

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761052Orig1s000**

**OTHER REVIEW(S)**



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** April 27, 2017

**To:** Jean-Marc Guettier, MD, Director  
Division of Gastroenterology and Inborn Errors Products (DGIEP)

**Through:** Silvia Calderon, PhD, Senior Pharmacologist  
Controlled Substance Staff

Martin Rusinowitz, PhD, Senior Medical Officer  
Controlled Substance Staff

**From:** Jovita Randall-Thompson, PhD, Pharmacologist  
Controlled Substance Staff

**Subject:** Brineura intraventricular electrolytes injection, BLA 761052  
**Generic Name (Trade Name):** cerliponase alfa or BMN 190  
**Dosages:** 300 mg administered once every other week as an intracerebroventricular infusion followed by infusion of intraventricular electrolytes over approximately 4.5 hours  
**Formulations:** 150 mg/5 mL (30 mg/mL) of solution per single use vial (2X) and co-packaged with an intraventricular electrolytes injection of 5 mL in a single-dose vial  
**Routes:** intracerebroventricular (ICV)  
**Indication(s):** Treatment for patients with CLN2 disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency  
**IND:** 122742  
**Sponsor:** BioMarin

**Materials Reviewed:**

- BLA 761052, submission date May, 27, 2016
- 3.2.P.1 – Description and Composition
- 3.2.S.1.3 – General Properties
- 3.2.S.1.2 – Structure
- Phase 1/2 Study Reports 190-201 and Phase 4 Study Reports 190-501

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I. Summary

Background

This memorandum responds to a consult request dated 06/02/2016 from the Division of Gastroenterology and Inborn Errors Products (DGIEP) regarding cerliponase alfa, trade name Brineura (BLA 761052). Cerliponase alfa is being developed as an enzyme replacement therapy (ERT) for patients with ceroid lipofuscinosis type 2 (CLN2) disease. Cerliponase alfa is administered intracerebroventricularly at 300 mg once every other week followed by an infusion of intraventricular electrolytes over approximately 4.5 hours.

Cerliponase alfa is a recombinant form of the human tripeptidyl peptidase-1 (TPP1), an enzyme that is deficient in CLN2 patients. The enzyme deficiency is typically associated with a TPP1 gene mutation. The deficiency of TPP1 results in the accumulation of neurotoxic lysosomal storage material in CNS cells which results in an infantile and toddler age onset of developmental symptoms. CLN2 is a rapidly progressive and fatal neurodegenerative lysosomal storage disease characterized by normal development until age 2 to 4 years followed with neurocognitive decline including seizures, ataxia, deterioration of speech, loss of motor skills, progressive cognitive and developmental decline, loss of vision, and eventual progression to a vegetative state and death. It is also known as classical late-infantile CLN2, cLINCL, or Jansky-Bielschowsky disease and is categorized as a form of Batten Disease.

As an enzyme replacement therapy, cerliponase alfa is administered directly into the brain to slow the progression of the disease. The primary endpoint of the Applicant’s pivotal trial uses an adapted CLN2 disease-specific rating scale assessing motor and language function, in comparison with natural history data after 48 weeks of treatment.

Cerliponase alfa is not a scheduled substance under the Controlled Substances Act (CSA) and it is not chemically or pharmacologically similar to a known drug of abuse that is scheduled. It is directly injected into the brain and is CNS active. The Sponsor did not perform an abuse potential assessment;

however, nonclinical and clinical data from studies with cerliponase alfa was evaluated by CSS from an abuse prospective given that it is a CNS active substance.

## Conclusions

1. CSS conducted a review of the adverse events (AEs) collected during Phase 1/2 trials. No abuse related AEs were reported with cerliponase alfa. Movement-related (i.e., increased jitteriness, head drops, abnormal movements, myoclonus) were reported, but not accompanied by any AEs typically associated abuse (i.e., sedation, euphoric or elevated mood), thus alone these are not considered a signal of abuse in this case.
2. Based on cerliponase alfa's AE profile, and subject to completion of the Agency's safety review, an abuse assessment of cerliponase alfa is not required, and no section 9 is necessary for the prescribing information.

## Recommendations

1. Based on the lack of abuse potential signals, CSS recommends not to include Section 9 DRUG ABUSE AND DEPENDENCE in the prescribing information for Brineura (cerliponase alfa) product label.

## II. Discussion

Based on regulations under the Controlled Substance Act (CSA), if a marketing application is submitted for a drug that has a stimulant, depressant, or hallucinogenic effect on the central nervous system (21 U.S.C. 811(f)) also see 21 CFR 314.50(d)(5)(vii)), an abuse assessment is necessary because these effects are signals indicating that the drug may have abuse potential. To determine if an abuse assessment of cerliponase alfa should be conducted, nonclinical findings and clinical AEs were evaluated for any signals of abuse.

Cerliponase alfa is new molecular entity, structurally not similar to any scheduled drugs. It is a recombinant form of the human TPP1 enzyme, administered as an inactive pro-enzyme until taken up into the lysosome. The recombinant TPPI enzyme is expected to restore TPP1 enzyme activity in the CNS. The molecule is distributed widely in the CNS after ICV administration, and is detected proportionally lower in the systemic circulation; specifically the CSF  $C_{max}$  was 100- to 1000-fold higher than that in the plasma following a single dose.

Mechanistically cerliponase alfa activation is confined to the lysosome. The pro-enzyme is trafficked to the lysosome, where it is cleaved in an acidic environment, yielding a 20 kDa (195 amino acid) inactive fragment and a 46 kDa active protease, an enzyme that digest proteins by cleaving peptide bonds. Thus, in terms of receptors/transporters associated with abuse potential, due to cerliponase alfa's mechanism, the drug will not bind to or directly activate CNS receptors (dopamine, norepinephrine, serotonin, GABA, acetylcholine, opioid, NMDA, or cannabinoid receptors) associated with abuse.



Although cerliponase alfa may not directly activate abuse associated receptor sites, it could indirectly produce abuse effects (e.g. stimulant, depressant, or hallucinogenic effects on the central nervous system). To determine whether this is likely to be the case with cerliponase alfa, safety findings from each of the below mentioned studies were assessed for abuse-related signals.

The nonclinical program consisted of 8 in vivo studies, including:

3 single-dose studies-

- beagles (Study 0190-08-034/ 8, 33, or 128 mg IT-C) and
  - monkeys (Study 0190-09-071/ 5, 14, or 20 mg ICV; Study BMN190-11-046/ 14 mg IT-L), and
- 5 repeat-dose studies-
- TPP1 KO mouse (Study BMN190-12-010/ 3 daily doses of 0.27 mg and 0.4 mg IT-L) and
  - TPP1-null and WT Dachshund dogs (Study 0190-09-066/ 32 mg IT-C; Study 0190-10-077/ 0, 4, or 16 mg ICV, IT-L, and IT-C; Study (BMN190-12-009/ up to 48 mg ICV, IT-L, and IT-C; Study BMN190-12-027/ up to 16 mg ICV, IT-L, and IT-C).

According to the Sponsor, given the small number of patients eligible for a clinical trial, directed efforts were made to understand the dosing regimen (dose level, route and frequency), translatable pharmacodynamic (PD) endpoints and safety of cerliponase alfa prior to the start of the clinical trial.

This marketing application includes safety data from 2 clinical studies:

- 190-201 is a completed first-in-human Phase 1/2, open-label, dose escalation, multinational, study of cerliponase alfa administered via an ICV access device for at least 48 weeks at 300 mg every other week.
- 190-202 is an ongoing Phase 1/2 open-label extension study which enrolled subjects who completed treatment in 190-201.

A review of these findings did not reveal any abuse-related behavioral signals among the nonclinical findings (PK/PD and toxicity data), nor were there any clinical AEs reported after cerliponase alfa ICV administration that were abuse-related. These findings do not support the position that cerliponase alfa indirectly produces abuse-related effects.

Based on the information under the current BLA, cerliponase alfa does not induce a behavioral profile or characteristics indicative of abuse, and thus it does not potentially pose any abuse risk. There was a lack of psychoactive effects (e.g., euphoria, stimulant, depressant, hallucinations, or changes in mood) produced by the biologic. Thus, an abuse assessment on the drug is not warranted.

## 1. Chemistry

Cerliponase alfa is a recombinant human tripeptidyl peptidase-1 (rhTPP1) pro-enzyme. It is secreted by recombinant CHO cells as an enzymatically-inactive, 544 amino acid zymogen (pro-enzyme) with a calculated isotope average molecular mass of 59.31 kDa (including three disulfide bridges).

The primary amino acid sequence for cerliponase alfa is identical to the human tripeptidyl peptidase-1 (hTPP1) zymogen. The protein (cerliponase alfa) is secreted by the production cells as a pro-enzyme (zymogen) that does not have enzymatic activity at neutral pH. The pro-enzyme must be taken up by

the Cation Independent Mannose-6-Phosphate Receptor (CI-MPR; also known as M6P/IGF2 receptor) and translocated to the lysosomes. It is enzymatically inactive *in vivo* until it is activated into a mature protease through a series of proteolytic cleavages in the lysosome. The activated proteolytic enzyme (rhTPP1) cleaves tripeptides from the N-terminus of polypeptides that accumulate in the lysosome. Biological activity of rhTPP1 is measured by enzymatic activity, cellular uptake, and glycosylation profiling.

Cerliponase alfa is a clear to slightly opalescent and colorless to pale yellow solution. The recommended dosage is 300 mg administered once every other week as an ICV infusion followed by infusion of an intraventricular electrolytes injection (clear to colorless solution) over approximately 4.5 hours. Each infusion consists of 10 mL of cerliponase alfa (150 mg/5 mL (30 mg/mL) solution followed by 2 mL of Intraventricular Electrolytes.

Cerliponase alfa is introduced into the cerebrospinal fluid (CSF) via a reservoir or catheter (intraventricular access devices) implanted in a lateral ventricle of the brain. Thus, cerliponase alfa is administered by, or under the direction of a physician knowledgeable in intraventricular administration. Intraventricular access devices used in the cerliponase alfa clinical trial include the Codman® HOLTER RICKHAM Reservoirs (Part Numbers: 82-1625, 82-1621, 82-1616) with the Codman® Ventricular Catheter (Part Number: 82-1650). Cerliponase alfa is intended to be administered with the B Braun Perfusor® Space Infusion Pump System at a delivery rate of 2.5 mL/hr with delivery accuracy of +/- 1 mL/hr.

## 2. Pharmacokinetics

A single exposure (or Day 1) to cerliponase alfa at 300 mg measured in the CSF had a median (min, max):

- $C_{max}$  of 1260 (359, 4380)  $\mu\text{g/mL}$ ,
- $T_{max}$  of 4.50 (4.25, 5.75) hours
- $t_{1/2}$  of 6.15 (5.49, 16.3) hours

A single exposure (or Day 1) to cerliponase alfa at 300 mg measured in the plasma had a median (min, max):

- $C_{max}$  of 1.28 (0.176, 3.87) hours
- $T_{max}$  of 12.0 (4.25, 24.5) hours
- $t_{1/2}$  of 6.15 (5.49, 16.3) hours

## 3. Pre-clinical Studies

The cerliponase alfa nonclinical assessment included single dose studies in normal animals (beagle dog and cynomolgus monkey) and repeat dose studies in normal and disease models of CLN2 (TPP1-knockout [KO] mouse, and wild type (WT) and TPP1-null Dachshund dog). According to the Sponsor, the TPP1 amino acid sequence identity between the human and mouse, dog and monkey is 91%, 95% and 98%, respectively (Nonclinical Overview, page 3). Because CLN2 disease affects pediatric

patients, most of the pharmacology, pharmacokinetics, and toxicology evaluations of BMN 190 were characterized in normal and disease animal models.

To target the CNS, all animal studies administered cerliponase alfa into the CSF compartment using ICV administration catheters and dosing ports (via intrathecal-cisternal (IT-C), intrathecal-lumbar (IT-L) administration) that are similar in principle and design to the CNS delivery system used in the clinical setting. The animal PD studies (Study BMN190-12-010, Study 0190-09-066, Study 0190-10-077, BMN190-12-009, Study BMN190-12-027) indicated that cerliponase alfa administered via the CSF distributes widely in the CNS where it is taken up to the lysosome and activated.

To evaluate the safety of cerliponase alfa, toxicity was evaluated in six in vivo studies, including the two single dose studies in cynomolgus monkeys (Study 0190-09-071, Study BMN190-11-046) and the four repeat-dose studies in dogs (Study 0190-09-066, Study 0190-10-077, BMN190-12-009, Study BMN190-12-027).

- In monkeys, multiple recovery periods of 3, 7 and 14 days enabled a longitudinal assessment of potential early and late CNS findings or neuronal toxicity after a single 14 mg cerliponase alfa administration. No cerliponase alfa-related CNS or systemic findings were observed throughout the recovery period. The NOAEL for BMN 190 when administered as a single ICV infusion (~4-hour infusion) to monkeys was 20 mg, the highest dose tested. There were no cerliponase alfa - related toxicities observed in this program.
- CNS and CV safety pharmacology parameters were assessed in the repeat dose studies in WT and TPP1-null Dachshund dogs. The NOAEL was 32 mg BMN 190. The NOAEL in dogs given cerliponase alfa every two weeks for 9 months was 16 mg/dose. Neurological examinations were performed monthly on Dachshund dogs (WT and TPP1-null) chronically administered cerliponase alfa for up to 18 months. No clinical signs were observed in either WT or TPP1-null dogs indicative of cerliponase alfa-related systemic or CNS adverse effects. Hypersensitivity was reported in male and female WT and TPP1-null dogs given 32 mg of cerliponase alfa in a 3-month repeat dose study. This AE was reported as unrelated to cerliponase alfa. These reactions are common after human enzyme replacement therapy (ERT) or heterologous human protein administration to dog models of disease (Shull, 1994<sup>1</sup>); (Brooks, 1999<sup>2</sup>) and are likely related to anti-human protein antibody formation.

The safety and efficacy profile of cerliponase alfa, as assessed in the nonclinical program, supported the chronic ICV administration of cerliponase alfa at doses up to 960 mg administered every other week to CLN2 pediatric patients.

No other significant toxicity effects were reported, and no abuse-related effects were found.

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<sup>1</sup> Shull, RM, Kakkis, ED, McEntee, MF, Kania, SA et. al. Enzyme Replacement in a Canine Model of Hurler Syndrome. Proc Natl Acad Sci USA 91[26], 12937-12941. 1994.

<sup>2</sup> Brooks, DA. Immune response to enzyme replacement therapy in lysosomal storage disorder patients and animal models. Mol Genet Metab 68[2], 268-275. 1999.

#### 4. Treatment Emergent Adverse event profile through all Phases of development

The following is a review of those CNS-related (nervous system disorders and psychiatric disorders) treatment emergent AEs (TEAEs) reported in Phase 1/2 open-label Study Reports 190-201 (N=23 (completers); 30, 100 and 300 mg of cerliponase alfa administered) and 190-202 (300 mg of cerliponase alfa administered). These two Phase 1/2 studies assessed doses of cerliponase alfa in CLN2 patients age 3 to 16 years.

For those abuse-related TEAEs reported in Phase 1/2 Study Report 190-201<sup>3</sup> among the system organ categories, nervous system disorders and psychiatric disorders, the following was reported:

Event	Total count	Total counts per dose			Serious adverse event
		30 mg	100 mg	300 mg	
Deterioration of epilepsy	7	3	0	4	No
Dystonia	2	0	0	2	No
Increased jitteriness	12	0	4	8	No
Increase Head drops	4	0	0	4	No
Abnormal movements	6	0	0	6	No
Headache	8	0	0	8	No
Staring	6	0	0	6	No
Myoclonus	7	0	0	7	No
Irritability	4	0	0	4	No
Pain in head	4	0	0	4	No
Absence	1			1	
Seizure (epileptic/ epilepsy, atypical, first grand mal, multiple astatix, atonic, increase	61	2	2	57	No

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<sup>3</sup> Study 190-201 was titled, *A Phase 1/2 Open-Label Dose-Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Intracerebroventricular BMN 190 in Patients with Late-Infantile Neuronal Ceroid Lipofuscinosis (CLN2) Disease*. The study's primary objectives were to evaluate the safety, tolerability and effectiveness of BMN 190 (cerliponase alfa) administered to subjects diagnosed with CLN2 disease. Cerliponase alfa solution, given at escalating doses of 30 mg, 100 mg, and 300 mg, was administered via an implanted ICV access device (reservoir and cannula) continuously at a rate of 2.5 mL/hour for approximately 4 hours. The infusion was given every 14 days in the morning after a minimum fast of 2 hours. Each subject received at least 4 weeks of treatment and a safety clearance before moving to the next higher dose level. The motor/gait and language scale score was the primary efficacy outcome measure. Twenty-three subjects completed the study. Concomitant medications use was minimal (4% (1 subject) of overall sample population (N=24), see Study 190-201 Report, page 267, Table 14.1.8.2).

For those abuse-related TEAEs reported in Phase 1/2 Study Report 190-202<sup>4</sup> among the system organ categories, nervous system disorders and psychiatric disorders, the following was reported:

Event	Total count/ 300 mg	Serious adverse event
Deterioration of epilepsy	4	No
Dystonia	3	No
Increased jitteriness	12	No
Increase Head drops	4	No
Abnormal movements	6	No
Headache	18	No
Pain in the head	4	No
Staring	6	No
Myoclonus	6	No
Irritability	4	No
Deterioration of gait	2	No
Seizure (epileptic/ epilepsy, atypical, first grand mal, multiple astatix, atonic, increase	64	No

There were abnormal movement-related AEs reported with cerliponase alfa mainly at the highest dose of 300 mg. Drugs such as cocaine and amphetamine known to be abused that have stimulant effects on the CNS and mobility also tend to elevate a person's endurance and energy, these characteristics do not appear to apply to cerliponase alfa. The movement-related AEs do not appear to be stimulant-like. The other CNS AEs reported are more dysphoric (i.e., headache, irritability, seizure) in nature and there weren't any abuse-related symptoms reported, such as euphoria, sedation or hallucinations, symptoms which are typically reported with drugs having abuse potential. There were no adverse events reported as serious, and there were no subjects who discontinued any study due to an AE. Furthermore, there were no incidences of unaccounted medication, deaths or overdoses.

The AE profile of cerliponase alfa demonstrates and supports that it has no abuse potential.

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<sup>4</sup> Study 190-202 was titled, *A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 190 in Patients with CLN2 Disease*. The study's primary objectives were to evaluate the long-term safety and effectiveness (change in motor and language subscales) of BMN 190 (cerliponase alfa) given at of 300 mg (ICV infusion every 14 days in the morning after fasting for at least 2 hours) to CLN2 subjects who complete Study 190-201. The dose and regimen for this study (190-202) are based on the results of Study 190-201. Twenty-three subjects completed the study. Concomitant medications use included 25% (6 subjects) use of non-therapeutic products (undefined) and 4% (1 subject) use of an anesthetic among the overall sample population (N=24), see Study 190-202 Report, page 257, Table 14.1.8.2).

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JOVITA F RANDALL-THOMPSON  
04/27/2017

SILVIA N CALDERON  
04/27/2017

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

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BLA # 761052  
Product Name: Brineura (cerliponase alfa)

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PMR Description: 3207-1 Conduct an observational post approval safety study (Study 190-501) to evaluate the long-term safety of Brineura (cerliponase alfa) in patients with neuronal ceroid lipofuscinosis Type 2 (CLN2 disease), and further assess the occurrence of serious hypersensitivity reactions (including anaphylaxis), serious cardiovascular adverse events, and serious device related complications in patients followed for a minimum of ten years. In addition, this study will evaluate the effects of serious adverse events on patient performance on the CLN2 motor and language clinical scales.

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PMR Schedule Milestones:	Final Protocol Submission:	12/2017
	Interim Report Submissions:	06/2018
		06/2019
		06/2020
		06/2021
		06/2022
		06/2023
		06/2024
		06/2025
		06/2026
		06/2027
		06/2028
		06/2029
		06/2030
		06/2031
		06/2032
		06/2033
		06/2034
		06/2035
	Study Completion:	12/2036
	Final Report Submission:	12/2037

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected

- ☐ Theoretical concern  
☐ Other

CLN2 is a progressive, neurodegenerative disease of early childhood for which there is no available therapy and an unmet medical need. Brineura (cerliponase alfa) slows down the progression of CLN2. The Brineura (cerliponase alfa) clinical program evaluated safety for 48 weeks. The treatment is intended to be given for a lifetime. It is important to collect reliable safety data for labeling the safety of Brineura beyond 48 weeks, particularly as it relates to immunogenicity and device-related complications.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal is to assess signals of serious risks of hypersensitivity reactions, cardiovascular adverse events, device related complications, and adverse effects on patient performance on the CLN2 motor and language scales resulting from use of Brineura (cerliponase alfa).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)  
☐ Animal Efficacy Rule  
☐ Pediatric Research Equity Act  
☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?  
☒ Assess signals of serious risk related to the use of the drug?  
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk



☒ **Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
**Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk

☐ **Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct an observational post approval safety study (Study 190-501) to evaluate the long-term safety of Brineura (cerliponase alfa) in patients with neuronal ceroid lipofuscinosis Type 2 (CLN2 disease), and further assess the occurrence of serious hypersensitivity reactions (including anaphylaxis), serious cardiovascular adverse events, and serious device related complications in patients followed for a minimum of ten years. In addition, this study will evaluate the effects of serious adverse events on patient performance on the CLN2 motor and language clinical scales.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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BLA # 761052  
Product Name: Brineura (cerliponase alfa)

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PMR/PMC Description: 3207-2 Develop and validate a cellular uptake assay with sensitivity adequate to evaluate the neutralizing capacity of anti-drug antibodies of Brineura (cerliponase alfa) detected in patient serum and CSF samples.

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Study Completion: 10/2018  
Final Report Submission  
(including Assay Validation Report/SOP): 12/2018

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The validated sensitivity of the Sponsor’s existing Nab assay is poor, making it impossible to ascertain if the neutralizing capacity of the ADAs has been accurately assessed. Therefore, the neutralizing capacity of the ADAs should be evaluated, since neutralization of BMN190 uptake is likely to impact the safety and efficacy of this therapy for an otherwise fatal disease.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☒ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Develop and validate a cellular uptake assay with sensitivity adequate to evaluate the neutralizing capacity of anti-drug antibodies of Brineura (cerliponase alfa) detected in patient serum and CSF samples.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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☐ Meta-analysis or pooled analysis of previous studies/clinical trials

☒ Immunogenicity as a marker of safety

☐ Other (provide explanation)

---

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)

☐ Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

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☐ Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?

☒ Are the objectives clear from the description of the PMR/PMC?

☒ Has the applicant adequately justified the choice of schedule milestone dates?

☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

☐ There is a significant question about the public health risks of an approved drug

☐ There is not enough existing information to assess these risks

☐ Information cannot be gained through a different kind of investigation

☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

☐ The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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BLA # 761052  
Product Name: Brineura (cerliponase alfa)

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PMR Description: 3207-3 Develop and validate an assay to measure the capacity of anti-drug antibodies detected in the patient serum and CSF samples to neutralize Brineura (cerliponase alfa) enzymatic activity using conditions mimicking lysosomal environment.

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PMR Schedule Milestones: Study Completion: 10/2018  
Final Report Submission  
(including Assay Validation Report/SOP): 12/2018

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

While cellular uptake of the drug is critical to the mechanism of action (MoA) of BMN190, the auto-activation of inactive and subsequent enzymatic activity are also critical components of the MoA. The enzymatic activity of BMN190 can potentially be affected by Nabs that could either prevent activation of the pro-enzyme to its active, mature form or bind to the catalytic site of the enzyme. In order to fully evaluate the potential neutralization of the product's activity, the Sponsor should develop additional assays that can measure the formation of ADAs capable of neutralizing the enzymatic activity of the drug after its uptake into the lysosome.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The validated sensitivity of the Sponsor's existing Nab assay is poor, making it impossible to ascertain if the neutralizing capacity ADAs has been accurately assessed. Therefore, the neutralizing capacity of the ADAs should be evaluated, since neutralization of BMN190 uptake is likely to impact the safety and efficacy of this therapy for an otherwise fatal disease.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☒ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Develop and validate an assay to measure the capacity of anti- drug antibodies detected in the patient serum and CSF samples to neutralize Brineura (cerliponase alfa) enzymatic activity using conditions mimicking lysosomal environment.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☒ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)
- 

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- 
- ☐ Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 
- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed



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**PMR/PMC Development Coordinator:**

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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BLA # 761052  
Product Name: Brineura (cerliponase alfa)

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PMR Description: 3207-4 Conduct an immunogenicity study to evaluate the relationship between Brineura (cerliponase alfa) treatment and neutralizing anti-drug antibody (ADA) status. ADA-positive serum and CSF samples detected in Studies 190-201 and 190-202 will be re-tested with validated neutralizing antibody assays (developed in PMRs 3207-2 and 3207-3) for enzyme neutralization and cellular uptake, and patient serum and CSF samples will be collected and analyzed for immunogenicity assessment in Study 190-203.

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PMR Schedule Milestones:	Final Protocol Submission:	06/2018
	Study Completion:	06/2023
	Final Report Submission:	12/2023

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1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The capacity of the ADAs to neutralize both cellular uptake and enzymatic activity should be evaluated, since neutralization of either of these aspects of BMN190 function has the potential to impact the efficacy and safety of this therapy. However, the validated sensitivity of Sponsor’s Nab assay for cellular uptake is poor, making it impossible to ascertain if the capacity of ADAs to neutralize uptake has been accurately assessed. Moreover, the Sponsor has not developed and validated an assay to assess ADA neutralization of enzymatic activity. Therefore, confirmed ADA positive serum and CSF samples from the clinical trials should be re-tested with the Nab assays developed and validated under 3207-2 and 3207-3.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☒ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct an immunogenicity study to evaluate the relationship between Brineura (cerliponase alfa) treatment and neutralizing anti-drug antibody (ADA) status. ADA-positive serum and CSF samples detected in Studies 190-201 and 190-202 will be re-tested with validated neutralizing antibody assays (developed in PMRs 3207-2 and 3207-3) for enzyme neutralization and cellular uptake, and patient serum and CSF samples will be collected and analyzed for immunogenicity assessment in Study 190-203.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials

- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
  - ☒ Immunogenicity as a marker of safety
  - ☐ Other (provide explanation)
- 

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

- 
- ☐ Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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BLA # 761052  
Product Name: Brineura (cerliponase alfa)

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PMR Description: 3207-5 Conduct a clinical trial (Study 190-203) to evaluate the short-term safety of Brineura (cerliponase alfa) in CLN2 patients below the age of 2 years. The trial will assess the risks of serious hypersensitivity reactions, and serious device related complications with short-term use. Perform a root-cause analysis on any device related complications and/or failures including, but not limited to, an analysis of the material integrity of the intraventricular access device reservoir. In addition, this trial will evaluate the effects of serious adverse events on patient performance on the CLN2 motor and language clinical scales.

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Final Protocol Submission:	07/2017
Interim Report Submission:	12/2018
Interim Report Submission:	12/2019
Interim Report Submission:	12/2020
Interim Report Submission:	12/2021
Trial Completion:	12/2022
Final Report Submission:	12/2023

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this study is to identify unexpected risks of serious hypersensitivity reactions, serious device related complications, and serious adverse effects on patient performance on the CLN2 motor and language scales with short-term use of Brineura (cerliponase alfa), particularly in patients below the age of 2 years.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a clinical trial (Study 190-203) to evaluate the short-term safety of Brineura (cerliponase alfa) in CLN2 patients below the age of 2 years. The trial will assess the risks of serious hypersensitivity reactions, and serious device related complications with short-term use. Perform a root-cause analysis on any device related complications and/or failures including, but not limited to, an analysis of the material integrity of the intraventricular access device reservoir. In addition, this trial will evaluate the effects of serious adverse events on patient performance on the CLN2 motor and language clinical scales.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
  - ☐ Immunogenicity as a marker of safety
  - ☐ Other (provide explanation)
- 

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

- 
- ☐ Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)



## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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BLA # 761052  
Product Name: Brineura (cerliponase alfa)

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PMC Description: 3207-6 For patients in Studies 190-203 and 190-501, obtain a blood sample prior to cerliponase alfa treatment to determine TPP1 enzyme activity at baseline and collect the *TPP1* genotype information. Evaluate the association of enzyme activity with efficacy and safety data from PMR 3207-1 and PMR 3207-5. Derive the predicted protein function from the *TPP1* genotype for each patient, and compare efficacy and safety in patients with different *TPP1* genotypes based on their predicted protein function. In addition, perform similar analyses using a combined dataset from 4 clinical studies, including Studies 190-203, 190-501, 190-201 and 190-202.

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Final Report Submission:

12/2037

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1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

CLN2 is a progressive, neurodegenerative disease of early childhood for which there is no available therapy and an unmet medical need. Brineura (cerliponase alfa) slows down the progression of CLN2. Due to the rarity of the disease and the small size of the patient population studied in the Brineura clinical program, efficacy analyses relating the genotype and residual protein function to clinical response could not be conducted. Such analyses could be conducted only after collection of additional data points across multiple patients, for longer periods of time. They have potential to further guide and optimize dosing, and help to better understand the impact of immunogenicity long term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The *TPP1* genotype of the patients could impact the efficacy and safety of cerliponase alfa. However, efficacy evaluation has been performed using *TPP1* genotype grouping based on the presence of two common alleles. Rather, grouping of *TPP1* genotype based on expected protein function as predicted by the mutation type of the alleles should better reflect patient's response to cerliponase alfa therapy. Because the original BLA contained only a small sample size, a larger database including data from all studies is necessary for the data analysis.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

For patients in Studies 190-203 and 190-501, obtain a blood sample prior to cerliponase alfa treatment to determine TPP1 enzyme activity at baseline and collect the *TPP1* genotype information. Evaluate the association of enzyme activity with efficacy and safety data from PMR 3207-1 and PMR 3207-5. Derive the predicted protein function from the *TPP1* genotype for each patient, and compare efficacy and safety in patients with different *TPP1* genotypes based on their predicted protein function. In addition, perform similar analyses using a combined dataset from 4 clinical studies, including Studies 190-203, 190-501, 190-201 and 190-202.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

---

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

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- ☒ Other  
A larger dataset is necessary for the data analysis.

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5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

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BLA #	761052
Product Name:	Brineura (cerliponase alfa)

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PMC #1 Description:	3207-7 To add cellular uptake as a release assay for drug product, Brineura (cerliponase alfa), and establish an appropriate acceptance criterion when a statistically significant number of drug product lots is tested.
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PMC Schedule Milestones:	Final Report Submission:	06/2019
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PMC #2 Description:	3207-8 To develop and validate an additional identity test method for the Intraventricular Electrolytes Injection (b) (4)
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PMC Schedule Milestones:	Final Report Submission:	09/2017
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PMC #3 Description:	3207-9 To revalidate RP-HPLC and SEC-HPLC release and stability assays using impurities generated by subjecting Brineura (cerliponase alfa) to stressed stability conditions.
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PMC Schedule Milestones:	Final Report Submission:	12/2017
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- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☒ Other

(b) (4)  
[REDACTED]. In order to improve control of BMN 190 drug product, the sponsor needs to determine its cellular uptake as part of the drug product release protocol.

(b) (4)  
[REDACTED]

The sponsor validated the chromatographic assays RP-HPLC and SEC-HPLC and demonstrated their suitability to properly quantify the main peak and the low levels of impurities present at release. However, because these assays are stability indicating additional validation is necessary to confirm their suitability to accurately quantify the different levels of impurities formed during storage.

2. Describe the particular review issue and the goal of the study.

BioMarin should measure cellular uptake of the final product to ensure consistency in this quality attribute. This change in the DP release protocol will allow BioMarin to confirm that they have appropriate control on their manufacturing process.

(b) (4)  
[REDACTED]

The sponsor should subject Brineura (cerliponase alfa) samples to forced degradation conditions and use these samples to confirm the accuracy and precision of the RP-HPLC and SEC-HPLC assays when the tested samples contain impurities formed during storage.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☒ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the agreed-upon study:

To add cellular uptake as a release assay for drug product, Brineura (cerliponase alfa), and establish an appropriate acceptance criterion when a statistically significant number of drug product lots is tested.

To develop and validate an additional identity test method for the Intraventricular Electrolytes Injection (b) (4)

To revalidate RP-HPLC and SEC-HPLC release and stability assays using impurities generated by subjecting Brineura (cerliponase alfa) to stressed stability conditions.

5. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JENNY N DOAN  
04/26/2017



**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)**

**Epidemiology: ARIA Sufficiency Memo  
Version: 2016-02-11**

Date:	April 26, 2017
Reviewer / Acting TL:	Kira Leishear White, PhD, MS Division of Epidemiology I
Acting Deputy Director:	Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Subject:	Active Risk and Identification Analysis (ARIA) Sufficiency Memo
Drug Name(s):	Brineura (cerliponase alfa)
Application Type/Number:	BLA 761052
Applicant/sponsor:	BioMarin
OSE RCM #:	2017-720

**EXECUTIVE SUMMARY** (place "X" in appropriate boxes)**Memo type**

-Initial	X		
-Interim			
-Final			
<b>Source of safety concern</b>			
-Peri-approval	X		
-Post-approval			
<b>Is ARIA sufficient to help characterize the safety concern?</b>			
<b>Safety outcome:</b>	Serious hypersensitivity reactions	Vital sign abnormalities	Device related complications
-Yes			
-No	X	X	X
<b>If "No", please identify the area(s) of concern.</b>			
-Surveillance or Study Population	X	X	X
-Exposure	X	X	X
-Outcome(s) of Interest	X	X	X
-Covariate(s) of Interest			
-Surveillance Design/Analytic Tools	X	X	X

**1. BACKGROUND INFORMATION****1.1. Medical Product**

Cerliponase alfa is a recombinant human replacement for tripeptidyl peptidase-1 (TPP1) delivered through an intracranial route by means of an implanted device. TPP1 is a lysosomal enzyme responsible for cleaving tripeptides; its absence leads to substrate accumulation in the CNS which is responsible for the loss of neurologic function and reduced lifespan. The proposed indication is to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as TPP1 deficiency. Brineura is the first drug in the class and is a drug-device combination product comprised of a syringe pump, intraventricular catheter and reservoir. This is required because it cannot cross the blood brain barrier. Brineura has been granted both orphan drug and breakthrough therapy designation.

CLN2 disease is a rare inherited neurodegenerative disorder characterized by accumulation of storage material (lipopigment) in lysosomes of neural tissues, with a relatively predictable phenotype of progressive, inexorable, neurological deterioration resulting in severe neurological deficits by 6 years of age and death in adolescence.<sup>1</sup> Approximately 250-350 patients in the United States have CLN2 disease.<sup>1</sup> Most children are diagnosed around the age of 3 years. There is currently no medical treatment available for CLN2 disease.

<sup>1</sup> Roman D. Division Director Summary Review for cerliponase alfa. April 25, 2017 (draft).

According to the draft label, Brineura (cerliponase alfa) is administered into the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter (intraventricular access device). The intraventricular access device is implanted prior to the first infusion, which is recommended for 5-7 days after device implantation. Only physicians knowledgeable in intraventricular administration should administer Brineura. Brineura must be administered using aseptic technique to reduce the risk of infection. The recommended dosage of Brineura in pediatric patients 3 years of age and older is 300 mg administered once every other week by intraventricular infusion in a healthcare setting. In the label, Warnings and Precautions include 1) Intraventricular Access Device-Related Complications, 2) Cardiovascular Adverse Reactions (including vital sign abnormalities), and 3) Hypersensitivity Reactions. The Division of Gastroenterology and Inborn Errors Products (DGIEP) determined the need for a post-marketing observational safety study during a meeting on April 12, 2017.

Limited clinical data exist for both safety and efficacy endpoints from single arm trials, with only 24 patients treated with Brineura in the safety database with only about 2 years of data, although the drug will be administered throughout a patient's lifetime.

Efficacy of Brineura was assessed in a single-arm, open-label clinical trial that enrolled 24 patients  $\geq$  3 years of age with symptomatic CLN2 disease and was compared with an independent historical control group with similar but not identical baseline characteristics.<sup>1</sup> Efficacy assessments were based on an observer reported outcome, the CLN2 Activity Score. Brineura treatment was associated with a slowing in the progression of motor deterioration relative to a matched control cohort, which accounted for differences in baseline characteristics. The Division Director concluded that efficacy has been established, a slowing of disease progression, specifically the loss in motor function. Because of no existing therapy for CLN2 disease, a severe neurodegenerative disease, the available clinical data present a favorable risk-benefit profile.

## 1.2. Describe the Safety Concerns

DGIEP determined a need for a post-marketing observational study to evaluate the following safety concerns: 1) serious hypersensitivity reactions (including anaphylaxis), 2) vital sign abnormalities, and 3) device related complications.

Prior to the initiation of human studies of Brineura, infusion related hypersensitivity reactions (including anaphylaxis) were identified as key safety issues as they commonly occur with enzyme replacement therapy and can be life-threatening.<sup>2</sup>

The safety population in the clinical studies was comprised of 24 patients who received at least one dose of Brineura. Subjects in the trial received Brineura for 0.1 to 107.6 weeks, with most of the patients (N=23) receiving Brineura for at least 48 weeks, and half of the patients (N=12) receiving Brineura for at least 96 weeks. The studies were single-arm trials so it was sometimes unclear whether the adverse events were due to the treatment, the device, or the underlying disease.

In the clinical studies, 11 serious adverse events in 8 patients were assessed as related to Brineura and were classified as **hypersensitivity or infusion related reactions**. Four patients experienced serious adverse events (SAEs) which required hospitalization or an extended hospital stay due to the adverse reaction. The reactions included pyrexia, vomiting, hypertension, hypotension, pleocytosis, cytopenia, and seizure. The reactions resolved over time or with administration of

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<sup>2</sup> Hart E, Baum V. Safety Review for cerliponase alfa. April 19, 2017 (draft).

antipyretics, antihistamines, and/or corticosteroids, and no patients discontinued treatment as a result of the reactions. No anaphylaxis cases were observed in the clinical studies; however, the draft labeling for Brineura specifically states that there is a potential for anaphylaxis and advises close observation of the patient during and after infusion.

**Device-related complications** occurred in 12 patients (50%) and included infection, delivery system-related complications, and pleocytosis. Nine patients (38%) experienced complications of the non-implanted delivery system components. Four patients (16%) had device-related adverse reactions, which required medical intervention, including two patients (8%) with intraventricular access device-related CNS infections treated with antibiotics, and one patient (4%) with leakage of the intraventricular access device and pleocytosis. While the Sponsor did not identify any SAEs related to the device, the DGIEP Clinical Reviewer identified 3 device-related SAEs.<sup>1</sup> The SAEs included one case of pyrexia, vomiting, seizure, intracranial hemorrhage and edema; a second case of hemiparesis; and a third case of a subdural hematoma. For the first two cases, device migration was identified. For the third case, no details were provided; however, subdural hematomas are not described to be related to CLN2 disease.

**Vital sign abnormalities** included the following adverse events (AEs): bradycardia (N=2), sinus bradycardia (N=1), postoperative fever (N=1), body temperature increased (N=1), grip strength decreased (N=1), and oxygen saturation decreased (N=1). All twenty-four subjects developed hypotension during an infusion; however, there were no reports of symptomatic hypotension and no AEs were assigned due to hypotension alone. None of the vital sign abnormalities were considered to be SAEs.

At the April 12, 2017 meeting to discuss post-marketing requirements (PMRs) and post-marketing commitments (PMCs), DGIEP discussed the need for a post-marketing observational study to evaluate the long-term safety of Brineura (cerliponase alfa) in patients with neuronal ceroid lipofuscinosis type 2 (CLN2) disease, including the occurrence of serious hypersensitivity reactions (including anaphylaxis), vital sign abnormalities, and device related complications. In DGIEP’s Safety Review, the clinical reviewer noted concerns about the safety database comprising roughly 10% of the disease population.<sup>1</sup> The safety population was comprised of 24 children aged 3-8 years with mild to moderate disease. Patients with severe disease or other serious conditions (e.g., renal dysfunction or hepatic dysfunction) were not included in the database. While the SAEs involving serious hypersensitivity reactions were able to be resolved in the clinical trials, there is concern that SAEs are possible which are unable to be resolved. Because cerliponase alfa is a foreign protein entered directly into the CSF, there is a serious concern about these reactions as well as anaphylaxis. Likewise vital sign abnormalities (e.g., pyrexia, hypotension) were common during and after infusion and have the capability of being severe, causing a life-threatening event. The clinical studies had limited duration, while the drug will be administered throughout the patients’ lifetimes. The safety database does not adequately assess long-term risks. The reviewer recommended post-marketing studies to supplement the safety database.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

<i>Purpose (place an “X” in the appropriate boxes; more than one may be chosen)</i>	
Assess a known serious risk	<input type="checkbox"/>
Assess signals of serious risk	<input type="checkbox"/>
Identify unexpected serious risk when available data indicate potential for serious risk	<input checked="" type="checkbox"/>

#### 1.4. Statement of Purpose

The conditions for a PMR under FDAAA are satisfied, as the purpose is to identify an unexpected serious risk when available data indicate the potential for a serious risk. In patients with CLN2 disease, treated with cerliponase alfa, the available clinical data indicate the potential for serious risk of serious hypersensitivity reactions (including anaphylaxis), vital sign abnormalities, and device related complications. Limited clinical data do not indicate the potential for serious risk of anaphylaxis, specifically; however, it is hypothesized that this may occur given that the drug is administered using an intraventricular access device directly into cerebrospinal fluid by infusion and cerliponase alfa is a foreign protein.

In Section 2 of this ARIA Sufficiency Memo, the FDA considers whether ARIA is sufficient to be used in the post-marketing setting to assess the risk of serious hypersensitivity reactions, vital sign abnormalities, and device related complications after cerliponase alfa exposure.

#### 1.5. Effect Size of Interest or Estimated Sample Size Desired

The regulatory goal for evaluating the risk of serious hypersensitivity reactions, vital sign abnormalities, and device related complications in ARIA is for signal detection (i.e., post-marketing surveillance), rather than a hypothesis-driven study. Therefore, *a priori* levels of risk to rule in or out have not been determined as they would be for a protocol-based assessment. Furthermore, because CLN2 is a very rare disease, a sufficient sample size with adequate statistical power is not obtainable and this study will be descriptive only.

#### 1.6. Desired PMR Study

The following is an ideal study design, if ARIA is deemed insufficient. The PMR study would be conducted as a 10 year study to assess long-term safety in a registry of patients with CLN2 disease. Enrollment would occur over an 8-year period in order to enroll as many patients as possible. Serious hypersensitivity reactions (including anaphylaxis), vital sign abnormalities, and device related complications would be the main safety concerns; however, all adverse events and serious adverse events would be captured during the 10 years of follow-up. Additionally, efficacy endpoints including language and motor scores would be collected, as clinical data were limited during the clinical studies.

(b) (4)

## **2. SURVEILLANCE OR DESIRED STUDY POPULATION**

### **2.1. Population**

The study population will consist of the indicated population of patients aged 3 years or older with CLN2 disease who are exposed to Brineura (cerliponase alfa). This will be a descriptive study only, and no comparator population has been identified.

### **2.2. Is ARIA sufficient to assess the intended population?**

According to DGIEP's clinical safety review, there are approximately 250-350 patients in the United States with CLN2 disease.<sup>1</sup> DGIEP does not anticipate any off-label use. Sentinel's large surveillance population would normally be considered well suited for capturing and evaluating drug safety in the setting of rare diseases. However, FDA is seeking long term follow up of 10 years following drug administration (see Section 4.2 for more information).

We deem Sentinel insufficient to identify an adequate number of patients with CLN2 disease for the requisite observation period. In order to adequately assess the safety, a larger sample size would be desirable, including populations outside of the United States, and a study design capable of long term observation.

## **3. EXPOSURES**

### **3.1. Treatment Exposure(s)**

Patients who received at least one treatment of Brineura (cerliponase alfa) would be included in the ARIA assessment.

### **3.2. Comparator Exposure(s)**

No comparator exposure is available, since there are currently no other treatments for CLN2 disease.

### **3.3. Is ARIA sufficient to identify the exposure of interest?**

ARIA allows for the identification of dispensings of both inpatient and outpatient prescriptions. However, coded data on any medications administered during hospitalization may not be available. Brineura is administered in a healthcare setting, by a physician trained in intraventricular administration. Infusions would likely occur in specialized facilities in a hospital or ambulatory care center, such as an infusion center. Since adverse reactions may occur during and after administration, including device-related complications and because patients with the disease are very ill, it is possible that patients may be hospitalized while receiving the infusions, especially for the first infusion. Because it is unclear how these infusions would be billed, and whether the infusions will be bundled into a larger treatment code, the ability to adequately capture the exposure is uncertain.

We believe that ARIA will be insufficient to capture these infusions since many may occur during hospitalization or in a hospital setting.

## **4. OUTCOME(S)**

### **4.1. Outcomes of Interest**

The outcomes of interest are serious hypersensitivity reactions (including anaphylaxis), vital sign abnormalities, and device related complications.

#### 4.2. Is ARIA sufficient to assess the outcome of interest?

The outcomes of interest are generally non-specific and can include numerous types of hypersensitivity reactions, vital sign abnormalities, and device related complications.

During the Mini-Sentinel pilot program, Schneider et al. conducted a systematic review of the literature examining validation studies for hypersensitivity reactions.<sup>3</sup> Five studies were identified and the positive predictive values (PPVs) for various definitions of hypersensitivity reactions ranged from 3% to 95%. PPVs were high (e.g., 90%-95%) when very specific exposures and diagnoses were identified. PPVs decreased when the definition of hypersensitivity was expanded. Because specific serious hypersensitivity reactions were not identified and the outcome of interest may include several different types of hypersensitivity reactions, it is difficult to determine whether the PPVs would be acceptable, given that the range of PPVs is wide and includes very low PPVs. We believe ICD-10 validation to have a similar range of PPVs for examining a wide variety of hypersensitivity reactions.

A systematic literature review of validation of anaphylaxis was performed by Schneider et al. during the Mini-Sentinel pilot program.<sup>4</sup> The review found limited studies validating algorithms used for anaphylaxis and related conditions. ICD-9 code 995.0 (anaphylactic shock) was the most commonly used anaphylaxis-specific diagnostic code; the PPV ranged from 38% to 72%. For all-cause anaphylaxis, the PPVs had a wider range of values (7%-72%) and the PPVs were low for drug-related anaphylaxis outcomes PPV (15%-38%). After the systematic review was conducted, Walsh et al. evaluated the validity of administrative and claims codes from 8 large health plans across the United States.<sup>5</sup> The PPV of the evaluated algorithm was 63%, which is not well validated.

The outcomes of vital sign abnormalities and device related complications are not well defined outcomes and may include numerous specific adverse events. Hougland et al. examined the validation of adverse events in inpatient AEs or AEs resulting in hospitalization using ICD-9-CM codes in hospital claims data.<sup>6</sup> Specifically, AEs for nervous system devices had a PPV of 50%; however, this was based on only 7 reviewed cases. We consider the validation of these broad categories of outcomes to generally not be feasible since well-defined abnormalities and complications were not identified. We consider the goal of evaluating these safety concerns to be broad-based signal detection, which is currently not feasible in ARIA. Furthermore, vital sign abnormalities and device related complications may not always appear as diagnosis codes in claims

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<sup>3</sup> Schneider G, Kachroo S, Jones N, et al. A systematic review of validated methods for identifying hypersensitivity reactions other than anaphylaxis (fever, rash, and lymphadenopathy), using administrative and claims data. *Pharmacoepidemiol Drug Saf* 2012;21:248-55.

<sup>4</sup> Schneider G, Kachroo S, Jones N, et al. A systematic review of validated methods for identifying anaphylaxis, including anaphylactic shock and angioneurotic edema, using administrative and claims data. *Pharmacoepidemiol Drug Saf* 2012;21:240-7.

<sup>5</sup> Walsh KE, Cutrona SL, Pawloski P, et al. Validity of administrative and claims data for the identification of cases of anaphylaxis in the Mini-Sentinel distributed database. February 15, 2013. [https://www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Mini-Sentinel\\_Validation-of-Anaphylaxis-Cases.pdf](https://www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Mini-Sentinel_Validation-of-Anaphylaxis-Cases.pdf)

<sup>6</sup> Hougland P, Nebeker J, Pickard S, et al. Using ICD-9-CM codes in hospital claims data to detect adverse events in patient safety surveillance. In: Henriksen K, Battles JB, Keyes MA, Grady ML, editors. *Advances in patient safety: new directions and alternative approaches (Vol 1: Assessment)*. Rockville (MD): Agency for Healthcare Research and Quality; 2008.

databases. Instead, these may be written in the medical records (e.g., pyrexia, device migration); medical records are not available in ARIA.

DGIEP indicated that all SAEs should be captured during a long-term post-marketing observational study. They are recommending ten years of follow-up, because patients will be receiving Brineura throughout their lives and they would like long-term safety data. Roughly 75% of patients in the Sentinel database have at most 3 years of follow-up data available [See Figure 1 below]. Thus, assessing patients over 10 years in ARIA would not be sufficient, as less than 2% of patients would have follow-up data for 10 years or more.

Also, a limitation in using ARIA is that clinical characteristics (e.g., narratives) which may be of interest are not available in claims data. Diagnostic or procedure codes cannot provide detailed narratives describing the clinical details of the adverse event. Because the sample size will be small and this would be a descriptive study, medical records with clinical narratives are critical for this study.

Because of the limitations of low PPVs, broad-based signal detection across general categories of outcomes, and lack of long-term follow-up data, we consider ARIA to be insufficient to assess the outcomes of interest.

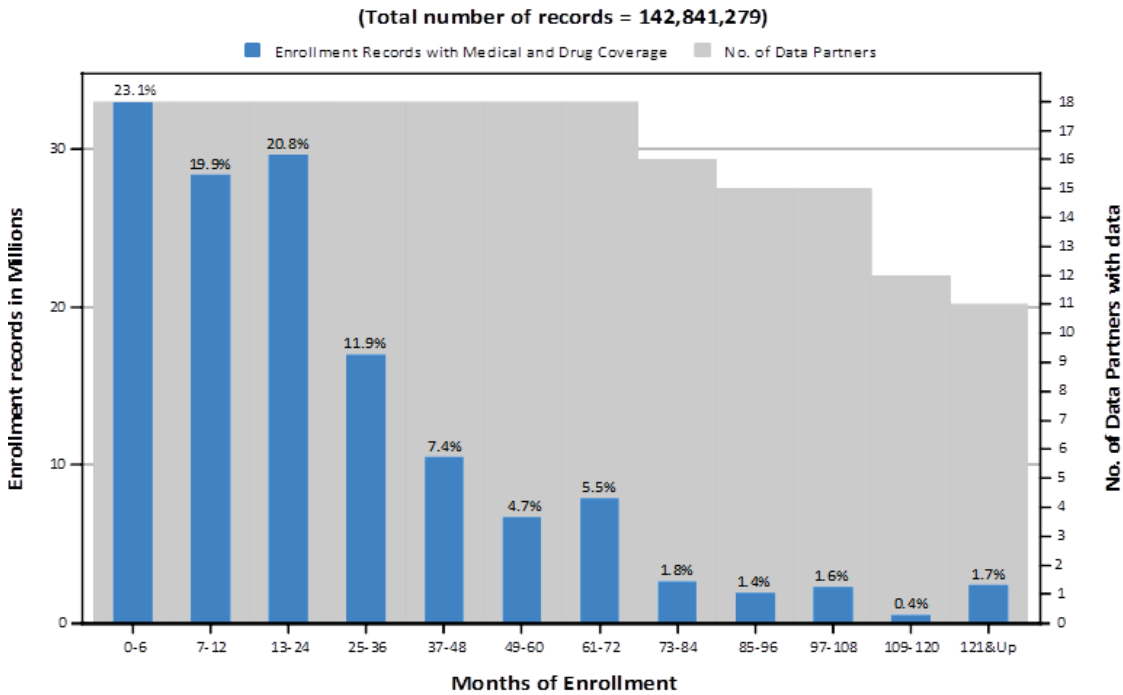


Figure 1. Number of Enrollment Records by Length of Enrollment in the Sentinel database<sup>7</sup>

<sup>7</sup> Source: Michael D. Nguyen, MD. FDA Sentinel Program Lead.



## **5. COVARIATES**

### **5.1. Covariates of Interest**

The covariates of interest include demographic characteristics (e.g., age, sex, calendar year, and geographic region) and clinical characteristics (e.g., comorbidities and concomitant medications).

### **5.2. Is ARIA sufficient to assess the covariates of interest?**

Because this study will only be descriptive, confounding control is not considered critical for this study. Code-based approaches to assess covariates would be adequate. Demographic characteristics (e.g., age, sex, calendar year, geographic region) are able to be assessed in ARIA. Other clinical characteristics (e.g., other medical conditions and concomitant medications) could also be assessed in ARIA. Therefore, we consider ARIA to be sufficient to assess the covariates of interest.

## **6. SURVEILLANCE DESIGN / ANALYTIC TOOLS**

### **6.1. Surveillance or Study Design**

A simple surveillance to determine the incidence of serious hypersensitivity reactions, vital sign abnormalities, and device related complications among cerliponase alfa users is the study design, as this will only be a descriptive study, given the rare disease population and no comparator treatments.

### **6.2. Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?**

ARIA includes sufficient analytic tools for a descriptive analysis. However, the capture of clinical narratives of adverse events is critical to this study, to better understand the adverse events in depth, as previously discussed. There is a need for detailed clinical narratives for attribution and timing of the adverse event. Therefore, we consider ARIA to be insufficient with respect to the design/analytic tools available to assess the risk of hypersensitivity reactions, vital sign abnormalities, and device related complications since detailed narratives on cases would not be available in ARIA.

## **7. NEXT STEPS**

ARIA is determined to be insufficient for all outcomes, due to a rare disease population, broad-based signal detection across non-specific outcomes (vital sign abnormalities and device related complications) and poor validation for hypersensitivity reactions overall, and the infusions likely given in hospital settings. A prospective cohort study (e.g., registry) would be a more appropriate post-marketing study design to better assess long-term safety including serious hypersensitivity reactions, vital sign abnormalities, and device related complications with detailed clinical characteristics of each adverse event.

The proposed PMR language for a post-marketing observational study is:

Conduct a non-interventional post approval safety study (Study 190-501) to evaluate the long-term safety of Brineura (cerliponase alfa) in patients with neuronal ceroid lipofuscinosis Type 2 (CLN2 disease), and further assess the occurrence of serious hypersensitivity reactions including anaphylaxis, vital sign abnormalities, and device related complications. In addition, this study will evaluate the CLN2 motor and language clinical scales.

Final Protocol Submission: 12/2017

Study Completion: 06/2036

Final Report Submission: 06/2037

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KIRA N LEISHEAR

04/26/2017

SIMONE P PINHEIRO on behalf of SUKHMINDER K SANDHU

04/26/2017

Memo cleared by Dr. Sandhu. I am signing this memo for Dr. Sandhu who is currently on leave

JUDITH W ZANDER

04/26/2017

MICHAEL D NGUYEN

04/26/2017

ROBERT BALL

04/26/2017

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

## Memorandum

**Date:** April 24, 2017

**To:** Jenny Doan, BSN, MSN, PMP, Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products (DGIEP)

**From:** Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer,  
Office of Prescription Drug Promotion (OPDP)

**Subject:** BLA 761052 – BRINEURA (cerliponase alfa) injection,  
for intraventricular use (Brineura)

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Reference is made to DGIEP's consult request dated June 8, 2016, requesting review of the proposed Package Insert (PI) and Carton/Container Labeling for Brineura.

OPDP has reviewed the proposed PI entitled, "Draft-BRI-US-001j-PI-Clean for Submission April 20, 2017.docx" that was sent via email from DGIEP to OPDP on April 24, 2017. OPDP's comments on the PI are provided directly on the attached marked-up copy of the labeling (see below).

OPDP has also reviewed the following proposed Carton/Container labeling entitled:

- "BRINEURA.pdf"
- "Brineura Vial.version Dec. 22, 2016.pdf"
- "Intraventricular Electrolytes Injection Vial version Feb. 13, 2017.pdf"
- "Administration Kit Carton version Feb. 13, 2017.pdf"
- "UDI Sticker for Administration Kit May 27, 2016.pdf"

that was sent from DGIEP to OPDP on April 18, 2017. OPDP has no comments at this time on the proposed Carton/Container labeling.

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or [adewale.adeleye@fda.hhs.gov](mailto:adewale.adeleye@fda.hhs.gov)

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ADEWALE A ADELEYE  
04/24/2017

**OFFICE OF DEVICE EVALUATION**DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,  
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES**GENERAL HOSPITAL DEVICES BRANCH  
INTERCENTER CONSULT MEMORANDUM**

<b>Date</b>	April 20, 2017
<b>To</b>	Jenny Doan, RPM CDER/OND/ODEIII/DGIEP
<b>Requesting Division</b>	DGIEP
<b>From</b>	John McMichael CDRH/ODE/DAGRRID/GHDB
<b>Through (Branch Chief)</b>	CDR Alan Stevens, Branch Chief CDRH/ODE/DAGRRID/GHDB
<b>Subject</b>	Consult for Submission BLA 761052, ICC 1600395
<b>Recommendation</b>	<b>Device Constituents Parts of the Combination Product are Approvable with Labeling and PMR Recommendations in Section 14.</b>

**Digital Signature Concurrence Table**

Lead Reviewer	John C. Mcmichael -S	Date: 2017.04.20 10:06:30 -04'00'
Clinical Consultant	Bennett Blumenkopf -A	2017.04.20 10:11:31 -04'00'
Branch Chief	Alan M. Stevens -S	Alan M. Stevens -S 2017.04.20 10:29:11 -04'00'

## 1. Submission Overview

Table 1. Submission Information	
ICC tracking # (Lead)	1600395
Submission Number	BLA 761052
Sponsor	Biomarin Pharmaceuticals
Biologic	Brineura aka BMN 190 (cerliponase alfa)
Indications for Use	BMN190 is indicated for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency
Device Constituent	BMN 190 Administration Kit

Table 2. Review Team		
CDER Lead Review Division		DGIEP
Submission RPM		Jenny Doan
Lead Device Reviewer		John McMichael
The CDRH review is being managed under ICC #: ICC1600395		
Below is a list of the Discipline Specific ICC# and CON#. The CON# are under ICC1600395 in CTS.		
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #
Biocompatibility	Sarah Mollo, PhD (CDRH/ODE/DAGRID/GHDB)	CON 1621711
Sterility	Christopher Dugard (CDRH/ODE/DAGRID/INCB)	CON 1612918
Labeling	Samuel Raben (CDRH/ODE/DNPMD/NIDB)	CON 1615882
Clinical	Bennett Blumenkopf, MD (CDRH/ODE/DNPMD)	CON 177956

**NOTE: All elements of this memo in which Dr. Blumenkopf contributed too are highlighted in YELLOW for recognition of his contribution.**

Table 3. Important Dates	
Dates of Information Requests	07/15/16, 08/05/16, 08/31/16, 09/23/16, 10/14/16, 10/28/16, 01/11/17, 01/18/17, 01/31/17, 02/08/17, 02/10/17
Final Lead Device Review Memo Due	April 11, 2017
Interim Due Dates	Meeting Date
Filing	06/28/16
Mid-Cycle	11/30/16
Internal Meetings	07/05/16, 07/27/16, 08/17/16, 08/31/16, 09/07/16, 09/14/16, 09/21/16, 09/27/16, 10/24/16, 11/10/16, 11/16/16, 11/28/16, 11/30/16, 12/01/16, 12/12/16, 12/14/16, 12/15/16, 01/17/17, 01/19/17, 01/25/17, 01/27/17, 01/31/17, 02/15/17, 03/22/17, 04/05/17, 04/12/17, 04/18/17, 04/19/17, 04/21/17
Sponsor Meetings	10/27/16, 11/16/16, 12/16/16, 12/20/16, 01/17/17, 02/01/17, 02/21/17, 04/12/17, 04/20/17

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**2. PURPOSE/BACKGROUND**

**2.1. Scope**

The purpose of this memo is to document the review of the device constituent parts of the combination product under BLA 761052. This review includes the Administration Kit device constituent parts, the drug product labeling as it pertains to the device constituents, the device compatibility with labeled off-the-shelf components that are not part of the combination product, and the clinical risks associated with the intended therapy in relation to the device constituent parts.

CDER/DGIEP requested a complete review of the devices in the BMN 190 Administration Kit in the context of the intended delivery system, the device related labeling, and the clinical risks associated with the device constituent parts of the combination product and delivery system as a whole.

It is important to note that the BMN 190 Administration Kit, which is the subject of this review, does not include the infusion pump, intraventricular access device, or syringe for patency checks that is labeled for use with the drug product. The entire delivery system includes the labeled infusion pump, intraventricular access device, patency syringe, and the BMN 190 Administration Kit.

NOTE: CDER/DGIEP determined that the route of administration for the combination product is ‘intraventricular’ and not ‘intracerebroventricular’. Anywhere in the memo where intracerebroventricular (ICV) is referenced should be read as intraventricular.



2.2. Prior Interactions

CDRH/ODE provided previous consultations (ICC 1600072) for Type C Meeting Requests from the Sponsor prior to submission of the original BLA for filing. Refer to the CDRH/ODE memos in DARRTS for more details.

2.3. Indications for Use

Product	Indications for Use
BMN 190 / Brineura / Cerliponase Alfa	BMN190 is indicated for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency

2.4. Device Constituents

BMN 190 Administration Kit Components:

Device Name (510(k) Number, Manufacturer Part Number)	Cleared/Approved Indications for Use
Infusion set with 0.2 micron filter (b) (4)	(b) (4)
(b) (4) Extension line Set (b) (4)	
(b) (4) needle - 16mm Port needle (b) (4)	
Syringe - (b) (4) 20 mL (b) (4) (b) (4)	
Hyprodermic needle - 21 gauge Syringe needle (b) (4)	

Labeled Device Components (Not part of combination product):

<b>Device Name (PMA/510(k) Number)</b>	<b>Cleared/Approved Indications for Use</b>
B Braun Perfusor Space Infusion Pump (K092313)	The Perfusor® Space Infusion Syringe Pump System is an electrical, external, syringe infusion pump system indicated for use with adults, pediatrics and neonates and is intended to provide infusions of parenteral fluids/medications, blood and blood products indicated for infusion through FDA approved routes of administration.
Codman HOLTER RICKHAM Reservoir PN 82-1625 (K853364)	This device is intended for use in diagnostic studies or therapeutic drug administration with or without shunting device. As a shunt component, this device is intended to help determine and alleviate blockage in the system and for use as the proximal fluid pathway.
Codman HOLTER Ventricular Catheter PN 82-1650 (K853362)	This device is intended for use as a means of access to the cerebral ventricles for the purpose of diagnostic studies, therapeutic drug administration, and/or the diversion of cerebrospinal fluid.

### 3. ADMINISTRATIVE

#### 3.1. Documents Reviewed

NOTE: Due to the large number of documents reviewed as part of this review memo not all documents are listed here below – instead the responses to information requests are listed and some high level documents that were critical to the review of the application. All links to documentation that was reviewed as part of this memo are referenced in Section 12 in the Information Requests responses from the Sponsor.

<b>Document Title / Number</b>	<b>Date - Version</b>	<b>Location</b>
Reviewer Guide		GSR Sequence 0001 / Module 1.2
Meeting Minutes	Multiple – see teleconference dates listed in Section 1 of memo	GSR Sequence 0001 / Module 1.6
Container Closure System	N/A	GSR Sequence 0001 / Module 3.2.P.7.
Design Input Requirements BMN 190 Administration Kit (DIR-190-001)	Rev 3, July 25, 2016	GSR Sequence 0009 / Module 3.2.P.7
User Requirements Specification BMN 190 Administration Kit (URS-190-001)	Rev 3, July 25, 2016	GSR Sequence 0009 / Module 3.2.P.7

Response to Quality RFI dated 18July2016	July 20, 2016	GSR Sequence 0009/ Module 1.11.1
Preliminary Hazard Analysis – BioMarin BMN190	RevA, August 2015	GSR Sequence 0001 / Module 3.2.P.7.
Draft Labeling		GSR Sequence 0001 / Module 1.14
Letter of Authorization – (b) (4)		GSR Sequence 0001 / Module 1.4
Letter of Authorization – (b) (4)		GSR Sequence 0001 / Module 1.4
TR-00565 Performance Syringe Pump Report_20160726	Rev 1, July 26, 2016	GSR Sequence 0009/ Module 1.11.1
Puncture Study Response for Brineura pdf (2)	04/19/17	Information Amendment, Module 1.11 in GSR
__cdsub1_evspod_bla761052_0100_m1_us_111-information-amendment_1111-quality-information-amendment_resp-qual-rfi-punct-study	02/17/17	Information Amendment, Module 1.11 in GSR
PVR-113755_ Accelerated Aging Report Of The Packaging Material For BMN190 Administration Kit, 55°C For 120 Days	02/01/17	Information Amendment, Module 1.11 in GSR
Response to IR #11 received 31Aug2016	02/01/17	Information Amendment, Module 1.11 in GSR
STN 761052_Response to Agency Question Puncture Study_SN 0087_30Jan2017	01/30/17	Information Amendment, Module 1.11 in GSR
CP-190-002 Repeated Septum Perforation Test protocol_Draft_17Jan2017	01/18/17	Information Amendment, Module 1.11 in GSR
Response to Agency Questions 17JAN2017	01/18/17	Information Amendment, Module 1.11 in GSR
Response To RFI Follow Up To OBP IR# 18 ICV Device Puncture dated 27Oct2016	12/19/16	Information Amendment, Module 1.11 in GSR
0060 Follow up to FDA IR # 16 dated 14Oct2016 and IR # 20 dated 28Oct2016 submitted 21Nov2016	11/22/16	Information Amendment, Module 1.11 in GSR

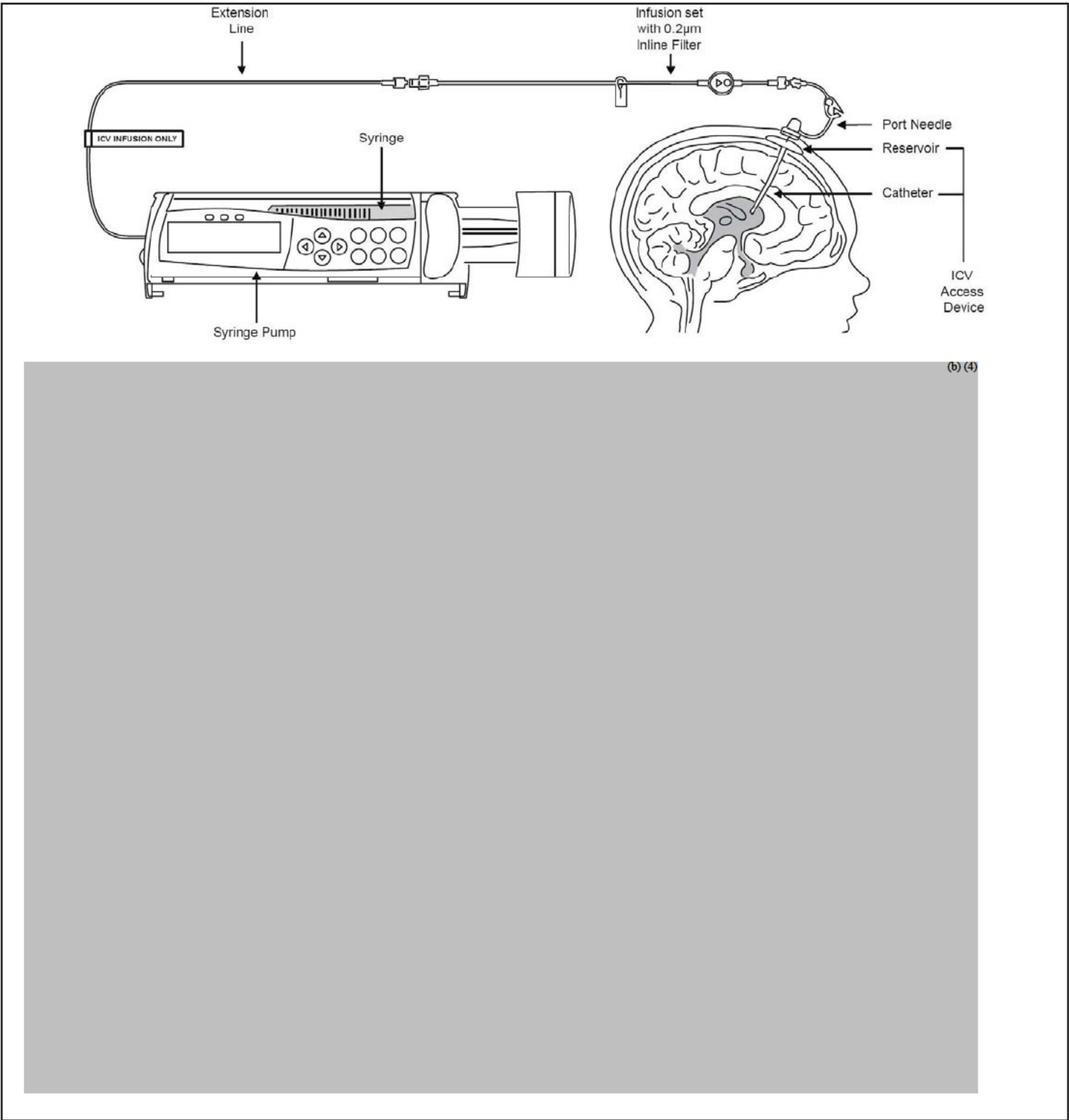
Response to FDA RFI #11 (Device) received 31Aug2016	11/19/16	Information Amendment, Module 1.11 in GSR
Response to FDA RFI #18 dated 27Oct2016	11/03/16	Information Amendment, Module 1.11 in GSR
Response to FDA Device RFI #20 dated 28Oct2016	11/03/16	Information Amendment, Module 1.11 in GSR
BLA STN 761052_IR18 Q3 (Device) received 27Oct2016_1.11.1 Quality Inform...	11/02/16	Information Amendment, Module 1.11 in GSR
Response to FDA RFI #16 (device) dated 14Oct2016	10/25/16	Information Amendment, Module 1.11 in GSR
SN0038 Response to FDA IR14 (Device_Labeling received 23Sep16)	10/24/16	Information Amendment, Module 1.11 in GSR
Response to FDA RFI #11 dated 31Aug2016	10/04/16	Information Amendment, Module 1.11 in GSR
Response to FDA RFI #11 Q10 and 12 dated 31Aug2016	09/22/16	Information Amendment, Module 1.11 in GSR
Response to Quality RFI dated 12Sep2016	09/15/16	Information Amendment, Module 1.11 in GSR
Response to Quality RFI Q9, 11, 13,14 dated 31Aug2016	09/15/16	Information Amendment, Module 1.11 in GSR
Information Amendment Labeling Response to FDA Day 74 Letter	09/01/16	Information Amendment, Module 1.11 in GSR

#### 4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

BMN 190 is intended for Intracerebroventricular (ICV) administration via a surgically implanted ICV access device (reservoir and catheter). A syringe pump is used to deliver BMN 190 drug product (DP) via a disposable syringe through the following set of components: an extension line, an infusion set (with a 0.2µm in-line filter), a port needle and ICV access device, including a reservoir and a catheter. The B. Braun (Perfusor® Space infusion pump) was selected for DP delivery and for inclusion in BMN 190 drug product labeling in the U.S.

The drug product solution (300mg dose in 10mL) is intended to be administered at a steady rate of 2.5 mL/hr over a 4-hour period.

The complete delivery system can be seen depicted below:



The device constituent parts of the combination product for BLA 761052 are depicted in the following table:

<b>BMN 190 Administration Kit Component</b>	<b>Image</b>
BMN 190 Administration Kit	
(b) (4) Port Needle (E)	

<div>(b) (4)</div> Extension Set (C)	<div>(b) (4)</div>
Infusion Set with 0.2 micron filter (D)	
20 mL Syringe (B)	
Syringe Needle (A)	

The components of the delivery system that are not a part of the combination proeduct under BLA 761052 (i.e. off-the-shelf components) are depicted below:

(b) (4)

Performance Requirement	Description / Specification
Infusion Pump Name	B Braun Perfusor Space Syringe Pump
Environments of use	Hospital
Flow Rate Accuracy	2.5 mL/hr ± 1.0 mL/hr
Infusion Site	Intraventricular
Priming Volume	0.4mL



Flushing Solution / Hold-Up Volume	2 mL
Total Dose / Drug Product Infusion Volume	300 mg / 10 mL administered every other week
Total Infusion Time	4 (b) (4) hours (including Drug Product – Flushing Solution transfer)
Occlusion Detection	(b) (4)  Requirement of pump under BLA 761052: Occlusion alarm setting to $\leq 281$ mm Hg
Audible / visual feedback	Syringe pump alarms, visibility of syringe during infusion
Tubing Length	10 – 12 Feet
Syringe Compatibility with Syringe Pump	Supported by hardware / software of pump Compatible with 20 mL syringe
Syringe Needle Specifications <ul style="list-style-type: none"> <li>Length</li> <li>Gauge</li> </ul>	Gauge: 21 G Length: 1 inch
Port Needle Specifications	90-degree (b) (4) port needle (b) (4) 22G, 5/8 inch
Port Needle Specifications and ICV Access Port Compatibility	The Administration Kit must provide a port needle which is capable of perforating the septum of the intraventricular access device at least four years without compromising the functionality of the intraventricular port.
Type of Use	Single-Use Only, Disposable
Sterility	Components purchased sterile, sterile packaging, maintain sterile barrier through shipping/aging
Endotoxin Limits	< 2.15 EU / Administration Kit, tested upon release
Biocompatibility	ISO 10993 Compliant Latex-free, Non-DEHP tubing
Luer Lock Connections	ISO 594 compliant
No Leakage	No leakage of Drug Product or ICV solution through Administration Kit connections
Storage conditions / Shelf Life	Packaging integrity and sterility through shipping / aging, tamper evident seal, kit name / lot # / expiration date on every carton is legible

The Sponsor provided the following 'Sources of Design Inputs' memo to establish the clinical rationale for the selection of design inputs:

The objective of this memo is to document background and justification for the design inputs defined for BMN 190. Sources of Design Inputs were captured from Medical Affairs and Clinical Sciences representatives based on direct experience in clinic, advisory boards with groups of physicians, and direct conversations with physicians, neurosurgeons, and pediatric neurologists. Clinical pharmacologists were consulted about the administration kit packaging and labeling. Below is a comprehensive summary of this information.

1) Administration Kit Components, Interfaces and Procedure

- 1.1 It is common practice for clinics that perform ICV delivery to already have an infusion pump available, which is intended for multiple infusions. Therefore an infusion pump should not be included in the Administration Kit, but the infusion pump used should be suitable for ICV administration.
- 1.2 The ICV Access Device must be implanted several weeks prior to the first infusion and therefore should not be included in the Administration Kit, but the ICV access device should be suitable for ICV administration.
- 1.3 Delivery of Drug Product therapeutic dose (300mg/10mL) is followed by 2mL of ICV Solution to flush all drug product from assembled infusion line to ensure that the full dose is administered. A deviation of  $\pm 1.0$  mL in the deliverable dose is considered clinically acceptable. The Drug Product and ICV Solution are provided in separate vials. Therefore, the administration kit requires 2 separate syringes and hypodermic.
- 1.4 BioMarin identified components for the Administration Kit based on recommendations from physician experts in the field of pediatric and adult neurosurgery, neuro-oncology and CLN diseases. All components selected were used in US clinical trials without serious adverse events. All administration kit components were identified as products commercially available in the U.S. Nonetheless, it is pertinent that drug/device compatibility is further demonstrated by non-clinical studies.
- 1.5 See Section 12 for information about the (b) (4) needle.

- 2) BMN 190 drug product contains (b) (4) particles that should not be infused to the brain, due to the risk of hypersensitivity reactions. It is also common practice for enzyme replacement therapies to be administered with an in-line filter. Therefore a filter is placed at the end of the infusion line, the sole intention of which is to filter out these particles.

- 3) Delivery of drug to cerebrospinal fluid (CSF) is necessary to bypass the blood-brain barrier. Therefore this drug is administered via an ICV access device with an infusion set and appropriate precautions must be taken to ensure safety of infusion components for this indication.
- 4) Development of ICV-specific infusion components or updating regulatory filings to add ICV indication would delay the availability of this life-saving drug. Therefore the preferred development strategy was to evaluate readily available, off-the-shelf infusion components for suitability and safety for ICV delivery.
- 5) It is common expectation in a clinical infusion environment that infusion components are delivered to the user in sterile condition. Therefore the Administration Kit components should be delivered sterile.
- 6) It is common expectation in a clinical infusion environment that infusion components are single-use and disposable. Therefore the Administration Kit components should be single-use and disposable.
- 7) Aseptic assembly using Luer Lock is standard clinical practice to prepare infusions. Therefore the Administration Kit components should be assembled using this method.
- 8) The therapeutic dose is 300mg. See Section 1.3 for information on the therapeutic dose.
- 9) The target delivery rate of 2.5mL/hour was determined to have low risk for causing overt clinical signs from increased intracranial pressure or alteration of CSF chemistry by comparing it to the natural CSF turnover rate in pediatric humans and the relative infusion flow rate to CSF turnover rate studied in the nonclinical program. The infusion flow rate of 2.5 mL/hour is approximately 12% of the natural CSF turnover rate in pediatric humans (2-5 years old) of 20.8 mL/hour (based on CSF turnover of 5x/day and a CSF volume of 100 mL). A deviation of  $\pm 1.0$  mL/hour in the target infusion rate is considered acceptable to neurosurgeons.
- 10) Minimum infusion time is 4 hours (10mL at 2.5mL/hour). Up to <sup>6</sup>/<sub>4</sub> hours is allotted to complete infusion to provide time to change from DP to FS, and to account for potential delays or interruptions in the infusion process such as patient adverse reactions or health complications.
- 11) The length provided by extension line is needed to reach from the pump to the hospital bed, while allowing enough slack in the line for the patient to adjust position. The appropriate length to provide sufficient length for the infusion, while not having excess length that could result in a tripping hazard, risk of dislodging the gripper needle, or increased infusion time due to increased tube length is 10-12 feet (width of bed is 4 feet, gap between pump and table ~3 feet, table with pump 2-3 feet wide, want 1-2 feet of slack to allow movement).

12) BMN 190 is delivered over a period of 4+ hours to young children, who are likely incapable of remaining still for this time period. The patient needs to be able to sit up, lay down, roll over, or even climb down from the bed for short periods of time. Therefore prior to the infusion, the (b) (4) needle is secured to the patient by wrapping the head with sterile transparent dressings and/or tape after inserting the needle. Butterfly needles are commercially available in small sizes (26G or smaller diameter), which are well-suited for accessing the ICV access port, however this type of needle cannot be securely fastened to the patient because it protrudes too far from the skull. Therefore the low-profile fixation provided by a 90-degree (b) (4) needle is required for secure fixation, to prevent the needle from being dislodged during the infusion. Commercially available 90-degree (b) (4) needles available are larger (22G) than the butterfly needles, however the need for secure fixation to the ICV access device supersedes the recommendation for a smaller needle diameter. Prior to every infusion, the ICV access device is checked for signs of damage or infection, such as swelling or bulging around the scalp, extravasation of fluid and patency. The larger needle gauge has not caused adverse events during clinical trials. However, it is necessary to ensure that the 90-degree (b) (4) needle does not cause coring or any other physical damage that would compromise the functionality of the ICV access device with repeated access. BMN 190 is administered every two weeks. Surgical revision/replacement of the ICV access device is only performed as needed, and should not be required more than once per year.

- 13) HCPs expect the following from the packaging
- i. It is highly important that sterility of components is maintained (delivered sterile, can be taken out of kit without compromising package integrity)
  - ii. Integrity and functionality of the infusion components are maintained
  - iii. No shedding, as fiber/particulates should be minimized in clinical environments
  - iv. That all components necessary for infusion are available in one place

- 14) HCPs will look at the labeling for the following information
- i. Sterile/non-sterile
  - ii. Single-use/disposable
  - iii. Contents of the kit and how those contents are used
  - iv. Storage requirements (anything other than room temperature is out of the ordinary for infusion components)

## 5. CLINICAL DEVELOPMENT

### 5.1. Current Study Summary

Titles	190-201
Phase	1/2 Open-label, dose-escalation study
Study Duration	Complete
Objectives	<ul style="list-style-type: none"> <li>• To evaluate safety and tolerability of BMN 190 administered to subjects with CLN2 disease by an implanted intracerebroventricular (ICV) reservoir</li> </ul>



	and cannula  <ul style="list-style-type: none"> <li>• To evaluate effectiveness using an adapted CLN2 disease-specific rating scale score in comparison with natural history data after 48 weeks of treatment</li> </ul>
Subjects	24; CLN2 patients age 3 to 16 years
Study Design	Dose Escalation Period: 30 mg, 100 mg, 300 mg every 14 days  Stable Dose Period: 300 mg every 14 days  Bi-weekly 4 hour ICV infusion
Duration of administration	48 weeks completed in the Stable Dose Period

Titles	190-202
Phase	Open-label, Extension study
Study Duration	Ongoing
Objectives	<ul style="list-style-type: none"> <li>• To evaluate the long-term safety and efficacy of BMN 190 administration at 300 mg every 14 days in patients with CLN2.</li> <li>• To assess change in motor and language subscales of the adapted CLN2 rating scale in subjects with CLN2 receiving BMN 190 at 300 mg every 14 days.</li> </ul>
Subjects	23; CLN2 patients age 3 to 16 years
Study Design	300 mg every 14 days  Bi-weekly 4 hour ICV infusion
Duration of administration	Up to 240 weeks

The following is a summary of the syringe pumps utilized for the above clinical studies that were not part of the Administration Kit:

**Table 1: Syringe Pumps Used in the Clinical Study and Performance Requirements**

Pump	Delivery Volume	Delivery Accuracy	Compatible with Admin. Kit Syringes	Alarms
<i>Essential Criteria</i>	<i>Syringe pump must be able to deliver at a rate 2.5 mL/hr</i>	<i>2.5 mL/hr ± 1.0 mL/hr</i>	<i>Must be compatible with administration syringes (20 mL (b)(4) syringe)</i>	<i>Syringe pump should have occlusion alarms</i>
Smiths Medical Medfusion 3500	Infusion rate range: 0.1 mL/hr to 200 mL/hr	Nominal ± 2%	Compatible with (b)(4) 20 mL	User can set the occlusion limit from High to Very Low. <ul style="list-style-type: none"> <li>• High: 16 psi (827 mmHg)</li> <li>• Normal: 12 psi (621 mmHg)</li> <li>• Low: 8 psi (413 mmHg)</li> <li>• Very Low: 4 psi (206 mmHg)</li> </ul>
Carefusion Alaris CC Pump 8003Med01	Infusion rate range: 0.1 mL/h to 600 mL/h for 20mL syringes	Nominal ± 2% for rates ≥ 1mL/h	Compatible with (b)(4) 20 mL	User can set the occlusion limit from L-10 to L-0. Examples: <ul style="list-style-type: none"> <li>• L-10: 1000 mmHg</li> <li>• L-5: 500 mmHg</li> <li>• L-3: 300 mmHg</li> <li>• L-0: 50mmHg</li> </ul>
Carefusion Alaris CC Guardrails 8003Med01-G	Infusion rate range: 0.1 mL/h to 600 mL/h for 20 mL syringes	Nominal ± 2% for rates ≥ 1 mL/h	Compatible with (b)(4) 20 mL	User can set the occlusion limit from L-10 to L-0. Examples: <ul style="list-style-type: none"> <li>• L-10: 1000 mmHg</li> <li>• L-5: 500 mmHg</li> <li>• L-3: 300 mmHg</li> <li>• L-0: 50 mmHg</li> </ul>
B Braun Perfusor Space <sup>1</sup>	Infusion rate range: 0.01 – 999.9 mL/h	Nominal ± 2%	Compatible with (b)(4) 20 mL	User can set the occlusion limit from L-9 to L-1. (0.1 to 1.2 bar / 75 to 900 mmHg). Levels separated by increments of approximately 0.1375 bar which corresponds to approximately 103 mmHg. Examples: <ul style="list-style-type: none"> <li>• L-9: 1.2 bar (~900 mmHg)</li> <li>• L-5: 0.65 bar (~487 mmHg)</li> <li>• L-3: 0.375 bar (~281 mmHg)</li> <li>• L-1: 0.1 bar (~75 mmHg)</li> </ul>

<sup>1</sup> The B Braun Perfusor FM was previously used at site 1244. It complies with these criteria, but is not currently in use and is not provided in this table.

See Appendix A for Dr. Blumenkopf's clinical consult regarding the adverse events related to the device constituent parts that were observed in the above clinical studies. There were 2 instances of device-related infection after explantation of the intraventricular access device, possibly related to the port needle-intraventricular access device compatibility.

## 6. DESIGN CONTROL REVIEW

### 6.1. Design Review Summary

This review constitutes a review of the device constituent components of the combination product and does not include human factors or review of the leachables/extractables of the primary container closure of the combination product.

After several pre-meetings with the Sponsor it was unclear if the Sponsor would be able to obtain the necessary sterilization validation information in order to file the BLA. The sterilization documentation necessary for review (subject of the pre-BLA meetings) appeared to have been included in the submission and therefore the submission was deemed adequate for filing. A sterility consultant (Christopher Dugard CDRH/ODE/DAGRID/INCB) has reviewed the submitted sterility information for completeness and adequacy.

Design control information was reviewed by the lead reviewer and after several rounds of interactive review, the lead reviewer has found the contents of the submission adequate to demonstrate the safety and effectiveness of the device constituent parts of the combination product in the context of the intended use of the combination product.

#### 6.1.1. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the BLA by the Combination Product Developer	X		GSR 0009 / Module 1.11.1
Design Verification Data included in the BLA or adequately cross-referenced to a master file.	X		GSR 0001 / Module 3.2.P.7 and GSR 0009 / Module 1.11.1
Risk Analysis supplied in the BLA by the Combination Product Developer	X		GSR 0001 / Module 3.2.P.7
Validation Data <ul style="list-style-type: none"> <li>Human factors</li> <li>Clinical data</li> </ul>	X		GSR 0009 / Module 1.11.1 and GSR 0001 / Module 3.2.P.7
	X		
Traceability Documentation	X		GSR 0009 / Module 1.11.1 and Module 3.2.P.7

## 7. DESIGN VERIFICATION AND VALIDATION REVIEW

Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		
Adherence to FDA Guidance: Infusion Pumps Total Product Life Cycle: Guidance for Industry and FDA Staff issued in December 2014			X (approved syringe pump adheres to FDA Guidance)

NOTE: The reliability of the intraventricular access device compatibility with the (b) (4) port needle was of particular importance due to concerns regarding port leakage and risk of infection leading to early replacement of the access port.

Discipline -Specific Design Verification / Validation adequately addressed						
	Consult needed			Consultant	Attributes Acceptable	
	Yes	No	N/A		Yes	No
Biocompatibility	X			Sarah Mollo	X	
Sterility	X			Christopher Dugard	X	
Clinical	X			Bennett Blumenkopf	X	

The following table identifies any standards or relevant FDA guidance documents not listed in the above table that might be referenced by the sponsor or determined to be relevant by the CDRH / ODE reviewer in the course of the design review.

Reference Standard / Guidance	Description / Extent of FDA Recognition	Documentation Adequate	
		Yes	No
IEC 60601-2-24, Infusion Pumps standard	Not recognized	X	
ISO 8536-8:2015, Infusion Equipment for Medical Use	Recognized	X	
FDA Guidance for Infusion Pumps Total product Life Cycle issued in 2014	FDA Guidance	X	
ISO 10993, Biocompatibility	Recognized	X – see biocompatibility consultant review in Appendix C	



Other standards were utilized as reference to test methods, including but not limited to, 1990 FDA *Guidance on 510(k) Submissions for Implanted Infusion Ports* and ISO 594-2 for luer lock connections.

#### Design Validation Review

<b>Design Validation Attributes</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>
Phase III Study utilized the to-be-marketed device	X		
Bioequivalence Study utilized to-be-marketed device			X
Simulated Actual Use Study utilized to-be-marketed device			X

See Section 12 of this memo for all information requests and information provided by the Sponsor in relation to the device constituent parts utilized for the clinical trial 190-201 and 190-202. It was determined that the B Braun Perfusor Space Syringe Pump and the Codman HOLTER RICKHAM intraventricular access device/catheter would be included as the specific off-the-shelf components to be used with Brineura along with the Administration Kit based on clinical and bench top validation/verification testing completed by the Sponsor.

#### Design Verification Review

Select Essential Performance Requirements of System	Specification	Verification	Validation	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
Infusion Time	4 <sup>(b)</sup> <sub>(4)</sub> hours	TR-00565	Clinical trial 190-202	N/A	N/A	N/A
Flow Rate Accuracy	2.5 ml/hr +/- 1.0 ml/hr	TR-00565	Clinical trial 190-202	Y	Y	N/A – pump not part of combination product
Tubing Length	10-12 feet	Yes – measurement	Clinical trial 190-202	N/A	N/A	N/A
Administration Kit Hold-Up Volume	NMT <sup>(b)</sup> <sub>(4)</sub> ml	TR-00585	Clinical trial 190-202	Y	Y	N/A – CoA/CoC provided on incoming
ICV Port Access Compatibility	No leakage/ material degradation of intraventricular access device after 4 years of punctures	Benchtop Puncture Study and Material Degradation SEM images	Clinical trial 190-202	Y	Y	N/A

**All individual component specifications that make up the Administration Kit were provided by the Sponsor and are adequate to the lead consultant reviewer. CoA and CoC documentation were provided and will be provided upon receipt of all components.**

The Sponsor supplied TR-00565 Rev 1 titled Performance Characterization Report for Perfusor Space Infusion Syringe Pump for BMN 190 as verification of the infusion system’s requirements with the intended drug product. A summary of the results of the test can be seen below:

Table 7.1: Design Input Requirements Related to Syringe Pump Performance					
URS -190-001 Rev. 1 <sup>(1)</sup>		DIR-190-001 Rev. 2 <sup>(2)</sup>		Results	Acceptable
DIR ID	Design Input Requirement	DIR ID	Design Input Requirement		
1.1	Syringe Pump delivery rate of 2.5 mL/hr	9.1	When connected to the label specified pump and ICV access device, the fully assembled Administration Kit can consistently deliver product at a rate of 2.5 ml/hr ± (b) (4)	(b) (4) mL/hr	Yes
1.2	Assembled component devices must allow ICV delivery of BMN 190 at rate of 2.5mL/hour				
1.4, 5.e	Syringes must be compatible with the syringe pump (supported by the pump hardware interface and software)				
Body of DIR	Drug will be administered as a controlled infusion of 10 mL	1.3	The fully-assembled Administration Kit components can deliver 10mL of Drug Product with the label-specified syringe pump	Fully assembled system can deliver controlled infusion of expected volume	Yes
		7.3	When connected to the label-specified pump and ICV access device, the fully assembled Administration Kit will not leak Drug Product or ICV Solution via connections	No leaks were detected	Yes
Body of DIR	The overall infusion time is approximately 4 hours	10	The fully-assembled Administration Kit components can deliver Drug Product within a time period of at least (b) (4) hours	Tests performed over a 4 hour period	Yes

(1) Revision 1 was a combined URS/DIR document.

(2) The requirements in DIR revision 2 are consistent with the requirements in DIR revision 1, with additional specificity.

The Sponsor provided TR-00581 titled In-Use Compatibility and Stability of BMN 190 Drug Product and Flushing Solution with BMN 190 Administration Kit Components. A summary of the results of the study can be seen below:

Table 4-2: Design Input Requirements Related to Compatibility, Leachables and Filter Performance		
DIR ID	Design Input Requirements <sup>(1)</sup>	Verification
1.5	The fully-assembled Administration Kit components must not alter the formulation composition of the BMN 190 Drug Product	Data presented in QC-1330-A and Section 3 of this report demonstrate that the formulation of BMN 190 Drug Product met specifications following its use with BMN 190 Administration Kit components.
1.6	The fully-assembled Administration Kit components, must not alter the chemical composition of the BMN 190 Drug Product	Data presented in QC-1330-A demonstrates that leachable levels were acceptable following simulated administration of Drug Product and ICV Solution with BMN 190 Administration Kit components with the 18G needle. Per Section 3 of this report, the material of construction of the 21G needle is the same as the 18G therefore no change to leachables results is expected with the 21G needle.
1.7	The fully-assembled Administration Kit components must not alter the formulation composition of the BMN 190 ICV Solution	Data presented in QC-1330-A demonstrates that the formulation of BMN 190 ICV Solution met specifications following its use with BMN 190 Administration Kit components with the 18G needle. The smaller gauge needle is not expected to have any impact on the ICV solution as it does not contain any protein which could be sheared.
2.1	The Administration Kit will contain a filter placed at the end of the assembled infusion set (closest to the patient) to filter out (b) (4) particulates	Data presented in QC-1330-A demonstrates that the filter reduces (b) (4) particles.
8.2	The in- line filter will have no effect on purity and strength of the Drug Product	Data presented in QC-1330-A demonstrates that the purity and strength of the Drug Product met specifications following filtration through the in-line filter

(1)These DIRs are consistent with DIR 1.4 of URS-190-001 Rev 1 “All administration kit component devices must be suitable for use for delivery to the intrathecal, and/or cerebrospinal fluid space” but with added specificity.

The Sponsor provided TR-00585 titled BMN 190 Administration Kit Hold-Up Volume and the results of the test can be seen below:

Table 6.1 Design Input Requirements Infusion Set Dead (Hold- Up) Volume			
DIR-190-001 Rev. 2 <sup>(1)</sup>		Results	Acceptable
DIR ID	Design Input Requirement		
8.1	Fully assembled Administration Kit will require (b) (4) mL of ICV Solution to expel Drug Product from dead volume in infusion lines	(b) (4) mL	Yes

(1) This DIR is more stringent than URS-190-001 Rev. 1 which indicated no more than 5 mL of flushing solution would be provided

A bench top verification study for the intraventricular access device compatibility with the 22G (b) (4) needle of the Administration Kit was conducted that looked at both leakage and material degradation of the septum after puncturing. The results and review of this study are detailed in the Information Requests in Section 13 of this memo.

## 8. DISCIPLINE SPECIFIC SUB-CONSULTED REVIEW

### 8.1. Biocompatibility

The following is the recommendation of Dr. Sarah Mollo (CDRH/ODE/DAGRID/GHDB) biocompatibility consultant:

**Recommendation:**

The sponsor has provided a biocompatibility evaluation of the device constituents including the following endpoints: cytotoxicity, sensitization, irritation, systemic toxicity, genotoxicity, hemolysis, and material-mediated pyrogenicity. To address the subchronic and genotoxic endpoints, the sponsor has performed a leachables study and provided a toxicological risk assessment for the 3 compounds identified in the leachables analysis. The biocompatibility evaluation provided by the sponsor is acceptable (see below for comments on leachable study and risk analysis).

The extraction method used to assess the leachables is appropriate for the intended use of the device in the clinical trial (4<sup>(b)</sup><sub>(4)</sub> hour infusion). The sponsor did not conduct an exhaustive extraction (i.e. exaggerated time and temperature); however, the extraction was conducted with the drug product under conditions that mimic the intended clinical use. This is acceptable as the device is being approved specifically for use with the drug/treatment protocol/patient population in this BLA. The biocompatibility evaluation should not be considered acceptable for clearance for a general indications for use (e.g. administration of other drugs, longer administration times).

**Notes:**

In <sup>(b) (4)</sup> the draft labeling there is a statement that

<sup>(b) (4)</sup>

The information reviewed by the biocompatibility consultant included the following documentation:

- 3.2.P.2 Pharmaceutical Development Compatibility
- 0060 Follow up to FDA IR # 16 dated 14Oct2016 and IR # 20 dated 28Oct2016 submitted 21Nov2016

- draft-labeling-text
- Response to FDA Device RFI #20 dated 28Oct2016
- Response to FDA RFI #16 (device) dated 14Oct2016
- Response to Quality RFI Q9, 11, 13,14 dated 31Aug2016
- Test Reports for Extension Line
- Test Reports for Infusion Set
- Test Reports (b) (4) Needle

The biocompatibility consultant's full review is included in Appendix C of this review for further information. The lead reviewer concurs with the consultant's recommendation.

## 8.2. Sterility

Chris Dugard (CDRH/ODE/DAGRID/INCB) was consulted by the lead reviewer to review the sterility of the device constituents of the combination product. The consultant's memo is in Appendix B of this memo. Below is a summary of the consultant's review and recommendation:

Summary of issues identified during sterility consult:

- The sponsor should describe the product challenge devices use in the (b) (4) validation
- The sponsor should provide (b) (4) testing
- Bioburden testing and tests for sterility are needed for the syringe and hypodermic needle
- A more detailed protocol for the bacterial endotoxin testing is needed
- Material-mediated pyrogen testing is needed

The above issues were resolved following the sponsor's response on 08/05/2016. No further concerns in regards to sterility.

The information reviewed by the sterility consultant included the following documentation:

- "Auto Tubing Dose Audit"
- "CoA 536040"
- "CoA FS116"
- "CoC 21-2737-24"
- "CoC 302830"
- "CoC 305165"
- "Container Closure System" (section 3.2.P.7)
- "Dose Audit Report 302830"

- “Dose Audit Report 305165”
- “Dose Validation Report 302830”
- “Dose Validation Report 305165”
- “Endotoxin 21-2737-24”
- “Endotoxin 302830”
- “Endotoxin 305165”
- “Endotoxin 536040”
- “Endotoxin FS116”
- “FM-SP 15-02-536040”
- “FM-SP 15-05 – FS116”
- “Manual Assembly Dose Audit”
- “Response to Quality RFI dated 18Jul2016”
- “sterilization process validation final report.VP 10499-03”

The design requirements related to sterility as defined by the Sponsor in DIR-190 Rev 2 are as follows:

3.1	Endotoxin content for the (b) (4) Administration Kit must be less than 2.15 EU per USP<161> and USP <85> requirements.
5.1	(b) (4)
5.2	
5.2	
7.1	Each component in the Administration Kit must have its own individual sterile packaging
14.1	The labeling shall instruct the user that the kit contains 'individual components that are sterile'

As noted in the sterility consultant memo in Appendix B the Sponsor provided the sterilization information for each component of the Administration Kit as well as the endotoxin testing of all components together at release (b) (4):

Table 3.2.P.7.2.1.4.1: Administration Kit Components				
Component	Certificate of Analysis/Conformity	Bacterial Endotoxin Test (BET)	Sterilization Validation	Sterilization Method
Infusion set with 0.2µm filter	(b) (4)	Endotoxin FS116	Auto Tubing Dose Audit Manual Assembly Dose Audit FM-SP 15-05 – FS116 FM-SP 15-02 – 536040	(b) (4)
Extension line		Endotoxin 536040		
(b) (4) needle (22G, 16mm Port needle)		Endotoxin 21-2737-24	Sterilization Validation VP 10499-03	
Syringe (b) (4) 20mL)		Endotoxin 302830	Dose Validation Report 302830 Sterility Dose Audit 302830	
Hypodermic needle (21 gauge Syringe needle)		Endotoxin 305165	Dose Validation Report 305165 Sterility Dose Audit 305165	

Sterilization of the individual components of the BMN 190 Administration Kit is conducted (b) (4) in accordance with (b) (4). The individual components are non-pyrogenic and tested per USP <85> and meet limits as specified in USP <161>.

Endotoxin testing (per USP <85> and <161>) was conducted on Administration Kit device components for (b) (4)

(b) (4) The Endotoxin levels for the Administration Kit system must meet the USP <161> limit (b) (4). The Device History Record and supporting documentation will be reviewed for compliance with cGMP and established written SOPs.

BioMarin performs endotoxin testing on (b) (4) Administration Kit according to the operating procedures described in Attachment 14 - Endotoxin SOP and Attachment 15 – Kinetic-Chromogenic LAL



Test.

Reviewer comment: The sponsor has provided endotoxin testing protocols for both the third party suppliers as well as their own internal endotoxin testing. Given that all provided protocols conform to cited standards (USP<85> and USP<161>) (b) (4)

this information is adequate.

The sterility consultant’s full review is included as an amendment to this review for further information. The lead reviewer concurs with the findings of the consultant reviewer.

### 8.5. Clinical

Please see Appendix A for Dr. Blumenkopf’s initial clinical consultant review. The lead consultant reviewer and Dr. Blumenkopf jointly reviewed all interactive review information requests regarding the intraventricular port access device and port needle compatibility.

The result of the clinical and lead reviewer’s review of the device related information can be seen in the labeling and PMR recommendations seen in Section 14 of this memo.

The clinical consultant’s signature on this memo represents the clinical consultant’s concurrence with the review and recommendations put forth in this memo.

### 8.6. Labeling

Samuel Raben (CDRH/ODE/DNPMD) performed an informal consult for this review which consisted of checking the cleared/approved labeling of the intraventricular access device port and catheters to ensure that they were indicated for drug administration and there would not be an outstanding device issue for the labeling of Brineura. The consult was performed via email and the initial Information Requests regarding the labeling of the intraventricular access device labeling were drafted in consultation with Mr. Raben. See Section 12 for more details.

## 9. RISK ANALYSIS

### 9.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		

### 9.2. Summary of Risk Analysis



ICC 1600395

BLA 761052, Brineura (cerliponase alfa), BMN 190 Administration Kit

Biomarin Pharmaceuticals

The following is the risk analysis deliverables and approach taken by the Sponsor to identify all risks associated with the device constituents of the combination product:

(b) (4)



4 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

The following was the summary of the risk analysis provided by the Sponsor:

In summary, the risk management process was conducted in accordance with BioMarin SOP-103956 Quality Risk Management, and per the requirements of the BMN 190 Risk Management Plan, RMP-190-001.

Based on a comprehensive assessment of risks and systematic implementation of mitigations/controls that are already in place, the risks to patient safety and product quality associated with the BMN 190 Administration Kit have been reduced to acceptable levels. The implemented risk control measures have been successful, and it is anticipated that the three remaining risk control measures (kit packaging validation, shipping validation and accelerated aging) will also be successful.

## 10.LABELING

The following is taken from the labeling related to the device constituents.

### **Drug Product Labeling:**

#### **-----DOSAGE AND ADMINISTRATION-----**

- Aseptic technique must be strictly observed. Brineura should be administered by, or under the direction of a physician knowledgeable in intraventricular administration. Brineura is administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter. (2.1)

-----**CONTRAINDICATIONS**-----

- Acute intraventricular access device leakage, device failure, or device-related infection. (4)
- Patients with ventriculoperitoneal shunts. (4)

-----**WARNINGS AND PRECAUTIONS**-----

- Intraventricular Access Device-Related Complications: Inspect the scalp for skin integrity and for signs of intraventricular access device leakage. Do not administer if there are signs of device leakage or infection. Routinely send CSF samples for testing to detect subclinical device-related infections. (5.1)

### **2.3 Method of Administration**

Brineura and the Intraventricular Electrolytes must only be administered by the intraventricular route, using the provided Administration Kit. Each vial of Brineura and Intraventricular Electrolytes is intended for a single dose only.

Each infusion consists of 10 mL of Brineura followed by 2 mL of Intraventricular Electrolytes. The complete infusion must be administered using an infusion set with a 0.2 micron inline filter. The Intraventricular Electrolytes is used to flush the infusion line, port needle, and intraventricular access device in order to fully administer Brineura and to maintain patency of the intraventricular access device.

### **2.4 Preparation for Infusion**

- *Gather supplies:*
  - Brineura and Intraventricular Electrolytes Injection vials (package 1 of 2) [*see How Supplied/Storage and Handling (16)*]
  - Administration Kit (package 2 of 2) [*see How Supplied/Storage and Handling (16)*]
  - Syringe pump (not supplied)
- 

Inspect the Administration Kit infusion components to ensure the components are in the individual packages and have not been compromised.

### **2.5 Intraventricular Infusion Procedure**

#### Intraventricular Infusion of Brineura

Figure 1 represents the intraventricular infusion system set up. Use aseptic technique during the infusion. Follow the steps below to proceed with the intraventricular infusion.

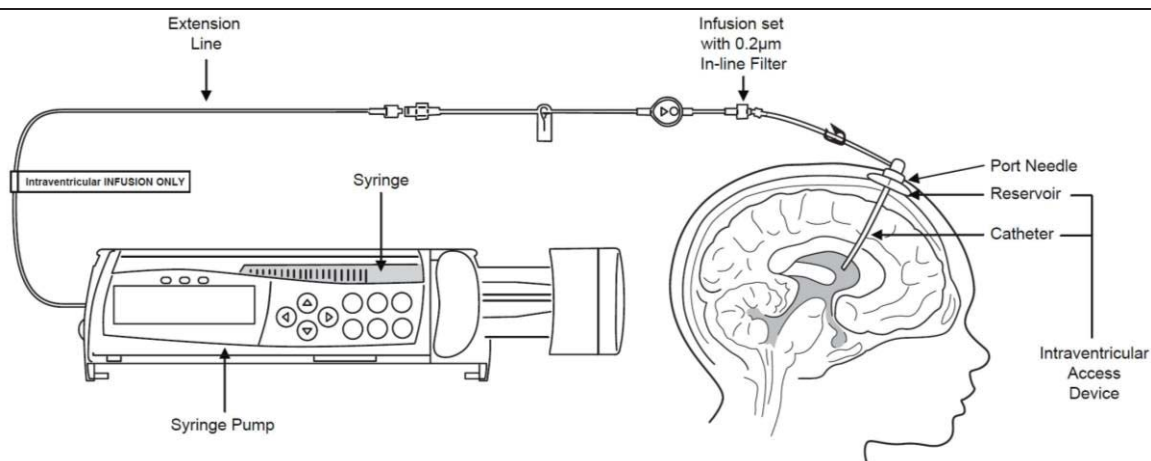


Figure 1

1. Label one sterile syringe “Brineura” and attach the syringe needle. Remove the green flip-off caps from the two Brineura vials. Use the “Brineura” labeled syringe to withdraw a total of 10 mL from the Brineura vials. **Do not** dilute Brineura. **Do not** mix Brineura with any other drug.
2. Label the infusion line “intraventricular infusion only” (see Figure 1).
3. Attach the syringe containing Brineura to the extension line (see Figure 2). Then connect the extension line to the infusion set with a 0.2 micron inline filter (see Figure 1).

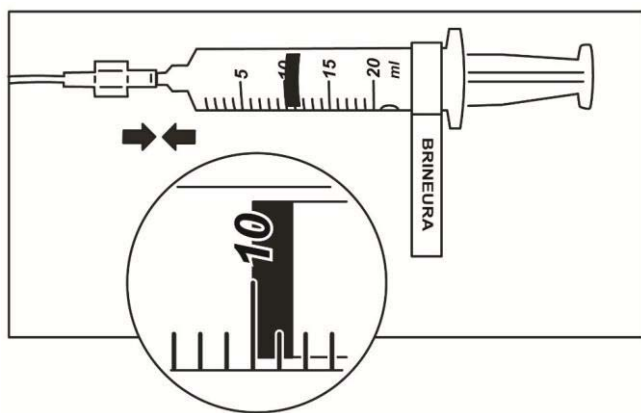
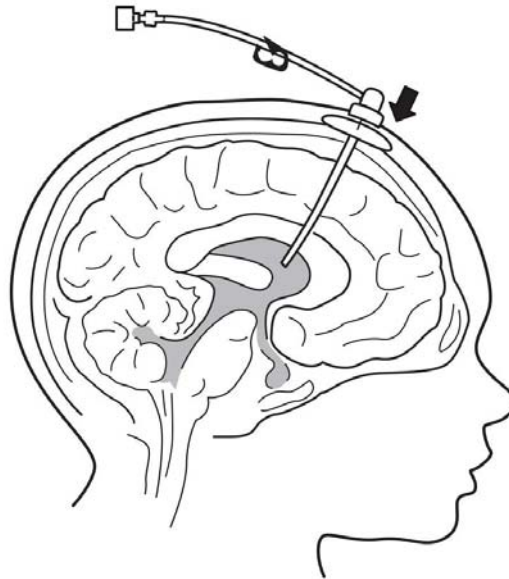


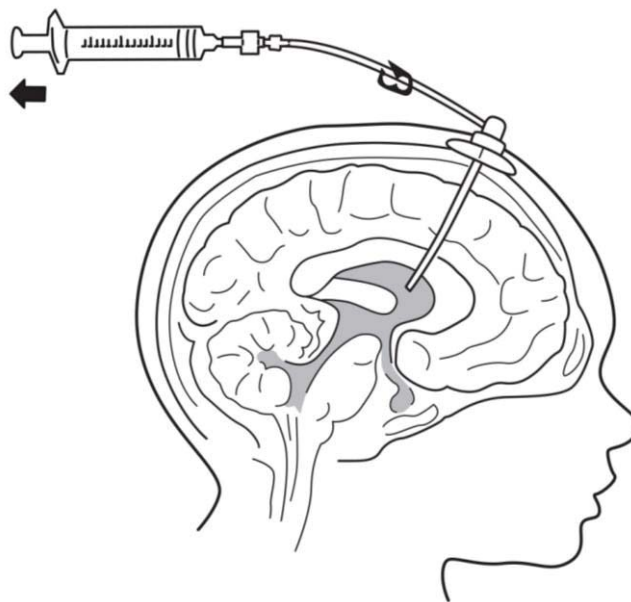
Figure 2

4. Prime the infusion components with Brineura.
5. Inspect scalp for signs of intraventricular access device leakage or failure and for potential infections [see Warnings and Precautions (5.1)].
6. Prepare the scalp for intraventricular infusion per institution standard of care.
7. Insert port needle into intraventricular access device (see Figure 3).



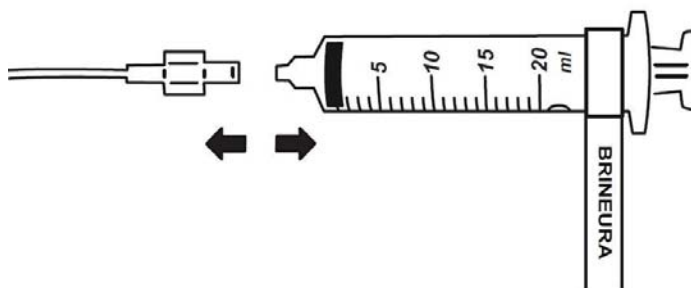
**Figure 3**

8. Connect a separate empty sterile (b) (4) luer lock syringe, no larger than 3 mL (not provided) to the port needle. Withdraw 0.5 mL to 1 mL of CSF to check patency of intraventricular access device (see Figure 4) and send specimen for culture.
- **Do not** return CSF to intraventricular access device.
  - Routinely send CSF samples for infection monitoring [see *Warnings and Precautions (5.1)*].



**Figure 4**

9. Attach the infusion set with 0.2 micron inline filter to the port needle (see Figure 1).
  - Secure the components per institution standard of care.
10. Place the syringe into the syringe pump and program pump to deliver at an infusion rate of 2.5 mL per hour. Set the occlusion alarm setting to alert at pressure  $\leq 281$  mm Hg. See syringe pump operating manual for details. **Do not** deliver as a bolus or manually.
11. Administer premedication 30 to 60 minutes prior to the start of infusion [see *Dosage and Administration (2.2)*].
12. Monitor vital signs (blood pressure, heart rate) prior to the start of infusion, periodically during infusion, and post-infusion [see *Warnings and Precautions (5.2)*].
13. Initiate infusion of Brineura at a rate of 2.5 mL per hour.
14. Periodically inspect the infusion system during the infusion for signs of leakage or delivery failure [see *Warnings and Precautions (5.1)*].
15. When the Brineura infusion is complete, detach and remove the empty syringe from the pump and disconnect from the tubing (see Figure 5). Proceed to Step 14 for Intraventricular Electrolytes infusion.



**Figure 5**

#### Intraventricular Infusion of Intraventricular Electrolytes

Administer the Intraventricular Electrolytes provided **after** Brineura infusion is complete.

16. Label one sterile syringe “Intraventricular Electrolytes” and attach the syringe needle. Remove the yellow flip-off cap from the Intraventricular Electrolytes Injection vial. Withdraw 2 mL of Intraventricular Electrolytes. Discard the remaining unused portion.
17. Attach the syringe to the extension line (see Figure 6).

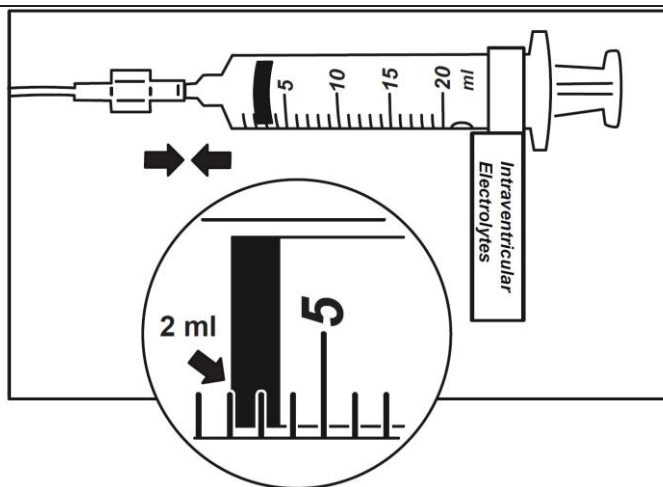


Figure 6

18. Place the syringe into the syringe pump and program pump to deliver at an infusion rate of 2.5 mL per hour. Set the occlusion alarm setting to alert at pressure  $\leq 281$  mm Hg. See syringe pump operating manual for details. **Do not** deliver as a bolus or manually.
19. Initiate infusion of Intraventricular Electrolytes at a rate of 2.5 mL per hour.
20. Periodically inspect the infusion system during the infusion for signs of leakage or delivery failure.
21. When the Intraventricular Electrolytes infusion is complete, detach and remove the empty syringe from the pump and disconnect from the infusion line.
22. Remove the port needle. Apply gentle pressure and bandage the infusion site per institution standard of care.

Dispose of the infusion components, needles, unused solutions and other waste materials in accordance with local requirements.

## 5 Warnings and Precautions

### 5.1 Intraventricular Access Device-Related Complications

Brineura must be administered using aseptic technique to reduce the risk of infection. Healthcare professionals should inspect the scalp for skin integrity to ensure the intraventricular access device is not compromised prior to each infusion [see *Dosage and Administration (2.5)*].

Brineura is contraindicated if there are signs of acute intraventricular access device-related complications (e.g., leakage, device failure or signs of device-related infection such as swelling, erythema of the scalp, extravasation of fluid, or bulging of the scalp around or above the intraventricular access device) [see *Contraindications (4)*]. In case of intraventricular access device complications, discontinue the Brineura infusion and refer to the device manufacturer's labeling for further instructions.

CSF samples should routinely be sent for testing to detect subclinical device infections [see *Dosage and Administration (2.5)*].

In clinical studies with Brineura, intraventricular access device-related infections were observed in two patients. In each case, antibiotics were administered, the intraventricular access device was replaced, and the patient continued on Brineura treatment.

Material degradation of the intraventricular access device reservoir may occur after approximately 105 perforations of the intraventricular access device. The intraventricular access device may require replacement as soon as, or prior to, 105 administrations of Brineura, equating to approximately 4.3 years of regular administrations.



**BMN-190 Administration Kit Shelf Life:**

Individual Components:

Administration Kit Component	Labeled Shelf Life
Infusion Set with In-line 0.2 µm Filter	3 years
Extension Line	3 years
(b) (4) Port Needle (16mm)	5 years
Syringe (20 mL)	5 years
Syringe Needle (21G, 1”)	5 years

The Sponsor provided the following information regarding the shelf life/expiration dating of the components of the Administration Kit:

BioMarin sets the expiry date of the BMN 190 Administration Kit based on the shortest expiry date of the



components used in the kit, as stated in the BMN 190 Administration Kit Specification Document PS-12632 and described by BioMarin procedure SOP-107751, Lot Number Creation, Issuance and Printing of Batch Records. (b) (4)

Protocols PVP-111690, “Accelerated Aging Qualification of the Packaging Configuration for BMN190 Administration Kit” and PVP-111693, “Real Time Aging Qualification of the Packaging Configuration for BMN190 Administration Kit” are designed to provide documented evidence that the printed folding paperboard carton, associated unique device identification (UDI) label, and tamper evident seal used for packaging of the BMN190 Administration Kit are capable of maintaining package integrity until the expiration date. Protocols are designed to measure performance for up to 36 months in accelerated and real time aging studies.

These studies confirm packaging seal integrity following the packaging processes and that the devices remain sterile throughout their assigned shelf-life. (b) (4)

(b) (4) therefore shelf-life studies consisted of packaging validation studies and sterilization validation. Confirmation of performance at the end of shelf-life was not required. Given that these products have been commercially available and successfully used for >30 years, and because of the low likelihood of time-dependent product degradation, end of shelf life performance was not verified by the manufacturer.

The purpose of this follow-up is to provide end of shelf-life performance testing results for the (b) (4) syringe and syringe needle. A response to Question #12 above, received from the Agency on August 31st, 2016, has already been submitted to the Agency on September 21, 2016 (refer to SN 0031). The response submitted to the Agency on September 21, 2016 included information regarding protocols PVP-111690 and PVP-111693, as well as long term and accelerated aging study reports for the (b) (4) components of the BMN 190 Administration Kit (infusion set with 0.2µm filter (b) (4), extension line (b) (4) and (b) (4) needle (b) (4)).

Long term and accelerated aging performance testing has been conducted by (b) (4) or the syringe and syringe needle. The shelf-life and aging study reports for the individual components are listed in the table below and provided with this response.

The (b) (4) syringe met the majority of acceptance criteria. The syringe failed one of the performance tests, the plunger rod retention test, at all time points for accelerated aging (60°C). Plunger rod retention forces measure the amount of force necessary to remove the plunger rod with the stopper from the barrel of the syringe. In this aging study, a few samples exhibited forces slightly above the high limit (for example: 2 samples out of 35 had pull forces above the upper specification limit of (b) (4) lbs (20.71 and 21.75 lbs) at 0 weeks) (b) (4) has initiated a CAPA and BioMarin will continue to follow-up with (b) (4) as results are obtained.

According to (b) (4) a higher force would make it difficult for the plunger to be inadvertently withdrawn from the syringe barrel. Since the administration of BMN 190 does not require removal of the plunger rod, this test result

would not impact the performance of the syringe. As stated in the response submitted to the Agency on September 21, 2016, BioMarin assigns the expiry date of the BMN 190 Administration Kit based on the shortest expiry date of the components used in the kit (refer to Table 2). The Administration Kit carton and labeling will include the expiration date of the Administration Kit.

**Table 2: Shelf Life of the BMN 190 Administration Kit Components**

Component	Part Number	Shelf Life (b) (4)
Infusion set with 0.2µm filter		
Extension line		
(b) (4) needle (16mm Port needle)		
(b) (4) Syringe		
(b) (4) Syringe Needle		

**Carton Labeling:**

(b) (4)

(b) (4)



Reviewer Comments:

The lead reviewer notes that the carton labeling of the Administration Kit be states the expiration date of commensurate with the shortest shelf life of the components within the kit when printed. The Sponsor agreed to this via IR response.

## **11.DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION**

The Sponsor provided the following statement regarding the administration kit release testing to be conducted by the Sponsor:

(b) (4)



the 510(k) of the release testing for the syringe and syringe needle are provided in the table below. The release testing specification for the BMN 190 Administration Kit is provided (see Specification Document PS-12632).

**Table 3: List of Specification Documents for the BMN 190 Administration Kit Components**

Component	Part Number	Specifications
Infusion set with 0.2µm filter		(b) (4)
Extension line		
(b) (4) needle (16mm Port needle)		
Syringe ( (b) (4) 20mL)		
Hypodermic needle (21G Syringe needle)		

(b) (4) kits will be released by Quality Assurance according to SOPs.

(b) (4). The Endotoxin levels for the Administration Kit system must meet the USP <161> limit of (b) (4). The Device History Record and supporting documentation will be reviewed for compliance with cGMP and established written SOPs. Expiration assigned to the Administration Kit will not exceed the shortest expiration dating of the individual components.

**Reviewer Comments:**  
**The Sponsor will conduct endotoxin testing at release** (b) (4)  
**This is to ensure that the sterility requirements of the Administration Kit are maintained** (b) (4). **The sterility validation and test methods have been reviewed by CDRH/ODE and found to be acceptable.**

## 12.INTERACTIVE REVIEW

Filing Review Information Request (sent with Filing Letter)  
 We note that the proposed labeling does not specify any particular intracerebroventricular (ICV) access device to be used in the delivery of BMN 190. In order to ensure the safe administration of BMN 190 please provide updated labeling that specifies the ICV access device, including the ventricular catheter, that was utilized in the clinical trials and verified for performance on the bench. Note that the indications for use of the ICV access device that you plan to label for use with your drug product should not prohibit delivery of medication into the ICV space.

**Sponsor Response (received on 09/01/16)**  
 The prescribing information has been revised to include the specific intracerebroventricular (ICV) access devices (reservoir and the ventricular catheter), used in the clinical trial and shown to be compatible with BMN 190 via drug-

device compatibility testing. Compatibility data for a representative Codman reservoir and catheter (part numbers 82-1625 and 82-1650, respectively) are provided in Section 3.2.P.2.6 of the BLA.

While additional ICV access devices were used in the clinical trial (outside of the United States), BioMarin is including only those devices which are appropriate for accessing the cerebral ventricles for therapeutic drug administration according to their approved 'indications for use statements'. The devices proposed in the prescribing information have clearance under 510(k) (b)(4). The 'indications for use' statement, applicable to all models being added to the prescribing information (reservoirs 82-1625, 82-1621, 82-1616 and catheter 82-1650), does not prohibit delivery of medication into the ICV space.

#### Reviewer Comments

The consultant reviewer found the response adequate; however, the labeling was later updated to specifically indicate the clinically used and bench verified intraventricular access device based on port needle compatibility.

#### Agency Information Request #2 (sent on 07/18/16)

In document DIR-190-001 Rev. 2 you list a table of Design Input Requirements.

1. Please provide a traceability matrix that denotes the verification and validation completed for each design requirement and the location of the V&V documentation.
2. Please provide any associated verification test reports and test methods, including acceptance criteria and justification of the acceptance criteria, for each design requirement. In particular, please be sure to address verification of requirements 9.1 for delivery accuracy ( $2.5 \text{ mL/hr} \pm (b)(4)\%$ ) and 13.9 for simulated shipping (maintenance of essential performance such as delivery accuracy and sterile barrier after shipping).
3. You provided Dose Audits and Validation reports for the components in the administration kit that are sterilized (b)(4). However, you did not provide the most recent cycle validation. While it does not appear you are changing the cycle as previously accepted, this information is useful to ensure the cycle is still adequate and to compare this validation with the provided dose audits. Please provide the most recent (b)(4) cycle validation in a full test report (much like what was provided for the (b)(4) validation).

#### Sponsor Response (received on 07/28/16)

During the development of the Verification and Validation (V&V) supporting documentation, it was recognized that the sources for the design inputs required additional clarification, therefore the "Sources of Design Inputs" memo was generated to provide documented justification for the requirements in the Design Input Requirement (DIR). As a result, DIR-190-001 Rev. 2 has been updated to revision 3; the update incorporates information from the "Sources of Design Inputs" memo that was approved by BioMarin Medical Affairs, Clinical Sciences, and Pharmacovigilance. An updated User Requirements Specification, URS-190-001 Rev 3, is also provided.

The attached trace matrix for DIR-190-001 Rev. 3 captures the status of the 51 identified input requirements; where 18 requirements have been completed, 16 requirements are in progress pending Agency review (labeling), 12 requirements have documents routing for approval and 5 requirements are in progress pending completion of validation. Target completion for 16 of the requirements routing for approval and in progress pending validation is August 19, 2016; the aging test requirement will be ongoing.

- a. The trace matrix provides the V&V document number and status of each document supporting the specific design input requirement. Refer to Table 1 for documents included in the trace matrix. Proposed labeling and letters of authorization for the device 510(k)s were provided in the original BLA and are not attached to this response.
- b. Associated V&V test reports are also provided where DIR expectations (acceptance criteria) are captured. As requested by the Agency, additional clarification are provided with respect to items 9.1 and 13.9 below.

Requirement 9.1 is designed to assess the accuracy of the labeled pump with the BMN 190 Administration Kit device components. The accuracy requirement of  $2.5 \text{ mL/hr} \pm (b)(4)$  in DIR-190-001 Rev. 2 is based on the pump



manufacturer's specification. BioMarin has performed testing (TR-00565) confirming acceptable performance of the pump. Subsequent to the verification of pump performance, DIR-190-001 Rev. 3 has been updated to define an acceptable target delivery rate range as 2.5 mL/hr  $\pm$  1.0 mL/hr based on process need and patient safety.

Requirement 13.9 was designed to assess the suitability of the carton to protect the device components from damage during shipping. Shipping validation is in progress. Post-shipping assessments include visual inspection of components for damage and container closure integrity testing per ASTN-D4169. Delivery accuracy is not expected to be impacted, provided that the individual components are not damaged during shipping. Requirement 13.9 in DIR-190-001 Rev. 3 has been combined with Requirement 13.1.

The documents listed in Table 1 are being provided with this response. The status of each of these attachments is defined in the trace matrix.

**Table 1: BioMarin V&V Supporting Documentation**

Document Number	Document Description
DVSR-190-002	DVSR-190-002 Rev 1 Clinical Data on Interface between (b) (4) Needle and ICV Access Device 20160720.pdf
Picture of component packaging label	Package labels for: Infusion set with 0.2µm filter (b) (4) Extension line (b) (4) needle (16mm Port needle) (b) (4)
PQ-16-4003	BMN 190 Administration Kit Packaging Process Performance Qualification Protocol
PS-12632	Drug Product Specification Brineura Administration Kit
PVP-111628	Qualification of the Packaging Configurations for the Distribution of BMN190 Administration Kit
PVP-111690	Accelerated Aging Qualification of the Packaging Configuration for BMN190 Administration Kit (55C)
PVP-111693	Real Time Aging Qualification of the Packaging Configuration for BMN190 Administration Kit
QC-1330-A	QC-1330-A Comparability Report-QCA and formulation-USA.pdf
QC-1640-A	QC-1640-A BMN190 Administration Kit Endotoxin Study Report 20160722.pdf
RM-Z112546	Raw Material Specification: 20ml (b) (4) Syringe with (b) (4) Luer-Lok tip
RM-Z112547	Raw Material Specification: 21 G x 1 in. (b) (4) general use sterile hypodermic needle
RM-Z112548	Raw Material Specification: (b) (4) Needle (b) (4) 22 gauge x 5/8 inch
RM-Z112549	Raw Material Specification: (b) (4) Extension Set with Male Luer Lock
RM-Z112550	Raw Material Specification: (b) (4) Extension Set with 0.22 Micron Filter
RMP-111333	Raw Material Packaging Specification: Carton, (b) (4) BMN 190
TR-00565	TR-00565 Performance-Syringe Pump Report_20160726.pdf
TR-00581	TR-00581 In-Use Compatibility Report 20160722.pdf
TR-00585	TR-00585 BMN 190 Administration Kit Hold-Up Volume 20160722.pdf

**Reviewer Comments:**

The Sponsor provided all documentation listed above and it was reviewed by the lead consultant reviewer. URS-190-001 Rev 3 for User Requirements Specifications was provided by the Sponsor and a trace matrix DIR-190-001 Rev 3 was provided that supplied the traceability between requirements and verification testing in the following manner with Inputs/Outputs/DVT Activity/Document Location/Status:

BMN 190 Administration Kit Design Control Trace Matrix Attachment 1, DVP-190-001 Rev 1						
DIR ID	Design Input Requirements	DVT ID	Design Output	DVT Activity Type	Document Number or Location	Status

Subsequent information requests were sent regarding incomplete testing.

For brevity, not all design input requirements are copied here but all requirements were reviewed. Particular requirements such as DIR 1.8/1.9 for the port needle/intraventricular access device compatibility were revised through subsequent information requests. The information provided by the Sponsor was adequate to satisfy the information request.

The second request of this IR is captured as part of Christopher Dugard’s sterility consultant review. Subsequent IR’s were sent to the Sponsor in relation to this request and the deficiency was resolved.

Agency Information Request #2 (sent on 08/05/16)

- In regards to the (b) (4) validation for the (b) (4) needle component, the provided test report indicates the product challenge devices used were a (b) (4). However, further details on these devices were not provided. Please describe the product challenge devices used and discuss how they represent a greater challenge to sterility than the subject component (i.e. the (b) (4) needle). This will help ensure the provided validation is representative of the subject component.
- You provided (b) (4) validation for the (b) (4) needle component. However, you did not provide (b) (4) testing. Please provide (b) (4) testing or justify why this testing is not needed. This will help ensure the (b) (4) are within the limits outlined in (b) (4).
- In regards to the syringe and hypodermic needle, you provided dose validation reports, dose audit reports, and dose mapping reports for the indicated (b) (4) cycles. However, you did not provide bioburden testing or a test for sterility as required by (b) (4) for auditing a sterilization dose. Please provide bioburden testing and tests for sterility in accordance with (b) (4) for both the syringe and hypodermic needle. This will help ensure that the average bioburden remains the same and that the delivered dose produces a sterile product.
- You provided results of endotoxin testing for the components in the administration kit. However, the method summary found in section 3.2.P.7.2.1.5 “Endotoxin Testing” is vague. Please provide a detailed protocol of the provided endotoxin testing for each component of the administration kit. This information will be useful in determining if the provided testing conforms to the cited standards.
- To support your claim that the administration kit is “non-pyrogenic”, you provided bacterial endotoxin testing. However, material-mediated pyrogens may also leach from the device and should be addressed as well. Please provide material-mediated pyrogen testing for all components of the administration kit following USP<151> or an

equivalent validated method. This will help ensure that the major sources of pyrogens are addressed, which will help prevent potential febrile reactions.

**Sponsor Response (received on 08/12/16)**

See sterility consultant memo.

**Reviewer Comments**

**The Sponsor's response and sterility consultant's comments can be seen in the sterility consultant's review memo. The lead consultant reviewer concurs with the recommendations of the sterility consultant.**

Agency Information Request #3 (sent on 08/31/16)

1. We note that you have not provided any testing for requirements or specifications for leakage or tensile strength of the appropriate Administration Kit components according to ISO 8536-8:2015. Please update your design requirements within DVP-190-001 to include these requirements and specifications and the associated testing to verify the requirements. If you intend to rely on the component manufacturers for the verification of these requirements be sure to provide reference to the location of this testing within each component's respective regulatory file.
2. In your response dated July 27, 2016, you state that Requirement 13.9 of DVP-190-001 was designed to assess the suitability of the carton to protect the device components from damage during shipping. You also state that the shipping validation is still in progress. Provide the test results of PQ-16-4003, PVP-111628, PVP-111690, and PVP-111693 to demonstrate that the sterile barrier remains intact for all administration kit components through kit assembly, aging, and shipping. Additionally, in order to ensure that the device constituent parts of the combination product can successfully maintain their performance requirements after shipping, you should provide verification of the device components specifications. If verification of the performance requirements of the components after shipping has been completed by the respective component manufacturers please provide reference to the location of the associated testing within the regulatory file for which each component is held.
3. You reference a completed design FMEA and risk management report within your submission; however, these documents are not provided in the BLA. Provide the design FMEA and risk management report. Also, be sure to address the risk of occlusion, kinking, leakage, improper component connections (i.e. luer lock connections), and other device specific risks associated with the Administration Kit within your design FMEA.
4. Provide the proposed shelf life of Administration Kit and provide the labeled shelf life for each of the device constituent parts. Note that the proposed shelf-life of the Administration Kit may not exceed that of the Administration Kit's individual components since they are to be packaged together and are disposable. The Administration Kit carton and labeling should state the expiration date of the Administration Kit. Additionally, provide a rationale for why the long-term and accelerated aging testing completed according to PVP-111690 and PVP-111693 verifies that the Administration Kit maintains its performance requirements up to the proposed shelf life. If you intend to rely on testing completed by the manufacturer of the device components to verify the



components' performance requirements through their intended shelf life, be sure to provide the location of the associated testing within the regulatory file for which each component is held.

5. Provide all completed testing that was noted as pending within your latest submission of BMN 190 Administration Kit Design Control Trace Matrix DVP-190-001 Rev 1. This should include all biocompatibility testing as well as a repeat of the drug product quality and leachables testing under QC-1330-A. If any testing remains pending or incomplete provide a rationale as to why the incomplete testing is acceptable for approval of the combination product. Alternatively, provide a timeline for submission of the completed testing.
6. Provide clarification regarding the release specifications of the Administration Kit components. It is noted that endotoxin limits will be tested prior to lot release, however no functional specifications (i.e. tensile strength, leakage, dimensional analysis, etc.) have been included. If you intend to rely on the respective manufacturer's certificate of analysis for the functional specifications of the kit components please reference the location of the release testing completed by the manufacturers of the components within the regulatory submission for which each component is held.

**Sponsor Response (received on 09/15/16)**

#1:

The BMN 190 Administration Kit Design Input Requirements (DIR-190-001 Rev 4) and the Design Control Trace Matrix (Attachment 1 of DVP-190-001) have been updated to address ISO 8536-8:2015 requirements for tensile strength and leakage. BioMarin has designed the Administration Kit to contain 510(k) cleared and commercially available devices which have been subjected to pre-market requirements and is relying on the vendors to perform applicable performance testing in compliance with their release specifications. As noted in DIR Revision 4.1, BioMarin will confirm that they are 510(k) cleared components, and BioMarin requires confirmation of adherence to the vendor specifications upon receipt.

Functional testing is conducted by the device manufacturers, (b) (4), for the components of the BMN 190 Administration Kit. A list of specifications documents, related to testing for leakage or tensile strength is provided in Table 1. The pull test and water leak tests performed by (b) (4) confirm its fitness for use and address the ISO 8536-8:2015 requirements. The applicable test methods are listed in Table 1 and attached to this response.

The (b) (4) syringe meets the requirements of ISO 594-2, which include leakage tests that confirm its fitness for use and satisfy the requirements of ISO 8536-8:2015. The syringe needle is not part of the infusion set used with pressure infusion apparatus and is not subject to ISO 8536-8:2015 requirements. The product specification for the syringe, and the syringe stopper test method are listed in Table 1.

**Table 1: Testing Requirements for the BMN 190 Administration Kit Components**

Component	Part Number	Test Method, Inspection Procedure, or Specification
Infusion set with 0.2µm filter	(b) (4)	MTY-M-181_101T (b) (4) Assembly Functional Specifications and Water/Leak Test
		MTY-M-35_101T (b) (4) Pull Test Criteria
		MTY-QC001 Assembly Specification
		FS116 (b) (4) Structure Report
Extension line		M-181 Assembly Functional Specifications and Water/Leak Test
		M-35 Pull Test Criteria
		SPC-QC001 Assembly Specification
		536040 (b) (4) Structure Report
(b) (4) needle		S21-2939.109 Product Specification
Syringe (b) (4) 20mL)		SP100001 Product Specification
		IT21-03 Leak Test

#2:  
 The packaging performance qualification (PQ), PQ-16-4003, is ongoing. The first packaging PQ run has been successfully completed. All samples passed the integrity testing, per ASTM F1886-09 (Visual Inspection), ASTM 2096-11 (Bubble Leak) and ASTM F1929-15 (Dye Penetration). An interim report has been generated and is attached with this response (see TS-16-1004-IR). The final report including the completion of the three performance qualification runs is expected to be available by the end of September 2016 and will be submitted to the Agency. Based on results from the first packaging run and the completed shipping validation studies (see PVR-111957 and summary below), the remaining two PQ packaging runs are expected to produce similar acceptable results for integrity testing.

The final report (PVR-111957) for the protocol (PVP-111628), “Qualification of the Packaging Configurations for the Distribution of BMN190 Administration Kit” provides documented evidence that the folding paperboard carton design used for packaging of the BMN190 administration kit is capable of withstanding transportation hazards while maintaining the integrity of its inner components. (b) (4)

(b) (4)

BMN190 Administration Kit were subjected to testing per ASTM F2096 to demonstrate that the packaging maintained the container closure integrity during the simulated transit. The entire test set of (b) (4) pouches passed the integrity test. The results were acceptable as no leaks were detected.

The interim report (PVR-112355) for the protocol (PVP-111690), provides data for the accelerated aging of the carton, label on the carton, and tamper evident seal, with simulated transit of the aged kits in the (b) (4) shipper. The BMN190 Administration kit carton was tested at 55°C for 30 days (representing 9 months at 23°C) per protocol.

(b) (4)

BioMarin has also subjected the infusion components to worst-case shipping conditions, as part of the Administration Kit shipping validation studies (refer to PVR-111957), and results demonstrate that all samples passed the testing, with no leaks or integrity issues. Supporting documents are listed in the table below and provided with this response.

**Table 1: List of Supporting Documents for the BMN 190 Administration Kit Components**

Component	Part Number	Supporting Documentation
Infusion set with 0.2µm filter	(b) (4)	Report 03186 – Packaging Distribution Testing Protocol 03186 – Packaging Distribution Testing Memo 03186 – Rationale for Representation
Extension line		Report 08052 – Packaging Distribution Testing Protocol 08052 – Packaging Distribution Testing
(b) (4) needle (16mm Port needle)		TR-1560 – Pack Verification

The packaging performance qualification (PQ), PQ-16-4003 has been successfully completed. Three performance runs were conducted and all samples passed the integrity testing, per ASTM F1886-09 (Visual Inspection), ASTM 2096-11 (Bubble Leak) and ASTM F1929-15 (Dye Penetration). The final report is being provided with this response (see Report PQ-16-4003-R).

#3:

The design FMEA is provided with this response, and the risk management report was submitted to the FDA on July 6, 2016 (SN#006).

The design FMEA (dFMEA-190-001 Rev. 2, attached) has evaluated risks associated with occlusions, kinking, leakage and improper component connections (i.e. luer lock connections). Table 2 below identifies the Hazard ID numbers from the dFMEA that are specific to these risks. The probability of occurrence of the failure mode for these risks has been reduced to the minimum level and residual risks are considered acceptable.

**Table 2: Risks and Hazard Identification**

<b>Risk</b>	<b>dFMEA-190-001 Rev. 2 Hazard ID</b>
Occlusions	17-20, 147, 149, 159-179
Kinking	159-179
Leakage	13, 14
Improper component connections	118-121

There have been no updates to the interim Risk Management Report (RMR-190-001 Rev. 1) since it was submitted to the FDA on July 6, 2016 (SN#006). Three risk mitigation measures were outstanding at the time of submission of this report; the status of the three remaining control measures are complete or in progress. Briefly, the shipping validation (PVP-111628) is complete: this study provides documented evidence that the folding paperboard carton design used for packaging of the BMN190 administration kit is capable of withstanding the transportation hazards associated with its distribution environment and maintain the integrity of its inner components. The packaging performance qualification (PQ), PQ-16-4003, is ongoing and will be completed in November 2016. The accelerated aging study is ongoing and results will be available in January 2017. Additional details related to the outstanding shipping studies will be provided with response to question 10 (to be submitted by September 21, 2016).

#4:

BioMarin sets the expiry date of the BMN 190 Administration Kit based on the shortest expiry date of the components used in the kit, as stated in the BMN 190 Administration Kit Specification Document PS-12632 and described by BioMarin procedure SOP-107751, Lot Number Creation, Issuance and Printing of Batch Records. (b) (4)

Protocols PVP-111690, "Accelerated Aging Qualification of the Packaging Configuration for BMN190 Administration Kit" and PVP-111693, "Real Time Aging Qualification of the Packaging Configuration for BMN190 Administration Kit" are designed to provide documented evidence that the printed folding paperboard carton, associated unique device identification (UDI) label, and tamper evident seal used for packaging of the BMN190 Administration Kit are capable of maintaining package integrity until the expiration date.

Protocols are designed to measure performance for up to 36 months in accelerated and real time aging studies. Long term and accelerated aging studies for labels and packaging of the individual components have been conducted by (b) (4)

(b) (4) The shelf-life and aging study reports for the individual components are listed in the table below and provided with this response.

These studies confirm packaging seal integrity following the packaging processes and that the devices remain sterile throughout their assigned shelf-life. (b) (4)

BioMarin has not been able to obtain performance data at the end of shelf life from (b) (4) for the syringe and syringe needle (b) (4). BioMarin continues to follow-up with (b) (4) and will provide these data to the Agency as they become available.

**Table 2: Shelf Life of the BMN 190 Administration Kit Components**

Component	Part Number	Shelf Life	Reference
Infusion set with 0.2µm filter	(b) (4)	(b) (4)	Report 02087 – Package Integrity Protocol 02087 – Package Integrity
Extension line			Report 08030 – Package Stability Study Protocol 08030 - Package Stability Study
(b) (4) needle (16mm Port needle)			Report 11/070/22 - Pack Shelf Life Verification MVP 10194 - Master Validation Plan

(update response on 11/19/16):

The purpose of this follow-up is to provide end of shelf-life performance testing results for the (b) (4) syringe and syringe needle. A response to Question #12 above, received from the Agency on August 31st, 2016, has already been submitted to the Agency on September 21, 2016 (refer to SN 0031). The response submitted to the Agency on September 21, 2016 included information regarding protocols PVP-111690 and PVP-111693, as well as long term and accelerated aging study reports for the (b) (4) components of the BMN 190 Administration Kit (infusion set with 0.2µm filter (b) (4), extension line (b) (4) and (b) (4) needle (b) (4)).

Long term and accelerated aging performance testing has been conducted by BD for the syringe and syringe needle. The shelf-life and aging study reports for the individual components are listed in the table below and provided with this response.

**Table 1: Shelf Life of the Syringe and Syringe Needle**

Component	Part Number	Shelf Life	Reference
(b) (4) Syringe	(b) (4)	(b) (4)	Functional Testing – HSE-TR-11-06-001
(b) (4) Syringe Needle			Functional Testing – HSE-TR-10-01-003



The (b) (4) syringe met the majority of acceptance criteria. The syringe failed one of the performance tests, the plunger rod retention test, at all time points for accelerated aging (60°C). Plunger rod retention forces measure the amount of force necessary to remove the plunger rod with the stopper from the barrel of the syringe. In this aging study, a few samples exhibited forces slightly above the high limit (for example: 2 samples out of 35 had pull forces above the upper specification limit of (b) (4) bs (20.71 and 21.75 lbs) at 0 weeks) (b) (4) has initiated a CAPA and BioMarin will continue to follow-up with (b) (4) as results are obtained.

According to (b) (4), a higher force would make it difficult for the plunger to be inadvertently withdrawn from the syringe barrel. Since the administration of BMN 190 does not require removal of the plunger rod, this test result would not impact the performance of the syringe. As stated in the response submitted to the Agency on September 21, 2016, BioMarin assigns the expiry date of the BMN 190 Administration Kit based on the shortest expiry date of the components used in the kit (refer to Table 2). The Administration Kit carton and labeling will include the expiration date of the Administration Kit.

**Table 2: Shelf Life of the BMN 190 Administration Kit Components**

Component	Part Number	Shelf Life
Infusion set with 0.2µm filter		(b) (4)
Extension line		
(b) (4) needle (16mm Port needle)		
(b) (4) Syringe		
(b) (4) Syringe Needle		

#5  
 BMN 190 Administration Kit Design Control Trace Matrix DVP-190-001 Rev 1 had 35 of 52 items noted as pending (34 via DVSR-190-001, 1 via PVR-111957). The updated version of the trace matrix captures that 29 of these pending items have been completed (see Attachment 1 DVP-190-001 and DVSR-190-001 Rev 2).

Four of the remaining six items are associated with the packaging, shipping and aging studies (PQ-16-4003, PVP-111628, PVP-111690, and PVP-111693); these studies are completed or in progress (the response to question 10 will provide a detailed status of each study). Results of the studies that have been performed to date indicate that the packaging, shipping and accelerated aging (first time point) performance were successful. These results provide confidence that the combination product is acceptable for approval. Ongoing accelerated and real-time aging studies are anticipated to provide further evidence of acceptability (results will be available in November 2016 and (b) (4), respectively).

The remaining two items are being addressed by repeating the drug product quality and leachables testing, which was originally performed under QC-1330-A. The original study, QC-1330-A demonstrated compatibility and stability of BMN 190 with the infusion components for an infusion time of 5 hours. Small levels of leachables were detected during this study. BioMarin identified these leachables as (b) (4) and found they were associated with the catheter of the ICV access device (b) (4). These study results were supportive of the standard infusion time in the clinical setting of approximately 4 hours. (b) (4)

(b) (4) The original report already supports the typical administration time of approximately 4 to 5 hours with respect to drug product quality and leachables, which provides confidence that the combination product is acceptable for approval.

#6:  
Part of the design criteria for the BMN 190 Administration Kit relies on the device manufacturers to perform the appropriate release testing as outlined in URS-190-001 ID4. Release testing is conducted by the device manufacturers according to the functional product specifications for each individual components. BioMarin will verify the Certificates of Analysis for each lot of components that are packaged in the Administration Kit. Product specification documents and representative Certificates of Analysis are listed in Table 3, and provided with this response. Reference to the location in the 510(k) of the release testing for the syringe and syringe needle are provided in the table below.


The release testing specification for the BMN 190 Administration Kit is provided (see Specification Document PS-12632).

**Table 3: List of Specification Documents for the BMN 190 Administration Kit Components**

Component	Part Number	Specifications
Infusion set with 0.2µm filter	(b) (4)	(b) (4)
Extension line		
(b) (4) needle (16mm Port needle)		
Syringe (b) (4) 20mL)		
Hypodermic needle (21G Syringe needle)		

**Reviewer Comments**  
The Sponsor provided all referenced updated/new documentation to support the device constituent review of the combination product. The remaining outstanding test results were submitted as part of a future IR response by the Sponsor. The risk assessment information provided by the Sponsor was adequate to address the specified hazards identified by the consultant reviewer. The CoA and CoC to be supplied to the Sponsor upon receipt of the off-the-shelf components of the Administration Kit and the specifications that are tested by the supplier's therein are acceptable to the consultant reviewer as a surrogate for the Sponsor opening and performing the same functional testing at release of the Administration Kits. The Sponsor adequately responded with testing to address the risk of leakage from the Administration Kit components. The shelf life of the remaining Administration Kit components was provided in a later IR response from the Sponsor. The shipping/aging validation of the Administration Kit is adequate to the consultant reviewer.

Agency Information Request #4 (sent on 09/23/16)

1. Provide a record of the use of the B Braun Perfusor Space Infusion Pump System to deliver your drug product during clinical trials (i.e. number of patients, number of administration procedures, etc.). Include a listing of the device-related adverse events, errors, or device failures that occurred during the administration of your drug product when the B Braun Perfusor Space Syringe Pump was utilized.
2. In the current version of your draft labeling you state that Brineura should be administered with the B Braun Perfusor Space Infusion Pump System (b) (4)  

- b. The alarm settings should be explicitly stated in the labeling. Establish and provide the rate, volume, and pressure limits required to safely infuse the drug product and flushing solution. Provide a rationale for the clinical acceptability of each alarm setting in the context of the administration of the drug product into the intended anatomical space.
3. Currently the administration kit includes two syringes, one for the delivery of the drug product and one for delivery of the flushing solution. However, it is noted that the current draft labeling states that a third syringe must be utilized during the administration procedure to check for patency. The labeling states that an empty sterile single-use luer-lock syringe no larger than 3 mL (b) (4). It is unclear to the Agency why the patency check syringe is not included in the administration kit, since it is a single-use disposable components necessary for the administration procedure. In order to avoid errors related to using off-the-shelf syringes, you should provide a qualified patency syringe in the administration kit that is shown to meet the essential performance requirements you establish for safe and effective completion of the patency check. Alternatively, a thorough risk analysis should be provided to establish the acceptability of the risk introduced from not including the patency syringe in the administration kit.

**Sponsor Response (received on 10/24/16)**

#1:

A record of the use of B Braun Perfusor Space Infusion Pump System to deliver BMN 190 during Studies 190-201/202 is included in Listing 16.2.5.7. A total of twelve patients at Site 1244 (Hamburg, Germany) each received 18-20 infusions of BMN 190 utilizing this pump from September 16, 2015 (date of first use) to June 3, 2016 (data cut-off). This B Braun Perfusor Space Infusion Pump System remains in use at Site 1244 for administration of BMN 190 in Studies 190-202 and 190-203.

One subject (1244-1010) in Study 190-202 had one device-related AE (preferred term of needle issue) as of June 3, 2016 which occurred when the B Braun Perfusor Space Infusion Pump was utilized to administer BMN 190. This AE was

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ICC 1600395  
BLA 761052, Brineura (cerliponase alfa), BMN 190 Administration Kit  
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categorized as CTCAE grade 1 and resulted in study drug interruption during the infusion (Listing 16.2.7.10). This subject continues to receive BMN 190 treatment as an active study participant in Study 190-202.

No device-related errors or device failures occurred during administration of BMN 190 when the B Braun Perfusor Space Infusion Pump was utilized (Listing 16.2.5.6).

#2:

(b) (4)



**Table 1: Syringe Pumps Used in the Clinical Study and Performance Requirements**

Pump	Delivery Volume	Delivery Accuracy	Compatible with Admin. Kit Syringes	Alarms
<i>Essential Criteria</i>	<i>Syringe pump must be able to deliver at a rate 2.5 mL/hr</i>	<i>2.5 mL/hr ± 1.0 mL/hr</i>	<i>Must be compatible with administration syringes (20 mL syringe)</i>	<i>Syringe pump should have occlusion alarms</i>
Smiths Medical Medfusion 3500	Infusion rate range: 0.1 mL/hr to 200 mL/hr	Nominal ± 2%	Compatible with 20 mL	User can set the occlusion limit from High to Very Low. <ul style="list-style-type: none"> <li>High: 16 psi (827 mmHg)</li> <li>Normal: 12 psi (621 mmHg)</li> <li>Low: 8 psi (413 mmHg)</li> <li>Very Low: 4 psi (206 mmHg)</li> </ul>
Carefusion Alaris CC Pump 8003Med01	Infusion rate range: 0.1 mL/h to 600 mL/h for 20mL syringes	Nominal ± 2% for rates ≥ 1mL/h	Compatible with 20 mL	User can set the occlusion limit from L-10 to L-0. Examples: <ul style="list-style-type: none"> <li>L-10: 1000 mmHg</li> <li>L-5: 500 mmHg</li> <li>L-3: 300 mmHg</li> <li>L-0: 50mmHg</li> </ul>
Carefusion Alaris CC Guardrails 8003Med01-G	Infusion rate range: 0.1 mL/h to 600 mL/h for 20 mL syringes	Nominal ± 2% for rates ≥ 1 mL/h	Compatible with 20 mL	User can set the occlusion limit from L-10 to L-0. Examples: <ul style="list-style-type: none"> <li>L-10: 1000 mmHg</li> <li>L-5: 500 mmHg</li> <li>L-3: 300 mmHg</li> <li>L-0: 50 mmHg</li> </ul>
B Braun Perfusor Space <sup>1</sup>	Infusion rate range: 0.01 – 999.9 mL/h	Nominal ± 2%	Compatible with 20 mL	User can set the occlusion limit from L-9 to L-1. (0.1 to 1.2 bar / 75 to 900 mmHg). Levels separated by increments of approximately 0.1375 bar which corresponds to approximately 103 mmHg. Examples: <ul style="list-style-type: none"> <li>L-9: 1.2 bar (~900 mmHg)</li> <li>L-5: 0.65 bar (~487 mmHg)</li> <li>L-3: 0.375 bar (~281 mmHg)</li> <li>L-1: 0.1 bar (~75 mmHg)</li> </ul>

<sup>1</sup> The B Braun Perfusor FM was previously used at site 1244. It complies with these criteria, but is not currently in use and is not provided in this table.

b) The intent of the pressure alarm is to indicate if an occlusion has occurred in the system. The setting of Level 3 (corresponds to approximately 281 mmHg) for the B Braun Perfusor Space Infusion Pump System has been demonstrated to provide timely notification of an occlusion and the infusion system has been used successfully at this setting in the clinic and during performance studies without issue. The PI has been updated with an example of an appropriate

numerical setting for the occlusion alarm ( $\leq 281$  mmHg). This example is compatible with each pump used in the clinical trial as noted in Table 1.

There are no alarms for flow rate or volume on the B Braun Perfusor Space Infusion Pump System. (b) (4)  
As indicated in the labeling, the flow rate (2.5 mL/hr) programmed into the pump and the instructions regarding administration of 2 mL of flushing solution provide assurance that the complete dose volume (10 mL) is delivered.

The infusion flow rate of 2.5 mL/hr was determined to have low risk for causing overt clinical signs from increased intracranial pressure or alteration of CSF chemistry by comparing it to the natural CSF turnover rate in pediatric humans and the relative infusion flow rate to CSF turnover rate studied in the nonclinical program. The infusion flow rate of 2.5 mL/hr is approximately 12% of the natural CSF turnover rate in the pediatric humans (2-5 years old) of 20.8 mL/hr (based on CSF turnover of 5x/day and a CSF volume of 100 mL). A  $\pm 1.0$  mL/hr deviation from 2.5 mL/hr is considered clinically acceptable and well within the performance tolerance set for each pump (target  $\pm 2\%$ ), as stated in Table 1.

#3:

As background, BioMarin met with the Agency to review requirements of the device-constituent part of Brineura at the Type C Meeting on September 30, 2015 (refer to Type C Meeting Minutes October 2015, Section 1.6.3 of the BLA). The Agency requested that BioMarin supply the components that are essential elements of the complete drug delivery pathway (product-contacting syringes, needles, infusion set with in-line filter, extension line and port needle). BioMarin agreed to create an Administration Kit with the above components to be used for the delivery of Brineura. The patency check syringe was not identified by the Agency as an essential element of the drug delivery pathway.

BioMarin has conducted a thorough risk assessment (uFMEA, refer to Section 3.2.P.7 of the BLA) to determine the required components for Brineura administration and the user errors that might occur. The risk analysis showed that provision of additional components could cause confusion or errors for end users, or may be in conflict with standard institution practice, or may be incompatible with the syringe pump (i.e., if provided in the kit, the end user may inadvertently select the 3 mL syringe to administer 2 mL of the flushing solution, which is not appropriate for delivery of the Brineura or ICV Solution with the syringe pump). The Design Input Requirements (DIR) document has been updated to clarify the rationale for including the components required only for Brineura administration and a statement was added in Section 6 (DIR-190-001): *“for clarity about the intended use of the administration kit, components not included in the administration kit are those that are readily available in a hospital setting and are not directly required for Brineura administration to the patient”*.

The intended use of the Administration Kit is to provide the components necessary to administer drug to the patient; materials required to prepare the patient prior to drug delivery are not included in the intended use of the Administration Kit as defined in the BMN 190 DIR, DIR-190-001 Rev.4 (SN# 0028), “Intended Use” statement:

*“The BMN 190 administration kit is intended to be used by healthcare professionals in a clinical setting. It will be used to deliver BMN 190 via ICV infusion through a previously implanted ICV access device (reservoir and catheter) using a Healthcare center-supplied pump to deliver BMN 190.”*

(b) (4)  
. A patency check is

performed as part of infusion preparation to ensure patency of the ICV access device. The syringe for the patency check has been removed from the list of required components for *administration* of Brineura in the PI.

**Reviewer Comments**

**The Sponsor provided all information regarding the use of particular syringe pumps during the 190-201/202 clinical trials. The B Braun Space Perfusor Syringe Pump was utilized most frequently and also the pump utilized to complete the bench performance testing. Therefore, the consultant reviewer recommends that Brineura be labeled specifically for use with the B Braun Perfusor Space Syringe Pump. This syringe pump has the capability of the essential performance requirements as outlined by the Sponsor, including, but not limited to the proper occlusion alarm backpressure detection settings.**

**The rationale for an occlusion detection of <281 mmHg is acceptable to the clinical and lead consultant based on the information from the clinical trial and scientific rationale provided by the Sponsor.**

**The Sponsor proposed that the patency syringe not be part of the BMN 190 Administration Kit. After discussion with CDER/OSE/DMEPA during a team meeting and revisions to the labeling to make it clear that the syringe would not be included in the kit and what type of syringe is necessary and its exclusive uses in the administration procedure the consultant accepts the Sponsor proposal.**

Agency Information Request #5 (sent on 10/14/16)

1. The 510(k) submissions for the Infusion Set with 0.2 um filter (b) (4), Extension line (b) (4), and (b) (4) needle/ 16 mm port needle (b) (4) do not appear to contain a biocompatibility evaluation. Please provide the location of the biocompatibility information for these device components, or provide the test summaries and/or test reports for the appropriate endpoints. For information on the endpoints that should be addressed according to the type and duration of contact, please refer to the FDA guidance, "Use of International Standard ISO 10993, "Biological Evaluation of Medical Devices - Part 1: Evaluation and testing within a risk management process"
  - a. Provide the updated Leachables/Extractables study for the administration kit that you stated would be completed by October in 'RESPONSE TO REQUEST FOR INFORMATION DATED AUGUST 31, 2016'. If the study and analysis has yet to be completed provide an expected date of completion and expected date of submission to the BLA.
  - b. In order to utilize the Leachables/Extractables study to address systemic endpoints (e.g. acute systemic toxicity, chronic systemic toxicity, genotoxicity) the Agency recommends that you provide a toxicological risk assessment in conjunction with the L/E study. The toxicological risk assessment should include an evaluation of the endpoints that you are using to support the intended use of the combination product. Please note that the toxicological risk assessment of the compounds detected within the chemical characterization (Leachables/Extractables study) should take into account the intended use of device and intended patient population (i.e. pediatric patients). The risk assessment should include, but is not limited to, a calculation of potential exposure to the patient, the results of a literature review of human and/or animal data on the toxicity of leachables and extractables, study end points, and uncertainty or modifying factors related to the estimated dose extrapolation.

- c. Provide the results of the (b) (4) pyrogenicity testing that was stated to be completed in October according to your response within 'RESPONSE TO REQUEST FOR INFORMATION DATED AUGUST 5, 2016' received by the Agency on August 12, 2016.

**Sponsor Response (received on 10/25/16)**

**Reviewer Comments**

**The Sponsor's responses and adequacy of the Sponsor's responses is denoted in the biocompatibility and sterility consultant's review memos seen in the Appendices of this memo. The lead consultant concurs with the recommendations of the consultants.**

Agency Information Request #6 (sent on 10/28/16)

1. You have provided biocompatibility test reports for the components of the administration set which includes an evaluation of the following endpoints: 1) cytotoxicity, sensitization, irritation, acute systemic toxicity, and hemolysis; however, the device is to be used for ICV administration, bi-weekly for up to (b) (4) hours for the duration of treatment (i.e. years). The patient contact would be considered to be > (b) (4) days based on the intended use of the device. Therefore, in addition to the endpoints that were addressed by the original 510(k) submissions, the BLA should include an evaluation of the subchronic systemic toxicity, genotoxicity, and pyrogenicity endpoints.

You have stated that given the history of clinical use and lack of complaints related to biological reactions, there is sufficient evidence to meet the current ISO 10993-1 requirements. You also state that an extractables study was not performed since administration kit components are approved for human use and have extensive commercial use history with a variety of aqueous drug product formulations. Please note that history of clinical use cannot be used to address subchronic toxicity and genotoxicity endpoints as the negative outcomes related to those endpoints are unlikely to be attributed to the device. This drug could be administered for the lifetime of the patient (> (b) (4) days) and therefore, should be evaluated for subchronic systemic toxicity and genotoxicity. The toxicological risk assessment of the leachables from the in-use compatibility study which you state you will be providing to the Agency on November 21, 2016 can be used to address these endpoints. If the toxicological risk assessment does not address subchronic systemic toxicity and genotoxicity endpoints, additional testing may be necessary.

2. You have provided the biocompatibility test reports for the individual components of the: Infusion Set with 0.2 µm filter (b) (4), Extension line (b) (4), and (b) (4) needle/ 16 mm port needle (b) (4)
- Please clarify if any manufacturing or processing steps of the of the final finished devices (included in the administration sets) could impact the biocompatibility of the final finished device. This may include a description of the manufacturing and/or processing that occurs after the device manufacturer receives the components that were tested for biocompatibility (tables 3, 4, and 5).
  - The reviewer was unable to locate the test reports referenced for the (b) (4) components of the (b) (4) Needle which contact the patient (externally communicating). Please provide the location of the test reports or submit the test reports if they were not included in the submission.
  - The "extension tubing (b) (4) components in "Table 5: Clearance for the (b) (4) Needle" appear to be referencing data from the " (b) (4) test reports. Please provide a certification statement that the materials, manufacturing, and processing are identical

between the tested and to-be marketed components, or provide a rationale for why any differences do not impact the biocompatibility of the device.

- d. The test reports for the individual components for the Infusion set with filter and the extension line include (b) (4) in the description of the test article. The test reports for the (b) (4) needle do not include the sterilization process. The biocompatibility testing should be performed on the final finished device. Please clarify if the component testing was performed on the sterilized components that will make up the to-marketed device. If not, provide a scientific rationale on why the sterilization process does not impact the biocompatibility of the device.

#### Sponsor Response (received on 11/03/16)

##### Reviewer Comments

The Sponsor's responses and adequacy of the Sponsor's responses is denoted in the biocompatibility consultant's review memo seen in the Appendices of this memo. The lead consultant concurs with the recommendations of the consultant.

#### Agency Information Request #7 (sent on 10/27/16)

You have not provided adequate data to support the use of the 22 gauge (b) (4) Needle with the labeled ICV access device, the Codman HOLTER Rickham. It is noted that the manufacturer of the ICV access device recommends a 25 gauge needle or smaller. It is also noted that your justification for the 22 gauge needle is that it is the only available size needle for the 90 degree (b) (4) Needle that you claim provides greater stability to the fluid path for the duration of the infusion of the biologic. However, the clinical evidence you have provided to support the compatibility of the 22 gauge needle with the ICV access device is limited and the Agency notes that there were observed membrane material deficiencies for the Rickham device under Subject 1244-1009. The reservoir material changes observed in the event noted above could conceivably result from the disparity between the gauge size of the (b) (4) ® Needle (22 gauge) and the size recommended for use with the Rickham device (25 gauge). The concern that over time the dome will sustain damage resulting in device leakage and the potential for wound complications, etc. may be confirmed by this event. Currently, your design requirement DIR 1.9 states that the port needle is capable of perforating the septum of the ICV

(b) (4)

1. Develop a design requirement and perform verification testing to assess the compatibility and functionality of the 22 gauge (b) (4) Needle with the labeled ICV access device for the entire duration of the intended life of the ICV access device.

2. Provide a clinical justification for the extent of preconditioning and aging that is performed on the devices prior to and during testing (e.g. shelf life, in-use life, number of perforations, etc.) in order to support longer term infusion schedules. The verification testing should include methods to assess integrity of the ICV access device dome, leakage, material degradation, and any other performance requirements of the port needle and ICV access device.

#### Sponsor Response (received on 11/02/16)

The design requirement for the ICV access device was established based on the clinical data collected to-date (see Table

- 1). The available clinical evidence was used to define the minimum criteria documented in the Design Input Requirements



(b) (4)

The Warnings and Precautions and Instructions for Use sections of the Prescribing Information, further details the importance of inspecting the device and surrounding scalp to ensure the access device is not compromised with each infusion.

The life span of the ICV access devices used in the clinical studies is unknown at this time and the maximum expected in-use life will be determined as more experience is gained. The observed membrane material deficiencies noted after removal of the ICV access device in 1244-1009 occurred in the setting of a microbial contamination rather than a device failure. The infection occurred after 34 infusions, resulting in the removal and replacement of the device. There were no reported ICV device malfunctions associated with the incident described above.

The current clinical data support the use of the ICV access devices for more than 3 years (approximately 80 infusions in one patient with a Codman ICV access device, as of October 2016) and the number of patients having received > 50 infusions is 11, as of June 3, 2016. Based on this information, the in-use life of the ICV access device is expected to be at least 3 years. BioMarin commits to continue collecting data regarding the in-use life of the ICV access device.

**Table 1: Number of infusions (June 3, 2016 data cut)**

	# of infusions*
Number of patients	22
Mean infusions per patient	51
Patients receiving 50 infusions or more	11
Total infusion count	1129

\*includes only infusions in patients implanted with Codman ICV access device.

(b) (4)

#### Reviewer Comments

**The information to support the clinical acceptability of the port needle and intraventricular access port compatibility is inadequate to support that the port will not have to be replaced due to leakage or possible infection in a time that introduces a significant amount of risk to the treatment (e.g. invasive surgery every 1-2 years to replace intraventricular port/catheter would introduce a significant amount of risk to the patients). The Sponsor submitted a protocol (Characterization Study Protocol – Repeated Septum Perforation Test BMN190 Document CP-190-002 Rev 1) to address the compatibility and material degradation concerns for the intraventricular access device which was deficient. See later information requests for more details.**

Agency Information Request #8 (sent on 01/11/17)

1. Your study protocol titled, “Repeated Septum Perforation Test BMN190” states (b) (4)

However, your acceptance criteria is based on the current design input requirement for the integrity of the intraventricular port and is as follows: (b) (4)

You should change your design input requirement to reflect a more appropriate length of time to be assured that the intraventricular port functionality will not be compromised (e.g. 4-5 years). Accordingly, you should update the acceptance criteria of the study protocol to reflect the revised design input requirement (b) (4)

2. With regards to the materials and methods outlined within the study protocol you should address the following concerns with a clear justification or update the protocol to reflect the recommended changes:

(b) (4)

3. Note that the Agency has determined intraventricular to be the appropriate terminology for this infusion route of administration and the term intracerebroventricular should therefore be replaced in the protocol.

**Sponsor Response (received on 01/18/17)**

As agreed during the teleconference meeting with FDA held on January 17, 2017, BioMarin has updated the perforation study protocol (Repeated Septum Perforation Test BMN190) with an acceptance criteria of (b) (4) perforations. The devices will be tested to failure; (b) (4)



The DIR will be updated to reflect the revised requirement of at least four years without compromising the functionality of the intraventricular access device.

The study protocol titled “Repeated Septum Perforation Test BMN190” has been updated to reflect the following changes:

- a. In order to replicate the clinical scenario, a new needle will be used for each perforation.
- b. The protocol has been updated to aim for the apex of the reservoir while simulating the expected clinical variability in locating the center of the reservoir under a layer of skin.
- c. BioMarin proposes to use the ‘Septum Puncture’ test method as described in the FDA Guidance document on 510(k) Submissions for Implanted Infusion Ports.

Justification for use of this method is provided below. A description of the equipment to be used for the study has also been provided in the revised protocol. (b) (4)

[Redacted]

[Redacted]

[Redacted]

Therefore, BioMarin believes the proposed Septum Perforation method

(b) (4)

[Redacted]

[Redacted] (b) (4)

(b) (4)

References to the route of administration for BMN 190 have been updated to intraventricular in the revised protocol as agreed with FDA.

**Reviewer Comments**

**The Sponsor's responses were reviewed by the clinical and lead consultant and found to be adequate except for the response regarding the dye-leak method rationale. See information request sent on 01/18/17 for deficiencies regarding the Sponsor's response.**

Agency Information Request #9 (sent on 01/18/17)- ADEQUATE/INADEQUATE

Upon further review of your response regarding the test method (b) (4), we are unclear as to why (b) (4) is a more representative test method (b) (4).

(b) (4)

Prior to initiation of the study, produce a sound rationale for why the leak test failed so prematurely (b) (4). In your response, justify why the test method you plan to utilize is truly clinically representative (b) (4).

**Sponsor Response (received on 01/30/17)**

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(b) (4)



(b) (4)



Based on clinical experience and benchtop testing performed to date, the access devices may need to be replaced after 3 to 5 years of use. Instructions to inspect the infusion site and monitor for device patency before and during each infusion will be provided to ensure best practices when dosing of

patients (as noted in Section 2.4 Infusion Procedure and Section 5.1 Warnings and Precautions of the current prescribing information).

#### Reviewer Comments

**The Sponsor's response was adequate to the clinical and lead consultant reviewer; however the method does not appear to assess the actual degradation of the material. See information request sent on 02/01/17 for more details.**

#### Agency Information Request #10/11 (sent on 02/01/17 and 02/07/17)

We acknowledge your responses to our latest information request regarding the benchtop study protocol you provided. Judging from your response we would recommend that you incorporate a method of assessing the degradation of the septum material over time as you puncture the septum (e.g. scanning electron microscopy analysis for surface porosity, holes, roughness, cracks, peeling, etc.). The Agency would be open to inclusion of measuring septum surface defects after discrete simulated time points throughout the study (e.g. after each subsequent simulated year of punctures) to determine when and if the surface material of the septum begins to deteriorate. These measurements would be in addition to the planned air leak detection testing that is outlined in the currently proposed study.

Your selected time points to study surface morphology appear to be adequate; however, the Agency is concerned that the study of surface morphology does not incorporate any accelerated aging to simulate the years of implantation that may contribute to material degradation following the repeated punctures. The Agency recommends aging the devices to the equivalent time point represented by the number of punctures you have outlined in your previous response prior to evaluating the surface morphology. The Agency believes that aging could be completed before or after puncturing the septum repeatedly. The Agency also suggests that the device be maintained in a normal saline or other physiological solution at 37 degrees Celsius to replicate its presence in the body if you plan to study the real-time aging effects on the septum.

#### **Sponsor Response (received on 02/17/17)**

BioMarin has completed the pressurized air puncture testing study per CP-19-002, "Repeated Septum Perforation Test BMN 190" (previously submitted in SN 0081) and results are being provided with this response (refer to Table 1). The study evaluated the compatibility of the Codman Holter Rickham access device with the (b) (4) port needle (22G). Results show that the Codman access device can be perforated 140 times, equivalent to 4 years of perforations, plus safety factor (test 5), without compromising the functionality of the access device.

Additional testing (test 6) was conducted to the point of device failure (air leak) and demonstrates that the ports are resistant to leaks for up to 160 perforations. These results support the use of the (b) (4) port needle (22G) as part of the BMN 190 Administration Kit.

(b) (4)

**Table 1: Results from Protocol CP-190-002, “Repeated Septum Perforation Test BMN 190”**

Test	Simulated Years	Port Number	Number of perforations	Port Quantity per Time Point	Leak Check Result (at 100 mm H <sub>2</sub> O air pressure)
5	4	5, 6, 7, 8, 9	140	5	No leaks detected after 2 minute hold
6	6.3	8	220	1	Leakage at 220 perforations
6	4.6	9	160	1	Leakage at 160 perforations

(Update 02/28/17):

**BMN 190 Septum Puncture Study**

BioMarin has completed the pressurized air puncture testing study per CP-19-002, “Repeated Septum Perforation Test BMN 190” (protocol previously submitted in SN 0081). Results from the test were submitted to the Agency previously in SN 0100 and the complete study report including Scanning Electron Microscopy (SEM) results from the test devices is being provided with this response (refer to CPR-190-002). The study evaluated the compatibility of the Codman Holter Rickham access device with the (b) (4) port needle (22G). Results show that the Codman access device can be perforated 140 times, equivalent to approximately 4 years of use, plus safety factor, without compromising the functionality of the access device. These results support the use of the (b) (4) port needle as part of the BMN 190 Administration Kit.

Additionally, as proposed in SN 0100, in order to address the Agency’s recommendation for device aging to assess degradation over time, an evaluation of suitable conditions for an accelerated aging study has been completed. BioMarin is providing the proposed study plan for the Agency’s consideration (refer to the description below).

(b) (4)

(b) (4)



Attachment #2: SEM Images

Figure 1: Port 1, no perforations

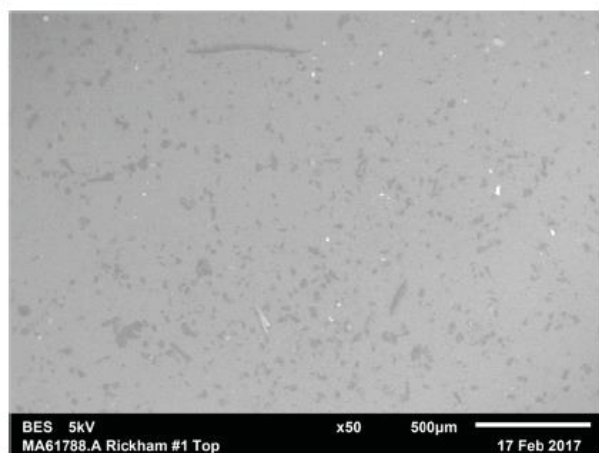
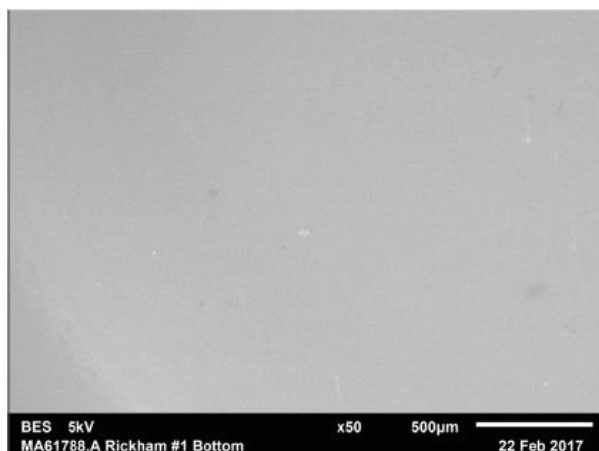


Figure 2: Port 2, 35 perforations

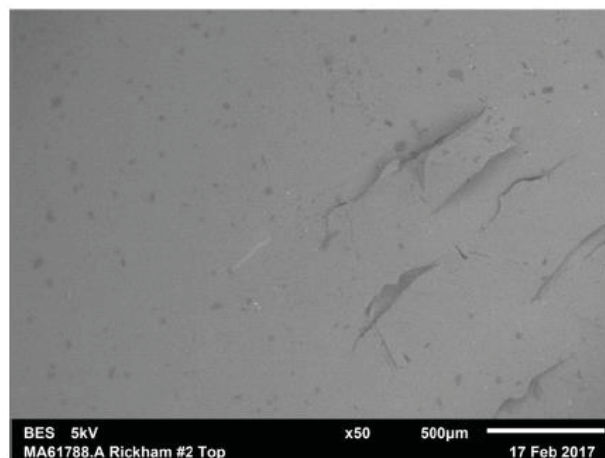
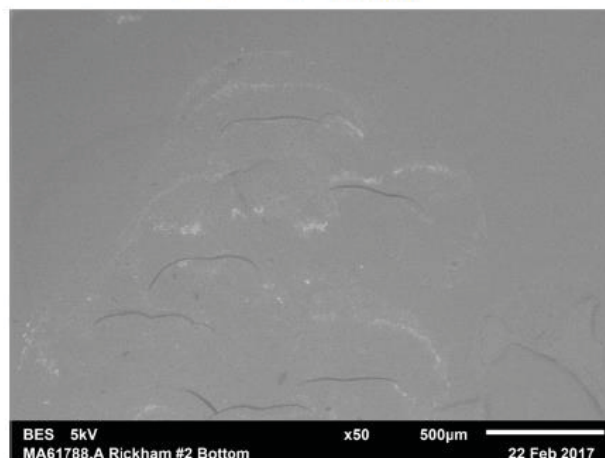


Figure 3: Port 3, 70 perforations

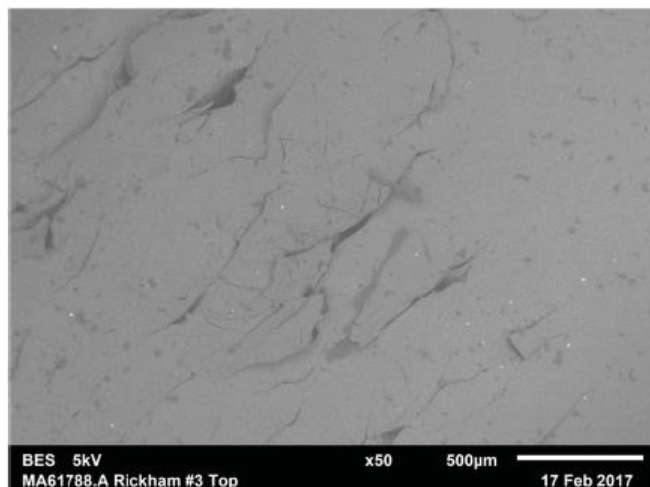
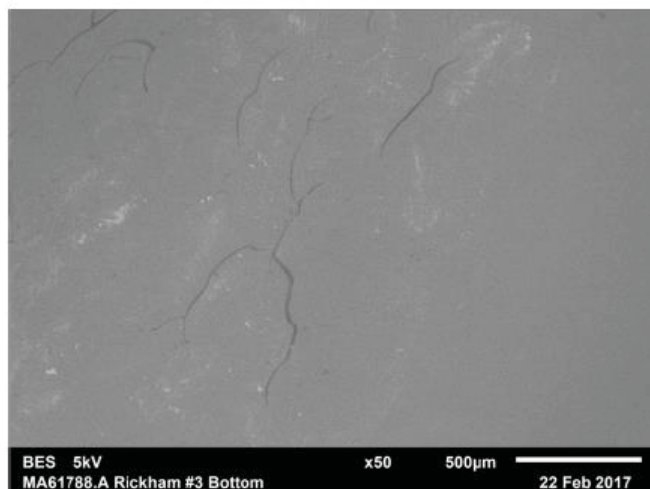


Figure 4: Port 4, 105 perforations

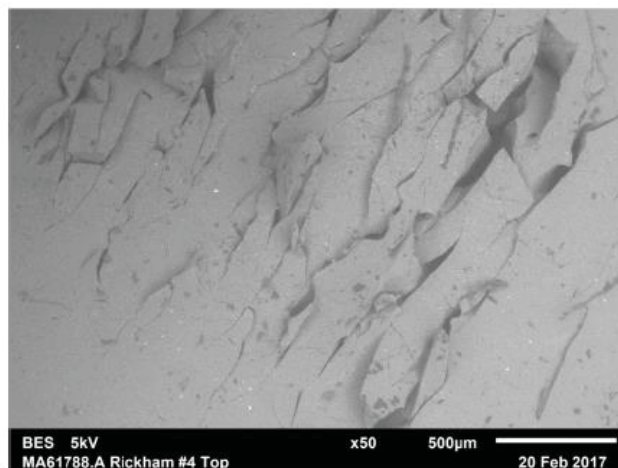
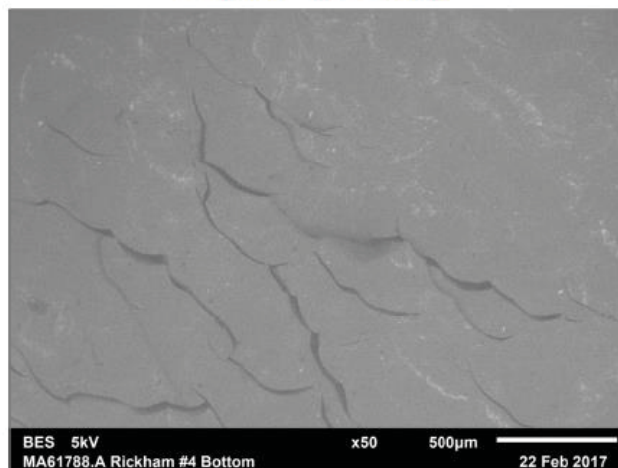




Figure 5: Port 5, 140 perforations

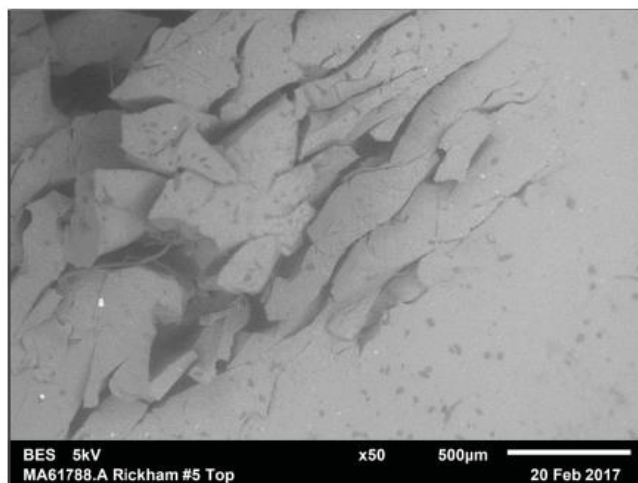
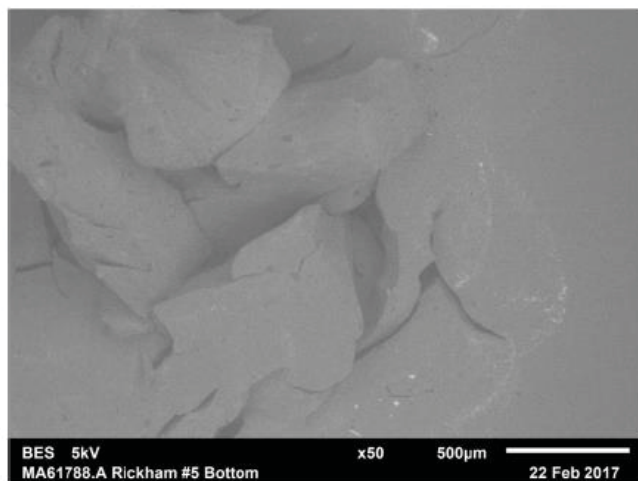


Figure 6: Port 6, 140 perforations

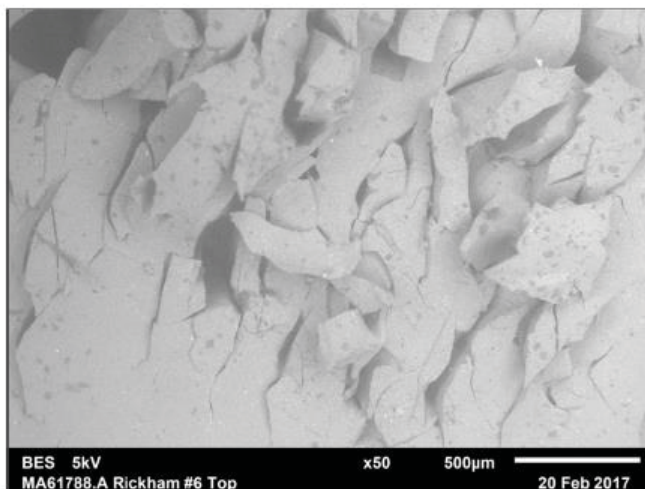
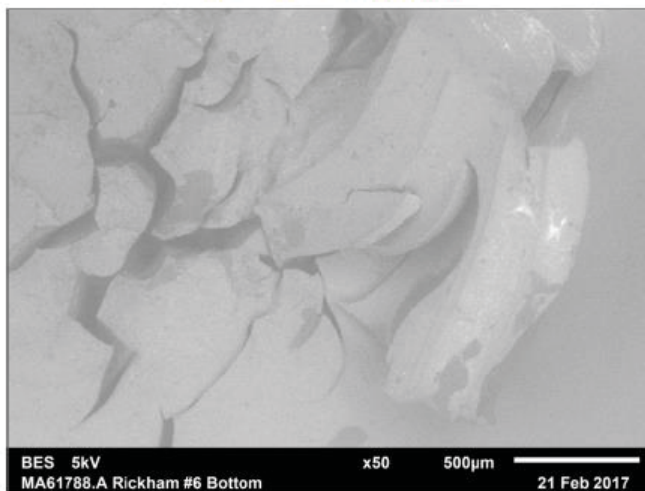


Figure 7: Port 7, 140 perforations

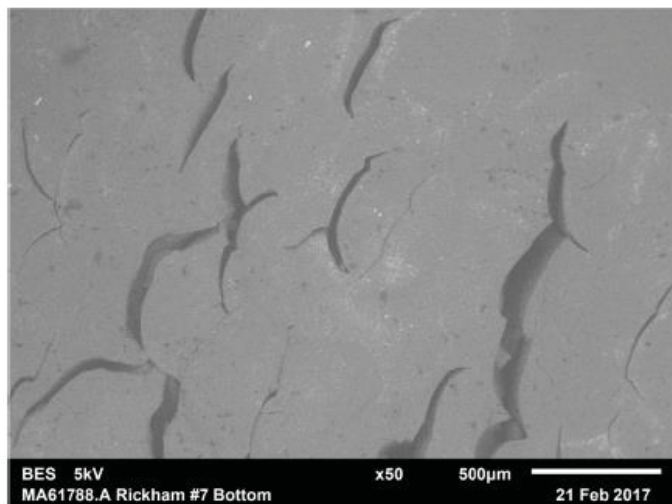


Figure 8: Port 8, 220 perforations

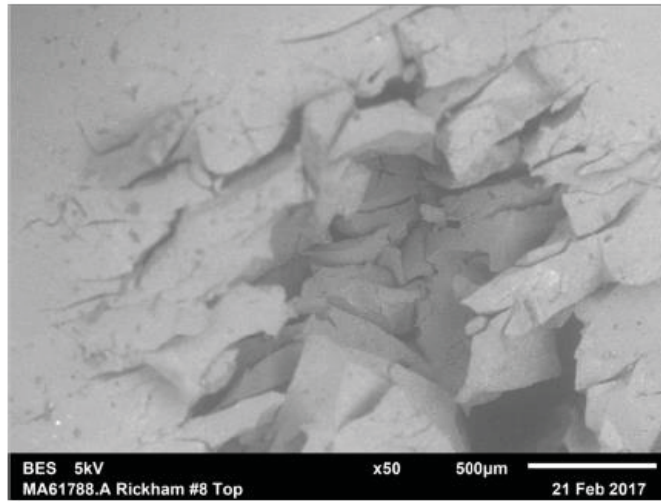
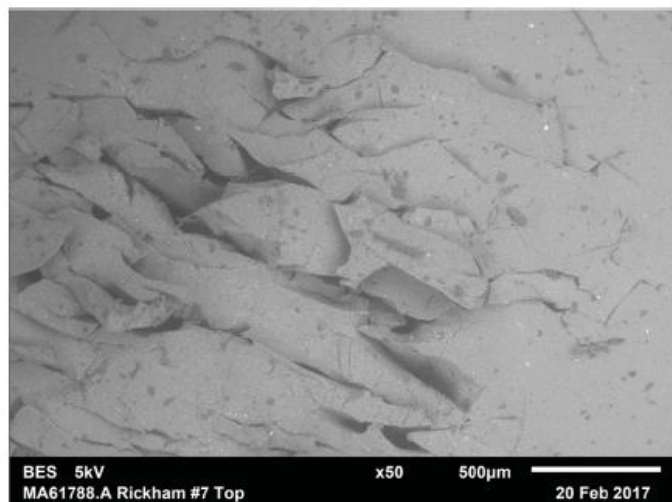
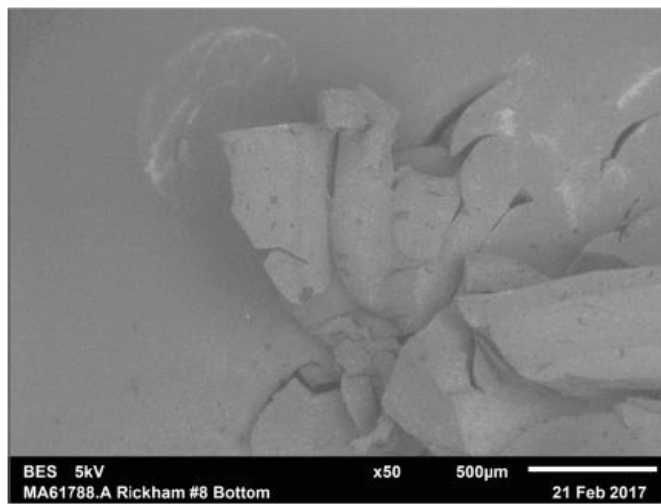


Figure 9: Port 9, 160 perforations

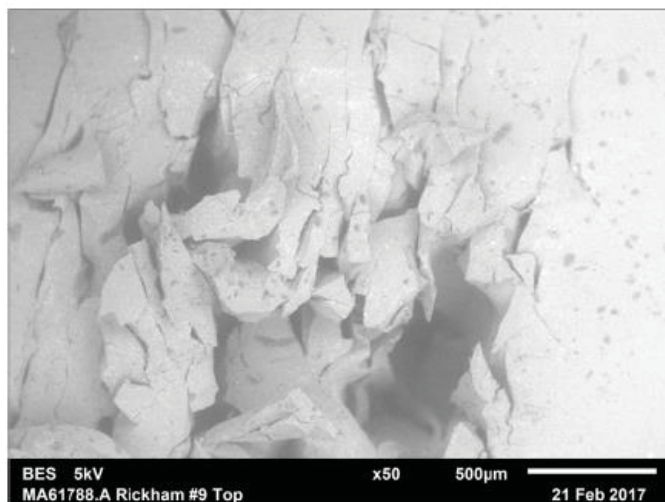
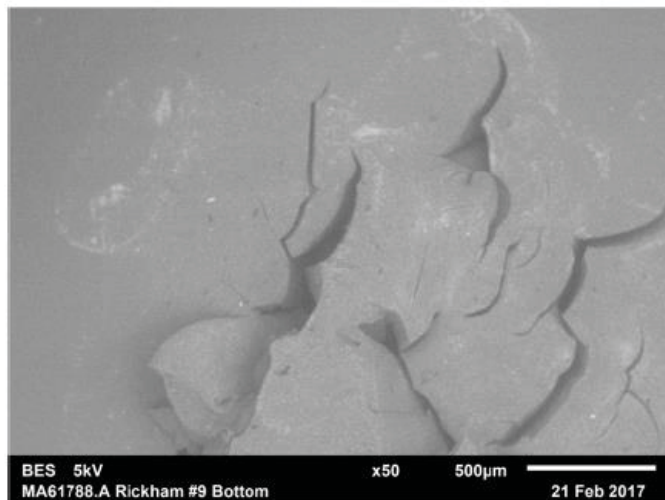


Figure 5: Rickham #3, 70 perforations.



Figure 7: Rickham #4, 105 perforations.



Figure 9: Rickham #5, 140 perforations.



Figure 10: Rickham #5 bottom, 140 perforations.



Figure 13: Rickham #8, 220 perforations.



Figure 14: Rickham #8 bottom, 220 perforations.

#### Reviewer Comments

The clinical consultant's review of the material degradation septum puncture study is as follows:



I have reviewed the report and offer these comments:

withstanding 100 mm H<sub>2</sub>O air pressure after 140 punctures. Test results are summarized below in Table 3.

Table 3: Summary of Air Bubble Leak Test Results

Test	Simulated Years	Port Number	Number of perforations	Port Quantity per Time Point	Leak Check Results (held for 2 minutes at 100 mm H <sub>2</sub> O air pressure)
5	4	5, 6, 7	140	3	All Pass
6	4+	8	220	1	Leakage at 220 perforations
		9	160	1	Leakage at 160 perforations

• Bennett.Blumenkopf  
 3/1/2017 11:37:10 AM  
 The sponsor should confirm that no leaks were demonstrable in Tests 1 - 4 with ports 1 - 4. The absence of data is not to be construed as fact.

least four years of use including a 1/3 safety factor (140 perforations) without compromising the functionality of the intraventricular port using the test method described in FDA Guidance on 510K Submissions for Implanted Infusion Ports (1990), thus satisfying design input requirement DIR 1.9.

SEM and optical microscopy images show the underside of the ports appears to be smooth for up to 105 perforations, which is consistent with clinical experience of acceptable functionality for more than 3 years of use.

• Bennett.Blumenkopf  
 3/1/2017 11:40:50 AM  
 Seems acceptable.

From: Attachment #2: SEM Images: *there is clearly material degradation following the repeated punctures, however. Clearly beyond the ~ 100 punctures there is clear material failure which should therefore be confirmed as the upper limit of use-life.*

The lead consultant concurs with the review of the clinical consultant and after meeting with the clinical consultant it was determined that the labeling include warnings/precautions and regarding the need to replace the intraventricular access device after approximately 105 perforations, which is equal to roughly 4.3 years of use of the device under the labeled treatment plan.

Also, the consultant recommended labeling so that only the studied intraventricular access devices could be used with this system since it is unknown how the larger 22G (b) (4) needle would impact the materials of other intraventricular access devices that are labeled for drug administration.

### 13.OUTSTANDING DEFICIENCIES

N/A

### 14.RECOMMENDATION

CDRH/ODE recommends approval of the device constituent parts of the combination product with the following recommended labeling changes and post-market commitment.

#### 14.1. Recommended Post-market commitments/post-market requirements

3207-5 Conduct a clinical trial (Study 190-203) to further evaluate the safety and immunogenicity of Brineura (cerliponase alfa) in CLN2 patients, including tolerability and device related adverse events and/or complications with routine use. Perform a root-cause analysis on any device related complications and/or failures including, but not limited to, an analysis of the material integrity of the intraventricular access device reservoir. In addition, this trial will evaluate the CLN2 motor and language clinical scales. Include at least 5 patients below the age of 2 years.

## 14.2. Labeling Recommendations:

### Section 2.1:

Aseptic technique must be strictly observed during preparation and administration.

Brineura should be administered by, or under the direction of a physician knowledgeable in intraventricular administration.

Brineura is administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter (intraventricular access device). Brineura is intended to be administered via the Codman® HOLTER RICKHAM Reservoirs (Part Numbers: 82-1625, 82-1621, 82-1616) with the Codman® Ventricular Catheter (Part Number: 82-1650). The intraventricular access device must be implanted prior to the first infusion. It is recommended that the first dose be administered 5-7 days after device implantation.

Brineura is intended to be administered with the B Braun Perfusor® Space Infusion Pump System<sup>1</sup>. The essential performance requirements for this syringe pump used to deliver Brineura are as follows:

Delivery rate of 2.5 mL/hr with delivery accuracy of +/- 1 mL/hr

Compatible with 20 mL syringes provided in the Administration Kit for use with Brineura

Occlusion alarm setting to  $\leq 281$  mm Hg

Administer Brineura and the Intraventricular Electrolytes using the provided Administration Kit components [see How Supplied/Storage and Handling (16)].

### Section 5.1:

Brineura must be administered using aseptic technique to reduce the risk of infection. Healthcare professionals should inspect the scalp for skin integrity to ensure the intraventricular access device is not compromised prior to each infusion.

(b) (4)

In clinical studies with Brineura, intraventricular access device-related infections were observed in two patients. In each case, antibiotics were administered, the intraventricular access device was replaced, and the patient continued on Brineura treatment.

Material degradation of the intraventricular access device reservoir may occur after approximately 105 perforations of the intraventricular access device. The intraventricular access device may require replacement as soon as, or prior to, 105 administrations of Brineura, equating to approximately 4.3 years of regular administrations.

## 15. APPENDIX A

Clinical Consultant initial review of BLA 761052:

## ODE CLINICAL REVIEW

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Date: October 21, 2016

Subject: BLA 761052  
BioMarin BMN 190

From: Bennett Blumenkopf, MD, FACS, FAANS  
Medical Officer NDNB/DNPMD/ODE/CDRH

To: John McMichael  
Biomedical Engineer  
CDRH/ODE/DAGID/GHDB

Elizabeth Hart, MD  
Medical Officer CDER/OND/ODEIII/DGIEP

Laurie Muldowney, MD  
Medical Officer CDER/OND/ODEIII/DGIEP

Sponsor's text: regular

Reviewer's/FDA text: *italicized*; comments **bold**

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***RECOMMENDATION: feedback/comments provided***

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### **SUMMARY**

*The infusion system detailed in the submission represents a hybrid of a number of marketed devices. However, as evidenced by the information provided in the Integrated Subject Narratives, the sponsor should:*

- 1. Provide further detail regarding a number of the adverse events noted below, or a root cause analysis of each, or provide a justification for not doing so;*
  - 2. Develop a strategy to deal with the patient compliance issues experienced at the time of drug infusion and noted below to avoid the potential risks associated with the event, e.g., wound infection, or provide a justification for not doing so;*
  - 3. The reservoir material changes observed in the event noted below could conceivably result from the disparity between the gauge size of the The (b) (4)® Needle and the (smaller) size recommended for use with the Rickham device. The concern that over time the dome will sustain damage resulting in device leakage and the potential for wound complications, etc. may be confirmed by this event. The sponsor should demonstrate the long term integrity of the reservoir dome following repeated infusions through a 22 gauge needle before proceeding with any longer-term infusion schedules or provide a justification for not doing so.*
- 

### **BACKGROUND**

## Introduction

BioMarin Pharmaceutical Inc. (BioMarin) developed BMN 190 as an enzyme replacement therapy (ERT) for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency. CLN2 disease is a rare genetic disease characterized by the deficiency of tripeptidyl peptidase-1 (TPP1) caused by mutations in the *CLN2* gene. In the absence of TPP1, lysosomal storage materials normally metabolized by this enzyme accumulate in many organs; accumulation in the CNS leads to the neurodegenerative symptoms and, ultimately, death. The onset of symptoms is typically between ages 2 and 4 (Chang 2011; Kurachi 2000) with an average age of diagnosis of 4 years.

BMN 190 is provided as a solution for intracerebroventricular (ICV) infusion to be administered every other week at a dose of 300mg over approximately 4.5 hours.

**Reviewer's comment:** *The sponsor previously inquired about the regulatory pathway for the syringe pumps under IND 122472. The appropriate clinical terminology was discussed in the Clinical Review dated September 16, 2015 (attached). The characterization of the compartment: "intracerebroventricular (ICV)" was the subject of an internal discussion on October 18, 2016. Please see this email:*

**From:** Brodsky, Eric  
**To:** Gallagher, John; Blumenkopf, Bennett; Roman, Dragos; Muldowney, Laurie; Dunn, Billy; Sohrabi, Farrokh; Best, Jeanine A; Beitzell, Debra; Trentacosti, Ann Marie; Monteleone, Michael V.; Peters, Tracy; Meyer, Joette M; Bastings, Eric  
**Cc:** Brodsky, Eric  
**Subject:** ROA terminology for use in the BRINEURA labeling - October 18th meeting  
**Date:** Thursday, September 29, 2016 9:25:18 PM

*"DNP recommends using the ROA terminology "intraventricular" (administration within a ventricle) and notes that the intracerebroventricular terminology is not commonly seen in journal articles.* (b) (4)

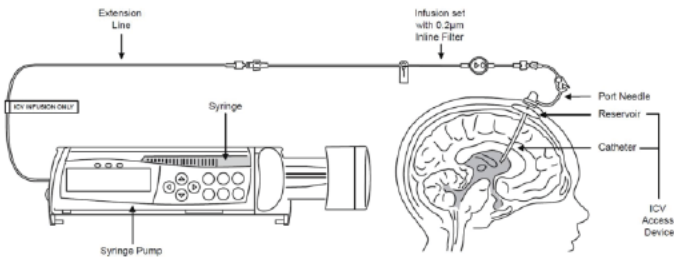
BMN 190 is a recombinant form of human tripeptidyl peptidase-1 (rhTPP1) expressed in Chinese Hamster Ovary (CHO) cells. rhTPP1 is produced as an enzymatically inactive 544 amino acid long zymogen (pro enzyme). The pro-enzyme is activated *in-vivo* following uptake into the lysosome to form the mature, active protease. Active TPP1 can catabolize lysosomal storage material and may, in the context of the present disease, reduce disease-related inflammation.

Following the administration of BMN 190 drug product, another solution (ICV solution) is used to complete the infusion. Throughout this marketing application, the term "flushing solution" is primarily used to describe this solution. (b) (4)



Combination Product Overview

Biomarin Pharmaceuticals	
Indication for Use	BMN190 is indicated for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency
Biologic Constituent	BMN190 (cerliponase alfa)
Device Constituent	BMN190 Administration Kit



BMN 190 Administration Kit

BioMarin will supply a BMN 190 Administration Kit for use with BMN 190 DP and FS containing two syringes, two hypodermic needles, an infusion set with an inline filter, an extension line, and a port needle. (b) (4)

Several ICV access devices (reservoir and catheter) as well as the recommended syringe pump are cleared for indications including ICV drug delivery and will not be supplied. The devices to be supplied for use with BMN 190 DP and BMN 190 FS were selected because they are commonly used for fluid delivery by healthcare professionals (HCPs), designed to aid in aseptic technique, and utilize standard luer lock fittings. The individual infusion components of the kit (single container) will be provided to the HCPs in the original manufacturer's, sterile-unit packaging. The devices specified are 510(k)-cleared devices commonly used for infusions, they have design features that allow them to be used as part of a system (leak-free fittings), and are designed to aid in aseptic technique (sterile and easy to open). Table 3.2.P.7.2.1 lists the device components that will be supplied for use with BMN 190 DP and FS.

Table 3.2.P.7.2.1: Medical Device Components

Component	Construction	Manufacturer	Manufacturer Part Number	510(k) Number <sup>1</sup>
Infusion set with 0.2µm filter	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Extension line				
(b) (4) needle (16mm Port needle)				
Syringe ( (b) (4) 20mL)				
Hypodermic needle (21 gauge Syringe needle)				

Reviewer's comment: The (b) (4) ® Needle (b) (4) is 22 guage. Please see: (b) (4) (b) (4) (b) (4)

(b) (4)

The sponsor addressed the disparity between the gauge size of the The (b) (4) ® Needle catalog # (b) (4) (22 g) and the (*smaller*) size recommended for use with the Codman® HOLTER RICKHAM Reservoirs (Part Numbers: 82-1625,

Please see: Response to Quality RFI dated 18Jul 2016 Re: Dome.Needel and Brineura (BMN-190)BLA 761052 Device Overview (power point presentation, attached):

(b) (4)  
(b) (4) the low-profile fixation provided by a 90-degree gripper needle (only commercially available in 22G and larger) is required for secure fixation to prevent the needle from being dislodged during the infusion. Therefore all port needles used in the BMN 190 clinical study as well as the port needle contained in the Administration Kit have 22G (b) (4) (b) (4) needles.

A number of precautions were taken to ensure that the port needle is compatible with the ICV access (b) (4)

Additionally, 22G needles have not caused serious adverse events during the clinical trials and no evidence of malfunction of the port has been observed. Patients are being monitored throughout the BMN 190 clinical studies for signs of ICV access device leakage or failure (e.g., swelling of skin around ICV access device site, difficulty with CSF extraction, erythema of the scalp, bulging of ICV access device, or extravasation of fluid on infusion) and a patency check was done before every infusion, during which malfunction of the ICV access device or infection could be identified. No ICV access devices have been replaced due to leakage/malfunction resulting from the 1173 infusions that have been performed during the BMN 190 clinical studies.

## 2. Conclusion

Based on a review of clinical data as discussed below, it can be concluded that the port needle included with the Administration Kit (b) (4) is capable of perforating the septum of the ICV access (b) (4)

APPEARS THIS WAY  
ON ORIGINAL

The sponsor further presented the current numbers of infusions employed with the system, which remains, however, somewhat limited:

### 3. Discussion

Twenty-four patients worldwide have been enrolled in the BMN 190 clinical studies 190-201 and 190-202, however one subject dropped out of the first clinical study after one dose for reasons not related to the ICV access device. The remaining 23 patients were enrolled for a minimum of 48 weeks, with ICV infusions being administered every 14 days, amounting to a total of 1173 infusions performed as of June 3<sup>rd</sup>. For these 23 patients, the mean number of infusions per patient was 51, with 11 patients receiving 50 infusions or more. Additionally the ICV access device septum was perforated additional times for PK/PD analysis, which is not included in the infusion counts below in Table 1.

Table 1. Number of infusions (June 3<sup>rd</sup> data cut) during clinical studies

Number of patients	23
Mean infusions per patient	51
Patients receiving 50 infusions or more	11
Total infusion count	1173

### Risk Management Summary

BMN 190 will be administered by healthcare professionals, experienced in the ICV administration of drugs. BMN 190 will be administered using infusion system components known to be compatible with both BMN 190 DP and FS and the other components of the system. Clinical usage and/or compatibility testing has been performed for all the components of the administration kit. Additionally, a pump study has been performed with the B.Braun Perfusor Space pump confirming acceptable compatibility and performance with the selected syringe. The risk evaluation conducted via the uFMEA for BMN 190

administration has revealed that the risks are classified as low or medium, with no risks classified as high. The dFMEA identified one risk related to the BET levels allowed for CSF delivery, which will be mitigated by testing and/or confirmation of low endotoxin levels in each lot of the Administration Kit.

*The proposed BMN 190 as an enzyme replacement therapy (ERT) for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency would be required throughout a subject's lifetime. This shall likely require biweekly infusions ultimately totalling at least an order of magnitude greater than those, heretofore, performed in the clinical study 190-201. The concern remains that over time the dome will sustain damage resulting in device leakage and the potential for wound complications, etc. The sponsor should demonstrate the long term integrity of the reservoir dome following repeated infusions through a 22 gauge needle before proceeding with any longer-term infusion schedules.*

*Please also see: Brineura (BMN-190)BLA 761052 Device Overview (power point presentation, attached):*

### Outstanding Review Issues

- Labeling for use with specific ICV Access Device / Syringe Pump or Specify Pump Requirements (i.e. back-pressure detection limits, etc.)

3 Page(s) have been Withheld in Full as b4 (CCI/tS) immediately following this page

**Reviewer's comment:** *The proposed BMN 190 as an enzyme replacement therapy (ERT) for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency is scheduled for **an additional 3 ½ years**. This shall require biweekly infusions totalling far greater than those, heretofore, performed in the clinical study 190-201. The concern remains that over time the dome will sustain damage resulting in device leakage and the potential for wound complications, etc. The sponsor should demonstrate the long term integrity of the reservoir dome following repeated infusions through a 22 gauge needle before proceeding with any longer-term infusion schedules. Please see discussion above.*

### **Summary of Clinical Safety**

#### **Studies Included in the Clinical Safety Summary**

This Summary of Clinical Safety is based on safety results from 1 completed clinical study and 1 ongoing extension study in 24 subjects with CLN2 disease exposed to BMN 190 for up to 107.6 weeks of treatment every other week (overall mean [standard deviation (SD)] of exposure was 65.5 [24.75] weeks). The 2 studies are:

- The completed Phase 1/2 study (190-201) (includes all safety data from the study, up to the study end date [30 November 2015])
- The ongoing Phase 1/2 extension (190-202) (includes safety data up to the data cutoff date [15 October 2015]).

In the Safety Population, a total of 24 subjects were treated with BMN 190 at doses of 30 mg, 100 mg, and/or 300 mg every other week for periods ranging from 0.1 weeks to 107.6 weeks; 18 of these subjects have been dosed in 190-202 and have been exposed to BMN 190 for more than 48 weeks.

Twenty-four subjects were enrolled at 5 investigative centers (one of which was discontinued following a sponsor audit):

The University of Hamburg (Germany);  
Bambino Gesù Children's Hospital (Italy);  
Evelina Children's Hospital (United Kingdom);  
Great Ormond Street Hospital (United Kingdom); and  
Nationwide Children's Hospital (United States).

Overall, the treatment group included 9 (38%) males and 15 (63%) females. Ages of subjects at enrollment ranged from 3-8 years. The mean (SD) age of the subjects at study baseline was 4.3 (1.24) years. Twenty-three subjects (96%) were White and 1 (4%) was Asian. Of the 24 subjects, 21 were enrolled in Europe; the remaining 3 subjects were enrolled in the United States.

### Adverse Events

Pooled data from 190-201/202 are presented. The pooled data are presented for all subjects combined. All subjects experienced at least one treatment-emergent AE while on study. Eleven subjects (46%) had at least 1 Grade 3 AE and 1 subject (4%) had 1 Grade 4 AE. Overall most AEs were graded mild (Grade 1) to moderate (Grade 2) in severity based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 severity criteria. Serious adverse events (SAEs) were reported for 19 (79%) subjects. There were no AEs leading to study discontinuation or permanent study drug discontinuation in 190-201/202.

No deaths have been reported. The most common AEs during 190-201/202 were pyrexia (67%), seizure (58%), vomiting (54%), upper respiratory tract infection (50%), epilepsy (46%), and hypersensitivity (38%). These events are consistent with a pediatric population, the underlying CLN2 disease, and/or exposure to BMN 190. The most commonly reported SAE was hypersensitivity (9 events in 7 subjects), epilepsy (3 events in 2 subjects), bacterial pharyngitis (3 events in 2 subjects), gastroenteritis (2 events in 2 subjects), pyrexia (2 events in 2 subjects), and infusion related reaction (2 events in 1 subject). No other SAE was reported more than once.

### Temporally Related Events

A temporally-related event (TRE) is an event that is temporally related to BMN 190 infusion and is defined as any AE with onset after initiation of a study drug infusion and within 24 hours after start or restart of study drug infusion, regardless of the investigator's assessment of relatedness to study drug administration. TREs with the highest incidences were nervous system disorders (79%), general disorders and administration site conditions (54%), infections and infestations (50%), gastrointestinal disorders (46%), and immune system disorders (38%).

### Device-Related Adverse Events

Nine subjects (38%) experienced a total of 20 device-related AEs. Needle issue (4 events in 3 subjects), pleocytosis (3



events in 3 subjects), and device leakage (2 events in 1 subject) are the only device-related AEs to occur more than once during 190-201/202. Two subjects have had ICV access device replacements during 190-201/202:

1244-1009: had an ICV access device replacement after developing a serious Grade 3 Propionibacterium infection

1323-1015: had an ICV access device replacement after developing a serious Grade 3 device-related infection with *Staphylococcus epidermidis*

Both events were detected by CSF monitoring and resolved after treatment with antibiotics and removal/replacement of the ICV access device. Subject 1244-1009 missed one dose of BMN 190 as a result of the infection; subject 1323-1015 had no interruption in dosing. Neither subject required discontinuation from study participation as a result of the events. All other device-related AEs were Grade 1 in severity.

**Table 2.7.4.2.2.3.4.1: Incidence of Adverse Events Assessed by Investigator as Device-Related, by SOC and PT (Safety Population, Total Dosing Period)**

System Organ Class/Preferred Term	Overall (n = 24)	
	Events	Incidence
Subjects with at Least 1 Reported Device-Related <sup>a</sup> AE	20	9 (38%)
General disorders and administration site conditions	10	5 (21%)
Device connection issue	1	1 (4%)
Device leakage	2	1 (4%)
Device malfunction	1	1 (4%)
Medical device complication	1	1 (4%)
Needle issue	4	3 (13%)
Pain	1	1 (4%)
Infections and infestations	2	2 (8%)
Device-related infection	1	1 (4%)
Propionibacterium infection	1	1 (4%)
Injury, poisoning and procedural complications	2	2 (8%)
Post procedural haematoma	1	1 (4%)
Wound complication	1	1 (4%)

During 190-201/202, of the 11 infusions which were interrupted but not completed, 5 were secondary to device-related adverse events: 2 events of needle issue, and 1 event each of device malfunction, medical device complication, and Propionibacterium infection. Three additional incomplete infusions were secondary to device problems that were not reported as AEs (2 instances of the needle being dislodged, and 1 instance of problems with the port).

**Reviewer’s comment:** *The adverse events characterized as Temporally Related Events (defined as any AE with onset after initiation of a study drug infusion and within 24 hours after start or restart of study drug infusion) or Device-Related Adverse Events are reviewed in the context of the individual narratives presented in Integrated*

***Subject Narratives (attached).***

Below are presented narrative summaries for the 24 subjects who enrolled in the 190-201 and/or 190-202 clinical treatment studies for BMN 190.

A summary of safety findings from 190-201 and 190-202, including:

- ☐ A figure depicting all AEs, including duration and severity, in each study
- ☐ Narrative summaries of all serious AEs
- ☐ Narrative summaries of AEs of interest (device-related events, hypersensitivity AEs, status epilepticus events)
- ☐ Narrative summaries of other notable AEs

**Subject 1244-1001**

**AEs of note during 30 mg dosing**

Non-serious grade 1 wound complication (device-related AE)

Wound complication

On (b) (6) (Study Day [SD] 8), the subject experienced a non-serious grade 1 wound complication (no further description provided). No treatment for the event was reported, and it was considered resolved on (b) (6) (SD 60).

***Reviewer's comment: The absence of detail regarding the wound complication makes a determination of the root cause impossible.***

**Subject 1244-1002**

**AEs of note during 30 mg dosing**

Non-serious grade 1 CSF pleocytosis (device-related AE)

CSF Pleocytosis

On (b) (6) (Study Day [SD] 15), the subject developed non-serious grade 1 granulocytic CSF. No action was taken with study medication in response to the event. Repeat testing on (b) (6) (SD 31) showed CSF leukocyte count within normal limits.

**Subject 1244-1003**

**Subject 1244-1004**

**AEs of note during 100 mg dosing**

Non-serious grade 1 CSF pleocytosis (device-related AE)

CSF

CSF Pleocytosis

On (b) (6) (Study Day [SD] 45), the subject experienced non-serious grade 1 CSF pleocytosis. The event was considered resolved on (b) (6) (SD 57); the event of CSF pleocytosis as not related to treatment with BMN 190.

**Subject 1244-1006**

**Subject 1287-1005**

**AEs of note during Stable Dose Phase**

Non-serious grade 1 device malfunction (device-related AE)



Non-serious grade 1 needle issue (device-related AE)

*Device malfunction/needle issue*

(b) (6) (SD 293), the subject experienced an incomplete BMN 190 infusion due to non-serious grade 1 AEs reported as device malfunction of the syringe pump and needle issue. It was not clear how much of the scheduled 300 mg infusion was not given as a result of these device-related issues.

**Reviewer's comment:** *The absence of detail regarding these issues makes a determination of the root cause impossible.*

Non-serious grade 1 device leakage (device-related AE)

*Device leakage*

On (b) (6) (SD 362), the subject developed non-serious grade 1 device leakage. No other details were reported, but the event reportedly continued until (b) (6) (SD 545, during 190-202).

**Reviewer's comment:** *The absence of detail regarding this issue makes a determination of the root cause impossible*

**AEs of note during 190-202**

Non-serious grade 1 device leakage (device-related AE)

*Device leakage*

On (b) (6) (SD 601), the subject experienced a non-serious grade 1 event of device leakage, described as device leakage at the reservoir site both prior to and after infusion. It was reported that the planned 300 mg infusion on that date was completed. No treatment for the event was reported, and it was considered resolved at the time of the next infusion.

**Reviewer's comment:** *The absence of detail regarding the leakage issue makes a determination of the root cause impossible.*

**Subject 1244-1008**

**Subject 1244-1009**

**AEs of note during 190-202**

Serious grade 3 device-related infection (device-related AE)

*Device-related infection*

(b) (6) (SD 457), the subject experienced a serious grade 3 device-related infection. On an unreported date, the Rickham device was examined; the membrane showed frequent puncturing and was brittle at the edges. The device was explanted on (b) (6) (SD 459)

**Reviewer's comment:** *The reservoir material changes observed could conceivably result from the disparity between the gauge size of the The (b) (4) ® Needle (b) (4) (22 g) and the (smaller) size recommended for use with the Rickham device. The concern that over time the dome will sustain damage resulting in device leakage and the potential for wound complications, etc. may be confirmed by this event. The sponsor should demonstrate the long term integrity of the reservoir dome following repeated infusions through a 22 gauge needle before proceeding with any longer-term infusion schedules. Please see discussion above.*

**Subject 1244-1010**

**AEs of note during 190-202**

Non-serious grade 1 needle issue (device-related AE) (Week 23 – (b) (6))

*Needle issue (4 September 2015)*

On (b) (6) (SD 520), the subject experienced an interrupted infusion secondary to a nonserious grade 1 needle issue. It was reported that the child became restless during the infusion, and the child's activity caused the needle to become dislodged. The needle was replaced, and the infusion was completed.

Non-serious grade 1 needle issue (device-related AE) (Week 25 – (b) (6))

On 18 (b) (6) (SD 534), the subject experienced an incomplete infusion secondary to a nonserious grade 1 needle issue. It was reported that the child became restless during the infusion, and the child's activity caused the needle to become dislodged. The needle was replaced, but the infusion was not completed.

**Reviewer's comment:** *The sponsor should develop a strategy to deal with this compliance issue to avoid the potential risks associated with the event, e.g., wound infection.*

**Subject 1287-1007**

**Serious AEs at the time of ICV access device placement**

**Grade 3 intracranial hemorrhage**

There was a small amount of hemorrhage and edema in the frontal lobe along the shunt track, without any significant mass effect. The investigator concluded that the fever and lethargy post-operatively were most likely secondary to a serious grade 3 intracranial hemorrhage occurring at the time of surgery (a recognized complication).

**Serious AEs during Safety Follow-Up**

**Grade 2 hemiparesis**

On (b) (6) (SD 21), the subject experienced serious grade 2 acute right hemiparesis. An MRI was performed on (b) (6) (SD 24); it revealed that the Ommaya reservoir catheter tip had advanced and was at the right foramen of Monro. Some hemosiderin staining and edema were present at the site of a previous hematoma. Ventricular dimensions were unchanged from the previous scans. No acute infarcts or hemorrhage were observed.

**Reviewer's comment:** *This is a recognized risk of the insertion of a ventricular catheter.*

**Subject 0119-1020**

Non-serious grade 1 CSF test abnormal (device-related AE)

Non-serious grade 1 medical device complication (device-related AE)

Non-serious grade 1 device connection issue (device-related AE)

*CSF test abnormal/Medical device complication*

On (b) (6) (SD 267), the subject experienced non-serious grade 1 CSF test abnormal, described as blood in the CSF following difficult access. CSF labs drawn prior to the infusion. the subject also experienced a leak in the in-line filter, which led to an incomplete infusion.

*Device connection issue*

On (b) (6) (SD 294), the subject experienced a non-serious grade 1 device connection issue, described as line disconnection and reconnection when the patient became restless.

**Reviewer's comment:** *The absence of detail regarding the leakage issue makes a determination of the root cause impossible. The sponsor should develop a strategy to deal with this compliance issue to avoid the potential risks associated with the event, e.g., wound infection.*

**Subject 0146-1021**

**Subject 0146-1022**

**Subject 0146-1023**

**AEs of note during Stable Dose Phase**

**Serious grade 1 subdural hematoma**

*Subdural hematoma*

On (b) (6) (SD 168), the subject experienced a serious grade 1 right parietal subdural hematoma.

No additional details were reported, and no treatment for the event was reported. The event of subdural hematoma was considered resolved on (b) (6).

**Reviewer's comment:** *The absence of detail regarding the subdural hematoma makes a determination of the root cause impossible. However, this may represent a recognized risk of the insertion of a ventricular catheter.*

**Subject 1244-1011**

**AEs of note during Stable Dose Phase**

Non-serious grade 1 CSF pleocytosis (device-related AE)

*CSF pleocytosis*

On (b) (6) (Study Day [SD] 1), the subject experienced non-serious grade 1 CSF pleocytosis.

**Reviewer's comment:** *The absence of detail regarding the leakage issue makes a determination of the root cause impossible.*

Non-serious grade 1 post-procedural hematoma (device-related AE)

*Post-procedural hematoma*

On (b) (6) (SD 2), the subject experienced a non-serious grade 1 small local post-procedural hematoma. No treatment for the event was reported.

**Reviewer's comment:** *The absence of detail regarding the hematoma makes a determination of the root cause impossible. However, this may represent a recognized risk of the insertion of a ventricular catheter.*

**AEs of note during 190-202**

Non-serious grade 1 needle issue (device-related AE)

*Needle issue*

On (b) (6) (SD 337), the subject had an incomplete infusion because of a non-serious grade 1 needle issue. It was reported that the needle became dislodged during the infusion.

**Reviewer's comment:** *The sponsor should develop a strategy to deal with this compliance issue to avoid the potential risks associated with the event, e.g., wound infection.*

**Subject 1244-1012**

**Subject 1244-1017**

**Subject 1244-1024**

**Subject 1323-1013**

**Subject 1323-1014**

**Subject 1323-1015**

**AEs of note during Stable Dose Phase**

Serious grade 3 motor dysfunction

The investigator considered the motor dysfunction to be secondary to the pharyngitis.

**Subject 1323-1016**

**Subject 1323-1018**

**Subject 1323-1019**

**CONCLUSIONS/RECOMMENDATIONS**

The infusion system detailed in the submission represents a hybrid of a number of marketed devices. The sponsor plans to supply an Administration Kit (b) (6)

Several ICV access devices (reservoir and catheter) as well as the recommended syringe pump are cleared for indications including ICV drug delivery and will not be supplied. The devices to be supplied were selected because they are commonly used for fluid delivery by healthcare professionals (HCPs), designed to aid in aseptic technique, and utilize standard luer lock fittings. The individual infusion components of the kit (single container) will be provided to the HCPs in the original manufacturer's, sterile-unit packaging. The devices specified are 510(k)-cleared devices commonly used for infusions, they have design features that allow them to be used as part of a system (leak-free fittings), and are designed to aid in aseptic technique (sterile and easy to open).

However, as evidenced by the information provided in the Integrated Subject Narratives, the sponsor should:

1. Provide further detail regarding a number of the adverse events, or a root cause analysis of each, or provide a justification for not doing so;

2. Develop a strategy to deal with the patient compliance issues experienced at the time of drug infusion to avoid the potential risks associated with the event, e.g., wound infection, or provide a justification for not doing so;

3. The reservoir material changes observed in the event noted above could conceivably result from the disparity between the gauge size of the The (b) (4) ® Needle (b) (4) (22 g) and the (smaller) size recommended for use with the Rickham device. The concern that over time the dome will sustain damage resulting in device leakage and the potential for wound complications, etc. may be confirmed by this event. The sponsor should demonstrate the long term integrity of the reservoir dome following repeated infusions through a 22 gauge needle before proceeding with any longer-term infusion schedules or provide a justification for not doing so.

**16. APPENDIX B**

The following is the sterility consultant's review memo:

**Summary:**

Please note that all comments are taken/summarized from the sponsor's submission, unless noted as a "Reviewer comment".

This is a follow-up consult to address deficiencies noted in CON1612918.

Summary of issues found in CON1612918:

- The sponsor should describe the product challenge devices use in the (b) (4) validation
- The sponsor should provide (b) (6) testing
- Bioburden testing and tests for sterility are needed for the syringe and hypodermic needle
- A more detailed protocol for the bacterial endotoxin testing is needed
- Material-mediated pyrogen testing is needed

The above issues were resolved following the sponsor's response. No further concerns in regards to sterility.

Please see **Review of Response** for more details.

**Background:**

**Device Description:**



BMN 190 is an enzyme replacement therapy indicated for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency.

BioMarin will supply a BMN 190 Administration Kit for use with BMN 190 DP and FS containing two syringes, two hypodermic needles, an infusion set with an inline filter, an extension line, and a port needle. (b) (6)

(b) (6)

The devices to be supplied for use with BMN 190 DP and BMN 190 FS were selected because they are commonly used for fluid delivery by healthcare professionals (HCPs), designed to aid in aseptic technique, and utilize standard luer lock fittings.

The individual infusion components of the kit (single container) will be provided to the HCPs in the original manufacturer's, sterile-unit packaging.

**Intended Use:**

Enzyme replacement therapy for the treatment of Neuronal Ceroid Lipofuscinosis type 2 (CLN2) or TPP1 deficiency, a form of Batten disease

I was asked to review the following:

*Please review the sterility information provided in the submission for the device constituent parts. The device system includes two syringes, two hypodermic needles, an infusion set with an inline filter, an extension line, and a port needle. As a reminder*

(b) (6)

I reviewed the following documents for the follow-up consult:

"Response to Quality RFI dated 05Aug2016"

I reviewed the following documents in the original consult (CON1612918):

"Auto Tubing Dose Audit"

"CoA 536040"

"CoA FS116"

"CoC 21-2737-24"

"CoC 302830"

"CoC 305165"

"Container Closure System" (section 3.2.P.7)

"Dose Audit Report 302830"

"Dose Audit Report 305165"

"Dose Validation Report 302830"

“Dose Validation Report 305165”  
“Endotoxin 21-2737-24”  
“Endotoxin 302830”  
“Endotoxin 305165”  
“Endotoxin 536040”  
“Endotoxin FS116”  
“FM-SP 15-02-536040”  
“FM-SP 15-05 – FS116”  
“Manual Assembly Dose Audit”  
“Response to Quality RFI dated 18Jul2016”  
“sterilization process validation final report.VP 10499-03”

**Review:**

**Reviewer comment:** The following section represents the original consult with comments summarizing the sponsor’s response in *italics*. Please see **Review of Responses** for more details.

**Reviewer comment:** All components noted in this consulting review have been previously approved. (b) (6)

(b) (6) and the sponsor has submitted certificates of analysis confirming package integrity. The sterilization for the following components are all carried out by their manufacturers (b) (6) This is acceptable.

The following components are provided in the administration kit and are the subject of this consulting review:



Table 3.2.P.7.2.1: Medical Device Components

Component	Construction	Manufacturer	Manufacturer Part Number	510(k) Number <sup>1</sup>
Infusion set with 0.2µm filter				(b) (6)
Extension line				
(b) (4) needle (16mm Port needle)				
Syringe ( (b) (6) 20mL)				
Hypodermic needle (21 gauge Syringe needle)				
(b) (6)				

<sup>1</sup> Letters of Authorization to the device 510(k) submission provided in in Module 1.4.1

The above components are sterilized via:

Table 3.2.P.7.2.1.4.1: Administration Kit Components

Component	Certificate of Analysis/Conformity (b) (4)	Bacterial Endotoxin Test (BET)	Sterilization Validation	Sterilization Method (b) (6)
Infusion set with 0.2µm filter		Endotoxin FS116	Auto Tubing Dose Audit Manual Assembly Dose Audit FM-SP 15-05 – FS116	
Extension line		Endotoxin 536040	FM-SP 15-02 – 536040	
(b) (4) needle (22G, 16mm Port needle)		Endotoxin 21-2737-24	Sterilization Validation VP 10499-03	
Syringe ( (b) (6) 20mL)		Endotoxin 302830	Dose Validation Report 302830 Sterility Dose Audit 302830	
Hypodermic needle (21 gauge Syringe needle)		Endotoxin 305165	Dose Validation Report 305165 Sterility Dose Audit 305165	

Sterilization of the individual components of the BMN 190 Administration Kit is conducted (b) (4) in accordance with (b) (4). The individual components are non-pyrogenic and tested per USP <85> and meet limits as specified in USP <161>.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JENNY N DOAN  
04/20/2017

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
BLA# 761052	NDA Supplement #: S- BLA Supplement #: S-	<b>Efficacy Supplement Category:</b> <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Brineura Established/Proper Name: cerliponase alfa Dosage Form: Solution for infusion Strengths: 30 mg per mL Route of Administration: Intracerebroventricular (ICV)		
Applicant: BioMarin Agent for Applicant (if applicable):		
Date of Application: May 27, 2016 Date of Receipt: May 27, 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: Jan. 27, 2017		Action Goal Date (if different):
Filing Date: 07/26/2016		Date of Filing Meeting: 06/28/2016
<b>Chemical Classification (original NDAs only) :</b> <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
<b>Proposed indication(s)/Proposed change(s):</b> Cerliponase alfa is indicated for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i>		

<a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499"><u>http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</u></a>	
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Type of BLA		<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)		
<b><i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i></b>				
Review Classification:		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority (requesting for Ped Rare Dz priority voucher)		
<b><i>The application will be a priority review if:</i></b> <ul style="list-style-type: none"> <li><i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i></li> <li><i>The product is a Qualified Infectious Disease Product (QIDP)</i></li> <li><i>A Tropical Disease Priority Review Voucher was submitted</i></li> <li><i>A Pediatric Rare Disease Priority Review Voucher was submitted</i></li> </ul>		<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input checked="" type="checkbox"/>  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>		<input checked="" type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)		
<input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:		<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)		
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 122472				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA/BsUFA and Action Goal dates correct in the electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b><i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i></b>				
Are the established/proper and applicant names correct in electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i></p>					
<p>Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i>  <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></p> <p><i>If no, ask the document room staff to make the appropriate entries.</i></p>		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i>  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></p> <p>If yes, explain in comment column.</p>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<p><b>If affected by AIP, has OC been notified of the submission?</b>  <b>If yes, date notified:</b></p>		<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?</p>		<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i></p>		<p>Payment for this application (check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a>):</p> <p> <input type="checkbox"/> Paid  <input checked="" type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required </p>			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i></p>		<p>Payment of other user fees:</p> <p> <input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears </p>			
<p><u>User Fee Bundling Policy</u></p> <p><i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i>  <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a></p>		<p>Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i></p> <p> <input checked="" type="checkbox"/> Yes  <input type="checkbox"/> No </p>			
<b>505(b)(2)</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>



(NDAs/NDA Efficacy Supplements only)				
Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). If yes, answer the bulleted questions below:	<input type="checkbox"/>	<input type="checkbox"/>	x	
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?	<input type="checkbox"/>	<input type="checkbox"/>		
<p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>				
<ul style="list-style-type: none"> <li>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</li> </ul> <p>Check the Electronic Orange Book at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p>	<input type="checkbox"/>	<input type="checkbox"/>		
If yes, please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, # years requested:				



<i><b>Note:</b> An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
<b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If yes, did the applicant:</b> (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i><b>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</b></i>				
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Claims 7 years of market exclusivity
<i><b>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</b></i>				
<i><b>Note:</b> Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Format and Content				
<i><b>Do not check mixed submission if the only electronic component is the content of labeling (COL).</b></i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission, does it follow the eCTD guidance?</b> <sup>1</sup> <b>If not, explain (e.g., waiver granted).</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<sup>1</sup> <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>



<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Because BMN 190 has an orphan drug designation (#13-3919), BioMarin is exempt from PREA requirements for the current application.
<b>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</b>  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</b>  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b><u>BPCA:</u></b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required<sup>3</sup>)</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Sponsor submitted a Pharmacovigilance Plan (Non-REMS)
<b>Prescription Labeling</b>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labeling <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input checked="" type="checkbox"/> Other (administration kit, UDI sticker, solution vial)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in Physician Labeling Rule (PLR) format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		administered by healthcare provider via intracerebroventricular (ICV)
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015:</b> Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>



<i>labeling in PLLR format before the filing date.</i>				
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? ( <i>send WORD version if available</i> )	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	No patient labeling; administered by healthcare provider via ICV intracerebroventricular
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDRH,DNP,COA,OSI,OSE, OPDP- complete 6/8/16
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> May 9	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>	<input type="checkbox"/>			None



ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:**

**BACKGROUND:**

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	JENNY DOAN	Y
	CPMS/TL:	KEVIN BUGIN	Y
Cross-Discipline Team Leader (CDTL)	LAURIE MULDONEY		Y
Division Director/Deputy	DRAGOS ROMAN		Y
Office Director/Deputy	JULIE BIETZ		Y
Clinical	Reviewer:		Y
	TL:		Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		N/A
	TL:		N/A
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		N/A
	TL:		N/A
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		Y
	TL:		Y
Clinical Pharmacology	Reviewer:		Y
	TL:		Y
• Genomics	Reviewer:		N/A
• Pharmacometrics	Reviewer:		Y
Biostatistics	Reviewer:		Y
	TL:		Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:		Y
	TL:		Y
Statistics (carcinogenicity)	Reviewer:		Y
	TL:		Y
Product Quality (CMC) Review Team:	ATL:		Y
	RBPM:		Y
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:		
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
<ul style="list-style-type: none"> <li><b>Discipline</b></li> </ul> <p><small>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</small></p>	Reviewer:		
	TL:		
Other attendees			
	<small>*For additional lines, right click here and select "insert rows below"</small>		

### **FILING MEETING DISCUSSION:**

<b>GENERAL</b> <ul style="list-style-type: none"> <li>505(b)(2) filing issues: <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> </li> </ul>		<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO   <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments	

<b>CLINICAL</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <b>If no, explain:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <b>Comments:</b>  <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input type="text"/> <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>CONTROLLED SUBSTANCE STAFF</b> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>CLINICAL MICROBIOLOGY</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<b>CLINICAL PHARMACOLOGY</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>BIOSTATISTICS</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<u><b>New Molecular Entity (NDAs only)</b></u>  <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u><b>Environmental Assessment</b></u>  <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <b>Comments:</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<u><b>Facility Inspection</b></u>  <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review (BLAs only)</u></b></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

REGULATORY PROJECT MANAGEMENT	
<b>Signatory Authority:</b> DRAGOS ROMAN  <b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V):  <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):  <b>Comments:</b>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTION ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: April 2016



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JENNY N DOAN  
04/18/2017

# REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Application:** BLA 761052

**Application Type:** New BLA

**Drug Name(s)/Dosage Form(s):** BMN-190

**Applicant:**

**Receipt Date:** May 27, 2016

**Goal Date:** Jan. 27, 2017

## 1. Regulatory History and Applicant's Main Proposals

IND 122472

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

**NOTE TO RPM:** SEE THE [LABELING DEVELOPMENT TEAM \(LDT\) INTRANET SITE](#) FOR ADDITIONAL PI LABELING RESOURCES.

## 3. Conclusions/Recommendations

### CHOOSE A OR B

#### A. USE IF NO LABELING DEFICIENCIES WERE IDENTIFIED

No SRPI format deficiencies were identified in the review of this PI.

#### B. USE IF LABELING DEFICIENCIES WERE IDENTIFIED

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

### IF APPLICABLE, LIST OTHER LABELING ISSUES

In addition, the following labeling issues were identified:

1.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by DATE (e.g., CHOOSE A DATE WITHIN THREE WEEKS OF THE LETTER). The resubmitted PI will be used for further labeling review.

### Instructions for copying items from SRPI to 74-day or advice letter

## **RPM PLR Format Review of the Prescribing Information**

The SRPI is “locked” to allow use of the drop-down menus and comment fields. However, the “locked” mode does not allow you to directly copy SRPI items into the 74-day or advice letter. To copy SRPI items in the letter, use the following instructions to unlock the document.

Word 2010: (1) Click the “Review” tab, (2) click on “Restrict Editing” tab, (3) in the “Restrict Formatting and Editing” window, click “Stop Protection” at the bottom of the window.

### **Instructions to allow use of drop-down menus and comment fields**

If you need to switch from the “unlocked” mode back to the “locked” mode to allow use of the drop-down menus and comment fields, use the following instructions.

Word 2010: (1) Click the “Review” tab, (2) click on “Restrict Editing” tab, (3) in the “Restrict Formatting and Editing” window, click on “Allow only this type of editing in the document:”, (4) click on “Yes, Start Enforcing Protection”, and (5) click “OK” (leave the password box blank).

**[End instruction: Delete all instructions before DARRTS check-in.]**

## Selected Requirements of Prescribing Information

### 4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

#### Instructions for completing the SRPI

There is one drop-down menu and one comment field for each item.

Drop-Down Menu: “NO” is the default option. For each SRPI item, click on the word “NO” and choose one of three following options:

- **NO**: The PI does not meet the requirement for this item (deficiency).
- **YES**: The PI meets the requirement for this item (no deficiency).
- **N/A**: This item does not apply to the specific PI under review (not applicable).

Comment Field: Comments are optional. To insert a comment for a particular item, click on the word “Comment” and insert your comment.

[End instructions: Delete all instructions before DARRTS check-in.]

## Highlights

See Appendix for a sample tool illustrating Highlights format.

### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

#### Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

#### Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
  - TOC from the Full Prescribing Information (FPI).

#### Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

#### Comment:

## Selected Requirements of Prescribing Information

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

**Comment:**

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

\* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading, "**HIGHLIGHTS OF PRESCRIBING INFORMATION**" must be **bolded** and should appear in all UPPER CASE letters.

**Comment:**

#### Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

## Selected Requirements of Prescribing Information

### Comment:

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

### Comment:

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

### Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

### Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

### Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

### Comment:

#### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

### Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

### Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

### Comment:



## Selected Requirements of Prescribing Information

### Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

*Comment:*

### Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

*Comment:*

### Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "To report **SUSPECTED ADVERSE REACTIONS**, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)."

*Comment:*

### Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION** and **FDA-approved patient labeling**
- See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**

*Comment:*

### Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "Revised: 8/2015").

*Comment:*



## Selected Requirements of Prescribing Information

---

### Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

**YES** 24. The TOC should be in a two-column format.

Comment:

**YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.

Comment:

**YES** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

**YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

**YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment: 5.1 ICV Access Device-related Compliance- does "related" have to be capitalized?

**NO** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

**NO** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS\***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- NO** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]."

**Comment:**

## Selected Requirements of Prescribing Information

- NO** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- NO** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

#### BOXED WARNING Section in the FPI

- NO** 35. All text in the BW should be **bolded**.

Comment:

- NO** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

#### CONTRAINDICATIONS Section in the FPI

- NO** 37. If no Contraindications are known, this section must state “None.”

Comment:

#### ADVERSE REACTIONS Section in the FPI

- NO** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- NO** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

## Selected Requirements of Prescribing Information

### PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
  - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

**Comment:**

- NO** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

APPEARS THIS WAY ON ORIGINAL



# Selected Requirements of Prescribing Information

## Appendix: Highlights and Table of Contents Format

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

**PROPRIETARY NAME** (non-proprietary name) dosage form, route of administration, controlled substance symbol  
Initial U.S. Approval: YYYY

#### **WARNING: TITLE OF WARNING**

*See full prescribing information for complete boxed warning.*

- Text (4)
- Text (5.x)

#### -----RECENT MAJOR CHANGES-----

Section Title, Subsection Title (x.x) M/201Y  
Section Title, Subsection Title (x.x) M/201Y

#### -----INDICATIONS AND USAGE-----

**PROPRIETARY NAME** is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

#### -----DOSAGE AND ADMINISTRATION-----

- Text (2.x)
- Text (2.x)

#### -----DOSAGE FORMS AND STRENGTHS-----

Dosage form(s): strength(s) (3)

#### -----CONTRAINDICATIONS-----

- Text (4)
- Text (4)

#### -----WARNINGS AND PRECAUTIONS-----

- Text (5.x)
- Text (5.x)

#### -----ADVERSE REACTIONS-----

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### -----DRUG INTERACTIONS-----

- Text (7.x)
- Text (7.x)

#### -----USE IN SPECIFIC POPULATIONS-----

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

### FULL PRESCRIBING INFORMATION: CONTENTS\*

#### **WARNING: TITLE OF WARNING**

#### **1 INDICATIONS AND USAGE**

#### **2 DOSAGE AND ADMINISTRATION**

2.1 Subsection Title

2.2 Subsection Title

#### **3 DOSAGE FORMS AND STRENGTHS**

#### **4 CONTRAINDICATIONS**

#### **5 WARNINGS AND PRECAUTIONS**

5.1 Subsection Title

5.2 Subsection Title

#### **6 ADVERSE REACTIONS**

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

#### **7 DRUG INTERACTIONS**

7.1 Subsection Title

7.2 Subsection Title

#### **8 USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

#### **9 DRUG ABUSE AND DEPENDENCE**

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### **10 OVERDOSAGE**

#### **11 DESCRIPTION**

#### **12 CLINICAL PHARMACOLOGY**

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### **13 NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### **14 CLINICAL STUDIES**

14.1 Subsection Title

14.2 Subsection Title

#### **15 REFERENCES**

#### **16 HOW SUPPLIED/STORAGE AND HANDLING**

#### **17 PATIENT COUNSELING INFORMATION**

\* Sections or subsections omitted from the full prescribing information are not listed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JENNY N DOAN  
04/18/2017

## CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

Template version: January 05, 2017

COA CONSULT TRACKING NUMBER	2016-115
IND/NDA/BLA NUMBER	761052
REFERENCED IND FOR NDA/BLA	122472
ESTABLISHED NAME/TRADE NAME	BMN 190 (cerliponase alfa)/Brineura
SPONSOR/APPLICANT	BioMarin
INDICATION	Treatment of patients with Neuronal Ceroid Lipofuscinosis type 2 (CLN2) disease or TPP1 deficiency (also known as Batten disease)
MEETING TYPE (A/B/C/WRO)	N/A
LETTER DATE/SUBMISSION NUMBER	SDN 0001
PDUFA GOAL DATE	27 April 2017
DATE OF CONSULT REQUEST	02 June 2016
REVIEW COMPLETION DATE	14 April 2017
REVIEW DIVISION	Division of Gastroenterology and Inborn Error Products
MEDICAL REVIEWER/TEAM LEADER (TL)	Elizabeth Hart, M.D./Victor Baum, M.D.
REVIEW DIVISION PM	Jenny Doan
COA REVIEWER	Selena Daniels, Pharm.D., M.S.
ASSOCIATE DIRECTOR, COA STAFF	Elektra Papadopoulos, M.D., MPH
INSTRUMENT(S)	CLN2 (Hamburg) rating scale
COA TYPE	Clinician-reported outcome
ENDPOINT(S) CONCEPT(S)	Motor functioning (gait/walking ability), Language functioning
INTENDED POPULATION(S)	Children $\geq$ 3 years old with mild to moderate CLN2 disease
<i>Please check all that apply:</i>	<input checked="" type="checkbox"/> Rare Disease/Orphan Designation <input checked="" type="checkbox"/> Pediatric



## Clinical Outcome Assessment Review

Selena R. Daniels, PharmD, MS

BLA 761052

BMN 190/Brineura

CLN2 (Hamburg) Rating Scale (motor and language functioning)

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### A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Gastroenterology and Inborn Error Products (DGIEP) regarding IND 122472. The targeted indication is for treatment of Neuronal Ceroid Lipofuscinosis type 2 (CLN2; also known as Batten disease).

DGIEP requested COA Staff to review the clinician-reported outcome assessment, CLN2 rating scale, used as the primary endpoint in Studies 190-901 (DEM-Child Natural History registry study used as external control) and 190-201/202 (single arm, open-label BMN 190 treatment/extension studies) to measure motor and language functioning using a motor-language (M-L) total score. The applicant's primary endpoint is the proportion of patients with absence of "0" or an unreversed 2-point rate of decline in the CLN2 M-L total score (where 0 = greater disability [i.e., profoundly impaired] and 6 = least disability [i.e., grossly normal]) over 48 weeks.

It was observed that two different instruments were used in each of the studies, despite the rating scales being identical in the case report forms (CRFs) (Appendix A). Study 190-901 administered the CLN2 rating scale without rating assessment guidelines (i.e., rater instructions for administration and training), whereas Studies 190-201/202 administered the CLN2 rating scale but trained clinicians with different category descriptors than the scale used in the CRF (Appendix B). Therefore, while the form of the scale contained in the CRF was identical to that used in Study 190-901, the addition of rating guidelines and training that were specific to Studies 190-201/202, led to concerns about differences in comparability in how the scales were used. Effectively, with the addition of these new rating guidelines and training, the applicant created a different instrument<sup>1</sup> from the one used in Study 190-901.

Because of the differences in the instruments administered in these studies, there is concern about the comparability of ratings produced. The applicant attempted to demonstrate scale comparability by conducting a Video Comparability study using the CLN2 rating scale instruments from Study 190-901 and Studies 190-201/202. For additional details of this study and its results, refer to the Statistical Review.

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<sup>1</sup> The FDA Patient-reported outcome (PRO) Guidance (2009) describes an instrument as a means to capture data (i.e., a questionnaire) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results in the target patient population.

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We have the following comments on the CLN2 rating scale, which primarily stem from the scale comparability issue:

- Although the applicant attempted to improve upon the scale with the use of rating assessment guidelines, there are some notable differences that affect comparability, specifically for a score of ‘2’ in the scale. For example, in Study 190-901, the motor item allows for ‘frequent falls,’ whereas in Studies 190-201/202 it allows ‘intermittent falls’ and quantifies a child’s walking distance. Similarly, the language item in Study 190-901 allows speech to be ‘recognizably abnormal’, whereas in Studies 190-201/202 it specifies that speech can include ‘some intelligible words’ and the use of ‘short sentences to convey concepts, requests, or needs.’ Based on these qualitative descriptors, a score of ‘2’ with the rating assessment guidelines in Study 190-901 scale may indicate a worse functional status than in Studies 190-201/202.
- Different methods of rating were used in the two studies. Patients from Study 190-901 were rated by clinicians both retrospectively and prospectively through live assessment and secondary sources (medical charts, parental interviews, etc.), whereas patients from Studies 190-201/202 were rated by clinicians prospectively through live assessment only. There is no evidence to show that these individual methodologies would generate the same clinician rating. These differences in rating methodology could potentially lead to systematic differences between the observed rates of decline observed between Studies 190-201/202 and Study 190-901. For additional details, refer to the Statistical Review.
- Different schedules of assessments were used in the two studies. The CLN2 scale was administered approximately every 12 weeks (range 2-61 months) and eight weeks in Study 190-901 and Studies 190-201/202, respectively. The studies do not have the same time points to compare between patients.
- Based on the findings from the applicant’s Video Comparability study, the language item weakens the interpretability of the CLN2 M-L total score. Overall, there was disagreement of ratings on the CLN2 scales used in Study 190-901 and Studies 190-201/202 indicating that the scales are not equivalent, particularly the language item. Greater concordance was shown with the CLN2 motor item ( $K_{\omega} = 0.88$ ), whereas there was greater discordance with the language item ( $K_{\omega} = 0.53$ ). Refer to the Statistical Review for more details.

To overcome some of these measurement challenges, we offer the following suggestions:

- Because the language item demonstrated greater discordance in the Video Comparability Study, the motor item would be a more reliable indicator to assess clinical benefit on its own rather than the use of a combined M-L total score.

## **Clinical Outcome Assessment Review**

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- In light of the analysis issues described above, the applicant should consider exploring other methods to analyze the CLN2 data. Another approach to mitigate this issue is to examine a 2-category change in the scale for each individual item, with an emphasis on the CLN2 motor item for the reasons described above. Refer to the Statistical Review for additional information regarding these analyses.

This review summarizes the measurement properties for the CLN2 rating scale used in Studies 190-201/202. It is important to note that its measurement properties are not translatable to the CLN2 rating scale used in Study 190-901 due to the fact that these are two different instruments.

For best practices for future drug development, we recommend the use of well-defined and reliable instruments in conjunction with the same rater training and instructions across comparator arms (e.g., treatment, placebo, etc.). These considerations apply to clinical trials, as well as natural history studies. Every effort should be made to ensure comparability between assessment methods used in clinical trials with the natural history control to allow meaningful comparison of changes over time. Instruments should also be culturally adapted and adequately translated for all intended study populations for use in multinational trials. Translation and cultural validation of outcome assessments can affect efficacy findings and it is important to ensure that assessments are standardized across sites. These issues should be considered and discussed with the Agency early in drug development.

## **B. BACKGROUND**

### Materials reviewed:

- Common Technical Document Summaries (2.5; 2.7.3; 2.7.4)
- Clinical Study Reports (Studies 190-201/202)
- Evidence Dossier including appendices
- Previous COA Consult Reviews:
  - AT 2015-040\_IND 122472\_Kovacs dated 19 June 2015 (Reference ID: 3777028)
  - AT 2015-103\_IND 122472\_Daniels dated 05 January 2016 (Reference ID: 3866091)
  - AT 2016-026\_IND 122472\_Daniels dated 19 March 2016 (Reference ID: 3904770)
  - AT 2016-131\_IND 122472\_Daniels dated 06 July 2016 (Reference ID: 3955081)
- Applicant responses to Information Requests
- Literature (see Section 10 for list of key references)

### Regulatory History

- Agency requested additional information about CLN2 rating scales (20 May 2015; 01 July 2015)
- Agency requested BioMarin to provide comparability data for the CLN2 rating scales (11 September 2015)

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- Agency provided feedback on BioMarin's proposal for scale comparability and requested some additional analyses to be added to their analysis plan (11 January 2016)
- Agency requested a full evidence dossier for the CLN2 rating scales (11 March 2016)

### Disease Background:

Neuronal Ceroid Lipofuscinosis type 2 (CLN2) disease, a form of Batten disease, is a progressive neurodegenerative disease. It is characterized as a lysosomal storage disease due to tripeptidyl peptidase 1 (TPP1) deficiency. The U.S. incidence of CLN2 is estimated to be 0.5-1/100,000 births/year. CLN2 disease symptom onset occurs typically between two and four years of age. The clinical presentation of CLN2 includes seizures, ataxia, loss of motor skills, speech degeneration, blindness, and cognitive/developmental decline. Death usually transpires between eight to fifteen years of age. There is currently no approved therapy.

### BMN 190

BMN 190 is a recombinant form of human TPP1, the enzyme deficient in patients with CLN2 disease. As an enzyme replacement therapy (ERT), BMN 190 is expected to restore TPP1 enzyme activity. BMN 190 is administered by intracerebroventricular (ICV) infusion.

## C. CLINICAL OUTCOME ASSESSMENT REVIEW

### 1 CONTEXT OF USE

#### 1.1 Clinical Trial Population

The target study population for Study 190-901 and Studies 190-201/202 includes children  $\geq 3$  years old with mild to moderate CLN2 disease, and a baseline M-L total score of  $\geq 3$  (using the CLN2 rating scale).

#### 1.2 Clinical Trial Design

Study 190-901 is a natural history registry study (using DEM-CHILD database). Studies 190-201/202 is a single arm, open-label dose escalation and 48-week stable dose study with an extension study. The clinical review provides further details of the study designs.

In Study 190-901, the CLN2 rating scale was administered at variable time points (median: every 3 months [12 weeks]; range: 2-61 months<sup>2</sup>). Data was collected prospectively and retrospectively (e.g., parental interviews, medical charts, etc.). In Studies 190-201/202 the CLN2 rating scale was administered every two months [8 weeks] when patients were on stable dose (see Tables 1 and 2). Data was collected prospectively. Additionally, a parent/caregiver interviewer is conducted prior to the clinician assessment. (Note: Clinicians did not rate the

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<sup>2</sup> Based on data entered in DEM-CHILD database

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same patients within Studies 190-201/202 and a patient could be rated by a different clinician at different time points.).

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**Table 1. Schedule of Assessment for Studies 190-201**

For Patients Enrolled After Dose Escalation is Completed											
Assessments and Events	Screening <sup>a</sup> (≤ 3 days prior to ICV Surgery)	ICV Surgery and Recovery (≤ 3 days) <sup>e</sup>	Baseline Visit	First Infusion (Days 1-6)						Study Completion / Early Termination	Safety Follow- Up
			Prior to First Dose	Week 1 Study Day					Stable Dose	Proximity to last dose (±3days)	6 months after last dose ±1week
			≤2 Days	1	2	3	4	5	6		
Informed consent/assent <sup>a</sup>	X										
Diagnosis <sup>b</sup>	X										
Genotype <sup>c</sup>			X <sup>d</sup>								
TPPI Activity (dried blood spot) <sup>a</sup>			X								
CLN2 disease rating scales with videotaping <sup>d</sup>	X		X			X			Q8W	X	
Criteria for study entry	X										
ECG, 12-lead <sup>e</sup>			X	X					Q24W	X	X
EEG, standard awake <sup>f</sup>			X						Q24W	X	X
MRI <sup>g</sup>	X		X						W 9, 25, 49	X	
CSF (cell count, protein, glucose) <sup>h</sup>			X				X		X	X	X
Administer study drug			X						X		

**Table 2. Schedule of Assessment for Studies 190-202**

Assessments and Events	Screening Period (2 weeks)	Q2 Weeks	Q8 Weeks	Q12 Weeks	Q24 Weeks	Study Completion or ETV (2 weeks ± 3 days after Week 239)	Safety Follow-Up (6 months after last dose ±1 week)
Informed consent/assent <sup>a</sup>	X						
Criteria for study entry <sup>b</sup>	X						
Medical history <sup>c</sup>		X (Week 1 only)					
CLN2 disease rating scales <sup>d</sup>			X			X	
Videotaping <sup>e</sup>					X	X	
ECG, 12-lead <sup>f</sup>					X	X	X
EEG, standard awake					X	X	X
MRI <sup>g</sup>					X	X	
CSF (cell count, protein, glucose) <sup>h</sup>		X				X	X
Device Patency/Infection <sup>i</sup>		X					
Administer study drug		X					
Phone follow-up <sup>j</sup>		X					
CSF/plasma for biomarkers <sup>k</sup>					X	X	
CSF/serum for immunogenicity <sup>l</sup>				X		X	X
Vital signs <sup>m</sup>		X				X	X
Complete physical examination <sup>n</sup>				X		X	X
Brief physical examination <sup>o</sup>		X					
Blood/urine for clinical lab tests <sup>p</sup>				X		X	X
CLN2 specific QoL questionnaire <sup>q</sup>					X	X	
PedsQL <sup>r</sup>					X	X	
EQ-5D-5L <sup>s</sup>	X				X	X	

*Reviewer's comments: There is no standard protocol for Study 190-901. Data collection for the CLN2 rating scale and frequency of assessments are different across studies, so the scores from each study cannot be directly compared as Study 190-901 is susceptible to lack of comparability among the data from the different modes of collection (retrospective and prospective assessment) and recall error. Further, the studies do not have the same time points to compare between patients.*

*Regarding the retrospective data collection for Study 190-901, multiple modes were used to collect data (medical charts and/or parental interviews). There is no evidence to show that these individual methodologies would generate the same clinician rating. There is also concern that parents may not have been able to recall the disability status of their child based on memory and/or any other aid (e.g., photographs, videos, etc.) appropriately.*

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*For the prospective data collection for Studies 190-201/202, the applicant noted that the role of the parent/caregiver interview was to ascertain whether the clinical appearance at the time of assessment was incongruous with the patient's functioning over the prior week. Based on multiple communications with the applicant and sites, they have stated that the parent interview was not used to score the patient. However, there is still some concern that the clinicians' rating could be influenced from the parental interview.*

### 1.3 Endpoint Hierarchy and Definition

Table 3. Endpoint Hierarchy

Concept	Endpoint	Assessment Tool
<b>Primary Endpoint</b>		
Motor and verbal (language) function	Proportion of patients with 0 or absence of rate of < 2-point decline (i.e., 1-point decline)	CLN2 rating scale
<b>Secondary Endpoints</b>		
Brain Atrophy	<ul style="list-style-type: none"><li>• Mean whole brain volume (WBV)</li><li>• Mean CSF volume (% of WBV)</li><li>• Mean total white matter volume (% of WBV)</li><li>• Mean total cortical grey matter (%WBV)</li></ul>	Magnetic Resonance Imaging (MRI)
<b>Other Endpoints</b>		
Developmental progress	Mean change from baseline	Denver Developmental Screening Test
Health-related Quality of Life	Mean change from baseline	Pediatric Quality of Life Inventory (PedsQL): the Parent Family Impact Module
Health-related Quality of Life	Mean change from baseline	CLN2 Disease Quality of Life

*Reviewer's comments: The applicant defined response as a rate of decline of less than 2 points per 48 weeks on the CLN2 total score (combined M-L). Based on the natural history study, the expected rate of decline is a 2-point change on CLN2 M-L total score per year. The applicant's rationale for this threshold is that the smallest possible change on the M-L total score of 1 point is clinically meaningful by design.*

### 1.4 Labeling or promotional claim(s) based on the COA

The applicant proposed labeling claims using the CLN2 M-L total score. However, given that there were discordant ratings resulting from different descriptors between the natural history study and the clinical trial with respect to the CLN2-language item, we recommend describing only the results of the CLN2-motor score in labeling.

## 2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest for the CLN2 rating scale are motor and language functioning. The figure below represents the instrument's conceptual framework.

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**Figure 1. CLN2 Conceptual Framework**



*Reviewer's comments: The results from the applicant's Video Comparability study suggests that the motor and language items should be scored separately as there are issues surrounding the reliability of the language item (see Statistical Review). It is also unclear whether the rate of decline in each of these functions is comparable.*

### 3 CLINICAL OUTCOME ASSESSMENTS

The CLN2 rating scale (Appendix A) is a two-item instrument measuring two key neurological symptoms of CLN2: motor and language functioning. Each item is scored on a scale of 0 to 3 characterized by milestone events in the loss of previously attained functions of ambulation and speech (where 0 = greater disability [i.e., profoundly impaired] and 3 = least disability [i.e., grossly normal]). Clinicians are responsible for rating the patients based upon their abilities at the time of assessment, independent of the parent interview. The clinician is intended to use observed evidence from the patient at the time of the rating to complete each item. The mode of administration of the CLN2 rating scale is pen and paper.

The full-length version of the CLN2 rating scale (2002) is shown below (on next page).

**Figure 2. Full-length version of the CLN2 rating scale**  
**COPYRIGHT MATERIAL WITHHELD**



From: (Steinfeld, 2002, Am J Med Genet.)



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*Reviewer's comments: The sponsor is using a short-form version of the CLN2 rating scale by using only the motor and language items. There are other versions of the CLN2 rating scale besides the full-length version and short form version used by the applicant in Study 190-901 and Studies 190-201/202. Worgall et al (2007) described another shorter version of the CLN2 rating scale, which only included motor, language, and seizures items. The category descriptors for this short form remained consistent with what is present in the full-length version of the scale.*

The CLN2 M-L total score is calculated as a sum of the two items, with lower scores indicating greater disease progression and higher scores indicating less disease progression.

Rating Assessment Guidelines were developed to train the clinicians on the use of the short form version of the CLN2 rating scale for Studies 190-201/202. A copy of the guidelines are found in Appendix B of this review. Training for Studies 190-201/202 was conducted by (b) (4)

The scale category descriptors used for the rater training are shown below (the text in red font indicates the notable changes between the guidelines for both studies).

**Figure 3. CLN2 category descriptors in Rating Assessment Guidelines**

CLN2 Rating Assessment Guidelines (RAG)	Study 901	Studies 201 and 202
		<b>Motor</b>
	3 Walks normally	3 Grossly normal gait. No prominent ataxia, no pathologic falls.
	2 <b>Frequent falls</b> , clumsiness obvious	2 Independent gait, as defined by the ability to walk without support for <b>10 steps (10 meters; n= 9 patients)</b> . Will have obvious instability, and may have <b>intermittent falls</b> .
	1 No unaided walking or crawling only	1 Requires external assistance to walk, or can crawl only.
	0 Immobile, mostly bedridden	0 Can no longer walk or crawl.
		<b>Language</b>
	3 Normal	3 Apparently normal language. Intelligible and grossly age-appropriate. No decline noted yet.
	2 Has become recognizable abnormal	2 Language has become recognizably abnormal: <b>some intelligible words, may form short sentences to convey concepts, requests, or needs</b> . This score signifies a decline from a previous level of ability (from the individual maximum reached by the child).
	1 Hardly understandable	1 Hardly understandable. <b>Few intelligible words</b> .
	0 Unintelligible or no language	0 No intelligible words or vocalizations.

*Reviewer's comments: There was no detailed information regarding how the raters were trained for Study 190-901 (i.e., no training manual). However, the raters from each study were trained on different category descriptors. Based on communication with the applicant and site, the rating assessment guidelines were not available to the clinicians during assessment. The clinicians had to rely on their memory of how they were trained to rate the patient. The case report forms (CRFs) that were used in Study 190-901 and Studies 190-201/202 only showed the motor and language category descriptors seen in the full-length version of the scale (shown in*

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*Figure 2 and Appendix A of this review). It is unknown whether the clinicians in Studies 190-201/202 consistently rated patients based on their recall of the category descriptors included in the rating assessment guidelines or based their assessment on how the scores were described on the CRF.*

## 4 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

- ☒ Literature review and/or publications
- ☒ Documentation of expert input
- ☐ Qualitative study protocols and interview guides for focus group or patient interviews
- ☐ Chronology of events for item generation, modification, and finalization (item tracking matrix)
- ☐ Qualitative study summary with evidence to support item relevance, item stems and response options, and recall period
- ☐ Qualitative support for meaningful change
- ☐ Quantitative study summary with evidence to support item retention and scoring
- ☐ Transcripts (if available)

The applicant performed the following instrument development activities to help support content validity of the CLN2 rating scale: a targeted review of the CLN2 measurement literature and input from a panel of experts for refining the rating assessment guidelines for the scale. Documentation of the development of the CLN2 rating scale is limited to the Steinfeld et al. (2002) publication.

The applicant's literature review was targeted to the textbook "The Neuronal Ceroid Lipofuscinoses" (Chang et al., 2011). The textbook summary referenced in the applicant's evidence dossier noted that the first symptoms of CLN2 include motor decline with clumsiness and ataxia, and deterioration of speech, these symptoms are often initially interpreted as delayed speech or general psychomotor development.

*Reviewer's comments: The synopsis of the literature review submitted within the evidence dossier supports that motor and language functioning are clinically relevant concepts for CLN2. The applicant elected not to assess seizure and vision, which were originally included in the full-length version of the CLN2 rating scale. The applicant did not include seizures as a part of the primary endpoint because the frequency of seizures becomes variable later in the course of disease progression despite their initial occurrence at the end of the third year of life. Per the applicant, vision was not included in the primary endpoint primarily because vision impairment is delayed in late infantile CLN2 compared to motor/gait and language impairment. Visual abnormalities typically present around the age of 4 years and complete blindness may not become obvious until age 10 (Chang, 2011). Based on discussion with DGIEP, the Division found the applicant's rationale for omitting measurement of seizures and vision for the purpose of the primary efficacy endpoint acceptable.*

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Expert input from clinicians from the first two clinical sites for Study 190-201 was obtained to operationalize the CLN2 rating scale items for a clinical trial setting in the attempt to standardize administration and training. These clinicians reviewed and rated video recordings of subjects in Study 190-901 as scale item category descriptors were revised until a consensus was reached on anchor point definitions and specific descriptions for the scores of each item. These anchor point definitions and category descriptors were incorporated into the rating assessment guidelines. Modifications were made to the category descriptors in the rating assessment guidelines for both the motor and language items.

*Reviewer's comments: Although modifications were made to the category descriptors (in the rating assessment guidelines) to improve standardization of administration and training, there are some notable differences between the category descriptors used by the clinicians in Study 190-901 and Studies 190-201/202 that impact scale comparability, specifically for a score of 2 for both Motor and Language items. For example, in Study 190-901, the Motor item allows for frequent falls, whereas in Studies 201/202 it allows intermittent falls and walking distance is quantified. Based on these qualitative descriptors, a score of 2 with the Study 190-901 scale may indicate a worse status than in Studies 201/202. Furthermore, the raters within Study 190-201 were trained on different guidelines. For a score of 2 in the Motor item, nine patients in Study 190-201 were scored based on the walking distance of 10m where the remaining patients were scored on 10 steps.*

## 5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The applicant evaluated the psychometric properties of the CLN2 rating scale using Study 190-201 clinical trial data. The psychometric analyses were limited in evaluating the reliability and validity of the CLN2 rating scale due to the study design.

*Reviewer's comments: The applicant was unable to perform these analyses with the data from Study 190-901. Note the sample size for these analyses are small and should be interpreted cautiously.*

- **Reliability:**
  - Intra-rater reliability: Evidence that clinician ratings are stable over time when no change has occurred in the patient's disease status.

*Reviewer's comments: This property was unable to be assessed as clinicians either were unable to rate the same patient throughout the trial or the patient was no longer stable.*

- Inter-rater reliability: Evidence that there is consensus (agreement) in ratings among clinicians.

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The applicant attempted to evaluate inter-rater reliability using two modes of assessments (i.e., live assessment and video assessment) as the Study 190-201/202 clinicians did not rate the same patients in the trial. A single clinician (b) (4) viewed the recorded study 190-201/202 visits from the Hamburg site and rated patients using the CLN2 rating scale from Study 190-201/202. The videotapes given to (b) (4) were in no specific order by patient or time period. The ratings from (b) (4) were then compared to Study 190-201/201 clinicians' ratings.

The weighted kappa ( $K_w$ ) results generated from (b) (4) ratings were as follows:

M-L total score (0-6): The  $K_w$  ranged from 0.89 - 0.93 for each time point and across all rating periods.

Motor Score (0-3):  $K_w = 0.93$  across all videos ( $n=36$ ) and  $K_w = 1.00$  at Week 25 ( $n=11$ ), Week 48 ( $n=10$ ), and Week 72 ( $n=3$ ). At Baseline, (b) (4) provided two ratings that were one-category lower than the clinical study ratings ( $K_w=0.76$ ;  $n=12$ ).

Language score (0-3):  $K_w = 0.82$  across all ratings. The  $K_w$  ranged from 0.67 (Week 48) to 0.93 (Baseline).

The shift table for the motor (Table 5) and language (Table 6) scores from videos across all ratings are shown below.

**Table 5. Rater Agreement on Motor Item Across All Videos (n= 36)**

Clinician Rating	Video Rating				Total
	0	1	2	3	
0	0	0	0	0	0
1	0	10	0	0	10
2	0	2	19	0	21
3	0	0	0	5	5
Total	0	12	19	5	36

**Table 6. Rater Agreement on Language Item Across All Videos (n= 36)**

Clinician Rating	Video Rating				Total
	0	1	2	3	
0	0	0	0	0	0
1	1	24	0	0	25
2	0	6	0	0	6
3	0	0	0	5	5
Total	1	30	0	5	36

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*Reviewer's comments: Although the weighted kappas demonstrated adequate reliability, when you examine the shift tables you can identify which categories were causing discordance. Based on Tables 5 and 6 above, the categories that were most frequently discordant were scores of 2 and 1, with more discrepancies with the language item (Note: Score category 2 had the most modifications in the rating assessment guidelines used for Studies 190-201/202). This could imply that the category descriptors are not as distinct as intended and that there may be greater discordance with the language item. Some of the observed discordance may also stem from differences in the two modes of assessment (live assessment vs. video assessment), which is a limitation of this inter-rater reliability analysis. Ideally, the study would include different raters using the same mode of assessment. There is concern that the live ratings might be influenced by other observed factors that would not have been made known during the video assessment.*

- **Construct validity:** Evidence that relationships among items, domains, and concepts conform to *a priori* hypotheses concerning logical relationships that should exist with other instruments or characteristics of patients and patient groups.
  - Convergent and discriminant validity: Evidence that relationships between results gathered using the instrument and results gathered using other instruments are consistent with pre-existing hypotheses concerning those relationships. The applicant examined construct validity by comparing the pattern and magnitude of the relationship between the CLN2 scores to other instrument scores using Spearman's correlation coefficients using baseline data. The instrument used in these comparisons were: Pediatric Quality of Life (PedsQL™) and CLN2 Quality of Life (QoL) Questionnaire. Despite the limitations of some of these instruments, the relationships demonstrated between the CLN2 scores with the concurrent instrument scores appeared reasonable on the surface.

*Reviewer's comment: The applicant did not pre-specify hypotheses about the expected relationships among the instruments.*

For the motor item, baseline correlations ranged from (b) (4) with the PedsQL™ Core, Family Impact Module, and CLN2 QL domain comparisons, with the strongest relationship seen with the PedsQL™ Physical Functioning measure (Table 7).

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(b) (4)



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(b) (4)





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(b) (4)

- Scale comparability: Evidence that the instruments administered in Study 190-901 and Studies 190-201/202 generated similar measurements.

The applicant attempted to support scale comparability by conducting a Video Comparability study using the CLN2 rating scales from Study 190-901 and Studies 190-201/202. The objective of this study was to demonstrate comparability of the scales used in both studies and bridge the similarities of the scales. The patient videos from Studies 190-201/202 were reviewed and scored by (b) (4) (Study 190-901 rater) without using the rating assessment guidelines specific to these studies (i.e., used the scale how it was administered in Study 190-901).

The Statistical Review describes the details of the study design of the Video Comparability study and its results. Overall, there was disagreement of ratings on the CLN2 scales used in Study 901 and Studies 201/202 indicating that the scales are not equivalent and have some reliability issues, particularly the language item. Higher rater agreement was shown with the CLN2 motor item ( $K_{\omega} = 0.88$ ), whereas there was inconsistent scale ratings across studies with the CLN2 language item ( $K_{\omega} = 0.53$ ).

*Reviewer's comments: The applicant was requested to score the videos from Study 190-901 using the same rating assessment guidelines for Studies 190-201/202. However, the applicant noted that this was not feasible as videotaping patients was not part of the clinical acquisition routine in Study 190-901 and there was not a sufficient supply patient videos. There are limitations to the design of this study as there is no evidence that supports that the two modes (live assessment and video assessment) are equivalent. There is concern that the live ratings would be influenced by other observed factors that would not have been made known during the video assessment.*

*Based on the results of the Video Comparability study, combining the motor and language items to form a composite score does not seem reasonable. A potential path forward is to analyze the motor and language items separately. Because the language item demonstrated greater discordance among raters, the motor item may be a more reliable indicator to assess treatment benefit.*

## 6 INTERPRETATION OF SCORES

The applicant states that the CLN2 rating motor and language scales are intended to represent meaningful changes in milestone activities in children, respectively. For example, in the motor item, a 1 point drop between a rating of 3 and 2 is the difference between a child who can walk normally to a child who can no longer walk normally and falls often. Another point

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drop to a score of 1 would be a child who could no longer walk at least 10 steps, but can still move by some self-process (crawl, etc.). Similarly, the applicant states that meaningful distinctions in levels are presented in the language item's ratings.

The applicant states that the smallest possible change on the summary (0 to 6) M-L total score (1 point) is clinically meaningful by design.

*Reviewer's comments: The applicant did not provide any evidence to support that a 1-point change in the M-L total score is clinically meaningful. (Note: this 1-point change is related to the rate of decline.). The general recommendation to support a threshold for meaningful change is to use anchor-based methods and cumulative distribution functions (CDFs). Additionally, input from clinicians and caregiver could help inform the responder threshold. Neither of these approaches were performed, as Studies 190-201/202 did not include suitable anchors to perform such analyses. It is acknowledged that even if the applicant had performed these analyses, the small sample size would have been a limitation to the interpretation of the data.*

## 7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

Five clinical sites/investigators participated in Studies 190-201/202: The University of Hamburg (Germany), Bambino Gesù Children's Hospital (Italy), Evelina Children's Hospital (United Kingdom), Great Ormond Street Hospital (United Kingdom), and Nationwide Children's Hospital (United States).

The CLN2 rating scale was not translated to any languages. All clinician assessors completed the instrument in English, the language that they were trained for completion in Studies 190-201/202. Certified translators were employed at each site to ensure that clinical assessments and parent interviews were conducted in either the native language of the parent or in a language that the parent is proficient in speaking and listening. For the CLN2 language item, the patient was rated for language, both intelligible words and sentence statements. If the assessor was not fluent in the native language of the patient, a certified translator was present to discern if the vocalizations were interpretable language. The clinician assessor was trying to ascertain the best function of the patient at the time of the visit, and only the clinician assessor made the language item assessment.

*Reviewer's comment: The applicant did not provide any qualifications for the translators besides noting that they were certified. Ideally, the CLN2 scale should have been culturally adapted and adequately translated for all intended study populations for use in multinational trials. Translation and cultural validation of outcome assessments can affect efficacy findings and it is important to ensure that assessments are standardized across sites.*

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### **8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION**

The CLN2 rating scale was not reformatted into a new mode of administration.

### **9 REVIEW USER MANUAL**

The applicant submitted Rating Assessment Guidelines for the CLN2 rating scale (Appendix 2 in the 190-201 clinical study protocol).

### **10 KEY REFERENCES FOR COA**

Steinfeld, R, Heim, P, von Gregory, H, Meyer, K et. al. Late infantile neuronal ceroid lipofuscinosis: quantitative description of the clinical course in patients with CLN2 mutations. Am J Med Genet 112[4], 347-354. 2002

Worgall, S, Kekatpure, MV, Heier, L, Ballon, D et. al. Neurological deterioration in late infantile neuronal ceroid lipofuscinosis. Neurology 69[6], 521-535. 2007

Worgall, S, Sondhl, D, Hackett, N, Kosofsky, B, et al. Treatment of Late Infantile Neuronal Ceroid Lipofuscinosis by CNS Administration of a Serotype 2 Adeno-Associated Virus Expressing CLN2 cDNA. Human Gene Therapy 19[5], 463-474. 2008

## **E. APPENDICES**

Appendix A: CLN2 Rating Scale

Appendix B: Studies 190-201/202 CLN2 Rating Assessment Guidelines

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### APPENDIX A: CLN2 Rating Scale

	Study 901	Studies 201 and 202
CLN2 scale (as seen on source document and CRF)	Motor	
	3	Walks normally
	2	Frequent falls, clumsiness obvious
	1	No unaided walking or crawling only
	0	Immobile, mostly bedridden
	Language	
	3	Normal
	2	Has become recognizable abnormal
	1	Hardly understandable
	0	Unintelligible or no language

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/s/  
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SELENA R DANIELS

04/14/2017

ELEKTRA J PAPADOPOULOS

04/14/2017

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**LABEL AND LABELING REVIEW AMENDMENT**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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<b>Date of This Review:</b>	April 12, 2017
<b>Requesting Office or Division:</b>	Division of Gastroenterology & Inborn Error Products (DGIEP)
<b>Application Type and Number:</b>	BLA 761052
<b>Product Name and Strength:</b>	Brineura (Cerliponase alfa) Injection, 150 mg/5 mL (30 mg/mL)
<b>Product Type:</b>	Single Ingredient Product
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Biomarin Pharmaceuticals
<b>Submission Date:</b>	May 27, 2016
<b>OSE RCM #:</b>	2016-1291
<b>DMEPA Primary Reviewer:</b>	Matthew Barlow, RN, BSN
<b>DMEPA Team Leader (Acting):</b>	Sarah K. Vee, PharmD
<b>OMEPRM Acting Deputy Director:</b>	Lubna Merchant, MS, PharmD

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**REASON FOR AMENDMENT:**

FDA recently issued a final guidance entitled *Nonproprietary Naming of Biological Products* on January 13, 2017 stating the Agency's intention to designate proper names for certain biological products that include four-digit distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix [and intend to work with the applicant post-approval to implement a proper name consistent with the principles outlined in the guidance].



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### **LABEL & LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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<b>Date of This Review:</b>	January 26, 2017
<b>Requesting Office or Division:</b>	Division of Gastroenterology & Inborn Error Products (DGIEP)
<b>Application Type and Number:</b>	BLA 761052
<b>Product Name and Strength:</b>	Brineura (Cerliponase alfa) Injection, 150 mg/5 mL (30 mg/mL)
<b>Product Type:</b>	Single Ingredient Product
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Biomarin Pharmaceuticals
<b>Submission Date:</b>	May 27, 2016
<b>OSE RCM #:</b>	2016-1291
<b>DMEPA Primary Reviewer:</b>	Matthew Barlow, RN, BSN
<b>DMEPA Associate Director (Acting):</b>	Mishale Mistry, PharmD, MPH

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## 1 REASON FOR REVIEW

This review is in response to DGIEP's request for DMEPA to review the submitted proposed labels and labeling for Brineura (cerliponase alfa) for any areas that may lead to medication errors. The proposed labels and labeling were submitted on May 27, 2016 under BLA 761052.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	N/A-D
FDA Adverse Event Reporting System (FAERS)*	N/A-E
Other	F
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

### Use-Related Risk Analysis (URRA)

As a part of their BLA submission, the applicant submitted a comprehensive use-related risk analysis (URRA) and their final conclusion regarding the necessity for a Human Factors study. DMEPA previously evaluated the URRA during a Type C meeting held on September 30, 2015.<sup>a</sup> DMEPA concluded that the proposed URRA and subsequent conclusion appeared reasonable and agreed that a Human Factors validation study was not needed at the time. However, DMEPA requested that the applicant submit any errors related to the safe use of this product or administration issues that occurred during the clinical trials, which will allow a greater understanding of the use-related risk.

DMEPA reviewed the errors, submitted on August 5, 2016, related to the safe use of this product or administration issues that occurred during the clinical trials. The reported errors involved device-related adverse events and were not attributed to the user interface/use of the product. With regard to the preparation and administration of Brineura, per discussions with

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<sup>a</sup>28 Oct 2015. IND 122472 BMN 190 Type C Meeting Minutes held on September 30, 2015.

the CDRH clinical reviewer, we note that experienced health care professionals familiar with this type of procedure will administer this product in clinics or infusion centers. Therefore, we agree with our previous assessment that the Applicant has adequately considered the risks associated with the proposed product and based on the FMEA data submitted, we agree that a human factors validation study is not needed at this time.

### **Labels, Labeling & Packaging**

The applicant submitted proposed carton labeling and container labels on May 27, 2016 and revised Prescribing Information (PI) on August 31, 2016. DMEPA performed a risk assessment of the proposed labels and labeling for areas of vulnerability that may lead to medication errors. Through our assessment, we note that the labels and labeling can be improved to increase clarity and understanding of the safe and effective use of this product.

As a result of an internal meeting between DGIEP, DNP, DCRP, and CDRH, it was agreed that the term “intraventricular” was most accurate to describe the route of administration for Brineura.

(b) (4)  
Per discussions with the Office of Biological Products (OBP), it was recommended that the nomenclature for (b) (4) “ (which is administered after Brineura) should be changed to “Intraventricular Mixed Electrolytes” to clearly convey the route of administration and mitigate the risk that health care providers use other types of electrolyte solutions in substitution for this product. Per the Prescribing Information, healthcare providers should withdraw 2 mL of the intraventricular mixed electrolytes, available in a net quantity of 5 mL. We discussed with the clinical reviewer the safety concerns associated with 1) administering 5 mL of the intraventricular mixed electrolytes, rather than 2 mL per the PI, and 2) administering the intraventricular mixed electrolytes injection prior to administration of Brineura. Per the clinical reviewer, due to the slow infusion rate, administering a volume of 5 mL over a prolonged time period does not prevent safety concerns. DMEPA provides recommendations for the labels and labeling to further clarify that the unused portion of the product should be discarded and that the product should be administered *after* administration of Brineura. We also note that Brineura will be packaged in a carton containing two vials of Brineura, with each vial containing 150 mg/5 mL (30 mg/mL), and one vial of the Intraventricular Mixed Electrolytes Injection. Per the PI, the dose is 300 mg administered once every other week. Therefore, there is a risk of underdose if healthcare providers do not withdraw the contents of both vials. We recommend that for future development, the applicant consider packaging Brineura in a single vial of 300 mg/10 mL to mitigate the risk of an underdose. We note that the carton labeling can be improved to further clarify the total drug amount per vial. We note that the size of the inline filter was “0.2 mcg”; however, we recommend the use of the units “microns” for consistency with other products using filters. Additionally, we note the use of the terminology (b) (4) throughout the labels and labeling. We defer to OBP on the appropriate terminology.

DGIEP, DMEPA and OBP held a teleconference with the applicant on December 20, 2016 to discuss the proposed container labels and carton labeling. DMEPA discussed with the applicant the recommendations listed in Section 4.2.

## 4 CONCLUSION & RECOMMENDATIONS

The proposed labels and labeling can be improved to mitigate any confusion and clarify information to promote the safe and effective use of the product. We provide recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these deficiencies.

### 4.1 RECOMMENDATIONS FOR THE DIVISION

#### A. Packaging Considerations

1. We recommend that for future development, the applicant consider packaging Brineura in a single vial of 300 mg/10 mL to mitigate the risk of an underdose.

#### B. Prescribing Information (PI)

1. We conveyed and discussed the following recommendations for Section 2 of the proposed PI with the Division on December 14, 2016:
  - i. The addition of a statement emphasizing the need for this product to be administered with the included 0.2 micron filter.
  - ii. The revision of step 16 to fully explain the necessary process for this step  
(b) (4)
  - iii. The inclusion and revision of statements regarding maintaining aseptic technique and the proper order and duration of administration to emphasize the safe and effective use of this product.

### 4.2 RECOMMENDATIONS FOR BIOMARIN PHARMACEUTICALS

We recommend the following be implemented prior to approval of this BLA:

#### A. Brineura Carton Labeling

1. Revise the route of administration (b) (4) to “For Intraventricular Infusion Only.” Avoid using any abbreviations for “intraventricular” to prevent misinterpretation and confusion.
2. Revise (b) (4) to read “Intraventricular Mixed Electrolytes.” Avoid using any abbreviations for “intraventricular” to prevent misinterpretation and confusion.
3. Revise the (b) (4) statement in the upper right corner of the Principal Display Panel to as follows for increased clarity on the total drug amount per vial in Brineura and the net quantity of the Intraventricular Mixed Electrolytes Injection:  
**Each carton contains:**  
2 vials, each containing Brineura (cerliponase alfa) Injection, 150 mg/5 mL  
1 vial of Intraventricular Mixed Electrolytes Injection, 5 mL
4. To further clarify the total drug amount per vial, we recommend bolding the following statement:  
**“Each vial of Brineura™ contains 150 mg cerliponase alfa in 5 mL of solution (30 mg/mL)”**

## B. Brineura Container Label

1. Revise the route of administration (b) (4) to “For Intraventricular Infusion Only.” Avoid using any abbreviations for “intraventricular” to prevent misinterpretation and confusion.
2. Revise (b) (4) to “Use before Intraventricular Mixed Electrolytes.” Avoid using any abbreviations for “intraventricular” to prevent misinterpretation and confusion.

## C. Intraventricular Mixed Electrolytes Container Label

1. Revise (b) (4) to read “Intraventricular Mixed Electrolytes Injection”. Avoid using any abbreviations for “intraventricular” to prevent misinterpretation and confusion.
2. Revise the route of administration (b) (4) to “intraventricular”. Therefore, the label should appear as:

**Intraventricular  
Mixed Electrolytes  
Injection**  
**Use after Brineura (cerliponase alfa)**  
**5 mL**  
For Intraventricular  
Infusion Only

3. Revise the statement (b) (4) to (b) (4) single dose only. Discard unused portion.’

## D. Administration Carton Labeling

1. Revise the size of the inline filter from “0.2 mcg” to “0.2 micron” for consistency in units as expressed by other products using inline filters.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Brineura that Biomarin submitted on August 31, 2016.

Table 2. Relevant Product Information for Brineura	
Initial Approval Date	N/A
Active Ingredient	Cerliponase Alfa
Indication	Brineura is indicated for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase (TPP1) deficiency.
Route of Administration	Intracerebroventricular Infusion
Dosage Form	Solution for Injection
Strength	150 mg/5 mL (30 mg/mL)
Dose and Frequency	The recommended dose of Brineura is 300 mg administered once every other week. The complete infusion, including the required Intracerebroventricular (ICV) Mixed Electrolytes solution, is approximately 4.5 hours.
How Supplied	<p>Brineura is supplied as a sterile solution for ICV infusion as package 1 of 2. The Administration Kit is supplied separately as package 2 of 2 [see <i>Dosage and Administration</i> (2.2)].</p> <p>Each Brineura vial (type I glass) with a stopper ( (b) (4) rubber) has a green flip-off cap (plastic) and green crimp seal (aluminum), and contains 150 mg per 5 mL of cerliponase alfa (30 mg/mL).</p> <p>Each ICV solution vial (type I glass) with a stopper ( (b) (4) rubber) has a yellow flip-off cap (plastic) and yellow crimp seal (aluminum), and contains 5 mL of ICV solution.</p> <p>The Administration Kit contains the following single-use, sterile infusion components:</p> <ul style="list-style-type: none"> <li>• Two 20-mL syringes</li> <li>• Two syringe needles (21 G, 25.4 mm)</li> <li>• One extension line</li> <li>• One infusion set with 0.2 micron inline filter</li> <li>• One port needle (22 G, 16 mm)</li> </ul>
Storage	<p>Store upright in a freezer ( -25°C to -15°C). (b) (4)</p> <p>The Administration Kit is supplied separately. Do not freeze.</p>

	<div>(b) (4)</div> <div>.</div> <p>Thawed Brineura and ICV solution should be used immediately. If immediate use is not possible, unopened vials of Brineura or ICV solution should be stored at 2 to 8°C and used within 24 hours.</p>
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## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On December 7, 2016, we searched the L:drive using the terms, Cerliponase, BMN 190, and Brineura, to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified two previous reviews which were not relevant to the labels and labeling<sup>bc</sup>.

---

<sup>b</sup> Barlow, M. Proprietary Name Review for Brineura (BLA 761052). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 28. RCM No.: 2015-370321.

<sup>c</sup> Abraham, S. Proprietary Name Review for Brineura (BLA 761052). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 AUG 05. RCM No.: 2016-8279583.

## **APPENDIX C. HUMAN FACTORS STUDY**

### **Comprehensive Use Related Analysis**

Refer to Applicant submission dated May 27, 2016



Brineura (cerliponase  
alfa) uFMEA.pdf

## **APPENDIX D. ISMP NEWSLETTERS—N/A**

## **APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)—N/A**

## **APPENDIX F. OTHER—N/A**

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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MATTHEW J BARLOW  
04/12/2017

SARAH K VEE  
04/12/2017

LUBNA A MERCHANT  
04/14/2017



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Food and Drug Administration  
Office of New Drugs/Office of Drug Evaluation IV  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9855

**Pediatric Labeling Review**

**From:** Amy M. Taylor, MD, MHS Medical Officer  
Division of Pediatric and Maternal Health

**Through:** Lily (Yeruk) Mulugeta, PharmD  
Division of Pediatric and Maternal Health

John J. Alexander, MD, MPH Deputy Director  
Division of Pediatric and Maternal Health

**BLA Number:** 761052

**Sponsor:** BioMarin Pharmaceutical Inc.

**Drugs:** Brineura (cerliponase alfa)

**Dosage Form and  
Route of Administration:** Injection, for intraventricular use

**Approved Indications:** none

**Proposed Indication:** For the treatment of patients with neuronal ceroid  
lipofuscinosis type 2 (CLN2) disease also known as  
tripeptidyl peptidase 1 (TPP1) deficiency

**Consult Request:** The Division of Gastroenterology and Inborn Errors  
Products (DGIEP) requests DPMH's input on the sponsor's  
proposed labeling.

**Background**

The sponsor has submitted an original BLA for Brineura, an enzyme replacement therapy indicated for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency. CLN2 is a rare, rapidly progressing, irreversible neurodegenerative disease.

Brineura is administered via the intraventricular route along with an infusion of Intraventricular Electrolytes over approximately 4.5 hours.

**Sponsor proposed labeling of specific sections with DPMH recommended edits  
(strikethroughs represent deletions and underlining represents additions)**

**Highlights of Prescribing Information**

**Indications and Usage**

Brineura is a hydrolytic lysosomal N-terminal tripeptidyl peptidase indicated for pediatric patients 3 years and older with CLN2 disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency (1).

(b) (4)

*Reviewer comment: The absence of information should not be included in highlights.*

**Full Prescribing Information**

**1 Indications and Usage**

Brineura is indicated <sup>(b) (4)</sup> of pediatric patients 3 years of age and older with CLN2 disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.

**8 Use in Specific Populations**

**8.4 Pediatric Use**


Safety and effectiveness of Brineura have been established in pediatric patients 3 years of age and older. Use of Brineura in pediatric patients 3 years and older for the treatment of CLN2 is supported by an open-label dose escalation clinical study and a long-term extension study in patients with CLN2 disease and compared to untreated patients with CLN2 disease from an independent historical control group [see Clinical Studies (14)]. Safety and effectiveness in patients <sup>(b) (4)</sup> less than 3 years of age have not been established. <sup>(b) (4)</sup>

*Reviewer comment: The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. Since the product will be indicated for use in pediatric patients 3 years and older, the information should be included throughout labeling.*

*A statement should be added to section 8.4 which describes the clinical studies supporting the use of Brineura in pediatric patients.*

**Recommendations**

The word “pediatric” should be added before patient in the Highlight’s Indication and Usage section. The intended population should be described as “3 years and older.” These same changes should be made in Section 1 Indication and Usage

 (b) (4)  
should be deleted. The absence of information should not be included in Highlights.

A statement should be added to section 8.4 which describes the support for the use of Brineura in pediatric patients. This statement should include a description of the clinical studies conducted which provided support for safety and effectiveness.

Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations (see approval letter).

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/s/  
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AMY M TAYLOR  
04/11/2017

YERUK A MULUGETA  
04/11/2017

JOHN J ALEXANDER  
04/11/2017



## Compliance Review

<b>Date</b>	April 6, 2017
<b>From</b>	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
<b>To</b>	Elizabeth Hart, M.D., Medical Officer, DGIEP
<b>NDA/BLA #</b>	BLA #761052
<b>Applicant</b>	BioMarin Pharmaceutical Inc.
<b>Biologic</b>	BMN-190, Cerliponase alfa
<b>NME (Yes/No)</b>	Yes
<b>Therapeutic Classification</b>	Therapeutic Inborn Errors
<b>Proposed Indication</b>	Treatment of Neuronal Ceroid Lipofuscinosis type 2 (CLN2) disease aka TPP1 deficiency
<b>Consultation Request Date</b>	January 25, 2017
<b>Summary Goal Date</b>	April 10, 2017
<b>Action Goal Date</b>	April 27, 2017 (three month extension due to submission of major amendment August 29, 2016)
<b>PDUFA Date</b>	April 27, 2017

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This memo is in response to a request from the Division of Gastrointestinal and Inborn Errors review division and statistical team to the Office of Scientific Investigations (OSI) to perform a verification of the genotype results for subjects analyzed for Studies 901-201 (active treatment) and Study 901-109 (registry study) and verification of the 2016 CLN2 motor and language scores for Study 901-202 that were submitted in the major amendment of August 29, 2017. This request to OSI was made in January 2017 after additional data for the 96 week follow up of subject population were submitted to the BLA. Inspections of three clinical investigators (CI) sites and the sponsor had been requested and were completed earlier in the review cycle. The clinical inspection summary (CIS) for these inspections was finalized in DARRTS on December 16, 2016. This memo is limited to the verification of the data requested above.

Verification of the CLN2 line listings was completed by comparing the line listings with the certified copies of the source documents provided by the sponsor in response to information requests in February and March, 2017. The CLN2 motor and language scores for all subjects could be verified. Verification of subject genotype for the Study 202 subjects and the 42 Hamburg patients in the registry that were to be used for comparison was conducted by

comparing the table of subject genotypes generated by the clinical pharmacology reviewer with the source documents provided by the sponsor on March 10, 2017 and March 28, 2017. All but 6 of the 56 records reviewed could be verified. Inability to verify was due to a variety of reasons including the source lacking a clear genotype and the presence of additional mutations that might have impact on the TTP1 mutation. Any discrepancies were referred to the review division for consideration. No source data were submitted for the subjects from Verona.

## II. BACKGROUND

The sponsor submitted this BLA for BMN-190, Cerliponase alfa for the indication of treatment of Neuronal Ceroid Lipofuscinosis type 2 (CLN2) Disease due to tripeptidyl peptidase-1 (TPP1) deficiency, a form of Batten Disease, a group of rare fatal pediatric dementias. There is currently no approved treatment for this disease. Patients receive symptomatic treatment for specific progressive problems such as seizures (anticonvulsants), motor control loss (bracing or wheelchairs) and feeding/aspiration risk (gastrostomy tube). Current treatment of patients with CLN2 disease, as described above, provides only temporary relief to certain symptoms of the disease. Due to the lack of approved pharmacologic interventions for CLN2 disease, the outcome is invariably fatal.

Biologic: BMN-190, Cerliponase alfa

Studies – Protocol number and title for all studies that were inspected:

1. Protocol 190-201 entitled “A Phase 1/2 Open-Label Dose-Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Intracerebroventricular BMN 190 in Patients with Late-Infantile Neuronal Ceroid Lipofuscinosis (CLN2) Disease”

Number of subjects: 24 subjects

Number of sites: 5

Number of countries where subjects were enrolled: 4 (U.S., Germany, Italy, and United Kingdom)

Dates that study was conducted: September 2013 to November 2015

Primary efficacy endpoint: Modified Hamburg and Cornell Neuronal Ceroid Lipofuscinosis (CLN2) rating scales at Week 48, assessment as change from baseline

2. Protocol 190-202 entitled, “A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN in 190 Patients with CLN2 Disease”

Number of subjects: 23 subjects (one subject withdrew due to inability to comply with assessments)

Number of sites: 5

Number of countries where subjects were enrolled: 4 (U.S., Germany, Italy, and United Kingdom)

Dates that study was conducted: February 2015 and ongoing

Primary efficacy endpoint: Modified Hamburg and Cornell Neuronal Ceroid Lipofuscinosis (CLN2) rating scales

3. Natural History Database DEM-CHILD is the natural history database which BioMarin relied on as a control group for the uncontrolled studies listed above. DEM-CHILD is a research database maintained by the clinical group in Universitätsklinikum Hamburg-Eppendorf Pediatric Clinic. The Hamburg site and Università degli Studi di Verona in Italy contributed data from subjects to this database. The database was developed for academic research to study the natural history of the neuronal ceroid lipofuscinoses (NCLs). BioMarin contracted with the clinic to use data from this database. The public web address for the database is:  
<http://www.dem-child.eu/index.php/background-16.html>

### III. RESULTS:

#### 1. Verification of CLN2 scores

The sponsor submitted certified copies of the CLN2 scoring sheets for all sites for the visits occurring in 2016 that included scoring of the Hamburg and Cornell scales. The scoring value of the Hamburg Motor and Language value and the Cornell Gait and Language and the “date performed” were compared with the line listings submitted to the BLA by the sponsor.

Values for all subjects were verified. The source documents for the June, August, and October 2016 visits for Subject 1287(0119) 1005 contained numerous cross outs and corrections. These were explained in a note to file and a memorandum explaining that a videotape of the August 22, 2016 visit was sent to (b) (4) for adjudication. Values on the source document were changed to reflect the results of the adjudication and then changed back to the original value.

For seven subjects, the “visit date,” on the top of the page, and the “date performed,” noted lower on the page, (see example below) did not agree. During the sponsor meeting held on February 21, 2017, the sponsor noted that the protocol and associated documents allowed for the visit to occur over several days while the subject was hospitalized so the visit could occur over several days. The date performed is the date of the actual performance of the CLN2 assessment and this is reflected in the line listings for all but Subject 1244-1004, starred in the table on the next page.

BIOMARKIN

0.1

Site Name

24.OCT.20

Visit Date

CLN2 DISEASE RATING SCALE ASSE

Date performed: 26/OCT/1

DD MM

**Table 1. Discrepancies: Line Listing Date, Visit date, Date Scoring of the Hamburg Motor and Language and the Cornell Gait and Language Performed**

Subject	Line Listing Date	Visit Date	Date Performed
0146-1022	16-May-2	16-May-3	16-May-2
0146-1023	16-Oct-26	16-Oct-24	16-Oct-26
1244-1004*	16-Mar-14	16-Mar-14	16-Mar-17
1244-1008	16-Mar-7	16-Mar-1	16-Mar-7
	16-Aug-22	16-Aug-9	16-Aug-22
1244-1017	16-Feb-12	16-Feb-8	16-Feb-12

*Reviewer note: The differences in the visit date and date performed are not protocol violations. For all but one value as indicated by the \*, the date on the line listing is the date of the date performed. For Subject # 0146-1022 the data for scoring of the Hamburg Motor and Language and the Cornell Gait and Language occurred two days prior to the Visit Date. The observation was isolated.*

Conclusion: The data are considered reliable for the CLN2 scores.

## 2. Verification of Genotype

The sponsor submitted certified source documents to use for verification of subject genotype for both Study 201 and subjects in the DEM-CHILD database. Source included various types of documents such as laboratory slips from commercial laboratories and correspondence from academic specialists to treating physician. All these were considered acceptable for use in the verification process. Documents were translated from the native language to English and certification of translation was submitted. The sponsor did not submit documents for the subjects from Verona in the DEM-CHILD database.

In the submission dated March 10, 2017 the sponsor noted that four discrepancies were noted in the database when preparing the documents for submission. These included

Subjects 1323-1016 and 1323-1019 and HAM subjects 00230002 and 01630001.

The data were able to be verified for all active treatment subjects and the 34 subjects from Hamburg in the DEM-CHILD registry except the following five subjects that were referred to the clinical pharmacology reviewer for further assessment:

**Table 2. Subject Genotype in Source and Data File**

Subject ID	Genotype in source	Genotype in data file	Comments
0119-1020	Compound heterozygous <b>754</b> _757 and c.1094G>A	Compound heterozygous <b>745</b> _757 and c.1094G>A	May be typographical error
0146-1023	TPP1 c.1094G>A homozygous and POLG c.32 G>A	TPP1 c.1094G>A homozygous	Additional mutation in POLG referred to review division
02850001	The letter from 1999 provided does not contain a definitive genotype.	c.622C>T homozygous	Letter contains crossed out items, does not clearly state genotype.
03290001	c.1057A>C c.509-1G>C c237C>G	c.1057A>C and c.509-1G>C	Source indicates additional mutation of c237C>G
03290002	c.1057A>C; c.509-1G>C c237C>G	c.1057A>C and c.509-1G>C	Source indicates additional mutation of c237C>G
04990001	Note on untranslated letter states “only enzyme result is available for this patient, genotype tested per sibling patient””	c.230-13T>A c.622C>T	This is a sibling of 4990002 enrolled as 1244-1009 in active study, whose data were able to be verified.

Conclusion: Discrepancies in the source and the line listing for the genotypes is noted above for six subjects. The significance of these discrepancies is deferred to the review division.

{See appended electronic signature page}

Susan Leibenhaut, M.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

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Review Division /Division Director/Donna Griebel  
Review Division /Medical Team Leader/Victor Baum  
Review Division /Project Manager/Jennie Doan  
Review Division/Medical Office/Elizabeth Hart  
OSI/Office Director/David Burrow  
OSI/DCCE/ Division Director/Ni Khin  
OSI/DCCE/Branch Chief/Kassa Ayalew  
OSI/DCCE/Team Leader/ Susan D. Thompson  
OSI/DCCE/GCP Reviewer/ Susan Leibenhaut  
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague  
OSI/Database PM/Dana Walters

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/s/  
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SUSAN LEIBENHAUT  
04/06/2017

SUSAN D THOMPSON  
04/06/2017

KASSA AYALEW  
04/06/2017



**U.S. FOOD & DRUG  
ADMINISTRATION**

Center for Drug Evaluation and Research  
Office of Pharmaceutical Quality  
Office of Biotechnology Products

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**LABELS AND LABELING REVIEW**

Date:	March 31, 2017
Reviewer:	Jibril Abdus-Samad, PharmD Office of Biotechnology Products (OBP)
Through:	Rukman De Silva, PhD, Quality Reviewer OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761052/0
Product:	Brineura (cerliponase alfa)
Applicant:	Biomarin Pharmaceuticals Inc.
Submission Dates:	May 27, 2016; December 22, 2016; February 13, 2017

**I) RECOMMENDATION**

The Applicant's revisions to the prescribing information are acceptable. Note: we await the Applicant's comment on our recommendation to include the dosage form in section 11 – Description in the prescribing information submitted on February 13, 2017. The container labels and carton labeling submitted on the following dates are acceptable from a quality perspective:

- Container Labels

Brineura Vial: December 22, 2016

<\\cdsesub1\evsprod\bla761052\0070\m1\us\114-labeling\1141-draft-labeling\11411-draft-carton-container-labels\brineura-vial.pdf>

Intraventricular Electrolytes Injection Vial: February 13, 2017

<\\cdsesub1\evsprod\bla761052\0093\m1\us\114-labeling\1141-draft-labeling\11411-draft-carton-container-labels\intraventricular-injection-vial.pdf>

Administration Kit Sticker: May 27, 2016

<\\cdsesub1\evsprod\bla761052\0001\m1\us\114-labeling\1141-draft-labeling\11411-draft-carton-container-labels\udi-sticker-for-administration-kit.pdf>

- Carton Labeling

Brineura Carton: December 22, 2016

<\\cdsesub1\evsprod\bla761052\0070\m1\us\114-labeling\1141-draft-labeling\11411-draft-carton-container-labels\brineura-carton.pdf>

Administration Kit Carton: February 13, 2017

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## II) BACKGROUND AND SUMMARY DESCRIPTION

The Applicant submitted BLA 761052/0 Brineura (cerliponase alfa) on May 27, 2016. Table 1 lists the proposed characteristics of Brineura (cerliponase alfa). This review evaluates the labels and labeling submitted on May 27, 2016 ([Application 761052 - Sequence 0001 - 0001 \(1\) 05/27/2016 ORIG-1 /Multiple Categories/Subcategories](#) ).

Table 1: Proposed Product Characteristics of Brineura (cerliponase alfa).

<b>Proprietary Name:</b>	Brineura
<b>Nonproprietary Name:</b>	cerliponase alfa
<b>Dosage Form:</b>	Injection
<b>Strength and Container-Closure:</b>	<ul style="list-style-type: none"><li>• 150 mg/5 mL Brineura (cerliponase alfa) in a single-dose vial</li><li>• 5 mL intracerebroventricular solution in a single-dose vial (sodium phosphate, dibasic, heptahydrate; sodium phosphate, monobasic, monohydrate; sodium chloride; potassium chloride; magnesium chloride hexahydrate; calcium chloride dehydrate; and Water for Injection, USP)</li><li>• Administration Kit</li></ul>
<b>Route of Administration:</b>	Intraventricular Infusion
<b>Storage and Handling:</b>	Store Brineura and ICV solution upright in the freezer at -25°C to -15°C (-13°F to 5°F)
<b>Indication:</b>	hydrolytic lysosomal N-terminal tripeptidyl peptidase indicated for patients with CLN2 disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency
<b>Dose and Frequency:</b>	300 mg administered once every other week as an intracerebroventricular (ICV) infusion followed by ICV solution infusion over approximately 4.5 hours.

### III) MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

**Table 2: Materials Considered for this Label and Labeling Review**

<b>Materials Reviewed</b>	<b>Appendix Section</b>
Proposed Labels and Labeling	A
Other	B (n/a)
Relevant Code of Federal Regulations and CDER Labeling Best Practices	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

### IV) DISCUSSION

The proposed labels were evaluated for compliance to the applicable code of federal regulations and CDER Labeling Best Practices (see Appendix C).

### V) CONCLUSION

The prescribing information, container labels, and carton labeling for Brineura (cerliponase alfa) Injection 150 mg/5 mL in single-dose vials reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100 and United States Pharmacopeia (USP). The Applicant's revisions to the prescribing information are acceptable. Note: we await the Applicant's comment on our recommendation to include the dosage form in section 11 – Description in the prescribing information submitted on February 13, 2017. The container labels and carton labeling submitted on the following dates are acceptable from a quality perspective:

- Container Labels

Brineura Vial: December 22, 2016

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Intraventricular Electrolytes Injection Vial: February 13, 2017

<\\cdsesub1\evsprod\bla761052\0093\m1\us\114-labeling\1141-draft-labeling\11411-draft-carton-container-labels\intraventricular-injection-vial.pdf>

Administration Kit Sticker: May 27, 2016

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- Carton Labeling

Brineura Carton: December 22, 2016

<\\cdsesub1\evsprod\bla761052\0070\m1\us\114-labeling\1141-draft-labeling\11411-draft-carton-container-labels\brineura-carton.pdf>

Administration Kit Carton: February 13, 2017

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## **APPENDICES**

### **Appendix A: Proposed Labeling**

- Prescribing Information  
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- Container Labels  
<\\cdsesub1\evsprod\bla761052\0001\m1\us\114-labeling\1141-draft-labeling\11411-draft-carton-container-labels\brineura-vial.pdf>



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<\\cdsesub1\evsprod\bla761052\0001\m1\us\114-labeling\1141-draft-labeling\11411-draft-carton-container-labels\udi-sticker-for-administration-kit.pdf>



- Carton Labeling

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(b) (4)

<\\cdsesub1\evsprod\bla761052\0001\m1\us\114-labeling\1141-draft-labeling\11411-draft-carton-container-labels\administration-kit-carton.pdf>

(b) (4)



**Appendix B:** n/a

## Appendix C: Applicant Code of Federal Regulations and CDER Best Labeling Practices

**Table 3:** Label<sup>1,2</sup> and Labeling<sup>3</sup> Standards

Container<sup>4</sup> Label Evaluation

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 610.60 Container Label				
(a) Full label.			x	The following items shall appear on the label affixed to the container of a product capable of bearing a full label: This product has a partial label (see below). However, there was space on the label to allow for placement of some of the items recommended for the full label.
(1) Proper Name			x	
(2) Name, address, and license number of manufacturer			x	
(3) Lot number or other lot identification			x	
(4) Expiration date			x	
(5) Recommended individual dose, for multiple dose containers			x	
(6) Statement: “Rx only” for prescription biologicals			x	
(7) Medication Guide			x	

<sup>1</sup> Per 21 CFR 1.3 (b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

<sup>2</sup> Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

<sup>3</sup> Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

<sup>4</sup> Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
(b) <i>Package label information</i>			x	
(c) <i>Partial label; proper name, lot, and manufacturer; individual dose for multiple dose containers; partial labels placed in a package with all items required for a package label</i>	x			DMEPA notified the Applicant: "As you have noted your 351(a) BLA is within the scope of our recently issued guidance for industry, Nonproprietary Naming of Biological Products. However, FDA issued the final guidance at a point in our review of your application that does not allow for sufficient time for FDA to designate a proper name that includes a suffix as described in the guidance at this time. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your 351(a) BLA be approved during this review cycle."
(d) <i>No container label</i>			x	Not applicable
(e) <i>Visual inspection</i>	x			Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e). <i>The Applicant confirms there is appropriate area to allow for visual inspection.</i>
<b>21 CFR 201.2 Drugs and devices</b>				
NDC numbers	x			Conforms
<b>21 CFR 201.5 Drugs</b>				
Adequate directions for use		x		On October 18, 2016, DGIEP, Division of Neurological and Physical Medicine Devices/Office of Device Evaluation/CDRH, DNP, DCRP, and LDT along with DGIEP met to obtain alignment on the appropriate route of administration (ROA) terminology to use in the BRINEURA labeling and other product labeling with similar ROA. The attendees agreed that the BRINEURA labeling and other future product labeling with the same ROA should: <ul style="list-style-type: none"> <li>- Include the "intraventricular" terminology in the product title: <b>BRINEURA (cerliponase alfa) injection, for intraventricular use</b></li> <li>- Clarify in several parts of the labeling (e.g.,</li> </ul>



Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				<p>DOSAGE AND ADMINISTRATION and CLINICAL STUDIES sections) that the ventricles refer to the ventricles of the brain rather than the heart.</p> <p>- (b) (4)</p> <p>Therefore we requested the Applicant: Revise the route of administration (b) (4) to "intraventricular. <i>The Applicant revised as requested.</i></p>
<b>21 CFR 201.6 Drugs</b>				
Misleading statements	x			Conforms
<b>21 CFR 201.10 Drugs</b>				
Statement of ingredients		x		<p>The proposed Intracerebroventricular solution is composed of the same inactive ingredients used in the drug product to aid in complete delivery of the drug and maintain patency of the ICV access device. However the label it too small to list all the ingredients. Additionally, considering this product will be infused into the patient we find the naming of this solution should follow the drug product nomenclature.</p> <p>Revise the name of the proposed (b) (4) to "Intraventricular Mixed Electrolytes Injection" to align with drug product and route of administration nomenclature. Here is our rationale:</p> <ol style="list-style-type: none"> <li>1. We aligned with drug product nomenclature because this product is specially formulated to be compatible with the CSF for infusion into the patient.</li> <li>2. We included intraventricular to highlight that this electrolyte solution should not be substituted with any other mixed electrolyte solution (e.g. Multiple Electrolyte Injection)</li> <li>3. We previously removed " (b) (4) " to prevent the end-user from flushing this product via a bolus injection rather than an infusion.</li> </ol>

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				<p><b>BIOMARIN RESPONSE December 22, 2016</b></p> <p>As discussed in the teleconference with FDA on December 20, 2016, BioMarin proposes to remove the word “Mixed” from the name. This word may confuse users that the solution may require mixing with Brineura drug product or other solutions prior to intraventricular infusion. Additionally as noted in FDA’s comments, this product is specially formulated to be compatible with the CSF and should not be substituted with any other mixed electrolyte solution. The alternative name, “Intraventricular Electrolytes Injection”, is distinctive enough not to be confused or substituted with other mixed electrolytes. BioMarin has incorporated “Intraventricular Electrolytes Injection” into the draft labeling artwork included for your review. BioMarin plans to incorporate this term into the draft Prescribing Information as well.</p> <p><i>The Applicant’s revisions are acceptable.</i></p>
<b>21 CFR 201.15 Drugs</b>				
Prominence of required label statements		x		<p>See 21 CFR 201.5 above regarding route of administration.</p> <p><i>The Applicant’s revisions are acceptable.</i></p>
<b>21 CFR 201.17 Drugs</b>				
Location of expiration date	x			Conforms
<b>21 CFR 201.25</b>				
Bar code label requirements	x			Conforms
<b>21 CFR 201.50 Statement of Identity</b>				
Statement of identity		x		<p>See 21 CFR 201.10 above regarding statement of ingredients.</p> <p><i>The Applicant’s revisions are acceptable.</i></p>
<b>21 CFR 201.51 Declaration of net quantity of contents</b>				
Declaration of net quantity	x			Conforms
<b>21 CFR 201.55 Statement of dosage</b>				
Statement of dosage	x			Conforms

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 201.100 Prescription drugs for human use				
Prescription drugs for human use		x		See 21 CFR 201.10 regarding statement of ingredients and 21 CFR 201.15 above regarding route of administration. Additionally, the Intraventricular Electrolytes vial is a small label and thus the list of ingredients appears on the carton labeling. <i>The Applicant's revisions are acceptable.</i>



#### Package Label<sup>5</sup> Evaluation

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 610.61 Package Label				
(a) Proper name	x			DMEPA notified the Applicant: “As you have noted your 351(a) BLA is within the scope of our recently issued guidance for industry, Nonproprietary Naming of Biological Products. However, FDA issued the final guidance at a point in our review of your application that does not allow for sufficient time for FDA to designate a proper name that includes a suffix as described in the guidance at this time. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your 351(a) BLA be approved during this review cycle.”
(b) Name, address, and license number of manufacturer	x			Conforms
(c) Lot number or other lot identification	x			Conforms
(d) Expiration date	x			Conforms

<sup>5</sup> Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus this includes the carton, prescribing information, and patient labeling.

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
(e) Preservative used and its concentration, if no preservative is use and the absence of a preservative is a safety factor, the words "no preservative"	x			Conforms
(f) Number of containers, if more than one	x			Conforms
(g) Amount of product in the container	x			Conforms
(h) Recommended storage temperature	x			Conforms
(i) "Shake Well", "Do not Freeze" or equivalent	x			Drug product vials requires freezing. Warnings regarding thawing and not refreezing appear in the PI within preparation instructions.
(j) Recommended individual dose if multiple-dose container			x	Single-dose vial.
(k) Route of administration		x		See the Container Label section above for rationale. Revise the route of administration (b) (4) to "For Intraventricular Infusion Only." <i>The Applicant's revision is acceptable.</i>
(l) Known sensitizing substances			x	Not applicable
(m) Type and calculated amount of antibiotics added during manufacturing			x	Not applicable
(n) Inactive			x	Not applicable

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
ingredients in case of safety factor				
(o) Adjuvant, if present			x	Not applicable
(p) Source of the product when a factor in safe administration			x	Not applicable
(q) Identity of each microorganism used in manufacturing			x	Not applicable
(r) Minimum potency of product expressed in terms of official standard of potency, or "No U.S. standard of potency"	x			Conforms
(s) "Rx only" statement for prescription biologicals	x			Conforms
<b>21 CFR 610.62 Proper name; package label</b> <i>This does not apply to specified biologics per 21 CFR 601.2(a). Brineura (cerliponase alfa) is a therapeutic recombinant DNA-derived product, therefore exempt.</i>				
(a) Position: proper name			x	
(b) Prominence			x	
(c) Legible type			x	
<b>21 CFR 610.63 Divided Manufacturing</b>				
Divided manufacturing			x	Only one Applicant.
<b>21 CFR 610.64 Name and address of distributor</b>				
Name and address may appear on the label provided the name, address,			x	Not applicable

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
and license number of manufacturer appears on the label				
<b>21 CFR 610.67 Bar code</b>				
Bar code	x			Conforms
<b>21 CFR 201.2 Drugs and devices</b>				
NDC numbers	x			Conforms
<b>21 CFR 201.5 Drugs</b>				
Adequate directions for use		x		<p>On October 18, 2016, DGIEP, Division of Neurological and Physical Medicine Devices/Office of Device Evaluation/CDRH, DNP, DCRP, and LDT along with DGIEP met to obtain alignment on the appropriate route of administration (ROA) terminology to use in the BRINEURA labeling and other product labeling with similar ROA.</p> <p>The attendees agreed that the BRINEURA labeling and other future product labeling with the same ROA should:</p> <ul style="list-style-type: none"> <li>- Include the “intraventricular” terminology in the product title: <b>BRINEURA (cerliponase alfa) injection, for intraventricular use</b></li> <li>- Clarify in several parts of the labeling (e.g., DOSAGE AND ADMINISTRATION and CLINICAL STUDIES sections) that the ventricles refer to the ventricles of the brain rather than the heart.</li> <li>-  (b) (4)</li> </ul> <p>Therefore we requested the Applicant: Revise the route of administration  (b) (4) to “intraventricular. <i>The Applicant revised as requested.</i></p>
<b>21 CFR 201.6 Drugs</b>				

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Misleading statements	x			Conforms
<b>21 CFR 201.10 Drugs</b>				
Statement of ingredients		x		<p>The proposed Intracerebroventricular solution is composed of the same inactive ingredients used in the drug product to aid in complete delivery of the drug and maintain patency of the ICV access device. However the label it too small to list all the ingredients. Additionally, considering this product will be infused into the patient we find the naming of this solution should follow the drug product nomenclature.</p> <p>Revise the name of the proposed (b) (4) to "Intraventricular Mixed Electrolytes Injection" to align with drug product and route of administration nomenclature. Here is our rationale:</p> <ol style="list-style-type: none"> <li>4. We aligned with drug product nomenclature because this product is specially formulated to be compatible with the CSF for infusion into the patient.</li> <li>5. We included intraventricular to highlight that this electrolyte solution should not be substituted with any other mixed electrolyte solution (e.g. Multiple Electrolyte Injection)</li> <li>6. We previously removed (b) (4) to prevent the end-user from flushing this product via a bolus injection rather than an infusion.</li> </ol> <p><b>BIOMARIN RESPONSE December 22, 2016</b>  As discussed in the teleconference with FDA on December 20, 2016, BioMarin proposes to remove the word "Mixed" from the name. This word may confuse users that the solution may require mixing with Brineura drug product or other solutions prior to intraventricular infusion. Additionally as noted in FDA's comments, this product is specially formulated to be compatible with the CSF and should not be substituted with any other mixed electrolyte solution. The alternative name, "Intraventricular Electrolytes Injection", is distinctive enough not to be confused or substituted with other mixed electrolytes. BioMarin has incorporated "Intraventricular Electrolytes Injection" into the draft labeling artwork included for your review. BioMarin plans to incorporate this term into the draft Prescribing Information as well.</p>

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				<i>The Applicant's revisions are acceptable.</i>
<b>21 CFR 201.15 Drugs</b>				
Prominence of required label statements		x		- See 21 CFR 201.5 above regarding route of administration. <i>The Applicant's revisions are acceptable.</i>
<b>21 CFR 201.17 Drugs</b>				
Location of expiration date	x			Conforms
<b>21 CFR 201.25</b>				
Bar code label requirements	x			Conforms
<b>21 CFR 201.50 Statement of identity</b>				
Statement of identity		x		See 21 CFR 201.10 above regarding statement of ingredients. <i>The Applicant's revisions are acceptable.</i>
<b>21 CFR 201.51 Declaration of net quantity of contents</b>				
Declaration of net quantity	x			Conforms
<b>21 CFR 201.55 Statement of dosage</b>				
Statement of dosage	x			Conforms
<b>21 CFR 201.100 Prescription drugs for human use</b>				
Prescription drugs for humans		x		<p>See 21 CFR 201.10 regarding statement of ingredients and 21 CFR 201.15 above regarding route of administration.</p> <p>Include the amounts of ingredients in the statement of ingredients per 21 CFR 201.100. Additionally, revise the list of inactive ingredients to appear in alphabetical order per USP General Chapters &lt;1091&gt; Labeling of Inactive Ingredients. For example:</p> <p>Each vial of Brineura provides 5 mL of solution containing 150 mg cerliponase alfa. Each vial of Intraventricular Mixed Electrolytes provides 5 mL of solution. Both Brineura and Intraventricular Mixed Electrolytes are formulated with the following excipients: calcium chloride dehydrate (1.05 mg); magnesium chloride hexahydrate (0.8 mg); potassium chloride (1.1 mg); sodium chloride</p>



Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				(43.85 mg); sodium phosphate, dibasic, heptahydrate (0.55 mg); sodium phosphate, monobasic, monohydrate (0.4 mg); and Water for Injection, USP. <i>The Applicant's revisions are acceptable.</i>

## Prescribing Information and Patient Labeling Evaluation

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
PRESCRIBING INFORMATION				
Highlights of prescribing information				
PRODUCT TITLE 21 CFR 201.57(a)(2)		x		Intraventricular is the preferred route of administration term for products infused exclusively into the ventricular system of the CNS (i.e., not administered into parenchyma)  <b>BRINEURA (cerliponase alfa) injection, for intraventricular use</b> <i>The Applicant accepts our revisions.</i>
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)				Delete (b) (4) and replace with “intraventricular” throughout the labeling, including Figure 1. We revised the name of the proposed (b) (4) to align with drug product nomenclature.  300 mg administered once every other week as an intraventricular infusion followed by Intraventricular Electrolytes solution infusion over approximately 4.5 hours <i>The Applicant's revisions are acceptable.</i>
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)				Revise the package type term for this product to “single-dose” here and throughout all labeling. See our current thinking in our Draft Guidance: <a href="#">Draft Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use,</a>

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				<p><a href="#">October 2015</a></p> <p>We revised the name of the proposed (b) (4) to align with drug product nomenclature.</p> <p>Injection: 150 mg/5 mL (30 mg/mL) solution in single-dose vials copackaged with 5 mL of Intraventricular Electrolytes solution in a single-dose vial</p> <p><i>The Applicant's revisions are acceptable.</i></p>
<b>Full Prescribing Information</b>				
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)				<p>We included a discard statement because there is 3 mL remaining in the single-dose vial of Intraventricular Electrolytes Injection.</p> <p>14. Label one sterile syringe "Intraventricular Electrolytes" and attach the syringe needle. Remove the yellow flip-off cap from the Intraventricular Electrolytes vial. Withdraw 2 mL of Intraventricular Electrolytes. Discard the remaining unused portion.</p> <p><i>The Applicant accepts our revisions.</i></p> <p>We relocated instructions from section 16 that explained thawing and storage after thawing which are more related to preparation. Although this product requires thawing, we find this information should appear with the preparation instructions consistent with 21 CFR 201.57(c)(3).</p> <p>We removed (b) (4)</p> <p>(b) (4)</p> <p>We also removed the information regarding (b) (4)</p> <p>(b) (4)</p> <p>We added storage instructions for product in syringes.</p>

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				<p><b>Storage of Thawed Product</b> Use thawed Brineura and Intraventricular Electrolytes immediately. If not used immediately, store unopened vials in the refrigerator at 2°C to 8°C and use within 24 hours.</p> <p><b>Storage of Product in Syringes</b> Use product held in labeled syringes immediately. If not used immediately, store product held in labeled syringes in the refrigerator at 2°C to 8°C up to 4 hours prior to infusion</p> <p><i>The Applicant accepts our revisions.</i></p>
3 DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(c)(4)				<p>Revise the package type term for this product to “single-dose” here and throughout all labeling. See our current thinking in our Draft Guidance: <a href="#">Draft Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October 2015</a></p> <p>We revised the name of the proposed (b) (4) to align with drug product nomenclature.</p> <p>We added the identifying characteristics. Injection: 150 mg/5 mL (30 mg/mL) solution, two vials per carton copackaged with 5 mL of Intraventricular Electrolytes solution in a single-dose vial. Brineura is a clear to slightly opalescent and colorless to pale yellow solution. Intraventricular Electrolytes is a clear to colorless solution. [see <i>How Supplied/Storage and Handling</i> (16)].</p> <p><i>The Applicant's revisions are acceptable.</i></p>
6.2 IMMUNOGENICITY		x		<p>We added the standard statement that addresses how comparison of incidence of antibodies between other products may be misleading.</p> <p><i>The Applicant accepts our revisions.</i></p>
11 DESCRIPTION 21 CFR		x		<p>We removed the proprietary name “Brineura” from the paragraph describing the drug substance</p>

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
201.57(c)(12)				<p>"cerliponase alfa."</p> <p>We deleted (b) (4)</p> <p>We revised the inactive ingredients to appear in alphabetical order per USP General Chapters &lt;1091&gt; Labeling of Inactive Ingredients. We also removed the trailing zeros (e.g. 0.40 mg to 0.4 mg).</p> <p><i>The Applicant accepts our revisions.</i></p> <p>We added the dosage form "Injection". The established name for injectable solution includes the dosage form, therefore "Intraventricular Electrolytes Injection". We note that you removed the dosage form from the name in other parts of the PI in section 2. However in this section that describes the product, we recommend using the full established name.</p> <p>Brineura (cerliponase alfa) Injection and Intraventricular Electrolytes Injection are administered by intraventricular infusion.</p> <p><i>We await the Applicant's response.</i></p>
16 HOW SUPPLIED/STORAGE AND HANDLING 21 CFR 201.57(c)(17)		x		<p>We added dosage forms (per USP nomenclature) and identifying characteristics.</p> <p>We deleted (b) (4)</p> <p>as this information is not useful to healthcare practitioners (HCP).</p> <p>We deleted (b) (4)</p> <p>. It is standard practice for HCPs and is not needed in the PI.</p> <p>We relocated information for storage of thawed product to section 2.</p> <p><i>The Applicant accepts our revisions.</i></p>

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
Manufacturer information For BLAs: 21 CFR 610.61, 21 CFR 610.64	x			

### Additional Labeling Recommendations

We provided the following request(s):

Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <1> Injections, Packaging, Labeling on Ferrules and Cap Overseals.

*The Applicant confirmed there is no text on the ferrule and cap overseal.*

## **APPENDIX D. Acceptable Labels and Labeling**

- Container Labels:



- Carton Labeling









Jibril  
Abdus-Samad

Digitally signed by Jibril Abdus-Samad  
Date: 3/31/2017 02:29:54PM  
GUID: 50814c7000007a3754a457f037f74915



Rukman  
De Silva

Digitally signed by Rukman De Silva  
Date: 3/31/2017 02:34:51PM  
GUID: 508da6db0002668622f9d73ac81c7d27

## Division of Neurology Consult memo

<b>BLA</b>	<b>761052</b>
<b>Sponsor:</b>	<b>Biomarin</b>
<b>Drug:</b>	<b>BMN-190/Brineura</b>
<b>Proposed Indication:</b>	<b>cLINCL/CLN2</b>
<b>Material Submitted:</b>	<b>BLA Submission</b>
<b>Submission Date:</b>	<b>5/27/16</b>
<b>Consult Date:</b>	<b>6/2/16</b>
<b>Date Review Completed:</b>	<b>2/6/17</b>
<b>Reviewer:</b>	<b>Teresa Buracchio, M.D.</b>

### Introduction

The sponsor, Biomarin, submitted a BLA for BMN 190 (recombinant human tripeptidyl peptidase-1) as enzyme replacement therapy for patients with phenotype classical late infantile neuronal ceroid lipofuscinosis (cLINCL) who had mutations in the CLN2 gene. The submission is based on reported positive efficacy results from a 48-week, open-label Phase 1/2 study (Study 190-201) that enrolled 24 subjects. The study uses a natural history study (Study 190-901) as a control group.

There have been prior DNP consults in DARRTS on this program from Dr. Buracchio on 3/37/2015 under IND122472 and Dr. Kasim on 6/11/2012 under PIND (b) (4).

DGIEP requests DNP's assistance in providing input on the following issues in the BLA submission:

- Input on the sponsor's efficacy data analyses of CLN2 related neurological disease and interpretability of these results based on the methodological limitations of the study
- Assistance on evaluation of videos provided by the Applicant to compare adapted CLN2 disease scale with scale used in NH study
- Advice and comment of neurological secondary and exploratory endpoints which may be considered in the totality of the evidence

### Background:

cLINCL is a progressive and fatal neurodegenerative lysosomal storage disease in childhood caused by a deficiency of the tripeptidyl peptidase-1 (TPP-1) enzyme. The cLINCL phenotype is commonly associated with mutations in the CLN2 gene and patients with the CLN2 genotype were specifically selected for inclusion in this study. The clinical course of the disease is generally characterized by normal development until age 2 to 4 years followed by a rapid decline in function with seizures, ataxia, deterioration of speech, loss of motor skills, progressive cognitive and developmental decline, loss of vision, and eventual progression to a vegetative state with death occurring between ages 10 to 15 years of age. As with other neurodegenerative diseases, there may be considerable heterogeneity in individual rates of decline with this disease.

In the Phase 1/2 study, Study 190-201, efficacy was assessed with a primary endpoint that is a composite of the Language and Motor domains of the Hamburg Scale. The disease course of cLINCL/CLN2 as established in the published literature and natural history studies support language and motor function as important and clinically relevant

symptoms for cLINCL/CLN2. However, extensive work done by the Clinical Outcomes Assessment (COA) has shown that these two domains were not assessed consistently and in a standardized fashion within Study 190-201 and when compared to the natural history study, 190-901. The COA staff has determined that the Motor Domain appears to be more reliable than the Language Domain; however, there is considerable bias that has been introduced in the scoring of these domains that calls into question the interpretability of these results.

Volumetric MRI data was designated as a secondary endpoint. Developmental milestones with Denver II Developmental Scale were designated as an exploratory endpoint. There were also other clinical domains on the Hamburg Scale and Weill Cornell Scale (another disease-specific cLINCL/CLN2 scale) as well as patient videos and datasets containing neurologic examinations that were included in the submission. Given the substantial limitations in interpretability of the primary endpoint, DGIEP requested DNP input on whether any of these sources of data could provide additional support for the primary endpoint.

#### **Questions from DGIEP**

**Provide input on the sponsor's efficacy data analyses of CLN2 related neurological disease and interpretability of these results based on the methodological limitations of the study.**

The Clinical Outcomes Assessment staff has taken a lead role in assessing the adequacy of the Motor/Language scale that was used as the primary endpoint. DNP defers to the primary review team and COA regarding the interpretability of the results of the primary endpoint that were obtained from this scale.

**Provide assistance on evaluation of videos provided by the Applicant to compare adapted CLN2 disease scale with scale used in NH study.**

A random selection of videos was reviewed. These appear to be short clips of the examinations and do not appear to contain the full clinical assessments that were used to score the CLN2. Because these do not contain the full assessments, the videos are not adequate to provide additional support for the accuracy of the scoring of the CLN2 disease scales.

**Provide advice and comment of neurological secondary and exploratory endpoints which may be considered in the totality of the evidence.**

*MRI brain volumes:* The sponsor presents a descriptive summary of percent change in different MRI volumetric brain measures from baseline to the end of the study; however, the natural history study used for the control group, Study 190-901, does not contain longitudinal MRI assessments.

There is a publication from more recent cLINCL/CLN2 natural history study, DEMCHILD, that describes expected annual change in gray matter in 13 patients. It is not clear that the study population in the DEMCHILD publication is comparable to that from Study 190-201 in order for it to serve as an adequate control. Additionally, there is large variability

in the volumetric MRI data in both Study 190-201 and in the data from DEMCHILD presented in the publication which leads to overlap in the rates of change between the two groups and no statistically significant difference between the two groups. Given the large amount of variability and the small number of patients in the two studies, the change in MRI brain volumes is not interpretable. It should be noted that the sponsor has also indicated in this submission that they do not feel that the MRI data is interpretable and they do not propose that that this data is supportive of efficacy findings nor that the MRI data be included in the label.

*Developmental Outcomes:* The sponsor included the Denver II Development Scale as an exploratory outcome in the study. This scale was not assessed in the natural history study. Given the lack of comparator data from the natural history control group, changes in this scale cannot be interpreted.

(b) (4)



(b) (4)



(b) (4)



**Recommendations**

Overall, the secondary and exploratory endpoints included in the study either do not provide adequate information or do not have an adequate control group to be used to support the findings for the primary endpoint.

**Appendix 1. Original POMA-G Scale**



(b) (4)

***Appendix 2. Modified POMA-G Scale***





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/s/  
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TERESA J BURACCHIO  
02/24/2017

ERIC P BASTINGS  
02/27/2017



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Pediatric and Maternal Health  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

**Division of Pediatric and Maternal Health Memorandum**

**Date:** January 27, 2017      **Date Consulted:** July 1, 2016

**From:** Jane Liedtka MD, Medical Officer, Maternal Health  
Division of Pediatric and Maternal Health (DPMH)

**Through:** Miriam Dinatale, DO, Acting Team Leader, Maternal Health  
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director  
Division of Pediatric and Maternal Health

**To:** Jenny Doan, BSN, MSN, PMP, Regulatory Project Manager (RPM)  
Division of Gastroenterology and Inborn Errors Products (DGIEP)

**Drug:** Brineura (cerliponase alfa)

**BLA:** BLA 761052

**Indication:** Brineura is an enzyme replacement therapy and a hydrolytic lysosomal N-terminal tripeptidyl peptidase indicated for patients with Neuronal Ceroid Lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency

**Applicant:** Biomarin Pharmaceutical Inc

**Subject:** Pregnancy and Lactation labeling

**Materials Reviewed:**

- Applicant's submitted background package for BLA 761052

**Consult Question:**

We request your assistance for the labeling review including the Pregnancy Lactation Labeling Rule (PLLR) implementation in this product label.

## INTRODUCTION

On July 1, 2016, DGIEP consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of Brineura (cerliponase alfa) labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

## REGULATORY HISTORY

On May 27, 2016, Biomarin Pharmaceutical Inc submitted an original BLA761052 for Brineura (cerliponase alfa) also known as (aka) BMN-190. Brineura is an enzyme replacement therapy and contains a hydrolytic lysosomal N-terminal tripeptidyl peptidase indicated for patients with CLN2 disease, aka TPP1 deficiency.

## BACKGROUND

### Cerliponase alfa and Drug Characteristics<sup>1</sup>

Cerliponase alfa is a purified human enzyme produced by recombinant DNA technology in a Chinese hamster ovary cell line. Cerliponase alfa is a proteolytic inactive proenzyme (zymogen) that is activated in the lysosome. Cerliponase alfa is taken up by target cells and translocated to the lysosomes through the Cation Independent Mannose-6-Phosphate Receptor (CI-MPR, aka M6P/IGF2 receptor). The activated proteolytic enzyme (rhTPP1) cleaves tripeptides from the N-terminus of the target protein with no known substrate specificity. Inadequate levels of TPP1 cause CLN2 disease, resulting in neurodegeneration, loss of neurological function and death during childhood.

Cerliponase alfa has an average molecular mass of 59 kilodaltons. Brineura is a fixed dose solution, 150 mg/5 mL (total dose 300 mg), administered by intracerebroventricular (ICV) infusion via an ICV access device at a dose of 300 mg once every other week. The mean half-life of cerliponase alfa was 7.35 hours with a standard deviation of 2.90 hours following the first ICV infusion (approximately 4 hours in duration) of 300 mg.

The most frequently reported adverse reactions in clinical studies of Brineura ( $\geq 10\%$ ) were pyrexia, vomiting, hypersensitivity, headache, irritability, and pleocytosis.

### Neuronal Ceroid Lipofuscinosis type 2 (CLN2) Disease

CLN2 disease, aka tripeptidyl peptidase-1 (TPP1) deficiency, aka Batten disease, is a predominantly late infantile form of neuronal ceroid lipofuscinosis. It is a rare genetic disease characterized by the deficiency of the lysosomal serine protease TPP1, caused by mutations in the CLN2 gene. In the absence of TPP1, lysosomal storage materials normally metabolized by this enzyme accumulate as characteristic intracellular deposits in many organs; accumulation in the CNS leads to the neurodegenerative symptoms and, ultimately death. The onset of symptoms is typically between ages 2 and 4<sup>2, 3</sup>. Children with CLN2

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<sup>1</sup> Brineura proposed package insert

<sup>2</sup> Chang, M. CLN2. The Neuronal Ceroid Lipofuscinoses. New York: Oxford Univ Press, 2011: 80-109.

disease are likely to be near normal until about the age of 3 years old. The rate of progression is significant once symptoms appear and the loss of all or substantial neurological function within three years after the first clinical symptom is common. CLN2 disease results in progressive, irreversible language decline, ambulation loss, involuntary movements, seizures, bulbar dysfunction, blindness, and, ultimately, death<sup>4</sup>. There is currently no form of treatment for this disease.

Most epidemiological studies of CLN2 disease originated before molecular diagnosis and suggest an incidence of about 0.46 per 100,000 live births and an estimated prevalence of 0.6 to 0.7 per million population in northern Europe<sup>5, 6</sup>. In the US, the estimated incidence of CLN2 is approximately 0.5 per 100,000 births<sup>5</sup>.

## **Pregnancy and Lactation Labeling**

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”<sup>7</sup> also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule<sup>8</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

## **REVIEW**

### **Pregnancy**

#### Nonclinical Experience

Animal reproduction studies have not been conducted using Brineura.

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<sup>3</sup> Kurachi, Y *et. al.* Rapid immunologic diagnosis of classic late infantile neuronal ceroid lipofuscinosis. *Neurology*. 2000; 54[8]: 1676-1680.

<sup>4</sup> Williams, R.E. *et al.* Diagnosis of the neuronal ceroid lipofuscinoses: An update. *Biochimica et Biophysica Acta*. 2006; 1762: 865–872.

<sup>5</sup> Claussen, M *et. al.* Incidence of neuronal ceroidlipofuscinoses in West Germany: variation of a method for studying autosomal recessive disorders. *Am J Med Genet*. 1992; 42[4]: 536-538.

<sup>6</sup> Uvebrant, P, Hagberg, B. Neuronal ceroid lipofuscinoses in Scandinavia. *Epidemiology and clinical pictures. Neuropediatrics*. 1997; 28[1]: 6-8.

<sup>7</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

<sup>8</sup> *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

### Applicant's Review of Literature

The Applicant was not asked to conduct a literature search since the development program for Brineura includes data from only two studies [one completed and one (the long term extension study) ongoing] involving a total of 24 subjects. The mean age of the subjects studied was 4.3 years with a range of 3 - 8 years of age. No pregnancies have been reported.

### DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase using the search terms "Cerliponase alfa and pregnancy," "Cerliponase alfa and pregnant women," "Cerliponase alfa and pregnancy and birth defects," "Cerliponase alfa and pregnancy and congenital malformations," "Cerliponase alfa and pregnancy and stillbirth," "Cerliponase alfa and spontaneous abortion" and "Cerliponase alfa and pregnancy and miscarriage." No reports of adequate and well-controlled studies of Cerliponase alfa use in pregnant women were found. No case reports were found.

### Summary

Human pregnancy outcome data for Cerliponase alfa were not identified in the published literature. There were no cases from the applicant's pharmacovigilance database. Animal reproduction studies have not been conducted using Brineura. There are no available data on Brineura use in pregnant women to inform a drug -associated risk of pregnancy-related outcomes.

### **Lactation**

#### Nonclinical Experience

There is no nonclinical information regarding the presence of Cerliponase alfa in milk.

### Applicant's Review of Literature

The Applicant did not perform a literature search.

### DPMH Review of Literature

DPMH conducted a search of *Medications and Mother's Milk*<sup>9</sup>, the Drugs and Lactation Database (LactMed),<sup>10</sup> and of published literature in PubMed and Embase using the search terms "Cerliponase alfa and lactation" and "Cerliponase alfa and breastfeeding." No reports

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<sup>9</sup> Hale, Thomas (2012) *Medications and Mothers' Milk*. Amarillo, Texas Hale Publishing, pg. 422-423.

<sup>10</sup> <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

of adequate and well-controlled studies of Cerliponase alfa use in lactating women were found. No mention of the use of Cerliponase alfa during lactation was found.

### Summary

There are no data on the presence of Cerliponase alfa in human milk. The lack of clinical data during lactation precludes a clear determination of the risk of Brineura to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Brineura and any potential adverse effects on the breastfed infant from Brineura or from the underlying maternal condition.

## **Use in Females and Males of Reproductive Potential**

### Nonclinical Experience

Animal reproduction studies have not been conducted using Brineura.

### Applicant's Review of Literature

The Applicant did not perform a literature search.

### DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase regarding Cerliponase alfa and its effects on fertility and found no relevant literature.

### Summary

Animal reproduction studies have not been conducted using Brineura. There are no human data available on the effect of Cerliponase alfa on fertility. Therefore, as there is no human or animal data available, Section 8.3, Females and Males of Reproductive Potential, will not be included in Cerliponase alfa labeling.

## **CONCLUSIONS**

Based on the literature review and review of the pharmacovigilance database, DPMH has the following recommendations for Brineura (Cerliponase alfa hydrochloride) labeling:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of Brineura labeling was structured in the PLLR format to include the "Risk Summary" section.<sup>11</sup>
- **Lactation, Section 8.2**
  - The "Lactation" subsection of Brineura labeling was formatted in the PLLR format to include the "Risk Summary" section.<sup>12</sup>

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<sup>11</sup> Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

## **LABELING RECOMMENDATIONS**

DPMH revised sections 8.1 and 8.2 of Brineura (Cerliponase alfa) labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DGIEP on 12/6/16. DPMH refers to the final NDA action for final labeling.

### **DPMH Proposed Brineura (Cerliponase alfa) Pregnancy and Lactation Labeling**

## **FULL PRESCRIBING INFORMATION**

### **8 Use in Specific Populations**

#### **8.1 Pregnancy**

##### Risk Summary

There are no available data on Brineura use in pregnant women to inform a drug -associated risk of pregnancy-related outcomes. Animal reproduction studies have not been conducted using Brineura.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### **8.2 Lactation**

##### Risk Summary

There is no (b) (4) on the presence of Brineura in human milk, the effects (b) (4) on the breastfed infant, or the effects (b) (4) on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of Brineura to an infant during lactation; therefore, the development and health benefits of breastfeeding should be considered along with the mother's clinical need for Brineura and any potential adverse effects on the breastfed infant from Brineura or from the underlying maternal condition.

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<sup>12</sup> Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

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JANE E LIEDTKA  
01/27/2017

MIRIAM C DINATALE  
01/27/2017

LYNNE P YAO  
02/06/2017



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## **LABEL & LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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<b>Date of This Review:</b>	January 26, 2017
<b>Requesting Office or Division:</b>	Division of Gastroenterology & Inborn Error Products (DGIEP)
<b>Application Type and Number:</b>	BLA 761052
<b>Product Name and Strength:</b>	Brineura (Cerliponase alfa) Injection, 150 mg/5 mL (30 mg/mL)
<b>Product Type:</b>	Single Ingredient Product
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Biomarin Pharmaceuticals
<b>Submission Date:</b>	May 27, 2016
<b>OSE RCM #:</b>	2016-1291
<b>DMEPA Primary Reviewer:</b>	Matthew Barlow, RN, BSN
<b>DMEPA Associate Director (Acting):</b>	Mishale Mistry, PharmD, MPH

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## 1 REASON FOR REVIEW

This review is in response to DGIEP's request for DMEPA to review the submitted proposed labels and labeling for Brineura (cerliponase alfa) for any areas that may lead to medication errors. The proposed labels and labeling were submitted on May 27, 2016 under BLA 761052.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	N/A-D
FDA Adverse Event Reporting System (FAERS)*	N/A-E
Other	F
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

### Use-Related Risk Analysis (URRA)

As a part of their BLA submission, the applicant submitted a comprehensive use-related risk analysis (URRA) and their final conclusion regarding the necessity for a Human Factors study. DMEPA previously evaluated the URRA during a Type C meeting held on September 30, 2015.<sup>a</sup> DMEPA concluded that the proposed URRA and subsequent conclusion appeared reasonable and agreed that a Human Factors validation study was not needed at the time. However, DMEPA requested that the applicant submit any errors related to the safe use of this product or administration issues that occurred during the clinical trials, which will allow a greater understanding of the use-related risk.

DMEPA reviewed the errors, submitted on August 5, 2016, related to the safe use of this product or administration issues that occurred during the clinical trials. The reported errors involved device-related adverse events and were not attributed to the user interface/use of the product. With regard to the preparation and administration of Brineura, per discussions with

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<sup>a</sup>28 Oct 2015. IND 122472 BMN 190 Type C Meeting Minutes held on September 30, 2015.

the CDRH clinical reviewer, we note that experienced health care professionals familiar with this type of procedure will administer this product in clinics or infusion centers. Therefore, we agree with our previous assessment that the Applicant has adequately considered the risks associated with the proposed product and based on the FMEA data submitted, we agree that a human factors validation study is not needed at this time.

### **Labels, Labeling & Packaging**

The applicant submitted proposed carton labeling and container labels on May 27, 2016 and revised Prescribing Information (PI) on August 31, 2016. DMEPA performed a risk assessment of the proposed labels and labeling for areas of vulnerability that may lead to medication errors. Through our assessment, we note that the labels and labeling can be improved to increase clarity and understanding of the safe and effective use of this product.

As a result of an internal meeting between DGIEP, DNP, DCRP, and CDRH, it was agreed that the term “intraventricular” was most accurate to describe the route of administration for Brineura.

(b) (4)  
Per discussions with the Office of Biological Products (OBP), it was recommended that the nomenclature for (b) (4) “ (which is administered after Brineura) should be changed to “Intraventricular Mixed Electrolytes” to clearly convey the route of administration and mitigate the risk that health care providers use other types of electrolyte solutions in substitution for this product. Per the Prescribing Information, healthcare providers should withdraw 2 mL of the intraventricular mixed electrolytes, available in a net quantity of 5 mL. We discussed with the clinical reviewer the safety concerns associated with 1) administering 5 mL of the intraventricular mixed electrolytes, rather than 2 mL per the PI, and 2) administering the intraventricular mixed electrolytes injection prior to administration of Brineura. Per the clinical reviewer, due to the slow infusion rate, administering a volume of 5 mL over a prolonged time period does not prevent safety concerns. DMEPA provides recommendations for the labels and labeling to further clarify that the unused portion of the product should be discarded and that the product should be administered *after* administration of Brineura. We also note that Brineura will be packaged in a carton containing two vials of Brineura, with each vial containing 150 mg/5 mL (30 mg/mL), and one vial of the Intraventricular Mixed Electrolytes Injection. Per the PI, the dose is 300 mg administered once every other week. Therefore, there is a risk of underdose if healthcare providers do not withdraw the contents of both vials. We recommend that for future development, the applicant consider packaging Brineura in a single vial of 300 mg/10 mL to mitigate the risk of an underdose. We note that the carton labeling can be improved to further clarify the total drug amount per vial. We note that the size of the inline filter was “0.2 mcg”; however, we recommend the use of the units “microns” for consistency with other products using filters. Additionally, we note the use of the terminology (b) (4) throughout the labels and labeling. We defer to OBP on the appropriate terminology.

DGIEP, DMEPA and OBP held a teleconference with the applicant on December 20, 2016 to discuss the proposed container labels and carton labeling. DMEPA discussed with the applicant the recommendations listed in Section 4.2.

## 4 CONCLUSION & RECOMMENDATIONS

The proposed labels and labeling can be improved to mitigate any confusion and clarify information to promote the safe and effective use of the product. We provide recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these deficiencies.

### 4.1 RECOMMENDATIONS FOR THE DIVISION

#### A. Packaging Considerations

1. We recommend that for future development, the applicant consider packaging Brineura in a single vial of 300 mg/10 mL to mitigate the risk of an underdose.

#### B. Prescribing Information (PI)

1. We conveyed and discussed the following recommendations for Section 2 of the proposed PI with the Division on December 14, 2016:
  - i. The addition of a statement emphasizing the need for this product to be administered with the included 0.2 micron filter.
  - ii. The revision of step 16 to fully explain the necessary process for this step (b) (4).
  - iii. The inclusion and revision of statements regarding maintaining aseptic technique and the proper order and duration of administration to emphasize the safe and effective use of this product.

### 4.2 RECOMMENDATIONS FOR BIOMARIN PHARMACEUTICALS

We recommend the following be implemented prior to approval of this BLA:

#### A. Brineura Carton Labeling

1. Revise the route of administration (b) (4) to “For Intraventricular Infusion Only.” Avoid using any abbreviations for “intraventricular” to prevent misinterpretation and confusion.
2. Revise (b) (4) to read “Intraventricular Mixed Electrolytes.” Avoid using any abbreviations for “intraventricular” to prevent misinterpretation and confusion.
3. Revise the (b) (4) statement in the upper right corner of the Principal Display Panel to as follows for increased clarity on the total drug amount per vial in Brineura and the net quantity of the Intraventricular Mixed Electrolytes Injection:

**Each carton contains:**

2 vials, each containing Brineura (cerliponase alfa) Injection, 150 mg/5 mL

1 vial of Intraventricular Mixed Electrolytes Injection, 5 mL
4. To further clarify the total drug amount per vial, we recommend bolding the following statement:

**“Each vial of Brineura™ contains 150 mg cerliponase alfa in 5 mL of solution (30 mg/mL)”**

## B. Brineura Container Label

1. Revise the route of administration (b) (4) to “For Intraventricular Infusion Only.” Avoid using any abbreviations for “intraventricular” to prevent misinterpretation and confusion.
2. Revise (b) (4) to “Use before Intraventricular Mixed Electrolytes.” Avoid using any abbreviations for “intraventricular” to prevent misinterpretation and confusion.

## C. Intraventricular Mixed Electrolytes Container Label

1. Revise (b) (4) to read “Intraventricular Mixed Electrolytes Injection”. Avoid using any abbreviations for “intraventricular” to prevent misinterpretation and confusion.
2. Revise the route of administration (b) (4) to “intraventricular”. Therefore, the label should appear as:

**Intraventricular  
Mixed Electrolytes  
Injection**  
**Use after Brineura (cerliponase alfa)**  
**5 mL**  
For Intraventricular  
Infusion Only

3. Revise the statement (b) (4) to (b) (4) single dose only. Discard unused portion.’

## D. Administration Carton Labeling

1. Revise the size of the inline filter from “0.2 mcg” to “0.2 micron” for consistency in units as expressed by other products using inline filters.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Brineura that Biomarin submitted on August 31, 2016.

Table 2. Relevant Product Information for Brineura	
Initial Approval Date	N/A
Active Ingredient	Cerliponase Alfa
Indication	Brineura is indicated for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase (TPP1) deficiency.
Route of Administration	Intracerebroventricular Infusion
Dosage Form	Solution for Injection
Strength	150 mg/5 mL (30 mg/mL)
Dose and Frequency	The recommended dose of Brineura is 300 mg administered once every other week. The complete infusion, including the required Intracerebroventricular (ICV) Mixed Electrolytes solution, is approximately 4.5 hours.
How Supplied	<p>Brineura is supplied as a sterile solution for ICV infusion as package 1 of 2. The Administration Kit is supplied separately as package 2 of 2 [see <i>Dosage and Administration</i> (2.2)].</p> <p>Each Brineura vial (type I glass) with a stopper (b) (4) rubber) has a green flip-off cap (plastic) and green crimp seal (aluminum), and contains 150 mg per 5 mL of cerliponase alfa (30 mg/mL).</p> <p>Each ICV solution vial (type I glass) with a stopper (b) (4) rubber) has a yellow flip-off cap (plastic) and yellow crimp seal (aluminum), and contains 5 mL of ICV solution.</p> <p>The Administration Kit contains the following single-use, sterile infusion components:</p> <ul style="list-style-type: none"> <li>• Two 20-mL syringes</li> <li>• Two syringe needles (21 G, 25.4 mm)</li> <li>• One extension line</li> <li>• One infusion set with 0.2 micron inline filter</li> <li>• One port needle (22 G, 16 mm)</li> </ul>
Storage	<p>Store upright in a freezer ( 25°C to 15°C). (b) (4)</p> <p>The Administration Kit is supplied separately. Do not freeze.</p>

	<div data-bbox="643 191 1393 310"><div>(b) (4)</div></div> <p>Thawed Brineura and ICV solution should be used immediately. If immediate use is not possible, unopened vials of Brineura or ICV solution should be stored at 2 to 8°C and used within 24 hours.</p>
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## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On December 7, 2016, we searched the L:drive using the terms, Cerliponase, BMN 190, and Brineura, to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified two previous reviews which were not relevant to the labels and labeling<sup>bc</sup>.

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<sup>b</sup> Barlow, M. Proprietary Name Review for Brineura (BLA 761052). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 28. RCM No.: 2015-370321.

<sup>c</sup> Abraham, S. Proprietary Name Review for Brineura (BLA 761052). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 AUG 05. RCM No.: 2016-8279583.



## **APPENDIX C. HUMAN FACTORS STUDY**

### **Comprehensive Use Related Analysis**

Refer to Applicant submission dated May 27, 2016



Brineura (cerliponase  
alfa) uFMEA.pdf

## **APPENDIX D. ISMP NEWSLETTERS—N/A**

## **APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)—N/A**

## **APPENDIX F. OTHER—N/A**

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MATTHEW J BARLOW  
01/26/2017

MISHALE P MISTRY  
01/27/2017

## Clinical Inspection Summary

<b>Date</b>	December 15, 2016
<b>From</b>	Susan Leibenhaut, M.D. , OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
<b>To</b>	Elizabeth Hart, M.D., Medical Officer, DGIEP
<b>NDA/BLA #</b>	BLA #761052
<b>Applicant</b>	BioMarin Pharmaceutical Inc.
<b>Biologic</b>	BMN-190, Cerliponase alfa
<b>NME (Yes/No)</b>	Yes
<b>Therapeutic Classification</b>	Therapeutic Inborn Errors
<b>Proposed Indication</b>	Treatment of Neuronal Ceroid Lipofuscinosis type 2 (CLN2) disease aka TPP1 deficiency
<b>Consultation Request Date</b>	June 7, 2016
<b>Summary Goal Date</b>	December 19, 2016
<b>Action Goal Date</b>	April 27, 2017 (three month extension due to submission of major amendment August 29, 2016)
<b>PDUFA Date</b>	April 27, 2017

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator (CI) sites and the sponsor were inspected for this application. One CI site has the final classification of voluntary action indicated (VAI), and the violations cited are not considered to have had an impact on data integrity. The two other clinical site inspections and the sponsor inspection have classifications of no action indicated (NAI).

The studies appear to have been conducted adequately, and the data generated by the studies appear acceptable in support of the respective indication.

The DEM-CHILD natural history data base was inspected in Hamburg and source scoring sheets for 16 patients were collected. The inspection had limitations because FDA did not have access to translated copies of subject record. Instructions for standardization and consistency of assessments and reporting were lacking. The ability of the data from the registry to contribute as a control group is referred to the review division.

## II. BACKGROUND

The sponsor submitted this BLA for BMN-190, Cerliponase alfa for the indication of treatment of Neuronal Ceroid Lipofuscinosis type 2 (CLN2) Disease due to tripeptidyl peptidase-1 (TPP1) deficiency, a form of Batten Disease, a group of rare fatal pediatric dementias. There is currently no approved treatment for this disease. Patients receive symptomatic treatment for specific progressive problems such as seizures (anticonvulsants), motor control loss (bracing or wheelchairs) and feeding/aspiration risk (gastrostomy tube). Current treatment of patients with CLN2 disease, as described above, provides only temporary relief to certain symptoms of the disease. Due to the lack of approved pharmacologic interventions for CLN2 disease, the outcome is invariably fatal.

Biologic: BMN-190, Cerliponase alfa

Studies – Protocol number and title for all studies that were inspected:

1. Protocol 190-201 entitled “A Phase 1/2 Open-Label Dose-Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Intracerebroventricular BMN 190 in Patients with Late-Infantile Neuronal Ceroid Lipofuscinosis (CLN2) Disease”

Number of subjects: 24 subjects

Number of sites: 5

Number of countries where subjects were enrolled: 4 (U.S., Germany, Italy, and United Kingdom)

Dates that study was conducted: September 2013 to November 2015

Primary efficacy endpoint: Modified Hamburg and Cornell Neuronal Ceroid Lipofuscinosis (CLN2) rating scales at Week 48, assessment as change from baseline

2. Protocol 190-202 entitled, “A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN in 190 Patients with CLN2 Disease”

Number of subjects: 23 subjects (one subject withdrew due to inability to comply with assessments)

Number of sites: 5

Number of countries where subjects were enrolled: 4 (U.S., Germany, Italy, United Kingdom)

Dates that study was conducted: February 2015 and ongoing

Primary efficacy endpoint: Modified Hamburg and Cornell Neuronal Ceroid Lipofuscinosis (CLN2) rating scales

3. Natural History Database DEM-CHILD is the natural history database which BioMarin relied on as a control group for the uncontrolled studies listed above. DEM-CHILD is a research database maintained by the clinical group in Universitätsklinikum Hamburg-Eppendorf Pediatric Clinic. The database was developed for academic research to study the

natural history of the neuronal ceroid lipofuscinoses (NCLs). BioMarin contracted with the clinic to use data from this database. The public web address for the database is:

<http://www.dem-child.eu/index.php/background-16.html>

### III. RESULTS (by site):

Name and type of inspected entity/Address	Protocol # /Site # # of Subjects	Inspection Dates	Classification
CI: Emily de los Reyes, M.D. Nationwide Children's Hospital 700 Children's Drive Columbus, OH 43205	Protocols 201 and 202/Site 0146/ 3 Subjects	August 10 to 24, 2016	NAI
CI: Nicola Specchio, M.D. Bambino Gesù Children's Hospital Piazza S. Onofrio 4 Rome 00165 Italy	Protocols 201 and 202/Site 1323/ 6 Subjects	September 26 to 30, 2016	VAI
CI: Angela Schulz, M.D. Universitätsklinikum Hamburg-Eppendorf Pediatric Clinic Martinistraße 52, 20246 Hamburg, Germany	Protocols 201 and 202/Site 1244/ 12 Subjects  DEM-CHILD natural history database	September 19 to 23, 2016	NAI
Sponsor: BioMarin Pharmaceutical, Inc. 105 Digital Drive Novato, CA 94949	Protocols 201 and 202	November 2 to 4, 2016	NAI

#### Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

#### 1. Emily de los Reyes, M.D.

##### **Nationwide Children's Hospital, Columbus, OH 43205**

At this site 3 subjects were screened, enrolled and completed Protocol 190-201. The subjects are continuing in the extension Protocol 190-202. No subjects participated in the dose escalation portion of the study. The first subject signed the informed consent on July 15, 2014 and the last subject completed the study on September 25, 2015. All subjects are enrolled in the extension study Protocol 190-202.

At this site, two investigators Dr. de los Reyes and Dr. Lenora Lehwald rated subjects on the CLN2 scale. Prior to initiation of the study at this site, both investigators attended training on September 25, 2014 (b) (4)

Both investigators also attended the CLN2 rater re-training in San Francisco,

California in February 2016, prior to the start of study 190-202. The sponsor provided source worksheets for ratings of Hamburg scale, Cornell scale, Denver II Developmental scale, electrocardiogram and electroencephalogram. The site used these worksheets during the study. The ratings were conducted by having the blank scoring sheet in front of the rater. Motor assessments were typically conducted in a quiet hallway near the clinic. The scores were then transferred to the CRF by study staff. . Ratings Assessment Guides dated April 28, 2014, June 26, 2015 and June 26, 2015 were at the site. The CI was unsure which version of the RAG were used during each point of the study or whether only one RAG was used throughout the study.

The records for all three enrolled subjects were reviewed and compared to line listings from the BLA provided for eligibility criteria, adverse events, and efficacy endpoints. The efficacy data for the Hamburg motor and language scores were compared to the scoring sheets and no discrepancies were noted. The following adverse events (AEs) were noted in the source documents but were not in the line listings provided in the BLA:

- a. Subject 0146-1022 experienced two adverse events, fever beginning on October 20, 2015 and insomnia beginning on August 26, 2015, that were not listed on the data listings.
- b. Subject 0146-1021 experienced two adverse events, a seizure on January 29, 2015 and hematuria that began on February 23, 2015, that were not reported on the data listings.

Study staff stated that these AEs were inadvertently not entered into the eCRFs. The review division can consider adding the AEs above in the review.

The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

## **2. Nicola Specchio, M.D.**

### **Bambino Gesù Children's Hospital, Rome 00165 Italy**

At this site six subjects were screened, enrolled and completed Protocol 190-201. No subjects participated in the dose escalation portion of the study. The first subject signed the informed consent on July 15, 2014 and the last subject completed the study on September 25, 2015. Four subjects continued into the extension study Protocol 190-202. Two subjects, Subjects 1323-1014 and 1323-1015 transferred to Site 0119 in the United Kingdom (UK).

At this site, two investigators, Dr. Nicola Specchio and Dr. Marina Trivisano rated subjects on the CLN2 scale. Prior to initiation of the study at this site, both CIs attended training on June 12, 2014 [REDACTED] (b) (4). They also attended the CLN2 rater re-training in San Francisco, California in February 2016, prior to the start of study 190-202. During the study, the sponsor provided the Ratings Assessment Guide dated April 28, 2014 and this was version was used throughout the study. The sponsor provided source worksheets for ratings of

Hamburg scale, Cornell scale, Denver II Developmental scale, electrocardiogram and electroencephalogram. This site removed the sponsor's header and footer and added the hospital heading and footer to fit their hospital requirements. The scales on these forms were used throughout the trial without modification. The gait assessment was performed in a corridor that was approximately 22x14 meters, and the interviews were performed in the Neurology conference room or the Medicine conference room.

Line listings submitted by the sponsor to the BLA for the efficacy endpoints and the adverse events were compared with the source documents. There were no discrepancies between the data in the line listings and the source documents except for one instance of a discrepancy on the Hamburg visual scale at Week 9 for Subject 1323-1013.

A one item Form FDA 483 was issued because the CI did not provide the original written informed consent in the language understandable to the subject or the subject's parents. Although the original consent form document was not in the subject

Reviewer note:

*The CI responded to the Observations in a letter dated October 13, 2016 describing the consenting process at the site and also describing corrective action. Specifically, the original consenting process involves support or a cultural mediator so that the subjects and parents can be informed in the native language. The cultural mediator acts as a translator and has a high level of interaction with the family during their stay at the clinical site. Also, a translated form was implemented and signed later for the 190 Studies.*

The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

### **3. Angela Schulz, M.D.**

#### **Universitätsklinikum Hamburg-Eppendorf Pediatric Clinic, Hamburg, Germany**

At this site 12 subjects were screened, enrolled and completed Protocol 190-201. The subjects are continuing in the extension Protocol 190-202. The first subject was enrolled on September 13, 2013 and the last subject was enrolled on December 22, 2014. Eight of the nine subjects who participated in the dose escalation phase of the study were enrolled at this site.

At this site, four investigators (CIs) Drs. Schultz, Thies, Nickel and Schwering rated subjects on the CLN2 scale. Dr. Theis was no longer working on the study at the time of the FDA inspection. The CIs received training at least yearly from (b) (4). During the study, the sponsor provided the Ratings Assessment Guide dated April 28, 2014 and, once implemented, this was used consistently. The RAG was laminated so that it could be wiped clean between assessments. Assessments were conducted in the Gymnastics Hall and the hallway at the Pediatric Intensive Care Unit. A note to file at the site dated October 14, 2015, states that the site was performing the Hamburg and Cornell scales at additional time points that are not in the study protocol.

Line listings submitted by the sponsor to the BLA for the efficacy endpoints and the adverse events were compared with the source documents. There were no discrepancies between the data in the line listings and the source documents.

Reviewer note:

*The additional training and performing of additional subject efficacy assessments could have contributed to the increased consistency in scoring seen at this site over time. The significance of this is deferred to the review division.*

Concerning Protocol 190-201 and Protocol 190-202, these studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

**DEM-CHILD DATABASE**

DEM-CHILD is the natural history database which BioMarin relied on as a control group for the uncontrolled studies. DEM-CHILD is a research database maintained by the clinical group in Universitätsklinikum Hamburg-Eppendorf Pediatric Clinic. The database was developed for academic research to study the natural history of the neuronal ceroid lipofuscinoses (NCLs). BioMarin contracted with the clinic to use data from this database. The public web address for the database is:

<http://www.dem-child.eu/index.php/background-16.html>

For the DEM-CHILD database, the CLN2 score at each time point was determined by review of source documents and entered into the “Late Infantile NCL-Scoring sheet” (aka Scoring Sheet) prior to being entered into the DEM-CHILD database. Source documents consisted of letters from the child’s local physician as the initial entry for DEM-CHILD or records from the Hamburg clinic once the patient was identified as having CLN2. For the initial entry, the score was determined from a letter provided by the local physician. Dr. Schultz read the letter containing a detailed account of the child’s health history and wrote the score on the physician’s letter. Dr. Schulz transferred this score from the physician’s letter to the Score Sheet. Once the child was seen in the Hamburg clinic, the score was determined by the “NCL database list of questions” and the clinic notes. The score was entered onto the Scoring Sheet.

OSI was able to collect Scoring Sheets for 16 selected subjects, but, because the line listings were not updated with the corrections, the scoring sheets were not compared to the line listings to verify the data. OSI was able to view the letters from physicians, but, limitations of the inspection are that OSI was not able to determine whether there was a standard for scoring the physician letters and was not able to review clinic notes from which the scores were determined to be entered on the Scoring sheets. OSI was not able to assess the quality or the consistency of the process of scoring.

FDA noted that the DEM-CHILD data base is password protected. The data base is designed to have audit trails and nightly backup to a hospital server. These features were not verified on inspection.



Concerning the DEM-CHILD database, the inspection noted that there were not adequate procedures and controls in place to prevent or detect data entry errors. Instructions for standardization and consistency of assessments and reporting were lacking. The inspection of the DEM-CHILD database had limitations because FDA did not have access to translated copies of subject record. The accuracy of the scoring determinations could not be assessed because the source documents were in German and, due to German laws, could not be copied or submitted to the BLA. The scoring sheets were collected on 16 subjects and these can be used to compare with line listings if the sponsor submits updated, corrected data. The ability of the data from the registry to contribute as a control group is referred to the review division.

#### **4. BioMarin Pharmaceuticals Inc., Novato, CA 94949**

This inspection evaluated compliance with sponsor responsibilities concerning the conduct of Protocol 190-201 and Protocol 190-202 including selection and oversight of contract research organizations, monitoring, financial disclosure, FDA Form 1572s, quality assurance (QA), and handling of data. The inspection included review of general correspondence and study master files, site monitoring for the clinical sites, and handling of adverse events and other sponsor/monitor related activities.

Review of the sponsor documents did not note any significant deficiencies. Monitoring practices at the sites inspected above were reviewed in detail. Results of the inspection indicated that, in general, monitoring of investigators was adequate and the sponsor maintained adequate oversight of the trials. All sites were audited by the sponsor. During the inspection, it was noted that Site 1287 in the UK was terminated for noncompliance in a letter sent on May 12, 2014 and the Institutional Ethics Committee (IEC) was notified on May 15, 2014. The letters noted that there was one missed serious adverse event (prolonged hospitalization due to catheter insertion) and “multiple missed adverse events”. At the time of the close-out of the site, there were no outstanding queries. The site enrolled two subjects. Subject 1287-1005, enrolled on December 4, 2013 and was transferred to Site 0119 when Site 1287 was closed. Subject 1287-1007, enrolled on February 18, 2014 and withdrew on March 9, 2014.

##### Reviewer comment

*The review division was notified of the occurrence of termination of this site. A copy of the letter of termination was sent to the primary reviewer on Dec 13, 2016. The site had been open for only five months. The perioperative complications that occurred for Subject 1287-1007 are contained in the line listings and the subject narrative. Because the site in the UK was terminated before the US IND was opened, the fact that FDA was not notified of the termination is not considered a violation.*

The studies appear to have been conducted adequately, and the data generated by this sponsor may be used in support of the respective indication.

*{See appended electronic signature page}*

Susan Leibenhaut, M.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Susan Thompson, M.D.  
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Kassa Ayalew, M.D., M.P.H  
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CC:

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Review Division /Division Director/Donna Griebel  
Review Division /Medical Team Leader/Laurie Muldowney  
Review Division /Project Manager/Jennie Doan  
Review Division/Medical Office/Elizabeth Hart  
OSI/Office Director/David Burrow  
OSI/DCCE/ Division Director/Ni Khin  
OSI/DCCE/Branch Chief/Kassa Ayalew  
OSI/DCCE/Team Leader/ Susan D. Thompson  
OSI/DCCE/GCP Reviewer/ Susan Leibenhaut  
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague

OSI/Database PM/Dana Walters

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/s/  
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SUSAN LEIBENHAUT  
12/16/2016

SUSAN D THOMPSON  
12/16/2016

KASSA AYALEW  
12/16/2016

**GENERAL HOSPITAL DEVICES BRANCH  
INTERCENTER CONSULT MEMORANDUM**

**Date:** July 12, 2016

**To:** Jenny Doan, RPM  
Division of Gastroenterology and Inborn Errors Products (DGIEP),  
Office of Drug Evaluation III (ODEIII),  
Office of New Drugs (OND),  
Center for Drug Evaluation and Research (CDER)

**From:** John McMichael, Biomedical Engineer  
General Hospital Devices Branch

**Through:** CDR Alan Stevens, Branch Chief  
General Hospital Devices Branch

**Subject:** Filing Review for BLA 761052

Applicant	Biomarin Pharmaceuticals
Indication for Use	BMN190 is indicated for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency
Biologic Constituent	BMN190 (cerliponase alfa)
Device Constituent	BMN190 administration kit

**Recommendation:** BLA 761052 contains the necessary device constituent information – FILEABLE

Digital Signature Concurrence Table	
Reviewer	John C. McMichael -S Date: 2016.07.12 08:13:48 -04'00'
Branch Chief	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2016.07.12 08:49:04 -04'00'

## I. Purpose / Background

The purpose of this memo is to record the filing review for the device constituent parts of the combination product submission, BLA 761052.

The BMN190 Administration Kit includes the following device constituent parts:

**Table 3.2.P.7.2.1: Medical Device Components**

Component	Construction	Manufacturer	Manufacturer Part Number	510(k) Number <sup>1</sup>
Infusion set with 0.2µm filter	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Extension line				
(b) (4) needle (16mm Port needle)				
Syringe ( (b) (4) 20mL)				
Hypodermic needle (21 gauge Syringe needle)				

## II. Administrative

### Documents Reviewed:

The following documents were evaluated to determine the availability of the required review information:

Document Title	Date -Version	Location
Reviewer Guide		GSR Sequence 0001 / Module 1.2
Meeting Minutes		GSR Sequence 0001 / Module 1.6
Container Closure System	N/A	GSR Sequence 0001 / Module 3.2.P.7.
Design Input Requirements BMN190 Administration Kit (DIR1-190-001)	Rev2, May 13, 2016	GSR Sequence 0001 / Module 3.2.P.7.
Preliminary Hazard Analysis – BioMarin BMN190	RevA, August 2015	GSR Sequence 0001 / Module 3.2.P.7.

Draft Labeling		GSR Sequence 0001 / Module 1.14
Letter of Authorization – (b) (4)		GSR Sequence 0001 / Module 1.4
Letter of Authorization – (b) (4)		GSR Sequence 0001 / Module 1.4

### III. Device Description and Performance Requirements

The draft labeling includes a diagram to demonstrate the set-up of the BMN190 infusion system.



The disposable BMN190 administration components are included as part of the combination product.

The infusion pump and ICV access devices are referenced in the BMN190 draft labeling, and are not listed as part of the combination product.

### IV. Design Control Review

#### A. Design Review Summary

The filing review only evaluates the presence of the documentation needed to initiate a complete review. The acceptability of the information to reach an approval decision is pending review.

After several pre-meetings with the Sponsor it was unclear if the Sponsor would be able to obtain the necessary sterilization validation information in order to file the BLA. The sterilization documentation necessary for review (subject of the pre-BLA meetings) appears to have been included in the submission. A sterility consultant (Christopher Dugard CDRH/ODE/DAGRID/INCB) has reviewed the submitted information for completeness and concurs that the necessary information has been included and the results of the information of the information provided will be a review issue, but there are no filing issues concerning the sterility information.

#### B. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		
Design Verification Data included in the NDA / BLA or cross-referenced to a master file or 510(k).	X		
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		
Validation Data <ul style="list-style-type: none"> <li>Human factors</li> <li>Clinical data</li> </ul>	X		
	X		
Traceability Documentation	X		

\*Sponsor may derive the regulatory requirements from 21 CFR 820.30 into multiple sets of documents. For example, injectors containing software may include separate software requirements and specification documents. In these circumstances, additional rows may need to be added to the table.

## V. Recommendation

BLA 761052 contains the necessary information for review of the device constituent parts.

We present the following recommendations:

1. File BLA 761052
2. The sponsor is not referencing a specific ICV access device. We recommend that the product be labeled for the ICV access device used in the clinical trials. This will be a review issue.
3. Send the following Information Requests to Biomarín:
  - Module 3.2.P.7 describes the device Risk Management Report. The BLA does not include this information. Please provide the device Risk Management Report to the BLA.
  - You provided Dose Audits and Validation reports for the components in the administration kit that are sterilized via (b) (4). However, you did not provide the most recent cycle validation. While it does not appear you are changing the cycle as previously accepted, this information is useful to ensure the cycle is still adequate and to compare this validation with the provided dose audits. Please provide the most recent (b) (4) validation in a full test report (much like what was provided for the (b) (4) validation).



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/s/  
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JENNY N DOAN  
07/14/2016