoms of this reaction reportedly included an urticarial skin eruption. Treatment for the event included IV chlorphenamine and IV hydrocortisone. The infusion rate was decreased to 9 ml/hr, where it remained until 12:50 PM. At that time, the subject's urticarial skin eruption worsened again, and the infusion rate was decreased to 4.5 ml/hr. Vital signs at that time included blood pressure 73/37 mm/Hg, which had improved to 110/70 by 1:00 PM. The subject was reported to be stable, so the infusion rate was increased again, to 9 ml/hr at 1:20 PM and to 18 ml/hr at 1:50 PM.

At 3:10 PM, the subject experienced a third urticarial skin eruption, and the infusion was discontinued. Treatment again included IV chlorphenamine and IV hydrocortisone, and the infusion reaction was considered resolved.

The investigator assessed the event of infusion related reaction to be possibly related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it meets the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #3:
Treatment Arm: BMN 110 1.0 mg/kg/week (Continuation Period)
Premedication(s): Acetaminophen, prednisolone, cetirizine
Timing: During 43rd infusion (65 minutes following start of infusion)
Adverse Event(s) and grade: Moderate drug eruption
Serious AE(s): Yes

On 9 March 2010, the subject received 1.0 mg/kg/week BMN 110, following premedication with prednisolone, cetirizine, and acetaminophen. His pre-infusion vital signs taken at 9:15 AM included pulse 120 bpm, blood pressure 137/98 mmHg, temperature 36.4°C, and respiratory rate 26/minute. The infusion was started at 9:35 AM at 3 ml/hr and gradually increased to 24 ml/hr by 10:38 AM.

At 10:40 AM, the subject experienced a serious, moderate drug eruption. Symptoms of this reaction reportedly included an urticarial rash and retching. Treatment for the event included IV chlorphenamine and IV hydrocortisone. The infusion was interrupted at that time, and restarted at 3 ml/hr at 12:00 PM. From there, the rate was gradually increased to 24 ml/hr by 1:00 PM.

At 1:15 PM, the rash reappeared and the infusion was stopped. The drug eruption was considered resolved by 2:40 PM. Vital signs remained stable throughout the infusion.

The investigator assessed the event of drug eruption to be possibly related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it meets the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #4:
Treatment Arm: BMN 110 1.0 mg/kg/week (Continuation Period)
Premedication(s): Acetaminophen, prednisolone, ranitidine, cetirizine
Timing: During 44th infusion (85 minutes following start of infusion)
Adverse Event(s) and grade: Moderate infusion related reaction
Serious AE(s): Yes

On 16 March 2010, the subject received 1.0 mg/kg/week BMN 110, following premedication with prednisolone, cetirizine, ranitidine, and acetaminophen. His pre-infusion vital signs taken at 9:55 AM included pulse 113 bpm, blood pressure 113/65 mmHg, temperature

36.6°C, and respiratory rate 36/minute. The infusion was started at 10:05 AM at 3 ml/hr and gradually increased to 12 ml/hr by 11:20 AM.

At 11:30 AM, the subject experienced a serious, moderate infusion related reaction. Symptoms of this reaction reportedly included an urticarial skin reaction on the face, lips, neck, and eyelids. Treatment for the event included IV chlorphenamine and IV hydrocortisone. The infusion was interrupted at that time, and restarted at 3 ml/hr at 12:45 PM. From there, the rate was gradually increased to 18 ml/hr by 1:30 PM.

At 1:40 PM, the subject reportedly developed a widespread rash and vomited. Starting at 1:55 PM, the subject's heart rate increased to the upper 130s (maximum 145 at 2:10 PM). The infusion was stopped. The infusion reaction was considered resolved by 2:35 PM. Heart rate at 3:05 PM had decreased to 120 bpm, increased again to 135 bpm at 4:20 PM, and then decreased to 118 bpm at 5:15 PM. Blood pressure and respirations remained stable.

The investigator assessed the event of infusion related reaction to be probably related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it meets the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #5:
Treatment Arm: BMN 110 1.0 mg/kg/week (Continuation Period)
Premedication(s): Acetaminophen, prednisolone, montelukast, cetirizine
Timing: During 45th infusion (27 minutes following start of infusion)
Adverse Event(s) and grade: Severe infusion related reaction
Serious AE(s): Yes

On 23 March 2010, the subject received 1.0 mg/kg/week BMN 110, following premedication with prednisolone, cetirizine, montelukast, and acetaminophen. His pre-infusion vital signs taken at 10:05 AM included pulse 134 bpm, blood pressure 111/61 mmHg, temperature 37.3°C, and respiratory rate 24/minute. The infusion was started at 10:18 AM at 3 ml/hr and increased to 6 ml/hr by 10:35 AM.

At 10:45 AM, the subject experienced a serious, severe infusion related reaction. Symptoms of this reaction reportedly included an urticarial rash on the face, trunk, and legs. Treatment for the event included IV chlorphenamine and IV hydrocortisone. The infusion rate was decreased back to 3 ml/hr, where it stayed until 12:25 PM. The subject developed vomiting and decreased oxygen saturation (95%), without clinical evidence of bronchospasm. The infusion was stopped at 12:25 PM, and the rash rapidly improved.

After a line change, the infusion was restarted at 1:18 PM at 3 ml/hr, then increased to 6 ml/hr again at 1:34 PM. At 1:49 PM, the rash recurred and the infusion was stopped. Treatment included hydroxyzine, and the rash improved. The event of infusion related reaction was considered resolved later that day.

The investigator assessed the event of infusion related reaction to be probably related to study treatment.

The investigator elected to discontinue further study treatment following this infusion.

Company comment: The Sponsor has reviewed this event and determined that it meets the NIAID/FAAN 2006 criteria for anaphylaxis.

Note: The angioedema and anaphylaxis MedDRA searches performed on the global safety database identified these potential anaphylactic reactions.

Subject No: MOR004-0020-4141 (18-year-old White male)

Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-004)
Premedication(s): Cetirizine
Timing: During the 5th infusion (2.5 hours after the start of the infusion)
Adverse Event(s) and grade: Severe hypersensitivity
Serious AE(s): Yes

This subject started treatment in MOR-004 (2.0 mg/kg/week) on 28 February 2012. On 27 March 2012, the subject received his 5th infusion with BMN 110, following premedication with cetirizine. His pre-infusion vital signs at 10:45 AM included pulse 79, blood pressure 123/83, temperature 36.3°C, and respiratory rate 28/minute. The infusion was started at 10:55 AM at 6 ml/hr, and gradually increased to 72 ml/hr by 12:25 PM.

At 1:16 PM, the subject developed a severe hypersensitivity reaction, with symptoms of vomiting, shivering, and paleness. The infusion was stopped at 1:16 PM, and vital signs at that time included BP 147/99, pulse 111, and temperature 37.4°C. Treatment included IV ranitidine. At 1:30 PM, the subject developed upper airway obstruction and was treated with prednisolone. Vital signs at that time were reportedly pulse 123, temperature 38.5°C, and oxygen saturation 99%. He continued to experience symptoms of hypersensitivity, and received additional treatment including epinephrine and inhalation therapy. At 1:50 PM, his temperature had risen to 39.2°C, with BP 140/100 and pulse 127.

Additional treatment with fluids, IV paracetamol, and inhalation therapy was continued. By 2:00 PM, the shivering had resolved, and the upper airway obstruction resolved as of

2:55 PM. Vital signs were BP 137/84, pulse 129, and temperate 38.6°C. The subject continued to show slow signs of improvement (3:30 PM vital signs were reported as BP 133/80, pulse 126, temperature 38.1°C), and he was taken by ambulance to the immediate care station for overnight observation. He experienced no further symptoms, and the event was considered resolved as of 28 March 2012.

Premedication for the next scheduled infusion (2 April 2012) included ranitidine, dimethindene, and prednisolone. The initial infusion rate was also decreased to start at 3 ml/hr. The infusion was completed as scheduled, without dose interruptions or dose reductions. The hypersensitivity event did not recur.

The investigator assessed the event of hypersensitivity as probably related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Subject No: MOR004-0021-4005 (5-year-old White female)

Event #1:
Treatment Arm: Placebo (MOR-004); BMN 110 2.0 mg/kg/qow (MOR-005)
Premedication(s): Cetirizine, acetaminophen
Timing: 1 day after 3rd infusion in MOR-005
Adverse Event(s) and grade: Grade 1 nasal obstruction, grade 1 pruritus
Serious AE(s): No

This subject started treatment in MOR-004 (placebo) on 8 April 2011, and in MOR-005 (2.0 mg/kg/qow) on 23 September 2011. On 7 October 2011, she received her 3rd infusion in MOR-005 following premedication with cetirizine and acetaminophen. No adverse events were reported during the infusion.

The next day, she reported non-serious grade 1 itching under her arms; on the day after that, she also reported non-serious grade 1 nasal obstruction. Treatment for the nasal obstruction included acetaminophen; no treatment for the pruritus was reported. The pruritus was considered resolved as of 10 October 2011, and the nasal obstruction was considered resolved as of 21 October 2011. No action was taken with study treatment as a result of these events.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #2:
Treatment Arm: Placebo (MOR-004); BMN 110 2.0 mg/kg/qow (MOR-005)
Premedication(s): Cetirizine, acetaminophen
Timing: On the day of 8th infusion in MOR-005 (timing of event in relation to dosing not reported)
Adverse Event(s) and grade: Grade 1 nasal obstruction
Serious AE(s): No

The subject received premedication with cetirizine and acetaminophen prior to her 8th infusion in MOR-005 on 11 November 2011. Her pre-infusion vital signs taken at 8:05 AM included pulse 122 bpm, blood pressure 93/61, temperature 37°C, and respiratory rate 22/minute. The infusion was started at 8:15 AM at 3 ml/hr and gradually increased to 36 ml/hr by 9:52 AM. The infusion was completed as scheduled at 12:03 PM without any dose changes or interruptions. Vital signs remained stable.

On the day of the infusion (timing not reported), the subject reported a non-serious grade 1 event of nasal obstruction. No treatment for the event was reported, and it was considered resolved as of 17 November 2011. No action was taken with study treatment as a result of the event.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #3:
Treatment Arm: Placebo (MOR-004); BMN 110 2.0 mg/kg/qow (MOR-005)
Premedication(s): Acetaminophen, chlorphenamine, ranitidine
Timing: 3 days after the 11th infusion in MOR-005
Adverse Event(s) and grade: Grade 1 nasal obstruction
Serious AE(s): No

On 2 December 2011, she received her 11th infusion in MOR-005 following premedication with acetaminophen, chlorphenamine, and ranitidine. A few minutes after the infusion started, the subject started vomiting; as a result, the infusion was restarted at 1.5 ml/hr, before being gradually increased and ultimately completed without further adverse events.

On 5 December 2011, she reported a non-serious grade 1 nasal obstruction. Treatment for the event included saline nose drops. The event was considered resolved as of 13 January 2012. No action was taken with study treatment as a result of the event.

Starting with the infusion on 21 December 2011, the initial infusion rate was started at 1.5 ml/hr, and montelukast was added as a pre-medication.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #4:
Treatment Arm: Placebo (MOR-004); BMN 110 2.0 mg/kg/qow (MOR-005)
Premedication(s): Acetaminophen, chlorphenamine, ranitidine, montelukast
Timing: During 17th infusion in MOR-005 (approximately 2 hours after start of infusion)
Adverse Event(s) and grade: Grade 4 anaphylaxis
Serious AE(s): Yes

On 13 January 2012, she received her 17th infusion in MOR-005, following premedication with acetaminophen, chlorphenamine, montelukast, and ranitidine. Her pre-infusion vital signs taken at 9:06 AM included pulse 112 bpm, temperature 36.8°C, respiratory rate 20, and BP 101/58 mmHg. The infusion was started at 1.5 ml/hr at 9:24 AM, then progressively increased to 18.0 ml/hr by 10:56 AM. Vital signs at 10:22 AM included BP 89/54, pulse 98, temperature 36.8°C, and respiratory rate 26. The infusion had to be stopped at 18 ml/hr because of leakage at the cannula site; the cannula was repositioned, and the infusion was restarted at 24 ml/hr, without a gradual rate increased despite being a higher rate than had been previously given.

At 11:15 AM, about 2 minutes after the infusion restart, the subject developed difficulty breathing. The infusion was stopped, and vital signs reportedly included elevated blood pressure (value not reported) and O_2 saturation 90% on 15 L of oxygen. A crash call was made 5 minutes later, and treatment for the life-threatening anaphylactic reaction included high flow oxygen, epinephrine, hydrocortisone, and chlorphenamine. The subject recovered, and the event resolved about 20 minutes after the onset of symptoms. The infusion was not restarted.

For the next scheduled infusion on 20 January 2012, additional premedications included prednisolone. During that infusion, she experienced a non-serious event of elevated temperature but no recurrence of her anaphylaxis symptoms.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #5:
Treatment Arm: Placebo (MOR-004); BMN 110 2.0 mg/kg/qow (MOR-005)
Premedication(s): Acetaminophen, chlorphenamine, ranitidine, prednisolone, montelukast
Timing: During 19th infusion in MOR-005 (approximately 3 hours after start of infusion)
Adverse Event(s) and grade: Grade 1 urticaria
Serious AE(s): No

On 27 January 2012, she received her 19th infusion in MOR-005, following premedication with acetaminophen, chlorphenamine, prednisolone, montelukast, and ranitidine. Her pre-infusion vital signs taken at 8:08 AM included pulse 124 bpm, blood pressure 105/64, temperature 37.6°C, and respiratory rate 32/minute. The infusion was started at 1.5 ml/hr at 9:24 AM, then increased gradually to 18 ml/hr by 10:03 AM. At that point, the subject complained of nausea, so the infusion rate was temporarily decreased to 9.0 ml/hr for approximately 15 minutes, before being increased again. By 11:27 AM, the infusion rate was 30 ml/hr. Vital signs taken at that time included pulse 122 bpm, blood pressure 127/69, temperature 37.2°C, and respiratory rate 28/minute.

When the infusion was increased to 30 ml/hr, the subject complained of non-serious grade 1 urticaria. The infusion rate was lowered to 15 ml/hr, and treatment for the event included acetaminophen and chlorphenamine. Vital signs taken at 12:36 PM included pulse 129 bpm, blood pressure 129/76, temperature 37.3°C, and respiratory rate 29/minute. The event persisted, and at 3:05 PM the infusion rate was lowered again, to 7.5 ml/hr. After 20 minutes, it was increased back to 15 ml/hr, and the infusion was completed at 4:29 PM.

The event of urticaria was considered resolved as of 5:25 PM. The subject received her next scheduled infusion on 3 February 2012 without recurrence of the urticaria, and the infusion was completed without dose interruptions or rate changes.

Prednisolone was discontinued as a premedication on 20 July 2012.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #6:
Treatment Arm: BMN 2.0 mg/kg/week (MOR-005 Part 2)
Premedication(s): Acetaminophen, chlorphenamine, ranitidine, montelukast
Timing: During 64th infusion in MOR-005 (approximately 90 minutes after start of infusion)
Adverse Event(s) and grade: Grade 1 urticaria
Serious AE(s): No

On 7 December 2012, the subject transitioned to Part 2 of MOR-005 and started receiving BMN 110 2.0 mg/kg/week.

On 14 December, she received her 64th infusion in MOR-005 (2nd infusion of 2.0 mg/kg/week in Part 2), following premedication with acetaminophen, chlorphenamine, montelukast, and ranitidine. Her pre-infusion vital signs taken at 10:20 AM included pulse 116 bpm, blood pressure 107/81, temperature 36.4°C, and respiratory rate 24/minute. The infusion was started at 1.5 ml/hr at 10:30 AM, then increased gradually to 24 ml/hr by 12:01 PM. Vital signs remained stable.

Around that time, the subject began to complain of non-serious grade 1 urticaria. At 12:19 PM, the infusion rate was decreased to 12 ml/hr, and the infusion was stopped completely at 12:28 PM. Treatment for the event included an unreported medication, and the event was considered resolved later that day.

Prednisolone was added as a premedication before the next infusion.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #7:
Treatment Arm: BMN 2.0 mg/kg/week (MOR-005 Part 2)
Premedication(s): Acetaminophen, chlorphenamine, ranitidine, montelukast, prednisolone
Timing: During 65th infusion in MOR-005 (approximately 2 hours after start of infusion)
Adverse Event(s) and grade: Grade 1 urticaria
Serious AE(s): No

On 14 December 2012, she received her 65th infusion in MOR-005 (3rd infusion of 2.0 mg/kg/week in Part 2), following premedication with acetaminophen, chlorphenamine, montelukast, prednisolone, and ranitidine. Her pre-infusion vital signs taken at 10:20 AM included pulse 118 bpm, blood pressure 121/88, temperature 37.3°C, and respiratory rate

24/minute. The infusion was started at 1.5 ml/hr at 9:52 AM, then increased gradually to 24 ml/hr by 11:24 AM. Vital signs remained stable.

Around that time, the subject began to complain of non-serious grade 1 urticaria. At 11:57 AM, the infusion rate was decreased to 12 ml/hr, and the subject was given IV chlorphenamine. The urticaria persisted, and the infusion was stopped completely at 2:16 PM. Vital signs remained stable throughout the event, which was considered resolved later that day (time not reported).

12:19 PM, the infusion rate was decreased to 12 ml/hr, and the infusion was stopped completely at 12:28 PM. Treatment for the event included an unreported medication, and the event was considered resolved later that day. This was the last dose administered prior to the BLA data cut-off, so no information was available concerning whether premedications were changed for the next dose, or whether the symptoms recurred.

The investigator considered all of the events of nasal obstruction, as well as the event of pruritus, to be unrelated to study treatment. The events of urticaria and anaphylaxis were considered to be probably related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Subject No: MOR004-0021-4103 (5-year-old White female)

Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-005)
Premedication(s): Prednisolone, hydroxyzine, ranitidine, acetaminophen
Timing: During 34th infusion (13 minutes following start of infusion)
Adverse Event(s) and grade: Grade 1 cough, grade 1 erythema
Serious AE(s): No

This subject started treatment in MOR-004 (2.0 mg/kg/week) on 20 February 2012, and in MOR-005 (2.0 mg/kg/week) on 7 August 2012. On 8 October 2012, she received premedication with prednisolone, hydroxyzine, ranitidine, and acetaminophen prior to her 34^{h} study infusion (10th infusion in MOR-005). Her pre-infusion vital signs taken at 10:06 AM included pulse 108 bpm, blood pressure 118/70 mmHg, temperature 36.8°C, and respiratory rate 24/minute. The infusion was started at 10:09 AM at 3 ml/hr.

At 10:22 AM, the subject experienced non-serious grade 1 cough and facial erythema, as well as grade 1 agitation and grade 2 decreased oxygen saturation (values not reported). The infusion was stopped and not restarted. Treatment for the events included oxygen and chlorphenamine. Vital signs taken at 10:38 AM included pulse 123 bpm, blood pressure

113/61 mmHg, temperature 37.2°C, and respiratory rate 36/minute. All events were considered resolved as of 10:53 AM. No further vital signs were reported.

Montelukast was added to the premedications for the next scheduled infusion on 15 October 2012. This infusion was completed successfully without recurrence of these symptoms.

The investigator assessed the events of cough and erythema as probably related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Subject No: MOR004-0050-4063 (9-year-old White female)

Event #1:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-004)
Premedication(s): Ranitidine, acetaminophen, diphenhydramine
Timing: During 16th infusion (45 minutes after start of infusion)
Adverse Event(s) and grade: Moderate throat tightness
Serious AE(s): No

This subject started treatment in MOR-004 (2.0 mg/kg/week) on 7 November 2011. On 24 February 2012, the subject received her 16th infusion with BMN 110, following premedication with ranitidine, acetaminophen, and diphenhydramine. The pre-infusion vital signs taken at 9:30 AM included pulse 92 bpm, blood pressure 94/54, temperature 36.6°C, and respiratory rate 28/minute. The infusion was started at 3 ml/hr at 9:35 AM, and gradually increased to 12 ml/hr by 10:05 AM.

At 10:05 AM, the subject developed a mild dry throat and dry mouth, and was offered some water. At 10:20 AM, she developed non-serious moderate throat closing, as well as mild nausea and shivering. The infusion was stopped, and treatment for the events included IV diphenhydramine. Vital signs at 10:35 AM included pulse 89 bpm, blood pressure 113/58, temperature 36.6°C, and respiratory rate 30/minute. The infusion was restarted at 12 ml/hr at 10:35, and gradually increased to 36 ml/hr by 11:35 AM. The events of throat tightness, nausea, shivering, dry throat, and dry mouth were considered resolved at that point. The infusion was completed by 1:40 PM. Vital signs remained stable for the remainder of the infusion.

No change was made in the premedications for the next infusion (29 February 2012). That infusion was started at 9:25 AM; at 9:50 AM, the subject developed non-serious abdominal pain and irritability, followed by dry throat, itching, shivering, and bilateral

extremity muscle twitching over the next 90 minutes; the throat tightness did not recur. Treatment for these events included IV diphenhydramine, hydrocortisone, and ranitidine. The infusion was not interrupted, nor was the dose reduced, in response to the events; the events were considered resolved by 11:40 AM, and the infusion was completed at 2:15 PM. Vital signs remained stable throughout the infusion.

Hydrocortisone was added as a premedication for the next infusion (9 March 2012). The subject continued to experience similar non-serious symptoms, including irritability, abdominal pain, dizziness, cough, dry throat/mouth, and nausea, through the infusion on 23 April 2012. The events were generally mild and resolved on the same day with similar treatments. Each infusion was completed without being interrupted. The throat tightness did not recur in any infusion.

The investigator considered the event of throat tightness to be possibly related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #2:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-005)
Premedication(s): Ranitidine, acetaminophen, loratadine
Timing: During 48th infusion (4.5 hours after start of infusion)
Adverse Event(s) and grade: Mild peripheral edema
Serious AE(s): No

This subject completed treatment in MOR-004 on 23 April 2012, and started treatment in MOR-005 (2.0 mg/kg/week) on 27 April 2012. On 12 November 2012, she received her 48th infusion of BMN 110 (25th infusion in MOR-005), following premedication with ranitidine, acetaminophen, and loratadine. The infusion was started at 3 ml/hr at 1:40 PM, and gradually increased to 36 ml/hr by 3:30 PM. The infusion was completed at 6:00 PM.

At 6:00 PM, the subject developed non-serious mild swelling in the left arm secondary to infiltration. No treatment for the event was reported, and the event resolved by the next morning. No action was taken with study treatment in response to the event.

The next scheduled infusion was given on 26 November 2012, and the infusion was completed as scheduled and without recurrence of the peripheral edema.

The investigator considered the event of peripheral edema to be not related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Subject No: MOR004-0109-4025 (5-year-old White female)

Event #1:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-004)
Premedication(s): Diphenhydramine, cetirizine
Timing: During 4th infusion
Adverse Event(s) and grade: Mild urticaria
Serious AE(s): No

This subject started treatment in MOR-004 (2.0 mg/kg/week) on 17 August 2011. On 7 September 2011, the subject received her 4th infusion with BMN 110, following premedication with oral diphenhydramine and cetirizine. The infusion was started at 3 ml/hr at 8:42 AM, and gradually increased to 36 ml/hr by 10:13 AM.

At 10:32 AM, the subject developed non-serious mild stomach pain and urticaria on the abdomen and face. The infusion was interrupted, and treatment for the events included IV diphenhydramine. The events were considered resolved by 11:15 AM, and the infusion was restarted at 18 ml/hr. The infusion was completed by 3:15 PM. Vital signs remained stable throughout the infusion.

Premedication for the next infusion (21 September 2012) was changed to IV diphenhydramine. The infusion was completed as scheduled, and the urticaria did not recur.

The investigator considered the event of urticaria to be probably related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #2:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-004)
Premedication(s): Diphenhydramine, acetaminophen
Timing: 5 days after 11th infusion
Adverse Event(s) and grade: Mild hypersensitivity
Serious AE(s): No

On 26 October 2011, the subject received her 11th infusion with BMN 110, following premedication with acetaminophen and IV diphenhydramine. The infusion was completed as scheduled without dose interruptions or rate changes. On 31 October 2011, 5 days after the

infusion, the subject developed mild cold symptoms secondary to allergies. Treatment for the event included diphenhydramine, and it was considered resolved as of 3 November 2011.

The investigator considered the event of hypersensitivity to be not related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #3:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-005)
Premedication(s): Diphenhydramine, acetaminophen, ranitidine
Timing: During 38th infusion (2.5 hours after start of infusion)
Adverse Event(s) and grade: Grade 1 urticaria
Serious AE(s): No

The subject completed treatment in MOR-004 on 26 January 2012, and started treatment in MOR-004 (2.0 mg/kg/week) on 3 February 2012. On 3 May 2012, she received her 38^{th} infusion of BMN 110 (14^{th} infusion in MOR-005), following pretreatment with acetaminophen, ranitidine, and IV diphenhydramine. The infusion was started at 3 ml/hr at 9:15 AM, and gradually increased to 36 ml/hr by 10:45 AM.

At 11:52 AM, the subject developed non-serious grade 1 hives on the mouth, chin, face, and right knee and thigh, as well as non-serious grade 1 abdominal pain and headache. The infusion was interrupted, and treatment for the events included oral diphenhydramine, acetaminophen, and ondansetron. At 12:45 PM, the subject experienced non-serious vomiting. The events were all considered resolved by 1:30 PM, and the infusion was restarted at 30 ml/hr. The infusion was completed later that day. Vital signs remained stable throughout the infusion.

The urticaria did not recur with the next infusion (10 May 2012), though the subject did experience headache and abdominal pain. No changes were made to premedications.

The investigator considered the event of urticaria to be probably related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Subject No: MOR004-0109-4028 (7-year-old White male)

Event #1:
Treatment Arm: Placebo (MOR-005); BMN 110 2.0 mg/kg/qow (MOR-005)
Premedication(s): Cetirizine
Timing: During 5th infusion in MOR-005 (75 minutes following start of infusion)
Adverse Event(s) and grade: Grade 1 cough, grade 1 flushing, grade 2 erythematous rash
Serious AE(s): No

This subject started treatment in MOR-004 (placebo) on 19 August 2011, and in MOR-005 (2.0 mg/kg/qow) on 3 February 2012.

On 2 March 2012, he received his 5th infusion in MOR-005, following premedication with cetirizine. His pre-infusion vital signs taken at 7:58 AM included pulse 100 bpm, blood pressure 120/79, temperature 37.6°C, and respiratory rate 24/minute. The infusion was started at 3 ml/hr at 8:00 AM, then increased gradually to 18 ml/hr by 8:45 AM. Vital signs remained stable.

At 8:56 AM, the subject experienced non-serious grade 1 vomiting, as well as upper abdominal pain. The infusion was temporarily stopped until the events resolved, then restarted at the same infusion rate at 9:05 AM and increased to 24 ml/hr at 9:11 AM. At 9:15 AM, the subject experienced a recurrence of non-serious abdominal pain, as well as a cough. The infusion was stopped again, and restarted at 10:08 AM at 12 ml/hr. At 10:23 AM the rate was increased to 18 ml/hr.

At that time, the subject complained of non-serious grade 1 flushing. The infusion was continued, and at 10:36 he developed a diffuse non-serious grade 2 rash across his arms, hands, and thighs bilaterally, as well as on his back, neck, groin, abdomen, and face. The infusion was stopped. Treatment for the events included IV diphenhydramine, and the flushing and rash were considered resolved as of 11:48 AM. Vital signs remained stable throughout the events. The infusion was not restarted.

Prednisolone and oral diphenhydramine were added as premedications for the next infusion, which was administered on 7 March 2012 and completed without dose interruptions or rate changes and without recurrence of the symptoms from the prior infusion.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #2:
Treatment Arm: Placebo (MOR-005); BMN 110 2.0 mg/kg/qow (MOR-005)
Premedication(s): Cetirizine, prednisolone, diphenhydramine
Timing: During 7th infusion in MOR-005 (approximately 3 hours following start of infusion)
Adverse Event(s) and grade: Grade 2 urticaria
Serious AE(s): No

On 16 March 2012, the subject received his 7th infusion in MOR-005, following premedication with cetirizine, prednisolone, and diphyenhydramine. His pre-infusion vital signs taken at 8:43 AM included pulse 112 bpm, blood pressure 101/64, temperature 36.9°C, and respiratory rate 24/minute. The infusion was started at 3 ml/hr at 8:45 AM, then increased gradually to 36 ml/hr by 11:47 AM. Vital signs remained stable.

At 11:51 AM, the subject experienced non-serious grade 2 hives on the arms bilaterally, face, abdomen, left knee, and right foot. The infusion was stopped, and treatment for the events included IV diphenhydramine. The hives were considered resolved as of 12:20 PM, and the infusion was restarted at 24 ml/hr. Vital signs remained stable.

At 2:45 PM, the diffuse hives recurred, again on the face, abdomen, knee, and bilaterally on the arms. The infusion was stopped, and IV diphenhydramine was administered again. The hives were considered resolved as of 3:30 PM, and the infusion was restarted at 12 ml/hr and completed by 3:50 PM.

Premedication for the next infusion on 23 March 2012 included cetirizine, IV diphenhydramine, and IV methylprednisolone. The infusion was completed without dose interruptions or rate changes and without recurrence of the symptoms from the prior infusion.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #3:
Treatment Arm: Placebo (MOR-005); BMN 110 2.0 mg/kg/qow (MOR-005)
Premedication(s): Ranitidine, prednisolone, diphenhydramine
Timing: During 14th infusion in MOR-005 (95 minutes following start of infusion)
Adverse Event(s) and grade: Grade 1 urticaria
Serious AE(s): No

On 18 May 2012, the subject received his 14th infusion in MOR-005, following premedication with ranitidine, prednisolone, and diphenhydramine. His pre-infusion vital

signs taken at 8:34 AM included pulse 104 bpm, blood pressure 105/69, temperature 36.8°C, and respiratory rate 22/minute. The infusion was started at 3 ml/hr at 8:39 AM, then increased gradually to 30 ml/hr by 10:25 AM. Vital signs remained stable.

At 10:15 AM, the subject complained of mild hives around the groin area. The infusion was continued, and no treatment was given. At 12:00 PM, he developed blotchy redness in the groin, around the left knee, as well as on the buttocks and in the left axilla. Again, no treatment was given and the infusion was continued. In each instance the events resolved within 5 minutes, with the last event having resolved by 12:09 PM.

At 12:30 PM, the subject developed mild blotchy hives in the groin and left leg. The infusion was stopped temporarily, and the hives had resolved by 12:40 PM. The infusion was restarted at 24 ml/hr at 12:45 PM and completed by 2:00 PM. Vital signs remained stable through all events of hives, rashes, and erythema.

No change was made to premedications for the next infusion on 18 May 2012, and that infusion was completed without dose interruptions or rate changes and without recurrence of the symptoms from the prior infusion.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #4:
Treatment Arm: Placebo (MOR-005); BMN 110 2.0 mg/kg/qow (MOR-005)
Premedication(s): Ranitidine, prednisolone, diphenhydramine
Timing: 6 days after the 17th infusion in MOR-005
Adverse Event(s) and grade: Grade 1 wheezing
Serious AE(s): No

On 12 June 2012, 6 days following the most recent infusion, the subject developed a non-serious grade 1 wheezy-sounding cough. Treatment for the cough included inhaled albuterol, and the event was considered resolved as of 14 June 2012.

The next scheduled infusion on 15 June 2012 was given, and that infusion was completed without dose interruptions or rate changes and without recurrence of the wheezing.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Subject No: MOR004-0111-4019 (11-year-old White female)

Event #1:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-004)
Premedication(s): Betamethasone, desloratadine, acetaminophen, prednisolone, ondansetron, dexchlorpheniramine
Timing: Prior to 16th infusion (16 minutes before start of infusion)
Adverse Event(s) and grade: Mild flushing, mild dyspnea
Serious AE(s): No

This subject started treatment in MOR-004 (2.0 mg/kg/week) on 26 July 2011.
On 9 November 2011, she received premedication with betamethasone, desloratadine, acetaminophen, prednisolone, ondansetron, and dexchlorpheniramine prior to her 16th study infusion. Her pre-infusion vital signs taken at 9:39 AM included pulse 112 bpm, blood pressure 102/69 mmHg, temperature 36.9°C, and respiratory rate 24/minute.

At 9:40 AM, prior to starting the infusion, the subject developed non-serious mild flushing and shortness of breath, without clinical signs of respiratory distress. No treatment for the events was reported. The flushing was reported as having resolved by 9:43 AM. The infusion was started at 9:56 AM at a lower rate of 2 ml/hr, then gradually increased to 36 ml/hr and completed as scheduled. Vital signs at 10:26 AM included pulse 113 bpm, blood pressure 112/69 mmHg, temperature 37.3°C, and respiratory rate 38/minute.
The subject's respiratory rate remained elevated (33-41/minute) for the remainder of the infusion. The dyspnea resolved at an unreported time on that date.

Premedications for the next infusion on 15 November 2011 included betamethasone, ondansetron, prednisolone, acetaminophen, and alprazolam. The infusion was completed as scheduled without recurrence of these symptoms.

Company Comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #2:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-005)
Premedication(s): Betamethasone, EMLA patches, acetaminophen, hydroxyzine, ondansetron
Timing: During 26th infusion (80 minutes following start of infusion)
Adverse Event(s) and grade: Grade 2 cyanosis, grade 2 hypotension
Serious AE(s): No

This subject completed treatment in MOR-004 on 3 January 2012, and she started treatment in MOR-005 (2.0 mg/kg/week) on 17 January 2012. On 31 January 2012, she received premedication with betamethasone, EMLA patches, acetaminophen, hydroxyzine, and ondansetron prior to her 26th study infusion (3rd infusion in MOR-005). Her pre-infusion vital signs taken at 9:33 AM included pulse 95 bpm, blood pressure 90/67 mmHg, temperature 37.4°C, and respiratory rate 33/minute. The infusion was started at 9:35 AM at 3 ml/hr, and gradually increased to 24 ml/hr by 10:50 AM. Vital signs at 10:35 AM included pulse 100 bpm, blood pressure 89/68 mmHg, temperature 37.3°C, and respiratory rate 27/minute.

At 10:55 AM, the subject experienced non-serious grade 2 cyanosis and hypotension, as well as non-serious grade 2 events of vomiting, shivering, fatigue, fever, and headache. Vital signs at that time were not recorded. Treatment for the events included acetaminophen, hydroxyzine, ibuprofen, methylprednisolone, and IV fluids. The infusion rate was decreased, and then the infusion was interrupted at 11:01 AM. The cyanosis, hypotension, and shivering all were considered resolved by 11:15 AM. Vital signs at 11:30 AM included pulse 98 bpm, blood pressure 90/61 mmHg, temperature 38.4°C, and respiratory rate 34/minute. The infusion was restarted at 12 ml/hr at 12:00 PM.

The remaining events persisted until 2:45 PM, when they were considered resolved. The infusion was completed at 3:45 PM. No changes were made to the premedications for the next infusion, and it was given as scheduled without recurrence of these symptoms.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #3:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-005)
Premedication(s): None
Timing: 3 weeks following 37th infusion
Adverse Event(s) and grade (Third reaction): Grade 3 erythema, grade 3 hypotension, grade 3 dyspnoea
Serious AE(s): No

The subject received the scheduled infusion (her 14th in MOR-005 and 38th overall) on 24 April 2012, then missed the next 2 infusions for vacation. On 15 May 2012, the subject was scheduled to receive her next infusion. However, prior to starting the infusion, the subject experienced a non-serious grade 3 presyncopal event, as well as non-serious grade 3 dyspnea. Other AEs reported on that date, but without an onset time, include non-serious grade 3 events of vomiting, hypotension, and erythema (described as "red patches"). Treatment for the events included oxygen and IV fluids. No infusion was given as a result of these events. The events of dyspnea and presyncope were considered resolved by 1:40 PM, while the other events also resolved later that date (but at unreported times).

The next scheduled infusion on 22 May 2012 was successfully administered without recurrence of these symptoms.

The investigator assessed the events of flushing and dyspnea (9 November 2011) and cyanosis and hypotension (31 January 2012) as possibly related to study treatment, and the events of erythema, hypotension, and dyspnea (15 May 2012) as not related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis. The event occurred prior to infusion.

Subject No: MOR004-0121-4139 (5-year-old Asian male)

Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-004)
Premedication(s): Hydrocortisone, cetirizine
Timing: Day of the 9th infusion (timing not reported)
Adverse Event(s) and grade: Moderate urticaria
Serious AE(s): No

This subject started treatment in MOR-004 (2.0 mg/kg/week) on 1 March 2012. On 3 May 2012, the subject received his 9th infusion with BMN 110, following premedication

with hydrocortisone and cetirizine. The infusion was completed as scheduled without dose interruptions or rate changes. On the day of the infusion (timing not specified), the subject developed non-serious moderate urticaria and vomiting, as well as mild fever (temperature 37.6°C following the end of the infusion). Treatment for the events included chlorphenamine, and they were all considered resolved by the end of the day.

Premedications for the next infusion (10 May 2012) were changed to ranitidine, cetirizine, and prednisolone. The infusion was completed as scheduled, and none of the events recurred.

The investigator considered the event of urticaria to be probably related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Subject No: MOR004-1075-4007 (6-year-old White male)

Event #1:
Treatment Arm: BMN 110 2.0 mg/kg/qow (MOR-004)
Premedication(s): Clemastine, acetaminophen
Timing: During 7th infusion (48 minutes following start of infusion)
Adverse Event(s) and grade: Severe anaphylactic reaction
Serious AE(s): Yes

This subject started treatment in MOR-004 (2.0 mg/kg/qow) on (b) (6) On 28 July 2011, he received premedication with clemastine and acetaminophen prior to his 7th study infusion. His pre-infusion vital signs taken at 10:45 AM included pulse 102 bpm, blood pressure 100/59, temperature 37°C, and respiratory rate 22/minute. The infusion was started at 11:19 AM at 3 ml/hr, increased to 6 ml/hr at 11:35 AM, to 12 ml/hr at 11:50 AM, and to 18 ml/hr at 12:05 PM.

At 12:07 PM, the subject complained of abdominal pain and mild nausea; vital signs were stable. After going to the bathroom, the subject noted no improvement in his symptoms, and the infusion rate was decreased to 9 ml/hr. At 12:17, a dose of oral clemastine was given.

At 12:22, the subject developed urticaria (mostly on the face and abdomen), severe itching, restlessness, and swollen eyes and mouth. Vital signs at that time were BP 121/86, pulse 142 bpm, and respiratory rate 28. Treatment for the event included IV clemastine and IV prednisone. The study treatment infusion was stopped at 12:33. By 12:45, the subject's symptoms had started to subside. Vital signs at that time were BP 112/69 mm Hg, pulse 118 bpm, and respiratory rate 24/min. The subject remained in observation, and at 13:00 his

vital signs were BP 80/53 mm Hg and pulse 112 bpm. He was treated with IM epinephrine and an IV fluid bolus, and by 13:16 his BP was 129/72; he was reported to be doing well, with ongoing resolution of the urticaria and swollen eyes and mouth. The subject's BP at 13:31 was 99/32, with a pulse of 103 and a respiratory rate of 29, and he received a second IV fluid bolus. At 13:46, his BP was 97/80 with a pulse of 109 and a respiratory rate of 33. It was reported that, throughout this episode, his oxygen saturation levels never dropped below 94-95%. He was admitted to the hospital for overnight monitoring. The event of anaphylaxis was considered resolved later that day, and the subject was stable overnight.

The next scheduled infusion was given on 4 August 2011. Pre-medications for this infusion were changed to cetirizine, acetaminophen, prednisone, and ranitidine. The subject continued to receive these pre-medications for the remainder of MOR-004, and all remaining infusions in the study were completed.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #2:
Treatment Arm: BMN 110 2.0 mg/kg/qow (MOR-005)
Premedication(s): Cetirizine, acetaminophen
Timing: 47th infusion (70 minutes following start of infusion)
Adverse Event(s) and grade: Grade 3 anaphylactic reaction
Serious AE(s): No

This subject started treatment in MOR-005 (2.0 mg/kg/qow) on 30 November 2011. Pre-medications at the start of MOR-005 included cetirizine, acetaminophen, and prednisolone. Prednisolone was discontinued as a premedication on 24 February 2012. The subject successfully completed the first 22 infusions in MOR-005 without infusion interruptions or discontinuations due to adverse events. He received his 47th dose overall (23rd dose in MOR-005) on 4 May 2012. Premedications for this dose included cetirizine and acetaminophen. His pre-infusion vital signs taken at 10:00 AM included pulse 93 bpm, blood pressure 98/53, temperature 36.6°C, and respiratory rate 22/minute. The infusion was started at 10:05 AM at 3 ml/hr, increased to 6 ml/hr at 10:20 AM, to 12 ml/hr at 10:35 AM, to 18 ml/hr at 10:50 AM, and to 24 ml/hr at 11:05 AM.

At 11:14 AM, the patient developed a non-serious grade 3 anaphylactic reaction. His vital signs at the time included BP 81/33, pulse 110, temperature 36.1°C, and respiratory rate 24/minute. The infusion was temporarily discontinued, and treatment with IV antihistamines and IV steroids was given. His vital signs for the next 2 hours were as follows:

Time	Pulse (bpm)	BP (mmHg)	Temperature (°C)	Respiratory rate (/minute)
11:40 AM	129	121/77	37.1	28
11:55 AM	123	112/65	37	28
12:11 PM	141	100/54	36.8	28
12:27 PM	141	119/64	36.8	28
12:45 PM	71	103/85	37.2	28
12:59 PM	130	90/34	36.8	28
13:19 PM	125	95/42	37.2	28

The infusion was restarted at 12 ml/hr at 11:45 AM and gradually increased to 36 ml/hr by 1:00 PM. The event of anaphylactic reaction was considered resolved as of 1:15 PM, and the infusion was completed at 2:41 PM. The next scheduled infusion on 11 May 2012 was not given, and when treatment was resumed on 18 May 2012, prednisolone had been added back to the premedication regimen. Subsequent infusions were completed without a recurrence of similar symptoms.

The investigator assessed both events of anaphylactic reaction as probably related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Subject No: MOR004-1159-4109 (12-year-old Asian male)

Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-005)
Premedication(s): Loratadine
Timing: During 45th dose (2.5 hours following start of infusion)
Adverse Event(s) and grade: Grade 1 cough, grade 1 rash, grade 2 dyspnea
Serious AE(s): No
This subject started treatment in MOR-004 (2.0 mg/kg/qow) on 20 February 2012, and in MOR-005 (2.0 mg/kg/qow) on 6 August 2012. On 3 December 2012, he transitioned to Part 2 of MOR-005 and started receiving BMN 110 2.0 mg/kg/week.

He received his 45th dose overall (21st dose in MOR-005, and 4th dose on the 2.0 mg/kg/week dosing regimen) on 26 December 2012. Premedications for this dose included loratadine. His pre-infusion vital signs taken at 9:32 AM included pulse 107 bpm, blood pressure 112/76, temperature 36.4°C, and respiratory rate 27/minute. The infusion was started at 9:50 AM at 3 ml/hr and gradually increased to 36 ml/hr by 11:20 AM.

At 12:25 PM, the subject developed non-serious events of grade 1 cough, grade 1 rash (location not specified), and grade 2 dyspnea. The infusion rate was reduced to 18 ml/hr at 12:27 PM, and the subject was given oxygen as treatment for the dyspnea. No treatments were reported for the cough or rash. His vital signs were as follows:

Time	Pulse (bpm)	BP (mmHg)	Temperature (°C)	Respiratory rate (/minute)
12:20 PM	101	106/76	36.5	31
12:45 PM	117	94/66	36.7	30
1:00 PM	107	92/64	37	26

The cough, rash, and dyspnea were all considered resolved by 12:50 PM. The infusion rate was increased again to 24 ml/hr at 12:47 PM, gradually back to 36 ml/hr, and was completed by 2:00 PM without recurrence of symptoms. This was the last dose administered prior to the BLA data cut-off, so no information was available concerning whether premedications were changed for the next dose, or whether the symptoms recurred.

The investigator assessed the events of cough, rash, and dyspnea as possibly related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Subject No: MOR004-1159-4117 (16-year-old Asian female)

Event #1:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-004)
Premedication(s): Loratadine
Timing: During 22nd infusion (45 minutes following start of infusion)
Adverse Event(s) and grade: Moderate urticaria
Serious AE(s): No
This subject started treatment in MOR-004 (2.0 mg/kg/week) on 24 February 2012. On 19 July 2012, one day prior to an infusion, she was bitten by an insect. On 20 July 2012, she received premedication with loratadine prior to her 22nd study infusion. Her pre-infusion vital signs taken at 10:15 AM included pulse 101 bpm, blood pressure 109/80, temperature 36.8°C, and respiratory rate 28/minute. The infusion was started at 10:28 AM at 6 ml/hr and gradually increased to 24 ml/hr by 10:58 AM.

At 11:10 AM, the subject experienced non-serious moderate urticaria (location not reported). The infusion was decreased to 12 ml/hr at 11:15 AM. Treatment for the event included

epinastine, topical betamethasone, hydroxyzine, and IV fluids. The infusion rate was gradually increased again, to 60 ml/hr by 1:43 PM, but had to be decreased again (to 30 ml/hr) at 2:01 PM. At 2:14 PM, the infusion was stopped, then restarted at 12 ml/hr at 3:51 PM. Around 5:15 PM, the subject began complaining of mild fatigue, and also had non-serious mild hypertension. The infusion rate was gradually increased, and the infusion was ultimately completed at 5:25 PM. A sampling of vital signs during this infusion:

Time	Pulse (bpm)	BP (mmHg)	Temperature (°C)	Respiratory rate (/minute)
11:10 AM	111	120/94	36.8	21
12:30 PM	107	114/86	37.4	33
1:55 PM	111	99/68	36.9	21
2:47 PM	111	113/88	37.2	22
3:18 PM	136	116/84	37.1	27
3:50 PM	146	126/88	36.9	24
4:48 PM	133	112/90	37.3	28
5:18 PM	136	142/108	36.8	30
5:48 PM	122	118/89	36.9	30
6:30 PM	115	108/80	37.2	26

The hypertension was reported resolved at 5:33 PM, while the urticaria and fatigue resolved by 6:30 PM.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #2:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-004)
Premedication(s): Loratadine
Timing: During 23rd infusion (1 hour following start of infusion)
Adverse Event(s) and grade: Moderate urticaria
Serious AE(s): No

On 27 July 2012, the subject received premedication with loratadine prior to her next infusion. Her pre-infusion vital signs taken at 9:51 AM included pulse 103 bpm, blood pressure 110/76, temperature 36.7°C, and respiratory rate 32/minute. The infusion was started at 9:58 AM at 6 ml/hr and gradually increased to 36 ml/hr by 10:43 AM.

At 10:55 AM, the subject again experienced non-serious moderate urticaria (location not reported). The infusion was decreased to 18 ml/hr at 10:58 AM, and then to 6 ml/hr at 11:56 AM. Treatment for the event included topical betamethasone, hydroxyzine, and hydrocortisone. The infusion rate was gradually increased again, to 60 ml/hr by 2:05 PM, before being decreased to 36 ml/hr, then increased again until the infusion finished at 5:33 PM. A sampling of vital signs during this infusion:

Time	Pulse (bpm)	BP (mmHg)	Temperature (°C)	Respiratory rate (/minute)
10:25 AM	101	102/81	37	24
10:55 AM	125	113/90	37.4	24
11:43 AM	117	109/84	37	22
12:16 PM	117	132/101	37.1	20
12:58 PM	115	117/80	36.9	28
2:02 PM	111	109/80	37	24
3:20 PM	115	120/95	36.6	27
4:20 PM	142	117/93	37.1	30
5:39 PM	136	119/75	37.1	27
6:38 PM	136	114/83	36.7	30

The urticaria was reported resolved as of 6:38 PM.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #3:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-004)
Premedication(s): Loratadine, hydrocortisone
Timing: During 24th infusion (75 minutes following start of infusion)
Adverse Event(s) and grade: Moderate urticaria, mild hypotension
Serious AE(s): No
On 3 August 2012, the subject received premedication with loratadine and hydrocortisone (newly added premedication) prior to her next infusion. Her pre-infusion vital signs taken at 10:54 AM included pulse 98 bpm, blood pressure 123/88, temperature 36.9°C, and respiratory rate 28/minute. The infusion was started at 11:02 AM at 6 ml/hr and gradually increased to 48 ml/hr by 12:02 PM.

At 12:15 PM, the subject again experienced non-serious moderate urticaria (location not reported). Treatment for the event included hydroxyzine. The infusion rate continued to increase to 72 ml/hr, but had to be decreased to 36 ml/hr at 1:02 PM. The subject vomited at 1:19 PM, and also experienced mild hypotension at 2:03 PM. The infusion was completed at 36 ml/hr at 5:27 PM. A sampling of vital signs during this infusion:

Time	Pulse (bpm)	BP (mmHg)	Temperature (°C)	Respiratory rate (/minute)
11:44 AM	109	120/86	36.9	31
12:15 PM	117	122/92	37.2	27
1:02 PM	146	119/88	37	30
2:03 PM	113	94/69	37.5	32
2:33 PM	120	122/83	37.1	32
4:03 PM	133	110/77	36.7	30
5:33 PM	117	132/91	37.2	32
6:27 PM	120	114/82	36.9	26

The hypotension was reported resolved at 2:33 PM, while the urticaria was reported resolved at an unreported time later that day. This was the last infusion of study treatment in study MOR-004.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #4:
Treatment Arm: BMN 110 2.0 mg/kg/week (MOR-005)
Premedication(s): Loratadine, prednisolone
Timing: During 25th infusion (75 minutes following start of infusion)
Adverse Event(s) and grade: Grade 2 anaphylactic reaction, grade 2 allergic reaction
Serious AE(s): No
This subject started treatment in MOR-005 (2.0 mg/kg/week) on 10 August 2012. She received premedications with loratadine and prednisolone, and her pre-infusion vital signs taken at 11:49 AM included pulse 113 bpm, blood pressure 114/83, temperature 36.7°C, and respiratory rate 27/minute. The infusion was started at 12:19 PM at 6 ml/hr and gradually increased to 48 ml/hr by 1:19 PM.

At 1:33 PM, the subject experienced a non-serious grade 2 anaphylactic reaction. Treatment included chlorphenamine, hydroxyzine, and oxygen. The infusion rate continued to increase, up to 72 ml/hr at 1:59 PM, then was decreased to 36 ml/hr at 2:13 PM, and oscillated between 36 and 48 ml/hr for the remainder of the treatment visit. The event of anaphylactic

reaction was considered resolved as of 6:19 PM, and the infusion was completed at 7:06 PM. A sampling of vital signs during this infusion:

Time	Pulse (bpm)	BP (mmHg)	Temperature (°C)	Respiratory rate (/minute)
12:47 PM	136	146/106	37.2	35
1:31 PM	130	122/93	37.6	27
2:22 PM	157	142/91	37.3	24
3:19 PM	127	126/95	36.6	21
4:48 PM	101	122/95	36.6	30
6:19 PM	115	90/60	37	30

At 10:01 PM, the subject experienced a non-serious grade 2 allergic reaction. Treatment for this event included oxygen, hydroxyzine, IV fluids, loratadine, and methylprednisolone. The event was considered resolved at an unreported time the next day (11 August 2012).

Time	Pulse (bpm)	BP (mmHg)	Temperature (°C)	Respiratory rate (/minute)
8:03 PM	136	123/98	37.5	27
9:58 PM	125	107/79	37.5	45
11:48 PM	111	115/87	NR	NR

The subject withdrew from the study following this infusion (subject's decision).

The investigator assessed the events of urticaria (20 July 2012, 3 August 2012), allergic reaction, and anaphylactic reaction (10 August 2012) as probably related to study treatment, and the events of urticaria (27 July 2012) and hypotension (3 August 2012) as possibly related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Subject No: MOR004-1167-4068 (9-year-old Asian female)

Event #1:
Treatment Arm: Placebo (MOR-005); BMN 110 2.0 mg/kg/qow (MOR-005)
Premedication(s): Acetaminophen, hydroxyzine
Timing: During 5th infusion in MOR-005 (110 minutes following start of infusion)
Adverse Event(s) and grade: Grade 2 urticaria, grade 2 chest discomfort
Serious AE(s): No

This subject started treatment in MOR-004 (placebo) on 21 November 2011, and in MOR-005 (2.0 mg/kg/qow) on 9 May 2012. On 3 June 2012, one day before a scheduled infusion, the subject complained of non-serious rhinorrhea.

On 4 June 2012, the subject received her 5th infusion in MOR-005, following premedication with acetaminophen and hydroxyzine. Her pre-infusion vital signs taken at 9:37 AM included pulse 99 bpm, blood pressure 95/62, temperature 36.7°C, and respiratory rate 22/minute. The infusion was started at 3 ml/hr at 9:45 AM, then increased gradually to 36 ml/hr by 11:15 AM. Vital signs remained stable.

At 11:35 AM, the subject developed non-serious grade 2 urticaria, followed at 12:00 PM by non-serious grade 2 chest discomfort. The infusion was interrupted at 12:30 PM when the subject started vomiting and developed non-serious grade 2 tachycardia and a diffuse whole body rash. Her vital signs at 12:30 PM were pulse 136 bpm, blood pressure 97/66, temperature 36.5°C, and respiratory rate 22/minute. Treatment for the events included oxygen, IV fluids, and IV chlorphenamine.

The chest discomfort was considered resolved by 1:30 PM, and the infusion was restarted at 36 ml/hr. Vital signs at 1:45 PM included pulse 94 bpm, blood pressure 100/62, temperature 36.6°C, and respiratory rate 22/minute. At 2:00 PM, the tachycardia recurred (pulse 132), and the infusion was stopped for the day. The event of tachycardia was considered resolved as of 2:30 PM, and the events of urticaria and generalized as of 3:15 PM.

Premedication for the next infusion was changed to include prednisolone, ranitidine, and IV chlorphenamine. That infusion was completed without dose interruptions or rate changes and without recurrence of the symptoms from the prior infusion.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #2:
Treatment Arm: Placebo (MOR-005); BMN 110 2.0 mg/kg/qow (MOR-005)
Premedication(s): Acetaminophen, chlorphenamine, ranitidine, prednisolone
Timing: During 7th infusion in MOR-005 (3 hours following start of infusion)
Adverse Event(s) and grade: Grade 1 urticaria
Serious AE(s): No

On 18 June 2012, the subject received her 7th infusion in MOR-005, following premedication with acetaminophen, ranitidine, prednisolone, and IV chlorphenamine,. Her pre-infusion vital signs taken at 9:45 AM included pulse 83 bpm, blood pressure 113/51, temperature 37.2°C, and respiratory rate 22/minute. The infusion was started at 3 ml/hr at 9:45 AM, then increased gradually to 36 ml/hr by 11:15 AM. Vital signs remained stable.

At 12:40 PM, the subject developed non-serious grade 1 urticaria and pruritus. The infusion was stopped, and treatment for the events included IV chlorphenamine. The events were considered resolved as of 1:40 PM, and the infusion was restarted at 18 ml/hr. The infusion was completed at 2:50 PM.

The next scheduled infusion on 25 June 2012 was completed without dose interruptions or rate changes and without recurrence of the symptoms from the prior infusion.

The investigator considered the events of 4 June 2012 (urticaria and chest discomfort) to be probably related to study treatment, and the urticaria from 18 June 2012 to be possibly related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Subject No: MOR007-0018-7005 (2-year-old Asian male)

Event #1:
Treatment Arm: BMN 110 2.0 mg/kg/week
Premedication(s): Loratadine
Timing: During 14th infusion (50 minutes after start of infusion)
Adverse Event(s) and grade: Grade 2 urticaria
Serious AE(s): No

This subject started treatment in MOR-007 (2.0 mg/kg/week) on 23 March 2012. On 26 June 2012, the subject received his 14th infusion with BMN 110, following premedication

with loratadine. The infusion was started at 3 ml/hr at 10:25 AM, and gradually increased to 18 ml/hr by 11:12 AM.

At 11:17 AM, the subject developed non-serious grade 2 urticaria and abdominal pain. Treatment for the urticaria included oral diphenhydramine. The infusion was continued at a lower dose rate (6 ml/hr), then gradually increased to 36 ml/hr by 1:02 PM and completed at 3:12 PM. The events of urticaria and abdominal pain were considered resolved by 4:20 PM. Vital signs remained stable throughout the infusion.

No change was made for the premedications for the next scheduled infusion.

The investigator considered the event of urticaria to be possibly related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #2:
Treatment Arm: BMN 110 2.0 mg/kg/week
Premedication(s): Loratadine
Timing: During 15th infusion (1 hour after start of infusion)
Adverse Event(s) and grade: Grade 2 urticaria
Serious AE(s): No

On 3 July 2012, the subject received his 15th infusion with BMN 110, following premedication with loratadine. The infusion was started at 3 ml/hr at 9:35 AM, and gradually increased to 24 ml/hr by 10:35 AM.

At 10:40 AM, the subject developed non-serious grade 2 urticaria and abdominal pain. Treatment for the urticaria included oral diphenhydramine, and the infusion was interrupted. The events were considered resolved as of 11:10 AM, and the infusion was restarted at that time at a lower dose rate (12 ml/hr). The infusion was gradually increased to 36 ml/hr and was completed later that day. Vital signs remained stable throughout the infusion.

Premedications for the next scheduled infusion (10 July 2012) were changed to levocetirizine and diphenhydramine. During that infusion, the abdominal pain recurred as a non-serious grade 1 event; the urticaria did not recur. There were no events of urticaria during the infusions when diphenhydramine was given as a premedication (10 July 2012 through 29 August 2012).

The investigator considered the event of urticaria to be possibly related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #3:
Treatment Arm: BMN 110 2.0 mg/kg/week
Premedication(s): Loratadine, levocetirizine
Timing: During 26th infusion (2 hours after start of infusion)
Adverse Event(s) and grade: Grade 1 urticaria
Serious AE(s): No

On 19 September 2012, the subject received his 26th infusion with BMN 110, following premedication with loratadine and levocetirizine. The infusion was started at 3 ml/hr at 9:50 AM, and gradually increased to 36 ml/hr by 11:20 AM.

At 11:53 AM, the subject developed non-serious grade 1 urticaria on his right upper arm. Treatment for the urticaria included oral diphenhydramine, and the infusion was continued at a reduced rate (18 ml/hr). The event of urticaria was considered resolved as of 12:45 PM. The infusion was gradually increased back to 36 ml/hr and was completed later that day. Vital signs remained stable throughout the infusion.

The investigator considered the event of urticaria to be probably related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #4:
Treatment Arm: BMN 110 2.0 mg/kg/week
Premedication(s): Loratadine, levocetirizine
Timing: During 27th infusion (2.25 hours after start of infusion)
Adverse Event(s) and grade: Grade 1 urticaria
Serious AE(s): No

On 26 September 2012, the subject received his 27th infusion with BMN 110, following premedication with loratadine and levocetirizine. The infusion was started at 3 ml/hr at 9:26 AM, and gradually increased to 36 ml/hr by 10:56 AM.

At 11:40 AM, the subject developed non-serious grade 1 urticaria in the antecubital region of his right arm. No treatment for the event was reported, and no change was made to the infusion rate. The event of urticaria was considered resolved as of 12:40 PM. The infusion

was completed later that day without interruption or dose change. Vital signs remained stable throughout the infusion.

This was the final infusion prior to the BLA data cutoff date, so it is not known whether the event of urticaria recurred after this infusion.

The investigator considered the event of urticaria to be probably related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Subject No: MOR008-0109-8106 (7-year-old White female)

Event #1:
Treatment Arm: BMN 110 2.0 mg/kg/week
Premedication(s): Diphenhydramine
Timing: 2 days after 4th infusion
Adverse Event(s) and grade: Mild urticaria
Serious AE(s): No

This subject started treatment in MOR-008 (2.0 mg/kg/qow) on 14 June 2012. On 3 July 2012, the subject received her 4th infusion with BMN 110, following premedication with diphenhydramine. Her pre-infusion vital signs taken at 9:44 AM included pulse 113 bpm, blood pressure 100/69 mmHg, temperature 36.8°C, and respiratory rate 24/minute. The infusion was started at 3 ml/hr at 9:45 AM, and gradually increased to 90 ml/hr by 11:33 AM.

At 12:20 PM, the subject developed non-serious moderate vomiting and mild pallor. The infusion was interrupted. The events of vomiting and pallor were considered resolved by 12:30 PM. At 12:47 PM, the subject became bradycardic and hypotensive. Vital signs:

Time	Pulse (bpm)	BP (mmHg)	Temperature (°C)	Respiratory rate (/minute)
12:00 PM	122	112/74	37	24
12:49 PM	64	76/34	37.6	24
12:55 PM	57	84/35	37.8	24
1:05 PM	102	93/62	37.7	26
1:30 PM	99	97/58	38.4	28
2:00 PM	120	103/54	38.2	24
2:30 PM	122	98/51	38	28
3:30 PM	107	82/63	37.4	24

4:14 PM	94	90/54	36.9	28
5:14 PM	110	97/65	36.8	24

Treatment for the events included diphenhydramine, IV fluids, methylprednisolone, acetaminophen, and ondansetron. The events of bradycardia and hypotension were considered resolved by 1:00 PM. The infusion was restarted at 2:00 at 30 ml/hr, and was completed by 4:15 PM.

On 5 July 2012, two days after the infusion, the subject developed non-serious mild urticaria. Treatment included diphenhydramine, and the event was considered resolved by 6 July 2012. On 7 July 2012, he developed non-serious mild pruritus on the hands and feet. No treatment was reported, and the event resolved the same day.

Premedications for the next infusion were changed to include prednisolone, ranitidine, and acetaminophen.

The investigator considered the event of urticaria to be possibly related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does meet the NIAID/FAAN 2006 criteria for anaphylaxis.

Event #2:
Treatment Arm: BMN 110 2.0 mg/kg/week
Premedication(s): Diphenhydramine, prednisolone, ranitidine, acetaminophen
Timing: During 5th infusion (3.25 hours after start of infusion)
Adverse Event(s) and grade: Mild urticaria
Serious AE(s): No

On 3 July 2012, the subject received her 4th infusion with BMN 110, following premedication with diphenhydramine, prednisolone, ranitidine, and acetaminophen. Her pre-infusion vital signs taken at 10:18 AM included pulse 95 bpm, blood pressure 93/47 mmHg, temperature 37.1°C, and respiratory rate 20/minute. The infusion was started at 3 ml/hr at 10:20 AM, and gradually increased to 60 ml/hr by 11:50 AM.

At 1:15 PM, the subject developed non-serious mild urticaria. The infusion was interrupted, and treatment for the event included IV diphenhydramine. Vital signs remained stable throughout the infusion. The event of urticaria was considered resolved as of 1:35 PM. The infusion was restarted at 1:50 PM at 40 ml/hr, and was completed as of 5:00 PM without recurrence of the urticaria.

No change was made to premedications for the next scheduled infusion (18 July 2012), and the infusion was completed without interruptions or dose rate changes and without recurrence of the urticaria.

The investigator considered the event of urticaria to be probably related to study treatment.

Company comment: The Sponsor has reviewed this event and determined that it does not meet the NIAID/FAAN 2006 criteria for anaphylaxis.