CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 125460
Drug Name:	VIMIZIM (BMN 110/elosulfase alfa) 2 mg/kg intravenous (IV) infusion once every week
Indication(s):	Mucopolysaccharidosis type IVA (MPS IVA; Morquio A Syndrome)
Applicant:	Biomarin Pharmaceuticals, Inc.
Date(s):	Stamp Date: March 29, 2013 PDUFA Goal date: February 28, 2014
Review Priority:	Priority with Major Amendment under the PDUFA V Program
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Keywords: BLA review, Clinical Studies

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1 EXECUTIVE SUMMARY

Mucopolysaccharidosis type IVA (MPS IVA; Morquio A Syndrome) currently remains as a serious and life threatening condition with an unmet medical need. There appears to be sufficient evidence to support efficacy claims on improving the 6-minute walk test (6MWT) distance for the VIMIZIM (BMN 110; elosulfase alfa) 2.0 mg/kg/week dose, and the claims reflected within the applicant's submitted product labeling are supported by the results shown in this review.

The efficacy of the BMN 110 2.0 mg/kg/week dose was primarily supported by a single trial MOR-004. In this pivotal trial, the BMN 110 2.0 mg/kg/week dose was demonstrated to be superior to placebo with respect to the Week 24 change from baseline in 6MWTdistance. The current long term extension data from the ongoing study MOR-005 suggest a reasonably sustained efficacy profile for the BMN 110 2.0 mg/kg/week dose with respect to 6MWT distance. These trial results collectively support the efficacy of VIMIZIM in improving 6MWT distance.

Exploratory subgroup analyses have shown that, separately, subjects who are white, who are 12 to 18 years of age, and who are from North America appeared to respond to the BMN 110 2.0 mg/kg/week dose better than their respective counterparts. An additional subgroup of patients who had a 6MWT distance of ≤ 200 meters at baseline were identified during the review cycle. This subgroup, which represents patients with greater morbidity, seems to drive the significant 6MWT efficacy results, and this suggests that these patients may respond better to the BMN 110 2.0 mg/kg/week dose than the patients with less morbidity at baseline. This finding, however, is exploratory in nature and thus cannot be used to support an efficacy claim in the ≤ 200 meters subgroup population. Consequently, if the results regarding this subgroup are to be included in the product labeling, they should be presented in a descriptive manner.

Overall, the design of study MOR-004 was deemed adequate from a statistical perspective, and the applicant's corresponding statistical analysis plan deemed appropriate. There were no statistical review issues identified for this application. However, currently there is no consensus regarding the clinical meaningfulness of the primary study endpoint of 6MWT distance. Consequently, it may be difficult to determine whether the MOR-004 study results, albeit statistically significant, were clinically significant for the BMN 110 2.0 mg/kg/week dose. The findings in the secondary efficacy endpoint of 3 Minute Stair Climb Test (3MSCT) did not show clinical or statistical significance. Without supportive data from the 3MSCT, the overall level of evidence for the efficacy of VIMIZIM on morbidity may be questionable. The clinical team also raised an issue regarding efficacious doses due to the fact that the dose finding investigation was inadequate during the clinical development of VIMIZIM. Another potential issue raised pertains to the optimal study duration necessary to observe a treatment effect. These issues will be discussed at the Advisory Committee meeting scheduled on November 18, 2013.

2 INTRODUCTION

2.1 Overview

Biomarin Pharmaceuticals, Inc. submitted this Biologics License Application (BLA) on March 29, 2013, for VIMIZIM (BMN 110; elosulfase alfa) in accordance with Title 21, Parts 314 and 601 of the Code of Federal Regulations (CFR). The active pharmaceutical ingredient (API) of BMN 110 (2 mg/kg of body weight to be administered once every week as an intravenous [IV] infusion over approximately four hours) is recombinant human N-acetylgalactosamine-6-sulfatase. Effective on December 28, 2007, the applicant had initiated clinical development of BMN 110 under IND 101,234 in patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A Syndrome), which is the proposed indication; and BMN 110 has been developed specifically to establish safety and efficacy in this patient population. The applicant obtained Orphan Designation from the Office or Orphan Products Development (OOPD) on May 15, 2009.

Mucopolysaccharidosis type IVA (MPS IVA; Morquio A Syndrome) is a rare inherited disorder resulting from deficiency of the lysosomal enzyme N-acetylgalactosamine-6-sulfatase (GALNS), which degrades glycosaminoglycans (GAGs) including keratan sulfate (KS) and chondroitin-6-sulfate (C6S). With insufficient GALNS, GAGs progressively accumulate in multiple organs and tissues. The pervasive and progressive accumulation of GAGs leads to significant morbidities and multisystemic clinical impairments resulting in diminished functional capacity, decreased endurance, impaired quality of life, and early mortality. The incidence of this disease estimated in the US is 1 in 200,000 to 300,000 live births, and the prevalence was approximately 520 to 800 patients. 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. Consequently MPS IVA remains as a serious and life threatening condition with an unmet medical need. BMN 110 is intended to provide the exogenous enzyme GALNS that will be taken up into the lysosomes and subsequently increase the catabolism of the GAGs KS and C6S. This mechanism of action is hypothesized to reverse the MPS IVA disease process.

There were a series of formal communications and meetings between the applicant and the Division of Gastroenterology and Inborn Errors Products (DGIEP) throughout VIMIZIM's development program. An advice meeting was held on March 11, 2008, for issues pertaining to the applicant's proposed nonclinical development program. An End of Phase 2 (EOP2) meeting was held on July 28, 2010, to discuss the clinical development program. Biomarin then submitted their single pivotal phase 3 study (trial MOR-004) through the Special Protocol Assessment (SPA) regulatory pathway on December 3, 2010. DGIEP subsequently issued a No-Agreement letter on January 20, 2011. Biomarin chose not to pursue the SPA any further but attempted to reach agreements on the outstanding clinical and statistical issues by an additional advice meeting held on July 9, 2012. The pre-BLA meeting between the applicant and DGIEP was held on December 11, 2012, to mainly discuss the format of the BLA submission. On March 29, 2013, Biomarin submitted the BLA under the PDUFA V Program. This is a priority

review; however, the review cycle was amended due to Chemistry, Manufacturing, and Control (CMC) issues.

This submission contained data from six clinical studies, including two completed studies and four ongoing studies. The clinical efficacy and safety of BMN 110 has been primarily evaluated in one trial (MOR-004): a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study, which serves as the single pivotal study in this clinical development program. The supportive data submitted are from a completed phase 1/2 study (MOR-002), two ongoing long-term extension studies (MOR-005 and MOR-100), and two ongoing ancillary phase 2 studies (MOR-007 and MOR-008). The applicant also mentioned a seventh ongoing phase 2 study (MOR-006) that is not included in this application due to incomplete enrollment and limited exposure at the data cutoff time-point. Table 1 below presents some summary information on the single pivotal clinical trial (MOR-004) and this trial will be the main focus of this BLA review.

Table 1
Summary Information for Relevant Clinical Trials

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Patients	Patient Diagnosis	Duration of Treatment
Efficacy, Safety and PK; Phase 3	MOR-004	To evaluate the ability of 2.0 mg/kg/week BMN 110 and 2.0 mg/kg/every other week BMN 110 compared with placebo to enhance endurance in patients 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	Multinational, Multicenter, Randomized, Double-blind, placebo-controlled, Parallel group	BMN 110; 2.0 mg/kg/week and 2.0 mg/kg/every other week; 4 hour IV infusions	Total: 176	MPS IVA patients age 5 years and older who are able to walk ≥ 30 and ≤ 325 meters in the 6MWT	24 weeks

Source: Reviewer's Table.

2.2 Data Sources

This BLA was submitted electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). The content, including the electronic data sets and labeling information, is located in the Center for Biologics Evaluation and Research (CBER) electronic document room

(EDR) at the location: \\cbsap58\m\eCTD_Submissions\STN125460. Sequences 0000 and 0017 contain all the contents relevant for this review.

The clinical study report (CSR), clinical datasets and analysis datasets for study MOR-004 were reviewed. The clinical datasets were compliant to the CDISC/SDTM v.3.1.2 implementation guide standard, and the analysis datasets were compliant to the CDISC/ADaM v.1.0 implementation guide standard. Adequate data definition files (in Define.XML and Define.PDF formats), a reviewer's guide and SAS program files (in .TXT format) were also submitted.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This study utilized paper Case Report Forms (CRF), and the submitted data quality appeared to be adequate. It was possible to reproduce the primary analysis dataset (along with the numerical results presented within the CSR), specifically the primary endpoint values, from the original data source. It was also possible to verify the randomized treatment assignments, and the applicant submitted documentation of data quality control/assurance procedures within Section 8.6 of the CSR.

The statistical analysis plan (SAP) was finalized on August 24, 2012. An addendum to the SAP, which was exclusively used to finalize the definition of the Per-Protocol (PP) analysis set, was issued on October 3, 2012. The SAP, along with the addendum, was submitted, and all relevant analysis decisions were made before the trial completion (August 23, 2012). Database hard-lock was on October 12, 2012, and the study was officially unblinded on October 19, 2012.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

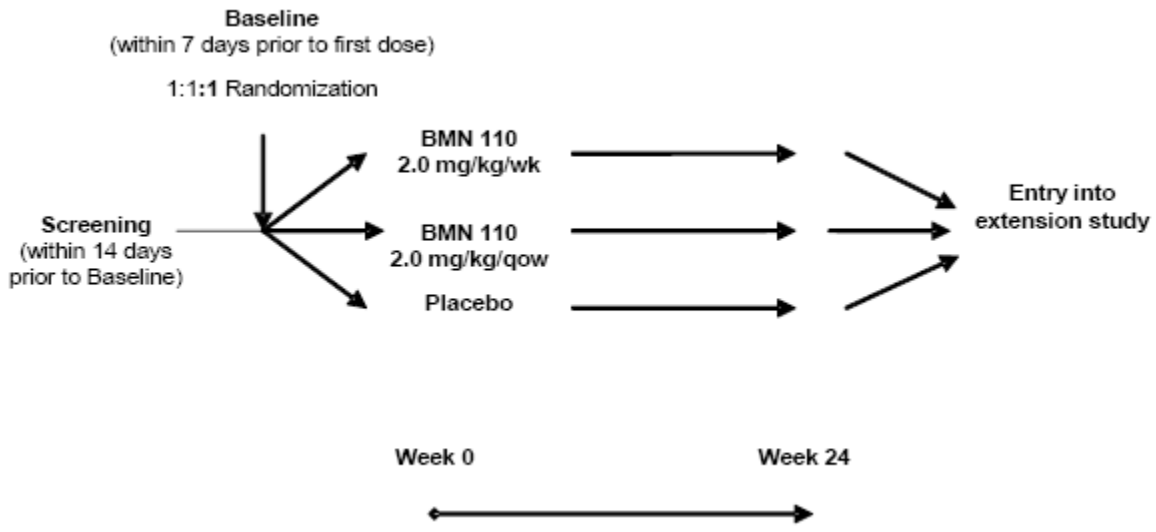
Phase 3 efficacy and safety study MOR-004 is an adequate and well-controlled study that is the main basis for the efficacy claims in the labeling. Due to the rare disease nature of MPS IVA and limited subjects available for clinical studies, there was only one additional clinical safety and efficacy study conducted by Biomarin Therapeutics prior to MOR-004. That was a Phase 1/2 study, MOR-002, which had 20 patients in total, and was a multicenter, open-label dose-escalation clinical trial. The study results from MOR-002 were utilized to choose the doses to be studied in trial MOR-004.

The MOR-004 trial protocol was finalized on October 4, 2010. Trial MOR-004 started on January 25, 2011, and ended on August 23, 2012. As stated previously, Biomarin submitted the MOR-004 trial protocol, under IND 101,234, through the SPA regulatory pathway on December 3, 2010, following the EOP2 meeting. DGIEP subsequently issued a No-Agreement letter on

January 20, 2011, and Biomarin consequently chose to reach agreements on the outstanding clinical and statistical issues by an additional advice meeting held on July 9, 2012. There were no changes made to the protocol as a result of this advice meeting. The main clinical concerns pertained to dosing and the study endpoints, and these issues will be the focus of the Advisory Committee meeting scheduled on November 18, 2013. The statistical advice (pertaining to analysis) from the Agency was incorporated by Biomarin into the MOR-004 SAP finalized on August 24, 2012.

This was a 24-week, multinational (with a total of 17 countries), multicenter (with a total of 33 clinical sites), out-patient, randomized, double-blind, placebo-controlled, parallel group study, whose primary objective was to evaluate the ability of 2.0 mg/kg/week BMN 110 and 2.0 mg/kg/qow (qow: every other week) BMN 110 compared with placebo to enhance endurance in patients with MPS IVA as measured by an increase in the number of meters walked in the 6MWT from baseline to Week 24. The study drug was to be administered as a four-hour IV infusion. To be enrolled into the study, treatment naïve patients must have had confirmed MPS IVA, been five years and older, and been able to walk ≥ 30 and ≤ 325 meters in the 6MWT. The full duration of a patient's participation was up to 27 weeks, which included up to three weeks for screening and baseline assessments, along with 24 weeks of treatment. The study scheme is shown below in Figure 1.

Figure 1
Study Diagram MOR-004



Source: MOR-004 October 4, 2010 Protocol - Figure 9.1.1 on pg. 40.

Subjects were randomized (1:1:1) to one of the three treatment groups: (1) BMN 110 2.0 mg/kg/week, (2) BMN 110 2.0 mg/kg/qow with placebo infusions on alternate weeks, or (3) placebo each week for 24 consecutive weeks. All infusions were to last approximately four hours. The randomization was conducted by a third party vendor so that Biomarin would be blinded to the treatment assignments. In addition, subjects, Investigators, and site personnel were also blinded to the treatment assignments throughout the study until the final analysis was

complete. The randomization was stratified by screening 6MWT categories (≤ 200 meters and > 200 meters) and age groups (5-11, 12-18, and ≥ 19 years old). A physical examination and endurance tests (6MWT and 3MSCT, in duplicates) were performed at Screening and/or baseline, Week 12, and Week 24 (or within one week of the Early Termination Visit [ETV]). The 6MWT measures the total number of meters walked in a six-minute period, and the 3MSCT measures the average number of stairs climbed per minute over a three-minute period, i.e., the total number of stairs climbed in three minutes divided by three. Urine samples for urinary Keratin Sulfate (urine KS), creatinine and blood samples for immunogenicity testing were collected at baseline, Weeks 2 and 4, and every four weeks thereafter (or within one week of the ETV).

It should be noted that all patients randomized into this study, upon completion were later given the opportunity to immediately roll over into a 240-week/5-year, multicenter, un-controlled extension study (trial MOR-005) which assesses the long term efficacy and safety of BMN 110. This extension study contains two parts. In Part 1, all patients rolling over from MOR-004 who were dosed with BMN 110 (i.e., 2.0 mg/kg/week or 2.0 mg/kg/qow) would stay on their MOR-004 dose in a double-blinded fashion. Placebo patients rolling over from MOR-004 would be randomized (1:1) to receive BMN 110 2.0 mg/kg/week or 2.0 mg/kg/qow in a double-blinded fashion. Part 1 assessments for 6MWT and 3MSCT will be made once every 12 weeks from the end of the MOR-004 study. After the closure of study MOR-004 and the final analysis of its primary efficacy and safety results, the optimal BMN 110 dose would be determined and Part 2 of study MOR-005 would subsequently begin. In Part 2, all participating MOR-005 patients would switch over to the chosen BMN 110 dose (if not already on it) in an open-labeled fashion. Part 2 assessments for 6MWT and 3MSCT will be made once every 48 weeks from the end of the MOR-004 study.

As stated above, the primary objective of study MOR-004 was 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 MPS IVA patients as measured by an increase in the number of meters walked in the 6MWT from baseline to Week 24. The two secondary objectives were: (1) 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 MPS IVA patients as measured by an increase in the number of stairs climbed per minute in the 3MSCT from baseline to Week 24; and (2) to evaluate the ability of 2.0 mg/kg/week BMN 110 and 2.0 mg/kg/qow BMN 110 compared with placebo to reduce urine KS levels in MPS IVA patients as measured by a decrease in normalized urine KS levels from baseline to Week 24. One central laboratory was utilized for the urine KS measurement in this study.

The following primary and secondary endpoints were pre-specified accordingly in the protocol by the applicant:

Primary Endpoint: Change from baseline in 6MWT at Week 24. It should be noted that a greater 6MWT distance may indicate a better disease state.

Secondary Endpoints:

- Change from baseline in 3MSCT at Week 24. It should be noted that greater 3MSCT numbers may indicate a better disease state.
- Percentage change from baseline in normalized urine KS levels at Week 24. It should be noted that a lower urine KS level may indicate a better disease state.

Approximately 162 patients (54 patients in each group) would be enrolled into the study to have more than 90% power to detect a difference of 40 meters in mean change in the 6MWT distance between each of the BMN 110 groups and the placebo group, assuming that the common standard deviation (SD) was 65 meters at an overall 0.05 two-sided significance level, α, with the Hochberg method for multiplicity adjustment. It should be noted that the standard deviation of 65 meters was somewhat conservative when compared to the standard deviation associated with the similar population subset found within study MOR-002. Study MOR-004 would be considered positive if both comparisons of the drug regimens to placebo render p-values less than 0.05 or the comparison of one of the drug regimens to placebo results in a p-value less than 0.025.

Overall, the design of study MOR-004 was deemed adequate from a statistical perspective and the estimated sample size was appropriate given the assumptions on the anticipated treatment effect. As stated previously, the pertinent clinical concerns may correspond to the dosing and the study endpoints, specifically the clinical meaningfulness of the 6MWT distance. The study duration may also be a potential issue. These clinical issues will be discussed at the Advisory Committee meeting.

3.2.2 Statistical Methodologies

3.2.2.1 Analysis Sets

The primary analysis set, i.e. the analysis set used for all primary and secondary efficacy endpoint analyses, was the Intent-to-Treat (ITT) analysis set, which included all randomized subjects who received at least one dose of study drug. In this analysis set, patients were included in the treatment group that they were randomized to receive regardless of the actual treatment received. Due to the fact that this was a randomized and double-blind study, the utilization of the applicant-defined ITT analysis set as the primary analysis set is acceptable per ICH E9.

As a sensitivity analysis, all analyses were re-conducted utilizing the Per-Protocol (PP) analysis set, which included all subjects in the ITT set who completed the study while being compliant with the study medication without any major protocol deviations.

Another sensitivity analysis conducted was utilizing an All-Randomized analysis set, which included all patients who were randomized into the study. As for the ITT set, patients were included in the treatment group that they were randomized to receive regardless of actual treatment received in this analysis set.

3.2.2.2 Multiplicity Adjustment

In order to control the overall study-wise Type I error rate (α), the Hochberg method was proposed for the multiple dose comparisons on the primary endpoint. A step-down procedure was pre-specified by the applicant to adjust for multiple comparisons in the analysis of the secondary endpoints in the order previously presented. The Hochberg method was nested within each step/endpoint testing when comparing each of the two doses to placebo. The applicant stated that the step-down can be carried to the next step if both doses at the current endpoint/step are found to be statistically significant (i.e., p-value < 0.05) in comparison to placebo. If at least one dose is found not statistically significant (i.e., p-value ≥ 0.05) compared to placebo at the current endpoint/step, all hypothesis testing for the subsequent endpoints/steps will be deemed as exploratory. It should be noted that this step-down procedure was not pre-specified in the finalized protocol, but was only described within the SAP after the trial initiated.

This step-down procedure was pre-specified in a dubious manner by the applicant. By not specifically stating if the step-down begins at the primary analysis level one could speculate that the applicant had assumed that formal hypothesis testing could still be conducted on the secondary efficacy endpoints after spending all of the Type I error rate on the primary endpoint comparisons. Consequently, the pre-specified step-down procedure was inherently flawed; however, study conclusions were not affected as neither BMN 110 dose was found to be statistically significant (i.e., p-value < 0.05) in comparison to placebo for the first secondary endpoint as discussed below in Section 3.2.4.

3.2.2.3 Primary Endpoint Analysis

As stated previously for the 6MWT, two assessments were conducted at each of the visit Weeks 0, 12, and 24. The arithmetic mean of the two measurements (in meters) was used as the score for the visit week. The primary analysis of the 6MWT distance was an Analysis of Covariance (ANCOVA) model of the Week 24 change from baseline in the 6MWT measurement with treatment, baseline 6MWT categories (≤ 200 meters and > 200 meters), and age groups (5-11, 12-18, and ≥ 19 years old) as factors. Each active treatment group was compared to the placebo group and p-values were calculated. Least-squares (LS) estimated means and confidence intervals (CIs) for the treatment effects of each BMN 110 dose regimen versus placebo were also calculated. The comparison is conducted in a pair-wise fashion, i.e., separately for each dose vs. placebo.

3.2.2.4 Secondary Endpoints Analysis

As stated previously for the 3MSCT, two assessments were conducted at each of the visit Weeks 0, 12, and 24. Similarly to the 6MWT, the arithmetic mean of the two measurements was used as the score for the visit week. The analysis of the 3MSCT score was an ANCOVA model of the Week 24 change from baseline in the 3MSCT measurement with baseline 3MSCT as a covariate, and treatment, baseline 6MWT categories (≤ 200 meters and > 200 meters), and age groups (5-11, 12-18, and ≥ 19 years old) as factors. The treatment comparisons conducted are identical to those for the primary endpoint of 6MWT.

Urine KS and urine creatinine (for normalization) were to be measured through quantitative laboratory analysis. As stated previously, samples for urine KS and urine creatinine were to be collected at baseline, Weeks 2, 4, 8, 12, 16, 20 and 24, as well as within one week of the ETV. Urine KS concentration normalized to creatinine will be calculated as follows: Normalized Urine KS = Urine KS / Urine Creatinine. Baseline values will be calculated as the average of the two measurements collected during the baseline week. Similar to that of 6MWT and 3MSCT, the analysis of the normalized urine KS was an ANCOVA model of the Week 24 percentage change from baseline in the normalized urine KS measurement with baseline normalized urine KS as a covariate, and treatment, baseline 6MWT categories (≤ 200 meters and > 200 meters), and age groups (5-11, 12-18, and ≥ 19 years old) as factors. The treatment comparisons conducted are identical to those for the primary endpoint of 6MWT and the secondary endpoint of 3MSCT.

3.2.2.5 Handling of Dropouts/Missing Data

For the 6MWT and 3MSCT, subjects who had died or were physically unable to perform the test(s) would have tests scored as 0. If only one of the two test scores was obtained, then that single score will be used instead of the arithmetic mean.

For subjects with missing 6MWT or 3MSCT data who had not died and were physically able to perform the test(s), and for subjects with missing urine KS data, the Multiple Imputation (MI) approach was conducted while assuming that these data were missing at random (MAR). It was expected that there would be few subjects dropping out, and any intermittent missing data would be infrequent and could satisfy the missing at random (MAR) assumption.

The imputation for each endpoint below was based on a sampling from the joint normal distributions of the corresponding continuous variables:

- 6MWT: baseline age and Weeks 0, 12, 24 of 6MWT
- 3MSCT: baseline age, Week 0 of 6MWT, and Weeks 0, 12, 24 of 3MSCT
- Urine KS: baseline age, Week 0 of 6MWT, and Weeks 0, 2, 4, 8, 12, 16, 20, 24 of urine KS

The sampling utilized a Markov-Chain-Monte-Carlo (MCMC) chain with five sets of imputations from SAS PROC MI. The imputation was performed for each treatment group separately using the randomly selected seed 38867.

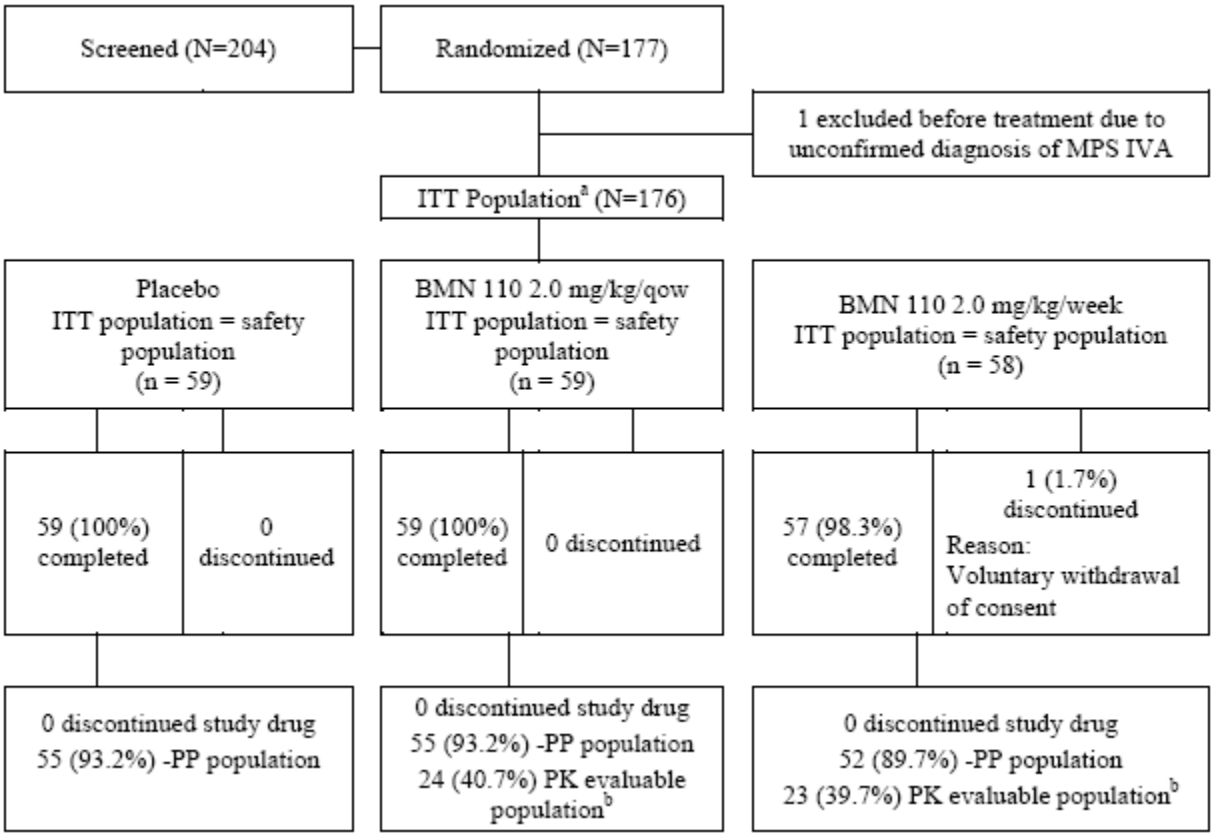
In addition, for subjects with missing 6MWT or 3MSCT data who had not died and were physically able to perform the test(s), and for subjects with missing urine KS data, a no-change-from-baseline imputation approach was conducted as a sensitivity analysis.

As discussed in Section 3.2.3 and 3.2.4 below, there were only two randomized patients (one before dosing and one after dosing) who dropped out of study MOR-004, and the sensitivity analyses consequently showed that it did not impact the study conclusions.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition information for all randomized patients is displayed in Figure 2 and Table 2 below. In this review, all the results presented in the reviewer's tables are agreeable to those reported by the sponsor.

Figure 2
Disposition – Study MOR-004



Source: MOR-004 CSR - Figure 9.1.1 on pg. 127.

[a]: Patient 1180-4161 was randomized to the placebo group but was ultimately excluded before treatment due to an unconfirmed diagnosis of PMS IVA. Patient 0050-4090 discontinued from the BMN 110 2.0 mg/kg/week group due to voluntary withdrawal of consent.

[b]: Note that the PK evaluable population is out of scope for this review.

Table 2
Disposition – Study MOR-004
(All Randomized)

	Placebo (N = 60)	BMN 110 2.0 mg/kg/qow (N = 59)	BMN 110 2.0 mg/kg/week (N = 58)	Total (N = 177)
Randomized	60 (100%)	59 (100%)	58 (100%)	177 (100%)
Intent-to-Treat (ITT)	59 (98.3%)	59 (100%)	58 (100%)	176 (99.4%)
Per-Protocol (PP)	55 (91.7%)	55 (93.2%)	52 (89.7%)	162 (91.5%)
Completed Study	59 (98.3%)	59 (100%)	57 (98.3%)	175 (98.9%)
Discontinued Study Early	1 (1.7%)	0	1 (1.7%)	2 (1.1%)
Adverse Event	0	0	0	0
Lost to follow-up	0	0	0	0
Patient decision (withdrew consent)	0	0	1 (1.7%)	1 (0.6%)
Investigator's decision	0	0	0	0
Protocol Deviation	0	0	0	0
Study Terminated by Sponsor	0	0	0	0
Other	1 (1.7%)	0	0	1 (0.6%)

Source: Reviewer's Table.
Note: Denominators for percentages are N. Patient 1180-4161 was randomized to the placebo group but was ultimately excluded before treatment due to an unconfirmed diagnosis of MPS IVA. Patient 0050-4090 discontinued from the BMN 110 2.0 mg/kg/week group due to voluntary withdrawal of consent.

The demographics and baseline characteristics for all randomized patients are presented in Table 3 below.

Table 3
Demographic and Baseline Characteristics – Study MOR-004
(All Randomized)

	Placebo (N = 60)	BMN 110 2.0 mg/kg/qow (N = 59)	BMN 110 2.0 mg/kg/week (N = 58)	Total (N = 177)
Age (years)				
n	60	59	58	177
Mean (SD)	15.0 (11.21)	15.3 (10.79)	13.1 (8.10)	14.5 (10.13)
Median	11.8	12.0	11.1	11.8
Min, Max	5, 57	5, 49	5, 42	5, 57
Age Group – n (%)				
5 to 11	31 (51.7%)	31 (52.5%)	32 (55.2%)	94 (53.1%)
12 to 18	15 (25.0%)	16 (27.1%)	16 (27.6%)	47 (26.6%)
≥ 19	14 (23.3%)	12 (20.3%)	12 (17.2%)	36 (20.3%)
Gender – n (%)				
Female	32 (53.3%)	25 (42.4%)	32 (55.2%)	89 (50.3%)
Male	28 (46.7%)	34 (57.6%)	26 (44.8%)	88 (49.7%)
Race – n (%)				
Asian	12 (20.0%)	15 (25.4%)	14 (24.1%)	41 (23.2%)
Black or African American	0	2 (3.4%)	2 (3.4%)	4 (2.3%)
Other	4 (6.7%)	7 (11.9%)	6 (10.3%)	17 (9.6%)
White	44 (73.3%)	35 (59.3%)	36 (62.1%)	115 (65.0%)
6MWT Distance (meters)				
n	60	59	58	177
Mean (SD)	211.5 (69.34)	205.7 (81.19)	203.9 (76.32)	207.1 (75.37)
Median	223.0	218.0	216.5	217.2
Min, Max	36, 312	47, 320	42, 322	36, 322
6MWT Distance Category – n (%)				
≤ 200 meters	24 (40.0%)	24 (40.7%)	23 (39.7%)	71 (40.1%)
> 200 meters	36 (60.0%)	35 (59.3%)	35 (60.3%)	106 (59.9%)
Geographic Region				
Europe	27 (45.0%)	21 (35.6%)	25 (43.1%)	73 (41.2%)
North America	16 (26.7%)	16 (27.1%)	15 (25.9%)	47 (26.6%)
Other	17 (28.3%)	22 (37.3%)	18 (31.0 %)	57 (32.2%)

Source: Reviewer's Table.
Note: Denominators for percentages are N.

There is no significant imbalance between the treatment groups regarding the presented demographic and baseline characteristics.

3.2.4 Results and Conclusions

The results displayed in this section correspond to the endpoint testing order specified in section 3.2.1 above.

Table 4
Analysis of 6MWT by Treatment Group – Study MOR-004
(ITT)

		BMN 110	
	Placebo (N = 59)	2.0 mg/kg/qow (N = 59)	2.0 mg/kg/week (N = 58)
Baseline 6MWT (meters)			
n	59	59	58
Mean (SD)	211.9 (69.90)	205.7 (81.19)	203.9 (76.32)
Median	228.9	218.0	216.5
Min, Max	36, 312	47, 320	42, 322
Week 24 6MWT (meters)			
n	59	58	57
Mean (SD)	225.4 (83.20)	220.5 (88.20)	243.3 (83.50)
Median	229.4	238.1	251.0
Min, Max	51, 501	44, 370	52, 400
Week 24 Change from Baseline (meters)			
n	59	58	57
Mean (SD)	13.5 (50.63)	14.9 (40.82)	36.5 (58.49)
Median	9.9	16.1	20.0
Min, Max	-99, 221	-106, 114	-58, 229
Modeled [1] Treatment Effect [2]			
n		59	58
LS Mean Difference (meters) (SE)		0.5 (9.29)	22.5 (9.35)
95% CI		(-17.8, 18.9)	(4.0, 40.9)
p-value [3]		0.9542	0.0174

Source: Reviewer's Table.
Note: Inference results under the BMN 2.0 mg/kg/qow column pertain to the comparison between BMN 2.0 mg/kg/qow and placebo. Inference results under the BMN 2.0 mg/kg/week column pertain to the comparison between BMN 2.0 mg/kg/week and placebo.
[1]: ANCOVA model adjusted for baseline 6MWT categories (≤ 200 meters and > 200 meters) and age groups (5-11, 12-18, and ≥ 19 years old).
[2]: Treatment effect defined as: (Change from Baseline to Week24, BMN 110) – (Change from Baseline to Week24, Placebo).
[3]: p-value from the ANCOVA model.

It can be observed that the BMN 110 2.0 mg/kg/week dose showed superior improvement in the change from baseline for 6MWT at Week 24 when compared to placebo while the BMN 110 2.0 mg/kg/qow dose failed to show a statistically significant treatment difference when compared to placebo. As explained previously, per the applicant's flawed multiplicity adjustment approach, all subsequent hypotheses testing corresponding to the secondary endpoints should be

exploratory in nature. It should be noted that the ANCOVA model assumptions, i.e. normality and constant variance of residuals, were appropriate based on graphically observing residuals along with the pertinent normal quantile-quantile plot.

These analyses were all repeated utilizing the PP and All-Randomized analysis sets, and the conclusions were consistent. From the 177 patients who were originally randomized, there were only two dropouts; sensitivity analysis consequently showed that these two dropouts did not impact the study conclusions. There were a large number of sites (31 in total) relative to the total number of patients randomized (177), however it is important to note that no single site influenced or drove the overall study results. There were three patients (0021-4022 [placebo], 1024-4033 [BMN 110 2.0 mg/kg/week], and 1073-4111 [BMN 110 2.0 mg/kg/week]) who were designated as outliers due to having studentized residual values greater than three. As a sensitivity analysis, these three patients were removed from the analysis, and the study conclusions remained the same. An additional sensitivity analysis was conducted by replacing the baseline 6MWT category (i.e. $\leq$ 200 meters and > 200 meters), as a factor in the ANCOVA model, with the baseline continuous 6MWT score as a covariate. One other sensitivity analysis was conducted by replacing the Week 24 change from baseline in 6MWT dependent variable, in the ANCOVA model, with Week 24 percentage change from baseline in 6MWT. The study conclusions from these two sensitivity analyses were consistent with the findings from the primary analysis.

Table 5
Analysis of 3MSCT by Treatment Group – Study MOR-004
(ITT)

		BMN 110	
	Placebo (N = 59)	2.0 mg/kg/qow (N = 59)	2.0 mg/kg/week (N = 58)
Baseline 3MSCT (stairs/min)			
n	59	59	58
Mean (SD)	30.0 (14.10)	27.1 (15.80)	29.6 (16.40)
Median	30.8	25.5	30.5
Min, Max	0, 59	0, 67	0, 72
Week 24 3MSCT (stairs/min)			
n	59	58	57
Mean (SD)	33.6 (18.40)	30.6 (17.90)	34.9 (18.40)
Median	32.0	28.6	34.7
Min, Max	0, 79	0, 75	0, 82
Week 24 Change from Baseline (stairs/min)			
n	59	58	57
Mean (SD)	3.6 (8.50)	3.4 (10.20)	4.8 (8.10)
Median	0.9	1.6	4.3
Min, Max	-13, 32	-19, 46	-12, 21
Modeled [1] Treatment Effect [2]			
n		59	58
LS Mean Difference (stairs/min) (SE)		-0.5 (1.66)	1.1 (1.66)
95% CI		(-3.7, 2.8)	(-2.1, 4.4)
p-value [3]		0.7783	0.4935

Source: Reviewer's Table.
Note: Inference results under the BMN 2.0 mg/kg/qow column pertain to the comparison between BMN 2.0 mg/kg/qow and placebo. Inference results under the BMN 2.0 mg/kg/week column pertain to the comparison between BMN 2.0 mg/kg/week and placebo.
[1]: ANCOVA model adjusted for baseline 3MSCT score, baseline 6MWT categories (≤ 200 meters and > 200 meters) and age groups (5-11, 12-18, and ≥ 19 years old).
[2]: Treatment effect defined as: (Change from Baseline to Week24, BMN 110) – (Change from Baseline to Week24, Placebo).
[3]: p-value from the ANCOVA model.

As discussed earlier, per the applicant's pre-specified multiplicity adjustment approach, all inferential statistics corresponding to the analysis of 3MSCT presented above in Table 5 should be exploratory in nature. Regardless, neither dose showed any benefit when compared to placebo with regards to the 3MSCT. Hence the study conclusion was left unaffected. It should be noted that these analyses were all repeated utilizing the PP and All-Randomized analysis sets as sensitivity analyses and the conclusions were consistent.

Table 6
Analysis of Normalized Urine KS by Treatment Group – Study MOR-004 (ITT)

		BMN 110	
	Placebo (N = 59)	2.0 mg/kg/qow (N = 59)	2.0 mg/kg/week (N = 58)
Baseline Normalized Urine KS (µg/mg)			
n	58	59	58
Mean (SD)	25.7 (15.10)	28.6 (21.20)	26.9 (14.10)
Median	26.7	27.4	24.1
Min, Max	3, 53	2, 117	2, 59
Week 24 Normalized Urine KS (µg/mg)			
n	56	57	54
Mean (SD)	24.3 (13.40)	16.4 (10.00)	14.2 (8.40)
Median	25.5	14.6	13.6
Min, Max	2, 50	2, 50	1, 38
Week 24 Percentage Change from Baseline (%)			
n	55	57	54
Mean (SD)	-4.4 (27.00)	-35.2 (20.70)	-45.1 (19.90)
Median	-12.3	-35.8	-50.8
Min, Max	-50, 74	-92, 45	-79, 5
Modeled [1] Treatment Effect [2]			
n		59	58
LS Mean Difference (%) (SE)		-30.2 (4.19)	-40.7 (4.23)
95% CI		(-38.5, -22.0)	(-49.0, -32.4)
p-value [3]		<0.0001	<0.0001

Source: Reviewer's Table.
Note: Inference results under the BMN 2.0 mg/kg/qow column pertain to the comparison between BMN 2.0 mg/kg/qow and placebo. Inference results under the BMN 2.0 mg/kg/week column pertain to the comparison between BMN 2.0 mg/kg/week and placebo.
[1]: ANCOVA model adjusted for baseline normalized urine KS concentration, baseline 6MWT categories (≤ 200 meters and > 200 meters) and age groups (5-11, 12-18, and ≥ 19 years old).
[2]: Treatment effect defined as: (Percentage Change from Baseline to Week24, BMN 110) – (Percentage Change from Baseline to Week24, Placebo).
[3]: p-value from the ANCOVA model.

As can be deduced, all inferential statistics corresponding to the analysis of normalized urine KS presented above in Table 6 are exploratory in nature. Nonetheless, both doses showed nominally significant improvement when compared to placebo with regards to the normalized urine KS concentration. It should be noted that these analyses were all repeated utilizing the PP and All-Randomized analysis sets as sensitivity analyses and the conclusions were consistent.

As stated previously in section 3.2.1, all patients participating in study MOR-004 were eligible, upon completion of the study, to roll over into the long term efficacy and safety trial MOR-005. In the end, out of the 177 patients randomized into the MOR-004 study, 173 participated in study MOR-005, and Table 7 and Figure 3 below displays the descriptive summary of long term

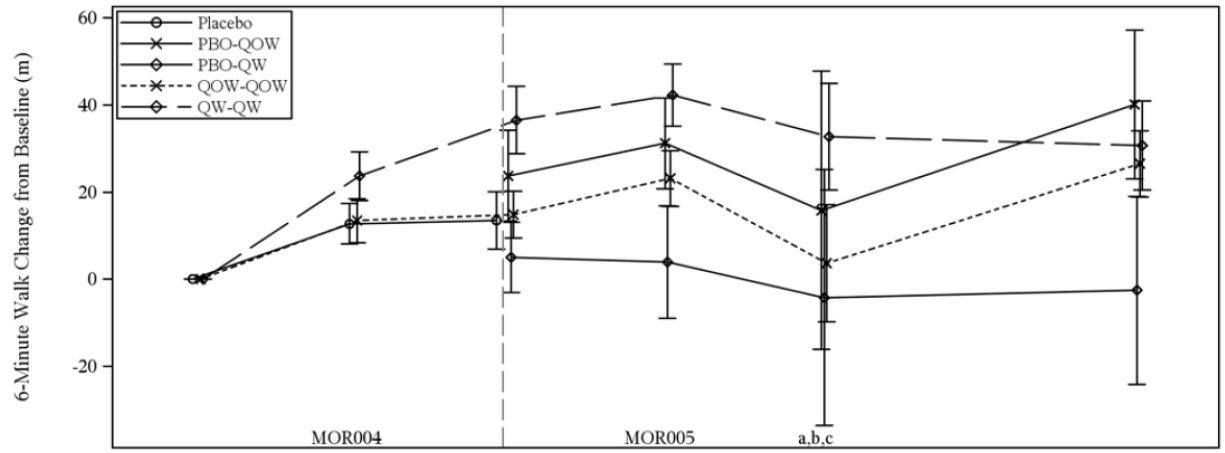
6MWT change from baseline scores (in meters), with baseline being Day 1 of the MOR-004 study, for these rollover patients. All 24 weeks of 6MWT data from the MOR-004 study is presented along with the subsequent finalized Part 1 results from study MOR-005 which presents an additional 24 weeks of treatment data in a double-blinded fashion. This study has been ongoing at the time of NDA filing, and the most up-to-date submission by the applicant includes the first assessment from Part 2 of the study (collected in an open-labeled fashion).

Table 7
Descriptive Summary of change from baseline in 6MWT Distance – Studies MOR-004/MOR-005
(MOR-004 ITT/MOR-004 Randomized patients rolling over into MOR-005)

		placebo – BMN 110		BMN 110 – BMN 110	
	placebo (N = 59)	PBO-QOW (N = 29)	PBO-QW (N = 29)	QOW-QOW (N = 59)	QW-QW (N = 58)
baseline 6MWT (meters)					
n	59	29	29	59	58
Mean (SD)	211.9 (69.90)	219.7 (74.20)	207.2 (64.90)	205.7 (81.19)	203.9 (76.32)
Median	228.9	239.5	217.2	218.0	216.5
Min, Max	36, 312	36, 310	93, 312	47, 320	42, 322
Week 24 CFB (meters)					
n	59	29	29	58	57
Mean (SD)	13.5 (50.63)	23.8 (56.21)	5.0 (43.27)	14.9 (40.82)	36.5 (58.49)
Median	9.9	13.8	0.4	16.1	20.0
Min, Max	-99, 221	-88, 221	-99, 95	-106, 114	-58, 229
Week 36 CFB (meters)					
n	NA	28	28	58	54
Mean (SD)		31.2 (55.36)	4.0 (68.48)	23.1 (48.70)	42.2 (52.13)
Median		23.3	3.1	18.8	41.7
Min, Max		-62, 182	-184, 128	-94, 130	-62, 229
Week 48 CFB (meters)					
n	NA	14	13	26	27
Mean (SD)		15.8 (119.49)	-4.2 (105.85)	3.7 (68.46)	32.7 (63.73)
Median		18.9	30.0	13.5	26.5
Min, Max		-310, 242	-234, 143	-239, 120	-120, 182
Week 72 CFB (meters) [1]					
n	NA	28	27	56	54
Mean (SD)		40.1 (90.57)	-2.5 (112.33)	26.5 (56.90)	30.7 (74.92)
Median		31.0	17.9	28.9	32.5
Min, Max		-101, 336	-312, 171	-125, 173	-149, 229

Source: Reviewer's Table.
Note: PBO = placebo; QOW = BMN 110 2.0 mg/kg/qow; QW = BMN 110 2.0 mg/kg/week; CFB = change from baseline with baseline being Day 1 of study MOR-004.
[1]: All cohorts were being administered BMN 110 2.0 mg/kg/week, i.e. the chosen MOR-004 BMN 110 dose, at Week 72.

Figure 3
Mean (± SE) Change from Baseline in 6MWT – Studies MOR-004/MOR-005
(MOR-004 ITT/MOR-004 Randomized patients rolling over into MOR-005)



MOR-005: Week	0	12	24	36	48	72
	MOR-004: 0	12	0	12	24	48
Placebo	59	59	59			
PBO-QOW			29	28	14	28
PBO-QW			29	28	13	27
QOW-QOW	59	59	58	58	26	56
QW-QW	58	58	57	54	27	54

Source: September 27, 2013 Information Request Submission - Figure 14.2.1.1 on pg. 221.
Note: PBO = placebo; QOW = BMN 110 2.0 mg/kg/qow; QW = BMN 110 2.0 mg/kg/week. All cohorts were being administered BMN 110 2.0 mg/kg/week, i.e. the chosen MOR-004 BMN 110 dose, at Week 72.

It can be seen from Table 7 and Figure 3 that MOR-004 patients who continued with their BMN 110 therapy (for either the 2.0 mg/kg/week or 2.0 mg/kg/qow dose) maintained their improvement of the 6MWT change from baseline scores through 36 weeks of total exposure (i.e. through Week 12 of study MOR-005). Study MOR-004 placebo patients who were randomized to either the BMN 110 2.0 mg/kg/week or BMN 110 2.0 mg/kg/qow dose appeared to maintain or improve, respectively, their 6MWT change from baseline scores through 36 weeks of total exposure.

It should be noted that less than half of the patients who rolled over into MOR-005 actually had existing data at 48 weeks of total exposure (i.e. through Week 24 of study MOR-005) when Part 1 of the study concluded and Part 2 subsequently commenced. The resulting sparseness of the 48 week data is due to the fact that these results were based on only those subjects who reached 48 weeks of total exposure while still in Part 1 of the MOR-005 study. And due to the difference in assessment schedules between Parts 1 and 2 as explained previously in Section 3.2.1 above, with Part 1 assessments being made once every 12 weeks from the end of the MOR-004 study and Part 2 assessments being made once every 48 weeks from the end of the MOR-004 study, data at 48 weeks of total exposure remain sparse in nature as they were acquired solely by a Part 1 assessment. This data sparseness is remedied at Week 72, which signifies the first Part 2 assessment, as can be seen by the increased Week 72 cohort sample size which is close to the sample size at the beginning of MOR-005. All cohorts shown in Table 7 and Figure 3 were being administered BMN 110 2.0 mg/kg/week, i.e. the chosen MOR-004 BMN 110 dose, at

Week 72. It can be seen that the patients who were administered the BMN 110 2.0 mg/kg/week dose throughout both studies reasonably maintained their improvement of the 6MWT change from baseline scores through 72 weeks of total exposure.

It should also be noted that when the MOR-004 placebo patients were randomized (1:1) to either the BMN 110 2.0 mg/kg/week or BMN 110 2.0 mg/kg/qow dose, there was a notable separation between these two MOR-005 randomized treatment groups (i.e. the PBO-QW and PBO-QOW groups in Table 7 and Figure 3 above) in terms of change from baseline in 6MWT distance. This separation is due to patient 0021-4022. This patient in placebo group was an outlier in study MOR-004 with a relatively large change from baseline in 6MWT distance at Week 24. Hence the treatment group he was randomized to (in this case the BMN 110 2.0 mg/kg/qow dose group) in Study MOR-005 would have a greater change from baseline in 6MWT distance, for all time points in Study MOR-005, relative to the other study dose group (in this case the PBO-QW group). Consequently, no clinical interpretation should be made in regard to this nominal and arbitrary difference between the PBO-QOW and PBO-QW arms.

3.3 Evaluation of Safety

As discussed in the clinical review, there is a high probability of developing anti-drug antibodies, including those that neutralize uptake of BMN 110 into cells. It should be noted that all patients treated with BMN 110 developed anti-drug antibodies by Week 4. There were no deaths during the entire BMN 110 development program, but there were risks pertaining to anaphylaxis and recurrent hypersensitivity reactions. Non-serious adverse events occurring in more than 10% of the BMN 110 patients were, in a descending order of the incidence rate, pyrexia, vomiting, headache, nausea, and fatigue. Please see Section 7 of the clinical review for the full details regarding the safety profile of BMN 110.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The primary efficacy analysis was re-assessed by gender, and it was found that the results were consistent across the female and male subgroups, and consistent with the whole population, for both dose comparisons. These results are presented in Table 8 below.

Table 8
Gender Subgroup Analysis of 6MWT by Treatment Group –
Study MOR-004
(ITT)

	BMN 110	
	2.0 mg/kg/qow (N = 59)	2.0 mg/kg/week (N = 58)
Female		
Week 24 Change from Baseline (meters)		
n	25	32
Mean (SD)	12.6 (32.78)	36.3 (59.07)
Median	7.9	23.8
Min, Max	-39, 79	-58, 229
Modeled [1] Treatment Effect [2]		
n	25	32
LS Mean Difference (meters) (SE)	-5.1 (13.49)	18.6 (12.65)
95% CI	(-31.7, 21.6)	(-6.3, 43.6)
p-value [3]	0.7076	0.1423
Male		
Week 24 Change from Baseline (meters)		
n	34	26
Mean (SD)	15.4 (46.30)	35.7 (58.06)
Median	16.7	19.4
Min, Max	-106, 114	-43, 194
Modeled [1] Treatment Effect [2]		
n	34	26
LS Mean Difference (meters) (SE)	6.4 (13.05)	27.0 (13.89)
95% CI	(-19.3, 32.2)	(-0.4, 54.4)
p-value [3]	0.6227	0.0538

Source: Reviewer's Table.
Note: Inference results under the BMN 2.0 mg/kg/qow column pertain to the comparison between BMN 2.0 mg/kg/qow and placebo. Inference results under the BMN 2.0 mg/kg/week column pertain to the comparison between BMN 2.0 mg/kg/week and placebo.
[1]: ANCOVA model adjusted for baseline 6MWT categories (≤ 200 meters and > 200 meters) and age groups (5-11, 12-18, and ≥ 19 years old).
[2]: Treatment effect defined as: (Change from Baseline to Week24, BMN 110) – (Change from Baseline to Week24, Placebo).
[3]: p-value from the ANCOVA model.

The primary efficacy analysis was re-assessed by race. It should be noted that due to the small sample sizes, the Asian, Black or African American, and other race groups were pooled into a single race group labeled 'Non-White'. It was found that the results were consistent across the White and non-White subgroups, and consistent with the whole population for the BMN 110 2.0 mg/kg/qow dose comparison. However, it was found that the BMN 110 2.0 mg/kg/week dose was markedly more efficacious in the White subgroup relative to the Non-White subgroup. This

finding, however, is exploratory in nature and thus cannot be used to support an efficacy claim in the White subgroup population. These results are presented in Table 9 below.

Table 9
Race Subgroup Analysis of 6MWT by Treatment Group – Study MOR-004
(ITT)

	BMN 110	
	2.0 mg/kg/qow (N = 59)	2.0 mg/kg/week (N = 58)
White		
Week 24 Change from Baseline (meters)		
n	35	36
Mean (SD)	11.2 (37.99)	48.4 (59.72)
Median	15.2	31.5
Min, Max	-61, 90	-39, 229
Modeled [1] Treatment Effect [2]		
n	35	36
LS Mean Difference (meters) (SE)	-5.9 (11.25)	31.4 (11.16)
95% CI	(-28.2, 16.3)	(9.4, 53.5)
p-value [3]	0.5981	0.0054
Non-White		
Week 24 Change from Baseline (meters)		
n	24	22
Mean (SD)	18.6 (45.10)	15.7 (50.24)
Median	16.1	10.6
Min, Max	-106, 114	-58, 119
Modeled [1] Treatment Effect [2]		
n	24	22
LS Mean Difference (meters) (SE)	14.4 (16.35)	11.6 (16.65)
95% CI	(-17.9, 46.6)	(-21.2, 44.5)
p-value [3]	0.3810	0.4859

Source: Reviewer's Table.
Note: Inference results under the BMN 2.0 mg/kg/qow column pertain to the comparison between BMN 2.0 mg/kg/qow and placebo. Inference results under the BMN 2.0 mg/kg/week column pertain to the comparison between BMN 2.0 mg/kg/week and placebo.
[1]: ANCOVA model adjusted for baseline 6MWT categories (≤ 200 meters and > 200 meters) and age groups (5-11, 12-18, and ≥ 19 years old).
[2]: Treatment effect defined as: (Change from Baseline to Week24, BMN 110) – (Change from Baseline to Week24, Placebo).
[3]: p-value from the ANCOVA model.

The primary efficacy analysis was re-assessed by age group as well. It was found that the results were consistent across all age subgroups**,** and consistent with the whole population, for the BMN 110 2.0 mg/kg/qow dose comparison. However, it was found that the BMN 110 2.0 mg/kg/week dose was notably more efficacious in the 12-18 year old subgroup relative to the other age

subgroups. This finding, however, is exploratory in nature and thus cannot be used to support an efficacy claim in the 12-18 years old subgroup population. These results are presented in Table 10 below.

Table 10
Age Subgroup Analysis of 6MWT by Treatment Group – Study MOR-004
(ITT)

	BMN 110	
	2.0 mg/kg/qow (N = 59)	2.0 mg/kg/week (N = 58)
5-11 years old		
Week 24 Change from Baseline (meters)		
n	31	32
Mean (SD)	9.3 (40.87)	34.7 (63.08)
Median	15.2	15.8
Min, Max	-61, 114	-51, 229
Modeled [1] Treatment Effect [2]		
n	31	32
LS Mean Difference (meters) (SE)	-11.7 (12.92)	13.8 (12.81)
95% CI	(-37.2, 13.8)	(-11.5, 39.1)
p-value [3]	0.3678	0.2844
12-18 years old		
Week 24 Change from Baseline (meters)		
n	16	16
Mean (SD)	18.5 (44.07)	42.9 (65.10)
Median	12.0	23.0
Min, Max	-106, 90	-58, 194
Modeled [1] Treatment Effect [2]		
n	16	16
LS Mean Difference (meters) (SE)	23.8 (18.12)	48.2 (18.12)
95% CI	(-12.0, 59.6)	(12.4, 84.0)
p-value [3]	0.1914	0.0086
≥19 years old		
Week 24 Change from Baseline (meters)		
n	12	10
Mean (SD)	21.0 (37.91)	29.3 (21.76)
Median	31.4	23.8
Min, Max	-29, 79	0, 72
Modeled [1] Treatment Effect [2]		
n	12	10
LS Mean Difference (meters) (SE)	2.3 (19.84)	10.4 (20.95)
95% CI	(-36.8, 41.5)	(-30.9, 51.8)
p-value [3]	0.9063	0.6194

Source: Reviewer's Table.
Note: Inference results under the BMN 2.0 mg/kg/qow column pertain to the comparison between BMN 2.0 mg/kg/qow and placebo. Inference results under the BMN 2.0 mg/kg/week column pertain to the comparison between BMN 2.0 mg/kg/week and placebo.
[1]: ANCOVA model adjusted for baseline 6MWT categories (≤ 200 meters and > 200 meters).
[2]: Treatment effect defined as: (Change from Baseline to Week24, BMN 110) – (Change from Baseline to Week24, Placebo).
[3]: p-value from the ANCOVA model.

Finally, the primary efficacy analysis was re-assessed by geographic region. It was found that the results were consistent across all regional subgroups**,** and consistent with the whole population, for the BMN 110 2.0 mg/kg/qow dose comparison. However, it was found that the BMN 110 2.0 mg/kg/week dose was markedly more efficacious in the North American subgroup relative to the other regional subgroups. This finding, however, is exploratory in nature and thus cannot be used to support an efficacy claim in the North American subgroup population. These results are presented in Table 11 below.

Table 11
Geographic Region Subgroup Analysis of 6MWT by Treatment Group – Study MOR-004
(ITT)

	BMN 110	
	2.0 mg/kg/qow (N = 59)	2.0 mg/kg/week (N = 58)
North America		
Week 24 Change from Baseline (meters)		
n	16	15
Mean (SD)	21.6 (41.52)	55.9 (68.83)
Median	16.6	45.7
Min, Max	-35, 114	-27, 229
Modeled [1] Treatment Effect [2]		
n	16	15
LS Mean Difference (meters) (SE)	9.4 (17.81)	43.4 (18.16)
95% CI	(-25.8, 44.5)	(7.5, 79.3)
p-value [3]	0.5988	0.0180
Europe		
Week 24 Change from Baseline (meters)		
n	21	25
Mean (SD)	9.1 (38.56)	39.9 (57.67)
Median	7.1	34.8
Min, Max	-60, 73	-51, 194
Modeled [1] Treatment Effect [2]		
n	21	25
LS Mean Difference (meters) (SE)	-7.5 (14.63)	23.2 (13.94)
95% CI	(-36.3, 21.4)	(-4.4, 50.7)
p-value [3]	0.6112	0.0985
Other		
Week 24 Change from Baseline (meters)		
n	22	18
Mean (SD)	13.8 (43.44)	14.1 (42.97)
Median	20.0	14.1
Min, Max	-106, 90	-58, 119
Modeled [1] Treatment Effect [2]		
n	22	18
LS Mean Difference (meters) (SE)	3.6 (16.49)	4.7 (17.26)
95% CI	(-29.0, 36.2)	(-29.4, 38.8)
p-value [3]	0.8279	0.7867

Source: Reviewer's Table.
Note: Inference results under the BMN 2.0 mg/kg/qow column pertain to the comparison between BMN 2.0 mg/kg/qow and placebo. Inference results under the BMN 2.0 mg/kg/week column pertain to the comparison between BMN 2.0 mg/kg/week and placebo.
[1]: ANCOVA model adjusted for baseline 6MWT categories (≤ 200 meters and > 200 meters) and age groups (5-11, 12-18, and ≥ 19 years old).
[2]: Treatment effect defined as: (Change from Baseline to Week24, BMN 110) – (Change from Baseline to Week24, Placebo).
[3]: p-value from the ANCOVA model.

4.2 Other Special/Subgroup Populations

The special subgroup population of clinical interest was the 6MWT distance categories (≤ 200 meters and > 200 meters) at baseline. The primary efficacy analysis was re-assessed in these subgroups, and it was found that the results were consistent across the baseline category subgroups**,** and consistent with the whole population, for the BMN 110 2.0 mg/kg/qow dose comparison. However, it was found that the BMN 110 2.0 mg/kg/week dose was notably more efficacious in ≤ 200 meters subgroup relative to the > 200 meters subgroup. This finding, however, is exploratory in nature and thus cannot be used to support an efficacy claim in the ≤ 200 meters subgroup population. These results are presented in Table 12 below.

Table 12
Baseline 6MWT Category Subgroup Analysis of 6MWT by Treatment Group – Study MOR-004
(ITT)

	BMN 110	
	2.0 mg/kg/qow (N = 59)	2.0 mg/kg/week (N = 58)
≤200 meters		
Week 24 Change from Baseline (meters)		
n	24	23
Mean (SD)	18.0 (45.32)	53.3 (66.74)
Median	17.1	34.8
Min, Max	-106, 114	-58, 229
Modeled [1] Treatment Effect [2]		
n	24	23
LS Mean Difference (meters) (SE)	5.0 (14.69)	40.4 (14.88)
95% CI	(-24.0, 34.0)	(11.0, 69.8)
p-value [3]	0.7324	0.0074
>200 meters		
Week 24 Change from Baseline (meters)		
n	35	35
Mean (SD)	11.6 (37.89)	24.7 (49.42)
Median	15.2	13.9
Min, Max	-61, 90	-51, 119
Modeled [1] Treatment Effect [2]		
n	35	35
LS Mean Difference (meters) (SE)	-2.2 (11.95)	10.8 (11.95)
95% CI	(-25.8, 21.4)	(-12.8, 34.4)
p-value [3]	0.8550	0.3657

Source: Reviewer's Table.
Note: Inference results under the BMN 2.0 mg/kg/qow column pertain to the comparison between BMN 2.0 mg/kg/qow and placebo. Inference results under the BMN 2.0 mg/kg/week column pertain to the comparison between BMN 2.0 mg/kg/week and placebo.
[1]: ANCOVA model adjusted for age groups (5-11, 12-18, and ≥ 19 years old).
[2]: Treatment effect defined as: (change from baseline to Week24, BMN 110) – (change from baseline to Week24, placebo).
[3]: p-value from the ANCOVA model.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Overall, the design of pivotal study MOR-004 was deemed adequate from a statistical perspective, and the applicant's corresponding statistical analysis plan deemed appropriate. There were no statistical review issues identified for this application.

5.2 Collective Evidence

The efficacy of the BMN 110 2.0 mg/kg/week dose was primarily supported by a single trial MOR-004. In this pivotal trial, the BMN 110 2.0 mg/kg/week dose was demonstrated to be superior to placebo with respect to the Week 24 change from baseline in 6MWT distance. The current long term extension data from the ongoing study MOR-005 suggest a reasonably sustained efficacy profile for the BMN 110 2.0 mg/kg/week dose with respect to 6MWT distance. These trial results collectively support the efficacy of VIMIZIM in improving 6MWT distance.

However, currently there is no consensus regarding the clinical meaningfulness of the primary study endpoint of 6MWT distance. Consequently, it may be difficult to determine whether the MOR-004 study results, albeit statistically significant, were clinically significant for the BMN 110 2.0 mg/kg/week dose. The findings in the secondary efficacy endpoint of 3 MSCT did not show clinical or statistical significance. Without supportive data from the 3MSCT, the overall level of evidence for the efficacy of VIMIZIM on morbidity may be questionable. The clinical team also raised an issue regarding efficacious doses due to the fact that the dose finding investigation was inadequate during the clinical development of VIMIZIM. Another potential issue raised pertains to the optimal study duration necessary to observe a treatment effect. These issues will be discussed at the Advisory Committee meeting scheduled on November 18, 2013.

5.3 Conclusions and Recommendations

MPS IVA currently remains as a serious and life threatening condition with an unmet medical need. There appears to be sufficient evidence to support efficacy claims on improving the 6MWT distance for the VIMIZIM (BMN 110; elosulfase alfa) 2.0 mg/kg/week dose, and the claims reflected within the applicant's submitted product labeling are supported by the results shown in this review.

Exploratory subgroup analyses have shown that, separately, subjects who are white, who are 12 to 18 years of age, and who are from North America appeared to respond to the BMN 110 2.0 mg/kg/week dose better than their respective counterparts. An additional subgroup of patients who had a 6MWT distance of $\leq$ 200 meters at baseline were identified during the review cycle. This subgroup, which represents patients with greater morbidity, seems to drive the significant 6MWT efficacy results, and this suggests that these patients may respond better to the BMN 110

2.0 mg/kg/week dose than the patients with less morbidity at baseline. This finding, however, is exploratory in nature and thus cannot be used to support an efficacy claim in the ≤ 200 meters subgroup population. Consequently, if the results regarding this subgroup are to be included in the product labeling, they should be presented in a descriptive manner.

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/s/

BEHRANG VALI
10/25/2013

FREDA COONER
10/25/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 125460	Applicant: Biomarin Pharmaceuticals, Inc.	Stamp Date: 29MAR2013
Drug Name: VIMIZIM (BMN 110; elosulfase alfa)	NDA/BLA Type: Original BLA Priority	Indication: Mucopolysaccharidosis type IVA (MPS IVA; Morquio A Syndrome)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter for RTF	Yes	No	NA	Comments
1	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			This electronic submission was eCTD compliant and of satisfactory quality.
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)		X		There were adequate and complete clinical study reports (CSRs), which were ICH E3 compliant, along with ISS reports submitted. With one pivotal study, there was no ISE section submitted.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups (if applicable).	X			Subgroup analyses for Gender, Race, and Age were presented for the sole Phase 3 pivotal/confirmatory clinical study (i.e. trial MOR-004) in this submission.
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			All data sets provided were of satisfactory quality and were compliant with CDISC data standards (i.e. SDTM and ADaM). Appropriate data definition files in Define.XML and Define.PDF format were included.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____YES____

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			The design utilized for MOR-004 appears appropriate.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			For MOR-004, the endpoints and corresponding methods of analysis were specified in the CSR including the protocol and Statistical Analysis Plan (SAP).
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	There was no formal interim analysis planned for MOR-004.
Appropriate references for novel statistical methodology (if present) are included.			X	The statistical methodology in MOR-004 was not novel per se hence no references were presented.
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			Safety datasets were submitted for each study individually. In addition, ISS datasets were also submitted.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			The sponsor's investigation of the effect of dropouts on the statistical analyses was adequate for study MOR-004.

Background

On March 29, 2013, Biomarin Pharmaceuticals, Inc. submitted this Biologics License Application (BLA) for VIMIZIM (BMN 110; elosulfase alfa) in accordance with Title 21, Parts 314 and 601 of the Code of Federal Regulations. The active pharmaceutical ingredient of BMN 110 [2 mg/kg of body weight to be administered once every week as an intravenous (IV) infusion over approximately four hours] is recombinant human N-acetylgalactosamine-6-sulfatase. Effective on December 28, 2007, the applicant had initiated clinical development of BMN 110 under IND 101,234 in patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A Syndrome), which is the proposed indication; and BMN 110 has been developed specifically to establish safety and efficacy in this patient population. The applicant obtained *Orphan Designation* from the Office or Orphan Products Development (OOPD) on May 15, 2009.

Mucopolysaccharidosis type IVA (MPS IVA) is a rare and inherited disorder resulting from deficiency of the lysosomal enzyme N-acetylgalactosamine-6-sulfatase (GALNS), which degrades glycosaminoglycans (GAGs) including keratan sulfate (KS) and chondroitin-6-sulfate (C6S). With insufficient GALNS, GAGs progressively accumulate in multiple organs and tissues. The pervasive and progressive accumulation of GAGs leads to significant morbidities and multisystemic clinical impairments resulting in diminished functional capacity, decreased

endurance, impaired quality of life, and early mortality. 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. BMN 110 is intended to provide the exogenous enzyme GALNS that will be taken up into the lysosomes and subsequently increase the catabolism of the GAGs KS and C6S. This mechanism of action is hypothesized to reverse the MPS IVA disease process.

There were a series of formal communications and meetings between the applicant and the Division of Gastroenterology and Inborn Errors Products (DGIEP) throughout VIMIZIM's development lifecycle. An advice meeting was held on March 11, 2008, for issues pertaining to the applicant's proposed nonclinical development program. An End of Phase 2 meeting was held on July 28, 2010 to discuss the clinical development program. Biomarin then submitted their single pivotal phase 3 study (trial MOR-004; see below for details) through the Special Protocol Assessment (SPA) regulatory pathway on December 3, 2010. DGIEP subsequently issued a No Agreement letter on January 20, 2011. Biomarin chose not to pursue the SPA any further. Instead they attempted to reach agreements on the outstanding clinical and statistical issues by an additional advice meeting held on July 9, 2012. The pre-BLA meeting between the applicant and DGIEP was held on December 11, 2012 to mainly discuss the format of the BLA submission.

This BLA was submitted electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). The content, including the electronic data sets and labeling information, is located in the Center for Biologics Evaluation and Research (CBER) electronic document room (EDR) at the location: \\cbsap58\m\eCTD_Submissions\STN125460\0000**.**

Brief Overview and Summary of Relevant Trials

This application includes data from six clinical studies, including two completed studies and four ongoing studies. The clinical efficacy and safety of BMN 110 has been primarily evaluated in one trial: a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study (MOR-004), which serves as the single pivotal study in this clinical development program. The supportive data are from the completed phase 1/2 study, MOR-002, two ongoing long-term extension studies (MOR-005 and MOR-100), and two ongoing ancillary phase 2 studies (MOR-007 and MOR-008). The applicant also mentioned a seventh ongoing phase 2 study (MOR-006) that is not included in this application due to incomplete enrollment and limited exposure at the data cutoff time-point.

For study MOR-004, the clinical datasets were compliant to the CDISC/SDTM v.3.1.2 implementation guide standard, and the analysis datasets were compliant to the CDISC/ADaM v.1.0 implementation guide standard. Adequate data definition files (in Define.XML and Define.PDF formats), a reviewer's guide and software code (in .txt format) were also submitted for the study.

The following table presents some information on the single pivotal clinical trial MOR-004 contained in this submission.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Subjects	Patient Diagnosis	Duration of Treatment
Efficacy, Safety and PK; Phase 3	MOR-004	To evaluate the ability of 2.0 mg/kg/week BMN 110 and 2.0 mg/kg/every other week BMN 110 compared with Placebo to enhance endurance in patients 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	Multinational, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel group	BMN 110; 2.0 mg/kg/week and 2.0 mg/kg/every other week; 4 hour IV infusions	Total: 176	MPS IVA patients age 5 years and older who are able to walk ≥ 30 and ≤ 325 meters in the 6MWT	24 weeks

Review Issues

There are no additional statistical requests to the Applicant for the 74-day letter. Moreover, there are no review issues identified so far.

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/s/

BEHRANG VALI
05/14/2013

FREDA COONER
05/15/2013