CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761052Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Dragos Roman MD, Associate Director, Division of Gastroenterology and Inborn Errors Products
Subject	Division Director Summary Review (to serve also as primary/secondary/CDTL review)
BLA #	761052
Applicant	BioMarin Pharmaceutical Inc.
Date of Submission	5/27/2016
PDUFA Goal Date	January, 27, 2017 (major amendment issued on August 29, 2016)
Proprietary Name / Non-Proprietary Name	BRINEURA (cerliponase alfa) injection for intracerebroventricular use
Dosage Form(s) / Strength(s)/dosing Regimen and Route of Administration	150 mg/5mL (30 mg/mL) solution in vials; to be administered at 300 mg every other week via intracerebroventricular infusion
Applicant Proposed Indication(s)/Population(s)	Treatment of neuronal ceroid lipofuscinosis type 2 (CLN2 disease), also known as tripeptidyl peptidase-1 (TPP1) deficiency
Action/Recommended Action for NME:	Approval
Approved/Recommended Indication/Population(s) (if applicable)	Symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2).

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Elizabeth Hart MD, Victor Baum MD
Statistical Review	Lili Garrard, PhD, Min Min, PhD, Scott Komo, DrPH,

	Yeh-Fong Chen PhD, Laura Lee Johnson, PhD
Pharmacology Toxicology Review	Fang Cai, PhD, David Joseph, PhD, Abby Jacobs PhD
Clinical Pharmacology Review (OCP)	Christine Yuen-Yi Hon, Pharm.D., Justin Earp, Ph.D. Christian Grimstein, Ph.D., Nitin Mehrotra, Ph.D. Yow-Ming Wang PhD, Hae Young Ahn PhD
OPQ Review	Ralph Bernstein PhD, Rukman De SilvaPhD, Frederick Mills PhD, Gerald Feldman PhD, Laura Fontan PhD, Peter Qiu PhD, Cristina Ausin-Moreno PhD.
Microbiology Review	Candace Gomez-Broughton/ PhD, Reyes Candauchacon PhD, Natalia Pripuzova PhD, Patricia Hughes PhD
OSE/DRISK	Bob Pratt, Pharm.D., Donella Fitzgerald, Pharm.D., Jamie Wilkins Parker, Pharm.D.

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
OBP=Office of technology products
OCP=Office of Clinical Pharmacology

Reference ID: 4089891

Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Neuronal ceroid lipofuscinosis type 2 (CLN2) is rare neurodegenerative disorder of childhood characterized by accumulation of storage material (lipopigment) in lysosomes of neural tissues. It has a relatively predictable phenotype with onset at 2-4 years of age followed by progressive, inexorable, neurological deterioration resulting in profound neurological deficits by 6 years of age and death in adolescence. It is due to a deficiency of the lysosomal enzyme tripeptidyl peptidase-1 (TPP1).

Brineura (cerliponase alfa) is recombinant human TPP1. Because it cannot cross the blood-brain barrier, it is administered directly into the intracerebroventricular space via a surgically implanted device (containing a catheter and a reservoir) at a dose of 300 mg infused over 4.5 hours every two weeks. Tissue penetrance into the CNS has been clearly demonstrated in two animal models that recapitulate the human CLN2 phenotype; in these two animal models cerliponase alfa slows down the neurological manifestations of the disease and improves survival. Currently there are no approved pharmacological therapies for CLN2.

Efficacy of Brineura was assessed in a single-arm, open-label clinical trial that enrolled 24 patients ≥ 3 years of age with symptomatic CLN2 disease, and was compared with an independent historical control group with similar but not identical baseline characteristics. Efficacy assessments were based on a clinician reported outcome (ClinRo), the CLN2 rating scale (Motor domain). Brineura treatment was associated with a slowing in progression of motor deterioration relative to a reasonably matched control cohort. Efficacy conclusions are based on multiple analyses of the best matched patients in the two cohorts, analyses that accounted for several confounding factors (age, genotype, screening motor score). Motor function (walking or crawling ability) was assessed using the Motor domain of the CLN2 clinical rating scale which could range from a score of "3" (normal) to a score of zero (profoundly impaired). The main efficacy analysis measured a sustained decline of 2 categories or a sustained score of zero (loss of walking or crawling ability). There was a progressively larger difference with time between the treated and historical groups: 18%, 29%, and 59% at 48, 72 and 96 weeks respectively. Of note, at week 96, the 95% confidence interval for the odds ratio excludes 1 (this was not observed with shorter exposure of treatments).

Safety findings associated with the use of Brineura include: device-related complications (bleeding, mechanical failure, CNS infection, and need to replace the intraventricular catheter); hypersensitivity reactions (observed in the clinical trial and

addressed with appropriate premedication); hypotension (measured frequently during the clinical program but rarely symptomatic).

In my opinion, efficacy has been established for Brineura. Despite the small differences in patient characteristics between the two compared cohorts and the imperfections of the ClinRo, the 96 week data show a distinct difference in motor function favoring the treatment cohort over the natural history study. The safety findings associated with administering Brineura are not insignificant, particularly those related to the use of the device. Given the absence of any available therapy and the severity of the disease, they represent a reasonable risk in view of the demonstrated benefit. Therefore I recommend approval for Brineura for the treatment of CLN2 in children >3 years of age. Brineura is not curative but it does, however, slow down the disease progression, specifically the loss in motor function. Long-term safety data will be collected via a postmarketing study; safety in children younger than 3 years of age will also be collected in a postmarketing study.

There are no inspectional issues to preclude approval. Discussions regarding product labeling, postmarketing study requirements and commitments have been completed agreed with the applicant.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Neuronal ceroid lipofuscinoses (NCLs) are a group of progressive neurodegenerative disorders of children characterized by accumulation of storage material (lipopigment) in the lysosomes of neural tissues, with a phenotype of progressive, inexorable, neurological deterioration. Neuronal ceroid lipofuscinosis type 2 (CLN2) is the second most common form of NCL. It is due to a deficiency of the lysosomal enzyme tripeptidyl peptidase-1 (TPP1). The "classical" or late-infantile clinical presentation of CLN2 begins with seizures at age 2 to 4 years followed by progressive neurological deterioration with a spectrum of manifestations that include ataxia, myoclonus, impaired speech and swallowing, developmental regression, and loss of vision. Cognitive and motor functions are rapidly lost and patients become blind and wheelchair bound by approximately 6 years of age. Death	CLN2 is a rare, devastating neurological degenerative disease of early childhood with a relatively predictable clinical course.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	typically occurs between 10 and 16 years of age. There are also non-classic phenotypes (20-25% of patients) with slightly earlier or later presentation than the classical form. CLN2 is a very rare condition (incidence between 0.56-4 patients per 100,000 live births in the U.S. and Europe).	
Current Treatment Options	• There are no pharmacological treatments for CLN2. Current standard of care includes: seizure management; physical, occupational, and speech therapy to optimize residual motor function; nutritional management including G-tube feedings; general treatment of complications related to loss of mobility, loss of swallowing; management of sleep disturbances and behavior symptoms; social and educational interventions.	There are no pharmacological treatments for CLN2.
Benefit	• Brineura (cerliponase alfa) is recombinant human TPP1. It was developed as an enzyme replacement therapy aiming to restore TPP1 enzyme activity in the CNS of patients with CLN2 disease, and to attenuate or stabilize the neurological progression of the disease (it is not anticipated to reverse neurological findings of the disease). Because cerliponase alfa cannot cross the blood-brain barrier, it has to be administered directly into the intracerebroventricular space. For the Brineura to be administered, a catheter has to be first surgically inserted in the one of the large cerebral ventricles. The catheter is connected to a subcutaneous reservoir into which Brineura is administered at a dose of 300 mg once every 2 weeks as an infusion over 4.5 hours. Cerliponase alfa is the first pharmacologic treatment for CLN2. • Evidence from the Brineura clinical program (which consisted of a single-arm, open-label, clinical trial with an extension) shows that in a 24 patient cohort with CLN2, cerliponase alfa slows down the ineluctable progression of the motor deterioration of disease. Specifically, over 96 weeks of treatment, cerliponase alfa reduced the motor decline when compared to a similar group of 42 untreated CLN2 patients (a historical control). • There are several limitations of the Brineura clinical program which created obstacles in the analysis of the efficacy results. First of all, any comparison to	Brineura provided evidence of effectiveness. Treatment with Brineura over a period of 96 weeks was associated with a slowing in motor deterioration when compared to a reasonably matched external control cohort. Efficacy conclusions are based on multiple analyses conducted in matched patients from the two cohorts, analyses that accounted for confounding differences in baseline patient characteristics. The differences seen at 96 weeks were consistent with, and continued, an efficacy trend observed at two previous timepoints (48 weeks and 72 weeks). The differences between the Brineura and the historical cohort cannot be

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	a historical control poses methodological challenges because the clinical trial group cannot be identical with the historical cohort in all baseline characteristics (e.g., age, type of genetic mutations, etc.). Secondly, the clinician reported outcome (ClinRo) used to compare disease progression between the Brineura and the historical cohort (CLN2 rating scale) used different versions of the ClinRo; furthermore, this ClinRo was implemented differently in the interventional trial and across the historical cohort. • In addition, a longer duration of treatment was necessary to identify a treatment difference. The initial efficacy comparisons at 48 weeks were inconclusive, as were comparisons after 72 weeks of treatment (although an efficacy trend was observed at both timepoints, and more clearly at 72 weeks compared to 48 weeks). FDA requested additional efficacy data, and the 96 week timepoint provided evidence of effectiveness.	reasonably ascribed to differences in the ClinRo versions used (efficacy analyses took into account and attempted to minimize the potential effect of ClinRo differences).
Risk	• The risks associated with Brineura are those associated with the use of the accompanying device (CNS infection, bleeding, mechanical failure, and need to replace the intraventricular catheter/reservoir); hypersensitivity reactions (observed in the clinical trial and treated with appropriate premedication); hypotension (measured frequently but rarely symptomatic; of note blood pressure measurements were not well standardized in the clinical trial); immunogenicity (particularly long-term)	Risks associated with a therapy delivered directly into the intracerebroventricular space are significant. However, given the poor outcome of patients with CLN2, the risk benefit is in favor of the treatment. Approval should be for both the "classic" and "non-classic" forms of CLN2 deficiency, since all forms of CLN2 have the same final outcome (neurological deterioration to a vegetative state and subsequent death).
Risk Management	• The safety risks observed in the clinical trial can be communicated clearly and effectively via physician labeling as WARNINGS AND PRECAUTIONS. • The device to be used is a marketed device in the U.S. • Given that CLN2 patients are rare and seen at highly specialized centers by a	Risk can be managed via appropriate labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	limited group of physicians there is no need for a REMS (DRISK concurs). • The long-term immunogenicity effect of Brineura will be addressed by postmarketing safety studies.	

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1. Background

CLN2 disease and phenotype

Neuronal ceroid lipofuscinosis (NCL) encompasses several progressive neurodegenerative disorders characterized by accumulation of autofluorescent lipopigment in the lysosomes of neural and nonneural tissues. The general phenotype is that of developmental regression, seizures, loss of vision, and premature death. Historically, several broadly defined phenotypes were described: acute infantile, late-infantile, juvenile, and adult. Mutations in multiple genes (as many as 12) have been identified for neuronal ceroid lipofuscinosis.

Neuronal ceroid lipofuscinosis type 2 (CLN2) is the second most common NCL (after CLN3 or Batten disease). It is due to mutations in the CLN2 gene which encodes the lysosomal enzyme tripeptidyl peptidase-1 (TPP1), an exopeptidase responsible for cleaving tripeptides from the N-terminus of proteins. TPP1 has no known substrate specificity. TPP1 encodes a 563-amino acid preproenzyme with a 19-amino acid signal peptide and a 176-amino acid prodomain, both removed during maturation, yielding a 368-amino acid mature enzyme. An absent or functionally deficient (truncated or misfolded) TPP1 results in accumulation of substrates in the lysosomes of the central nervous system (CNS). Two common mutations, the splicing mutation c.509-1G>A and the nonsense mutation c.622 C>T, account for approximately 60% to 78% of all CLN2 mutations. These two mutations will be referred as "key mutations" in this review.

The clinical presentation of CLN2 is that of a classical late-infantile NCL phenotype, with onset of symptoms (generally seizures) typically between ages 2 and 4 years (evidence of delayed speech may precede seizures), followed by a broadening of neurological manifestations to include myoclonus, ataxia impaired speech and swallowing, developmental regression, and loss of visual function. Cognitive and motor regression is relatively rapid and most patients become blind and wheelchair bound by approximately 6 years of age. Death typically occurs between 10 and 16 years of age. There are variations to the above described "classic" form of CLN2, The non-classic CLN2 phenotypes may present earlier or later than the classical form and can be seen in about 20-25% of CLN2 patients.

The incidence of CLN2 has been estimated anywhere between 0.56-4 patients per 100,000 live births in the U.S. and Europe. CLN2 meets the regulatory definition of orphan disease.

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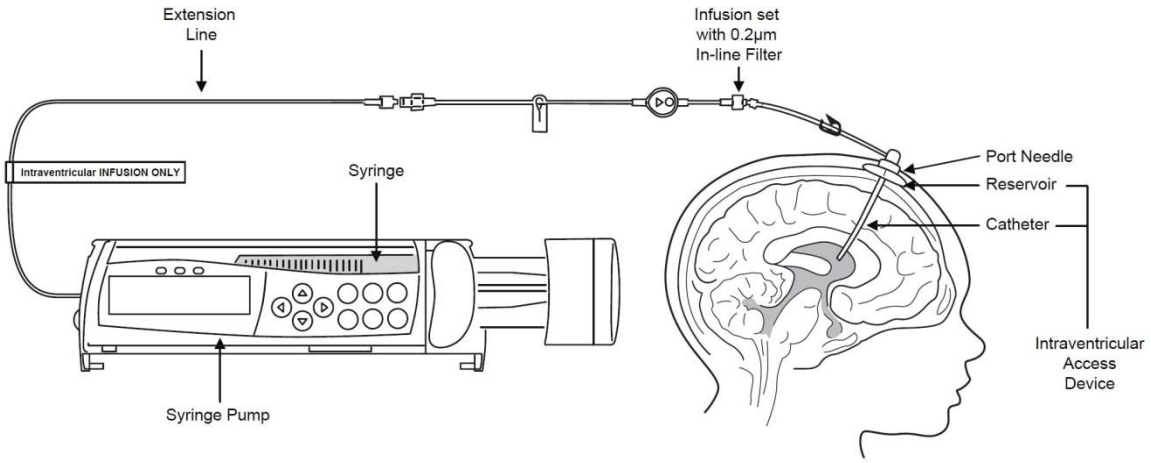
Brineura (cerliponase alfa)

Cerliponase alfa (BMN 190) was developed as an enzyme replacement therapy aiming at restoring TPP1 enzyme activity in the CNS of patients with CLN2 disease, and to attenuate or stabilize the neurological progression of the disease. Cerliponase alfa is recombinant human TPP1 expressed in a Chinese hamster ovary cell line. The purified form is a pro-enzyme of 544 amino acids which is taken up into the lysosome via the cation-independent mannose-6-phosphate receptor (CI-M6P). In the acidic lysosomal environment a 176 amino acid pro-peptide fragment is cleaved yielding the 368 amino acid mature enzyme.

Brineura, was formulated as a 150 mg/5 mL (30 mg/mL) aqueous solution of cerliponase alfa, and is to be administered as a 300 mg infusion once every other week in the intracerebroventricular (ICV) space via an ICV catheter; each administration is followed by an infusion of an electrolyte solution ("Intraventricular Electrolytes") over approximately 4.5 hours. The Intraventricular Electrolytes solution is meant to aid in complete delivery of the drug and to maintain patency of the ICV access device. Both Brineura and the "Intraventricular Electrolytes" are formulated with the same excipients.[1] The administration schematic is reproduced below from the final label:



Importantly, the to-be-marketed product is the same as the clinical trial material.

Brineura is a drug-device combination product. It is co-packaged with the Intraventricular Electrolytes Injection and with an administration kit containing syringes, needles, infusion set with filter, extension and a port needle. 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 pump to be used is the B Braun Perfusor® Space Infusion Pump System.

[1] 0.55 mg sodium phosphate, dibasic, heptahydrate; 0.40 mg sodium phosphate, monobasic, monohydrate; 43.85 mg sodium chloride; 1.10 mg potassium chloride; 0.80 mg magnesium chloride hexahydrate; 1.05 mg calcium chloride dehydrate; and Water for Injection, USP.

BioMarin is seeking an indication of treatment of CLN2 disease. The proposed indication is" "Brineura is a hydrolytic lysosomal N-terminal tripeptidyl peptidase indicated for patients with CLN2 disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency." For the final approved indication refer to the Labeling Section.

Rationale for cerliponase treatment and proof of concept in CL2 animal disease models

The drug development of cerliponase alfa as a treatment for patients with CLN2 benefited from the existence of animal models of CLN2, specifically the TPP1-knockout (KO) mouse and TPP1-null mutation Dachshund dog (discussed in detail in the nonclinical review). Both mice and dogs have greater than 90% amino acid sequence homology for TPP1, and greater than 80% homology for the CI-M6P receptor. Both animal models recapitulate the disease progression of CLN2, in that animals accumulate in neurons the characteristic auto-fluorescent lysosomal storage material, display progressive neurodegeneration, and show a loss of neurological function and reduced lifespan.

According to the nonclinical review, when administered in the central nervous system (CNS) of animals via the ICV or IT route, cerliponase alfa was widely distributed in CNS tissue, and tissue concentrations increased with dose. In both animal species administration of cerliponase alfa to the brain tissues resulted in reduction of lysosomal storage material, improvement in neurological function, and extension of lifespan. There was no effect on the retinal manifestations of the disease.

Regulatory history

The IND for cerliponase alfa was opened in July 2014 with an efficacy and safety study (Study 190-201). At the time of the original IND submission this study had been already initiated, and 12 of the 24 patients were already enrolled at sites in Germany and United Kingdom.

The Brineura (cerliponase alfa) development program was granted orphan drug designation on April 1, 2013. A Breakthrough Therapy Designation request for cerliponase alfa was initially denied, and after submission of additional analyses/data, Breakthrough Therapy Designation was granted on August 27, 2016. The protocol for the open-label extension study (Study 190-202) was submitted in February 2015. These two studies (190-201 and190-202) represent the main source of efficacy and safety data for the Brineura clinical program.

After granting Breakthrough Therapy Designation for cerliponase alfa for the CLN2 indication, multiple meetings took place to develop the Brineura clinical program. Issues of particular interest discussed at these meetings were: the use of the historical control study 190-901; regulatory issues concerning the drug-device combination for the application; and choice of endpoints for the efficacy analyses. Regarding the analyses required for demonstration of efficacy, FDA advised BioMarin that in absence of a concomitant control group, BioMarin should use conservative assumptions in statistical analyses, particularly given the anticipated

differences between the natural history study and the clinical trial patient populations. FDA advised that the primary efficacy analysis be responder analysis. A responder was defined as a patient who has an absence of an unreversed (sustained) 2-category (raw) decline or a score of 0 in the CLIN2 score. At that time, no particular domain (either Motor or Language) was specified.

The BLA was submitted on May 27, 2016 under the Public Health Service Act of the Food, Drug and Cosmetic Act. It was granted Priority Review. The BLA included efficacy data for up to 48 weeks of treatment. During the review of the BLA it became apparent that the efficacy data at the 48 week timepoint was not robust enough to demonstrate a treatment effect. The Agency requested sequentially efficacy data for the 72-week datapoint (the need to analyze these data resulted in a Major Amendment), and 96 weeks (on March 17, 2017). Given the complexity of the data analyses, particularly as they related to statistical issues and demonstration of efficacy, the review team had 33 information requests sent to the applicant. Three Center Director briefings were held for this BLA (December 15, 2016; January 27, 2017; and April 18, 2017).

Brineura received a Rare Pediatric Disease Priority Review Voucher.

Clinical program in CLN2 patients

The Brineura clinical program included one intervention clinical study (Study 190-201) with an extension (Study 190-201) and a historical control study (Study 190-901). Studies 190-201 and 190-202 are continuous and therefore they will be referred to in this memorandum as Study 190-201/202, unless reference is made specifically to one of the two components. There were 24 patients enrolled in Study 190-201 and 23 patients continued in Study 190-202.

Study 190-201 was a single,-arm, open-label efficacy and safety clinical trial. The critical efficacy assessments were based on a clinician reported outcome, the CLN2 rating scale. The natural history study (Study 190-901) included patients from the DEM-CHILD, an independent consortium that collects and analyzes clinical, genetic, and biomarker data in patients with neuronal ceroid lipofuscinosis, including CLN2 patients. Sixty-nine patients were enrolled in Study 190-901. The design of the 190-201/202 study will be discussed in more detail in the Efficacy Section, as will be the patients enrolled in Study 190-901. Key characteristics of the above-listed studies are summarized in Table 1 of the Statistical Review, reproduced below. Of note, while the table refers to CLN2 patients with "mild to moderate CLN2 disease," this should not be interpreted that the patients enrolled have mild-to moderate phenotype; this terminology acknowledges that patients were enrolled in the trial at a stage when the neurological deterioration was less pronounced ("mild to moderate") so that a treatment effect can be assessed; enrollment in a later stage ("severe") would not be expected to provide a real benefit. In a disease such as CLN2, a successful treatment in symptomatic patients is not expected to reverse the disease, but at most to stabilize it.

Table 1: List of Relevant Clinical Studies

Study ID	Phase and Design	Study Population	Treatment Arm(s)	Number of Subjects	Duration

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190-901	Non-treatment natural history control study based on registry data	Any child diagnosed with a type of neuronal ceroid lipofuscinosis (NCL; including CLN2) that has been confirmed through genetic testing	Do not apply	Overall: 69 Evaluable: 42	Range: 2-61 months (based on data entered in DEM-CHILD database)
190-201	Phase 1/2, first-in-human, single-arm, open-label, dose-escalation	Children ≥3 years old with mild to moderate CLN2 disease, and a baseline Motor-Language summary score of ≥3 (with a score of at least 1 in each of the Motor and Language domains)	ICV infusion every 8 weeks: • 30 mg • 100 mg • Stable dose 300 mg	Enrolled: 24 Completed: 23	Stable dose treatment period: 48 weeks
190-202	Treatment extension study for subjects who completed 190-201		ICV infusion every 8 weeks: • 300 mg	23	Stable dose treatment extension period: up to 240 weeks

Source: COA Statistical Reviewer's table

Brineura is not currently being developed for any other indication.

Data analysis challenges

There were several important challenges to reviewing the Brineura clinical trials. First of all, clinical trial 190-201/202 did not include a concurrent comparator, such as a placebo group or a no-treatment concurrent arm. Instead, the applicant decided to identify a historical cohort for efficacy comparisons. BioMarin identified patients with CLN2 in the DEM-CHILD database, and collected clinical information from records and patient interviews in 69 patients. Some of these patients were followed also prospectively but for relatively short periods of time (the majority of the data were retrospective). Not surprisingly, some differences in patient characteristics between the treatment trial and the untreated historical control were identified (see baseline characteristics the table, below). Therefore, an important question in reviewing this application is that of assessing if differences in baseline patient characteristics could have an impact on efficacy comparisons, and how significant such an impact could be. Table 16 of the Statistical Review illustrates the baseline patient characteristics of the two studies. The table describes such characteristics for the patients who were evaluated in the main efficacy analyses (of the 69 patients of Study 190-901 only 42 met the specific matching criteria for direct comparisons with patients from Studies 190-201/202). Three differences were noted: a predominance of male patients in the 190-901 study; a different percentage of patients who had the two typical CLN2 mutations (i.e. a larger proportion with "2 key mutations" in Study 190-901); and a difference in the distribution of the decades of birth (raising the issue that patients born at different times may have received different standard of care treatment). I do not believe that differences in sex are expected to affect in any meaningful way the clinical manifestations or response to treatment in this autosomal recessive condition. With respect to differences in the decade if birth, while standard of care can change with advances in medical care, CLN2 does not

have any effective treatment that may impact the neurological decline of the disease in any meaningful way. The differences in genetic background may be more significant, and will be addressed in the efficacy section (efficacy analyses focused on groups of patients with comparable genetic background, or accounted for such differences in the statistical models employed). The table lists 2 distinct patient groups in Study 201/202: 22/24 vs. all 24 patients enrolled. These are the main efficacy analysis populations.

Table 2. Patient Disposition, Demographic and Baseline Characteristics

	Study 901 (n=42)	Studies 201/202 (n=22)	Studies 201/202 (n=24)
Sex			
Male	25 (**60%**)	7 (**32%**)	9 (**37.5%**)
Female	17 (**40%**)	15 (**68%**)	15 (**62.5%**)
Genotype			
2 key mutations	24 (**57%**)	9 (**41%**)	9 (**38%**)
1 key mutation	11 (26%)	6 (27%)	8 (33%)
No key Mutation	7 (**17%**)	7 (**32%**)	7 (**29%**)
Decade Born			
Pre- 1980	4 (**10%**)	**0**	**0**
1980s	2 (**5%**)	**0**	**0**
1990s	19 (**45%**)	**0**	**0**
2000s	16 (**38%**)	12 (**55%**)	13 (**54%**)
≥2010	1 (**2%**)	10 (**45%**)	11 (**46%**)

Source: the primary statistical reviewer's results

Of similar relevance are differences in the ClinRO instrument that was used to collect data for the primary efficacy comparison and all other relevant comparisons. Efficacy in the clinical program was measured with a ClinRO developed specifically for CLN2 patients. Although the original instrument included four domains (Motor, Language, Visual, and Seizures), only two domains (Motor and Language) were measured in the historical cohort because accurate data could not be collected retrospectively for the other domains. Each domain in the CLN2 rating scale is scored on a 0 to 3 scale. A "3" represents preserved verbal or motor function, while "0" is loss of such function; scores of "1" and 2" represent different degrees of impairment in each domain.

As noted and detailed in the Clinical Outcome Assessment (CoA) review and in the statistical review, there were differences between the ClinRo versions used in the historical control and in the 190-201/202 study, as well as the manner in which the ClinRo was implemented. The CoA

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consult points out, among others, that descriptors in the scales in the natural history cohort and in the interventional study were not identical across all score categories, particularly with respect to the score category of "2." Patients in the interventional trial were scored prospectively by physicians through live assessments, while those in the historical cohort were rated by clinicians both retrospectively and prospectively through a combination of live assessment and secondary sources (medical charts, parental interviews). The schedule of assessments was different in the two studies and thus they did not have the same time points to compare. Finally, Study190-201/202 used additional rating guidelines and training that could not be implemented in the historical cohort due to the mostly retrospective design. Such differences raised important challenges in data analysis (see the CoA and statistical review for analyses and discussions regarding the impact of ClinRo differences on efficacy assessments – particularly Section 3.1.2 CLN2 Rating Scale in the statistical review); refer also to the Risk-Benefit section of this memorandum). For a better understanding of these differences, the Motor and Language domains are reproduced below, Table 3 of the Statistical Review.

Table 3: CLN2 Rating Assessment Guidelines for Study 901 and Studies 201/202

	Study 901		Studies 201 and 202	
CLN2 Rating Assessment Guidelines (RAG)	**Motor**			
	3	Walks normally	**3**	Grossly normal gait. No prominent ataxia, no pathologic falls.
	2	Frequent falls, clumsiness obvious	**2**	Independent gait, as defined by the ability to walk without support for 10 steps. Will have obvious instability, and may have intermittent falls.
	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.
	Language			
	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: some intelligible words, may form short sentences to convey concepts, requests, or needs. 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. Few intelligible words.
	0	Unintelligible or no language	**0**	No intelligible words or vocalizations.

Because the FDA reviewers had reservations regarding the comparability of CLN2 motor and language scores across studies, a Comparability Video Study was conducted by BioMarin at the request of the FDA (See Section 3.15 of the Statistical Review for details). This study identified inconsistent scale ratings in the Language domain, and recommended that the efficacy evaluation should focus primarily on the Motor domain, which has showed acceptable comparability across studies.

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Poor comparability between CLN2 activity scales in the historical cohort and Study 190-201/202 raises important data analysis issues. One concern raised by the CoA reviewers is that given the difference between the CLN2 scale descriptions (see table above) and subsequent different anchor point definitions used in Studies 201/202 and the historical cohort, the same patient could have been rated differently in the interventional and historical control study. For this and similar concerns, the FDA review team requested that the main efficacy analysis use a responder definition according to which a responder will be defined as a patient with an absence of an unreversed (sustained) 2-category (raw) decline or a score of 0 for the Motor domain. The purpose of such an analysis (see also the Efficacy Section) was to ensure that an observed change reflected an actual change, and was not due to differences in the ClinRo version used or to the way it was implemented. As demonstrated in the video comparability study, the majority of rating discrepancies observed in the Motor domain was in the 1-category difference; an analysis using a 2-category difference (e.g. change from 3 to 1 or from 2 to 0) would largely address this concern.

2. Product Quality

The office of Pharmaceutical Quality recommends approval of Brineura. The OPQ review concludes that the manufacture of Brineura "is well controlled and produces a product that is pure and potent." Both the drug substance and the drug product manufacturing sites were inspected (b) (4) and were approved based on inspectional assessment.

For recommendations of postmarketing studies refer to Section 12.

Immunogenicity
Immunogenicity was evaluated in 24 patients in studies 190-201/190-202; the duration of exposure to treatment ranged between 49 and 107 weeks. CSF and serum samples were tested for total anti-drug antibodies (ADA). Neutralizing antibodies (Nabs) were measured only in the CSF and not in serum; none were detected. The ADA assay was reviewed and found to be "adequately validated."

Antidrug antibodies were found in the serum of 19/24 (79%) of patients. Although serum ADA titers were generally low, three subjects had titers approaching or above 100,000. ADAs were first detected between weeks 5-13; the ADA response was either sustained (12/19, 63%), declined (5/19, 26%), or reverted to undetectable levels (2/19, 11%). In the CSF, ADAs were found in 5/24 (21%) of patients; 2 out of 5 ADA positive patients showing sustained antibody levels.

No neutralizing antibodies were detected, however, the assay (a cellular uptake assay) has relatively low sensitivity and as such it is unclear if the absence of detection of neutralizing antibodies reflects the *in vivo* process or the limitation of the assay. The immunology reviewer concludes that "there are no immunogenicity concerns that would preclude approval," and recommends the development of a more sensitive neutralizing antibody assay. For specific

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postmarketing studies refer to Section 12 of this memorandum. I agree with his recommendation.

3. Nonclinical Pharmacology/Toxicology

The nonclinical reviewers conclude that "[t]here are no approvability issues from a nonclinical viewpoint."

The nonclinical pharmacology and toxicology of cerliponase alfa have been characterized in several animal species (mice, dogs, and monkeys). The existence of animal models of CLN2 in mice (TPP1-KO mouse) and dog (Dachshund dog with TPP1-null mutation) has facilitated greatly the understanding of the cerliponase treatment effect. These two biological systems show good homology with humans for the TPP-1 gene and its lysosomal cognate receptor, suggesting conservation of function across species. Importantly, both animal models recapitulate the disease course of CLN2, displaying progressive neuronal degeneration, loss of neurological function, and reduced lifespan. In addition, in both models one sees accumulation in neurons of the characteristic auto-fluorescent lysosomal storage material seen in CLN2 disease in humans.

The observations in animal models regarding CNS tissue penetrance are very informative and may open a window into what may actually happen in patients following administration of cerliponase alfa in the intraventricular space. Following ICV or intrathecal (IT) administration in animals, cerliponase alfa was widely distributed in CNS tissues, with concentrations typically greater in superficial tissues compared to deep tissues. The mean CNS tissue half-life was approximately 2 weeks, and cerliponase alfa concentrations in CNS tissue increased with dose. In addition, immunohistochemical staining confirmed distribution of TPP1 in brain lysosomes. There was a reduction of lysosomal storage material (measured as subunit C of mitochondrial ATP synthase), along with improvement in neurological function, and extension of lifespan. As an example, in mice, cerliponase alfa treatment delayed disease progression and increased median lifespan to 164 days compared to 113.5 days in the vehicle-treated controls and 124.5 days in the untreated controls. There was no effect, however, on the retinal manifestations of the disease. Cerliponase was identified in plasma at a concentration that was 100-1000 times lower than in CSF.

In the Dachshund dog disease model, the effect of cerliponase on survival was evaluated with two doses: 4 mg/kg (0.08 mg/g brain weight given biweekly; 0.3 times the human dose based on brain weight) and 16 mg/kg/dose (0.32 mg/g brain weight given biweekly; 1.1 times the human dose based on brain weight). Lifespan in the Dachshund dog disease model increased by 21-30% at the 4 mg/dose and by 43-46%% at the 16 mg/dose, relative to the vehicle control group. Treatment was initiated at age 9 weeks, before any neurological deficits had appeared.

The adverse effects observed in toxicity studies with cerliponase alfa were limited to hypersensitivity reactions and inflammation associated with the implanted intracerebroventricular catheter. The potential impact of leachable from the vial, vial stopper,

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and/or infusion system was reviewed, and the estimated maximum exposure to individual leachables was judged to be low, and of no great concern.

No carcinogenicity studies were conducted. However, given the rapid clinical decline of CLN2 in children, I agree with the nonclinical reviewers' assessment that the carcinogenic potential of cerliponase alfa appears to be low, and that a carcinogenicity study is not necessary for approval in this rapidly progressive and lethal disease.

The established pharmacologic class (EPC) name proposed by the applicant (hydrolytic lysosomal N-terminal tripeptidyl peptidase) was found to be scientifically valid and acceptable by the FDA reviewers, and is reproduced as such in the final label.

4. Clinical Pharmacology

The clinical pharmacology team concludes that "[f]rom a clinical pharmacology perspective, information submitted to support this BLA is acceptable to support the product labeling."

The proposed dosing regimen and the pharmacokinetics (PK) characteristics of cerliponase alfa were evaluated in Study 190-201/202. Only one dose was assessed for efficacy (300 mg administered every 2 weeks). Because dose escalation was used early on in the trial until tolerability to the 300 mg dose was demonstrated, some PK information could be collected also for two lower doses (30 mg, 100 mg; refer to the Efficacy Section for a description of the design of Study 190-201/202).

The 300 mg dose is the human equivalent dose of the 16 mg dose which was associated with highest increased survival in the Dachshund dogs.

Single and multiple dose CSF and plasma PK data did not suggest any accumulation of cerliponase alfa. Despite the fact that PK for doses lower than 300 mg dose was measured, dose proportionality could not be assessed because of insufficient plasma PK data for the 30 mg and 100 mg doses.

Following single and multiple ICV dose administrations of cerliponase alfa, CSF concentrations peaked at 15 minutes post-infusion (this was also the first PK sampling timepoint) and declined in a biphasic manner with a median half-life of approximately 7 hours. Plasma concentrations peaked at approximately 12 hours after the end of the infusion and declined in a bi-exponential manner. The PK of cerliponase alfa showed high inter-subject and intra-subject variability. Exposure-response relationships for efficacy and safety could not be established in this small dataset. Because no intrinsic or extrinsic factors were identified to impact the cerliponase alfa PK, no treatment individualization recommendations were made by the clinical pharmacology reviewers.

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Regarding immunogenicity, the review team concludes that: "The assessment of the impact of immunogenicity on PK, efficacy, and safety is inconclusive because of the small number of subjects, the measurement of total concentration by the PK assay, high inter- and intra-subject PK variability, and lack of a sensitive neutralizing antibodies (NAb) assay."

5. Clinical Microbiology

The Microbiology Review states that "[t]he drug substance section of the BLA, as amended, is recommended for approval from a microbiology product quality perspective."

6. Clinical/Statistical-Efficacy

I am in agreement with the statistical reviewers who conclude:

> "All the analysis results based on 96-week data support the indication of Brineura (cerliponase alfa) 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 tripeptidyl peptidase 1 (TPP1) deficiency. To further assess the study drug's efficacy by exploring the extent of the efficacy, the primary statistical reviewer performed sensitivity analyses by imputing missing genotype information as different values. Those analysis results are supportive of the efficacy of the study drug."

A summary of the clinical studies in the Brineura clinical program is presented in the Background Section and will not be repeated here. The source of efficacy data for cerliponase alfa is Study 190-201 and its extension, Study 190-202. Study 190-201 used as single-arm, open-label design. It was conducted at multiple centers (Germany, US, UK, Italy). The objective was to assess safety/ tolerability and efficacy of cerliponase alfa in children > 3 years with CLN2 disease. Patients had a clinical diagnosis of CLN2 that was also was confirmed by genetic analysis and/or biochemical assay of enzymatic activity. Patients had to be medically stable, and had to have a combined Motor/Language score of 3-6 on CLN2 activity scale ("Hamburg scale") with a minimum Motor and Language score of 1 in each category. Efficacy was evaluated using a two-domain version of the CLN2 rating scale (Motor and Language domains) after 12 months of treatment; efficacy comparisons were made with data obtained from the historical cohort of Study 190-901.

The design of Study 190-201 is reproduced from the application, below.

Schematic of Study 190-201

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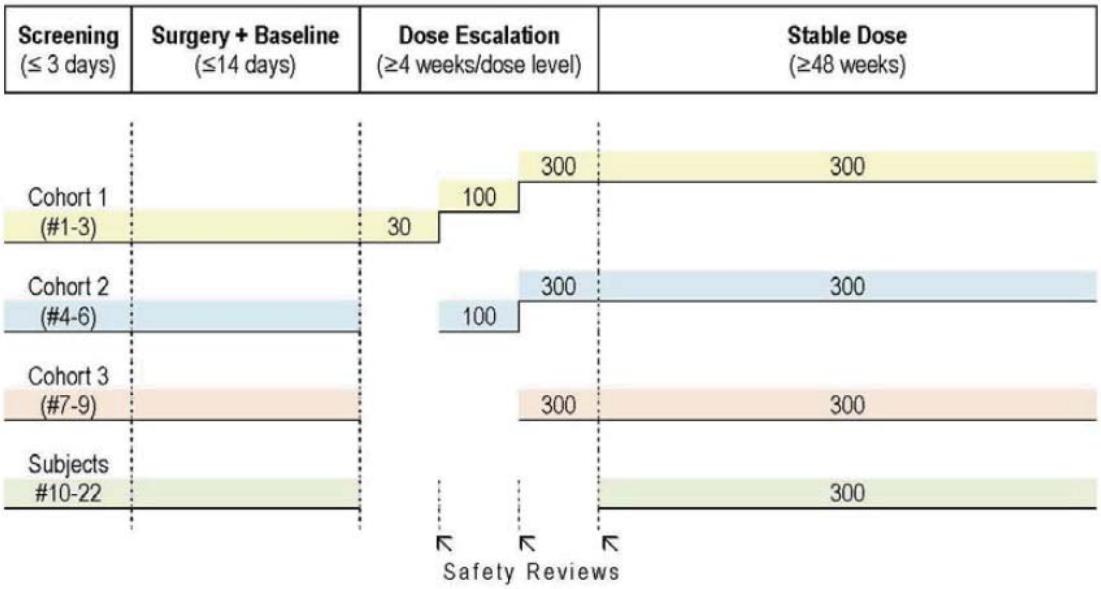

Subjects 1-9 are assigned to three 3-subject cohorts to participate in the Dose Escalation Period. Once this period is completed, all subjects (including Subjects 10 through 22) are administered a stable dose of BMN 190 (300 mg or the highest dose tolerated) every two weeks for at least 48 weeks (Stable Dose Period). During the Dose Escalation period, cohorts are managed independently; enrollment in the next higher dose level follows a safety review by an independent Data Monitoring Committee. A dose level will not be recommended for further use if two or more subjects experience unacceptable toxicity at that dose level. Escalation of cohort starting dose will not be recommended if one or more subject experiences unacceptable toxicity.

Following screening and enrollment, parents underwent surgical placement of an intracerebroventricular (ICV) catheter and after up to 14 days of postsurgical recovery they began cerliponase treatment starting with a 30 mg dose. Dose escalation to 100 mg and 300 mg was gradual and was done with the concurrence of an independent Data Safety Monitoring Committee. The final dose selected for the trial was 300 mg; once it was demonstrated to be well tolerated during the escalation phase, it became the starting dose for the remaining patients. The trial ensured that all patients were treated on a stable 300 mg dose for at least 48 weeks (including the initial escalation period, the trial had a total duration of 12 months). The study enrolled 24 patients, out of which 23 completed 12 months of treatment (one patient withdrew following the first dose).

As detailed in the clinical pharmacology section of this review the 300 mg dose was selected based on the highest dose that resulted in improvement in survival in the animal model (Dachshund dog with TPP1 deficiency). Cerliponase alfa was administered after brief fasting (2 hours). The protocol allowed for the use antihistamines and antipyretics prior to cerliponase alfa administration. Infusions lasted approximately 4.5 hours (occasionally infusions took longer due to hypersensitivity reactions which required additional medications/interventions). The infusion rate (2.5 ml/hour) is about 12% of the natural CSF turnover rate in children 2-5 years of age. The CDRH consultants note that a deviation of as much as ± 1 ml/hour is acceptable to neurosurgeons.

The applicant proposed that the primary efficacy comparison should use the proportion of patients with an absence of an unreversed (i.e. sustained) 2-point rate of decline (slope) or a score of 0 in the Motor-Language total score over 48 weeks. As already described, the FDA CoA and statistical reviewers disagreed with the use of the Language domain of the CLN2 scale given the lack of comparability in how this measurement was used in the intervention and historical studies. Therefore, the Agency focused on the Motor domain only. When the data were analyzed at 48 weeks, the efficacy findings were inconclusive. The Agency requested and analyzed sequentially efficacy data for two additional timepoints: 72 weeks and 96 weeks.

Following multiple discussions with the applicant, a new statistical analysis plan was finally agreed with BioMarin on March 09, 2017, a plan that incorporated Agency's recommendations. The agreed upon analyses included: a "best matching" analysis based on the 96-week timepoint; an ordinal analysis at 96 weeks that also included the 48- and 72-week timepoints for repeated measures analysis; a time to decline analysis (time to decline being defined as unreversed score of zero or a 2-category decline); and a binary logistic regression. It was agreed that these analyses were to be conducted in two patient populations (see Table 15).

Table 3. Two Analysis Populations (Screening Baseline Used for Studies 201/202)

Population #1 (42/22)	All subjects who entered the study with a baseline Motor/Language (ML) CLN2 scale score of 5 or less (N = 22) for Studies 201/202; Study 901 baseline is defined as the time of the first CLN2 assessment at age ≥ 36 months and ML scale score < 6
Population #2 (42/24)	All subjects who entered the study (N = 24). Study 901 baseline is defined as the time of the first CLN2 assessment at age ≥ 36 months (regardless of ML scale score value).

Source: the primary statistical reviewer's table

The FDA statistical reviewers were able to confirm applicant's results. Reproduced below are the best match and time to decline analyses. In the best match analysis patients were matched by baseline motor score, baseline age and genotype (genotype categories were defined as 0, 1 or 2 key mutations). This matching started with 22 patients in Studies 201/202 and 42 in Study 190-901. In case of a 1 to multiple or multiple to 1 match, further matching criteria were applied in the following order: specific genotype; gender; age of first symptom. In the end, 17 best matches were identified using this approach. Table 17 from the Statistical Review shows the analysis results for these best matched pairs at weeks 48, 72 and 96, comparing an unreversed 2-point decline or a score of zero for the Motor domain. The choice of an "unreversed" decline was made to overcome the many measurement issues with the ClinRo and reduce the "noise" created by the occasional observation of decline in score at one assessment followed by a subsequent return (generally such observations in the dataset were observed with one point decline only). An unreversed 2-category decline or a score of zero captured changes in the following numerical categories: 3 to 1, 3 to 0, 2 to 0, and 1 to 0 (of note, a score of zero was a final outcome of neurological/motor deterioration; once a patient reached a sustained score of zero there was no independent ambulation/crawling). According to this analysis there was a progressively larger difference with time, between the treated and historical groups 18%, 29%, and 59% at 48, 72 and 96 weeks respectively. Of note, at week 96, the 95% confidence interval for the odds ratio excludes 1 (this was not observed with shorter exposure of treatments).

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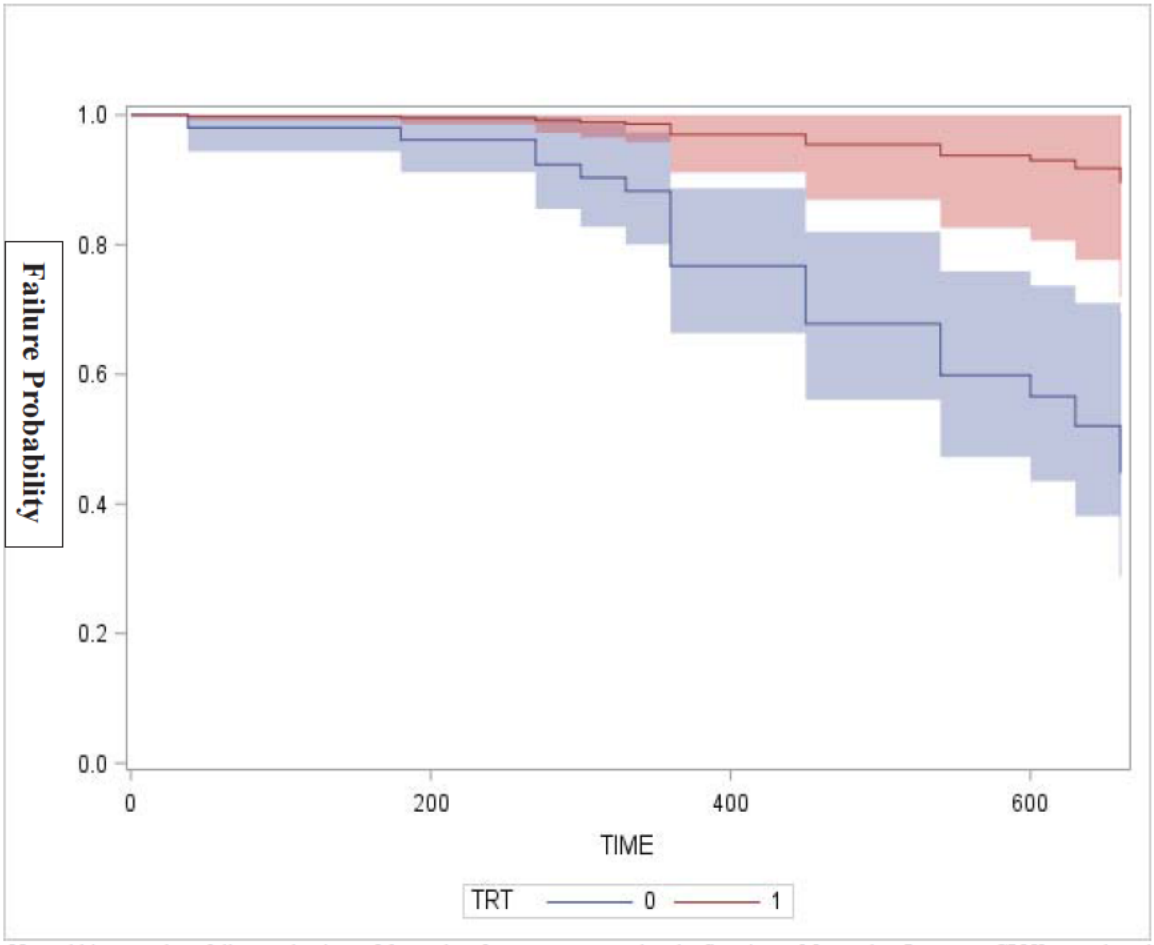
Table 4. Proportion of Patients
(Responder: Unreversed 2-Point Decline or Score of Zero in Motor Domain)

		190-901 (n=17)	190-202 (n=17)	Difference*	Odds Ratio**
	Time Point/Period			% (95% CI)	OR 95% CI
Response rate n (%)	Follow-up through Week 48	13 (76%)	16 (94%)	18% (-19, 51)	0.25 (0.005, 2.53)
	Follow-up through Week 72	11 (65%)	16 (94%)	29% (-7, 61)	0.17 (0.004, 1.37)
	Follow-up through Week 96	6 (35%)	16 (94%)	59% (24, 83)	0.09 (0.002, 0.63)

*confidence interval for odds ratio based on binomial distribution
**confidence interval for odds ratio based on McMemar's Exact test
Efficacy population based on full population minus two patients with baseline CLN2 score =6 (42/22)
Source: the primary statistical reviewer's table

A time to decline analysis using a Cox Proportional Hazards Model adjusted for initial motor score and genotype was used to evaluate time to unreversed 2-point decline or unreversed score of 0 in the Motor domain. It is reproduced below as Figure 6 of the Statistical Review. It displays graphically the separation of Motor domain CLN score over time, up to the 96 week timepoint.

Figure 1. Estimated Time to Unreversed 2-point Decline or Score of Zero in Motor Domain for Pediatric Patients In Single Group Clinical Study 1 and its Extension Up to 96 Weeks Compared to a Natural History Cohort Adjusting for Covariates



Natural history cohort follow up begins at 36 months of age or greater and at the first time a Motor plus Language CLN2 score less than 6 was recorded. The Brineura treated population is the full population (N=24) minus the two patients with baseline Motor plus Language CLN2=6

Covariates screening motor score and genome: 0 key mutations

Decline is defined as an unreversed (sustained) 2-point decline or unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale

Source: the primary statistical reviewer's figure

7. Safety

The safety review for this BLA is attached as an Appendix to this memorandum. It is based on Dr. Elizabeth Heart's preliminary review, finished by Dr. Victor Baum. An additional source of information for safety was Dr. Hart's presentation to the first two Center Director briefings.

The safety of Brineura was evaluated in 24 patients with CLN2 treated for one year and followed throughout the 120-day Safety Update.

There were no deaths in the trial and no discontinuations due to adverse events. Only one patient withdrew from the trial; this happened after receiving a single 300 mg dose of the study drug because of concerns related to the ability to comply with study procedures. This patient had complications following device placement (intracranial hemorrhage, device migration into the right foramen of Monro, and acute hemiparesis with complete recovery). While it is conceivable that these device-related complications may have influenced this patient's decision to discontinue participation in the trial, it should be noted that they were not related to Brineura itself.

The vast majority of SAEs observed in the Brineura clinical program were either device-related or hypersensitivity reactions occurring with the infusion of the product. A total of 52 SAEs were reported in 19 (79%) of subjects during studies 190-201/190-202 (32 SAEs during Study 190-201 and 20 SAEs during Study 190-202; 9 patients experienced a single SAE and 10 patients experienced more than one SAE (the largest number of SAEs in a single patient was eight). Of these, only 11 SAEs (in 8 subjects) were assessed as "related" to Brineura by the study investigators. Most SAEs were classified as hypersensitivity or infusion related reactions; (9 were mapped to the immune system disorder and 2 were mapped to procedural complications).

While every patient experienced at least one treatment-emergent adverse event for the duration of the trial, the following safety observations deserve special consideration: hypersensitivity reactions, device-related adverse events and abnormal blood pressure measurements.

Device-related adverse reactions

Nine subjects had a total of 20 device-related AEs (needle issues, pleocytosis, and device leakage). There were 2 SAEs (in 2 subjects) that were assessed as device-related by the investigators: propionibacterium (1) and staphylococcus epidermidis (1) CSF infections (both skin commensals), which required hospitalization, IV antibiotics, and removal/replacement of the ICV access device.

Device-related adverse events are not surprising given the complexity of administration of a drug directly into the intracerebroventricular space. They evoke similar complications seen with devices used for the treatment of increased intracranial pressure in children (device obstruction, migration, infection). Appropriate neurosurgical technique and expertise with accessing the subcutaneous reservoir are expected to minimize the occurrence of device-related adverse events. The Brineura label is very specific regarding the description of which device and infusion pump should be used for Brineura administration (both the device and the pump are currently marketed in the U.S.), as well as the appropriate infusion technique; it reflects the specific experience accumulated in the clinical program with these devices. Complications related to the intraventricular device and steps to reduce the risk of such complications are discussed in the WARNINGS AND PRECAUTIONS section of the label (it also provides approximate limits for device integrity following repeated needle punctures for access). The CONTRAINDICATIONS section clarifies that administration of the drug should not continue if there is evidence that calls into question the device integrity.

Hypersensitivity/infusion reactions
Eleven hypersensitivity AEs occurring within 24 hours of Brineura infusion were identified through the 120-day safety update. Nine were classified as SAEs because they resulted in prolongation of hospitalization. There were no AEs identified as anaphylaxis reactions. The most common signs and symptoms observed to occur at the time of hypersensitivity reactions included pyrexia, vomiting, or irritability. Patients were routinely pre-medicated with antihistamines, and also with antipyretics or corticosteroids prior to some of the Brineura infusions. Hypersensitivity reactions are highlighted in the current label as a WARNING AND PRECAUTION. The label emphasizes that appropriate medical support should be readily available when Brineura is administered, that patients need to be closely monitored during and after the Brineura infusion, and that appropriate steps should be taken in case of an anaphylactic event (i.e. discontinuation of the infusion and medical treatment).

Abnormal blood pressure measurements
Hypotension was reported as an adverse event in 2 (8%) patients, and occurred during or up to eight hours after Brineura infusion. These events resolved spontaneously or after intravenous fluid administration.

All subjects developed diastolic hypotension during an infusion at least once, according to the following definitions: decrease of at least 20% (82% of infusions), <45 mmHg (74% of infusions), <40 mmHg (49% of infusions), or <5th percentile for age, sex and height (39% of infusions). There were no reports of symptomatic hypotension associated with these low diastolic measurements. There were issues with the standardization of the methodology used for measuring blood pressure. It seems reassuring that the actual clinical events associated with these measurements were infrequent. The current WARNINGS AND PRECAUTIONS section of the label highlights this risk and the need for adequate blood pressure monitoring.

ECG evaluations identified at least one abnormal ECG finding in 50% of patients who had normal ECGs at baseline. All ECG changes were deemed to be not clinically significant, and none indicated prolongation of QT interval. Of note, no pathologic rhythm abnormalities were observed during a repeat dose study in TPP-1-null Dachshund dogs (study BMN190-12-027). In addition, it should be recognized that Brineura is administrated intracerebroventricularly and the serum concentration of cerliponase is low relative to then CSF concentration in both humans and animals. It seems prudent, however, to have ECG monitoring for patients with evidence of conductive disorder or structural heart disease; the current label contains such a recommendation for ECG monitoring.

8. Advisory Committee Meeting

There was no Advisory Committee Meeting. All scientific and methodological review issues regarding the Brineura clinical program were clarified and addressed by the different review teams.

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9. Pediatrics

Brineura received Orphan Drug Designation. PREA does not apply to this application.

10. Other Relevant Regulatory Issues

CDRH Consult

A review of the device constituent parts co-packaged with cerliponase alfa in Brineura was provided by the General Hospital Devices Branch of CDRH. The CDRH reviewers recommend approval of the device constituent parts of the Brineura combination product. They also recommend a postmarketing study (refer to Section 12 of the memorandum, Study 203).

The CDRH consult reviewed 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.

CDRH identified no issues with the design review, design verification, biocompatability, or sterility. The CDRH clinical reviewer had concerns about the use of a 22g access device needle rather than the recommended 25g needle as they relate to the membrane integrity of the subcutaneous reservoir after repeated needle punctures, a concerned shared by CDER's clinical reviewers.

At the request of CDRH/ CDER clinical reviewers, the Applicant studied *in vitro* the device integrity after multiple punctures with the 22g needle, by air pressure leak and by scanning electron microscopy. Results showed that the ICV access device can be perforated to an equivalent of approximately 4 years of use, without compromising the functionality of the access device. These results support the use of the gripper port needle as part of the Brineura Administration Kit and this has information been incorporated into the product label.

Potential design failure modes were identified and a probability of occurrence was assigned to each. None of the risks identified was categorized as high risk. CDRH categorized several potential failure modes as medium risk. Adequate risk control measures to minimize risk were identified.

The CDRH reviewers made several recommendations to improve labeling and these were incorporated into the final label. These included:

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- Withdrawal of CSF prior to each administration of Brineura for bacterial culture to detect subclinical device infections.

- Information that the ICV device reservoir may degrade and require replacement after approximately 105 perforations (approximately 4.3 years of routine use).

Office of Scientific Investigation Consults

The OSI review concludes:

> 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. In addition, following the issuance of the Major Amendment, OSI verified of the genotype results for subjects analyzed in Studies 901-201 and Study 901-109; OSI also verified the CLN2 motor and language scores for Study 901-202 that were submitted in the major amendment. No issues that would preclude reliance on the data were identified.

DPMH Consult

Labeling recommendations from DPMH were incorporated into the labeling.

11. Labeling

A final labeling has been agreed at this stage, and includes recommendations made by multiple FDA reviewers and contributors. Important elements include:

- The indication describes the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2; this description reflects the only efficacy component that could be assessed comparatively in the clinical program.
- There are no limitations of use to the indication.
- Although most patients included in the clinical trials had a phenotype of classic CLN2, there is no reason to restrict the indications given that the non-classic CLN2 is very similar and has the same unfavorable final outcome (neurological deterioration, progression to vegetative state, and death)

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- CONTRAINDICATIONS are limited to the presence of VP shunts, or to evidence of device malfunction, infection, or failure.
- The WARNINGS AND PRECAUTIONS section reflects the adverse events described in the safety section of the review (device-related, hypersensitivity reactions, and hypotension). There is no need for a BOXED WARNING.
- Given the fact that the treatment is administered under physician supervision, there is no need for a Medication Guide.

12. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

The Division of Risk Management (DRISK) evaluated whether a risk evaluation and mitigation strategy (REMS) is necessary for Brineura and concluded that a REMS is not necessary. I agree.

- Other Postmarketing Requirements and Commitments

The following postmarketing requirements and commitments have been discussed and agreed with the applicant:

- 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.
- 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.
- 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 a lysosomal environment.
- 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.

- 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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Appendix 1

Safety Review – Completed by Drs. Elizabeth Hart and Victor Baum

8.1 Safety Review Approach

The safety review is based on adverse events reported during studies 190-201 and 190-202 at the time of BLA submission, the 120 day Safety Update (through June, 2016) and assessments of information requests during the review process. The safety population is comprised of the 24 subjects who received at least one dose of Brineura during study 190-201. Three additional subjects are included from study 190-203 (a sibling protocol). Studies 190-201/202 are single-arm trials so it can occasionally be unclear whether specific adverse events are due to the underlying disease process or from the study drug or device. For example, subject 0146-1023, a 5 yo Caucasian non-Hispanic female, developed a subdural hematoma. The applicant assessed this as unrelated to the device, and related to vessel rupture from brain shrinkage as a natural consequence of disease progression.

Prior to the initiation of human studies of Brineura, infusion associated reactions (IAR), hypersensitivity and anaphylaxis, were identified as key safety issues as they commonly occur with enzyme replacement therapy (ERT) and can be life-threatening. In the non-clinical toxicology studies, anaphylactoid-type reactions and plasma and CSF anti-drug antibodies were seen in the repeat dosing of dachshund dogs, although human proteins can be immunogenic in other species and not in humans, limiting relevance to clinical studies. Other adverse events of special interest are device related complications.

8.2 Review of the Safety Database

8.2.1 Overall Exposure

The safety population is comprised of all subjects who received at least one dose of Brineura in studies 190-201 and 190-202. In addition three subjects in trial 190-203, an expanded use protocol, were reported in the 120 day Safety Update. No healthy subjects or patients with other conditions have received this drug.

At the time of BLA submission, 24 subjects in studies 190 201/202 had received Brineura for 0.1 to 107.6 weeks (see Table 1), with a per subject cumulative dose of 300 mg to 14,180 mg. The maximum duration any subject received 300mg of Brineura was 91 weeks. Following upward dose titration, all subjects received recurrent doses of 300 mg. The median duration subjects received any dose and the 300mg dose was 61 weeks. One subject withdrew after a single dose; the remainder of subjects received 300 mg every two weeks for at least 48 weeks [Additional efficacy data through 96 weeks of treatment were submitted by the applicant during the review process.] Safety data are reviewed through the 120 day Safety Update.

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The safety update, which had a data cut of June 3, 2016, was submitted on September 23, 2016. It includes a median of 30 weeks (26-32) of additional safety data from 23 subjects enrolled in the extension study 190-202. The Applicant also provided safety data from study 190-203, which included 3 subjects treated with 300mg Brineura every 2 weeks for 13-16 weeks. At the time of this review, no safety data were submitted from the treatment expanded access study, 190-502.

Table 1. Duration of Exposure to Brineura after Safety Update

	≥1 day	≥48 weeks	≥ 96 weeks
Any Dose	n=27	n=23	n=12
300mg Dose	n=27	n=23	n=12

8.2.2 Relevant characteristics of the safety population:

The safety population includes the 24 children treated with Brineura in study 190-201. There were 9 boys (38%) and 15 girls (63%). The mean age at first dose of Brineura was 4 years (range 3 to 8 years). The majority (92%) of these children were non-Hispanic Caucasians; there was 1 Hispanic (4%) and 1 Asian (4%) subject. All subjects in the safety database were included in the enrollment population of the efficacy study.

8.2.3 Adequacy of the safety database:

Reviewer Comment: The safety database is very small, based on 24 subjects. However, this appears to represent approximately 10% of the estimated population of patients with CLN2 in the U.S., as estimates indicate that there are about 250-350 patients in the United States with CLN2. Typically for rare disease, a safety database of 1-10% of the disease population is preferable for detecting important safety signals (O'Connell 2014)[1]. While the FDA agreed to review the BLA application as long as it included 12 months of safety data from subjects enrolled in study 190-201, it is possible that important safety signals will not be detected based on the small safety population and limited duration. Effects of drug-drug interactions cannot be detected based on this small safety population.

The safety database is further limited since it includes only subjects between 3-8 years of age who have mild to moderate CLN2. Therefore, there are no safety data on risks in younger patients, children less than 14.5 kg, end-stage disease patients with underlying complications, or patients with other forms of CLN2 disease including infantile NCL and juvenile NCL due to mutations in CLN2.

None of the subjects in the safety database had underlying renal dysfunction, hepatic dysfunction, or cardiac conduction abnormalities; the effect of Brineura in these populations is unknown. Conduction abnormalities are commonly reported in juvenile NCL patients and have been reported in older CLN2 patients.

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Lastly, the maximum exposure is limited to the study duration, yet the Applicant is seeking approval for the drug to be administered throughout these patients' lifetimes. The current safety database does not adequately assess for very long-term complications.

We believe that the safety database will require supplementation via postmarketing studies.

8.3 Adequacy of Applicant's Clinical Safety Assessments

8.3.1 Issues Regarding Data Integrity and Submission Quality

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Safety data were limited by the small population size and the lack of a concurrent control group. Interpretation of safety results was also limited due to missing data (including baseline values), brief narratives about adverse events (AEs), and heterogeneity with respect to classification of AEs. There was substantial variation in how investigators at sites classified AEs. For example, at the German site only 17% of subjects were classified as having seizures and 92% were classified as having epilepsy whereas at all other sites 100% of subjects were classified as having seizures and 0% were classified as having epilepsy.

Seizures (and epilepsy) were reported as AEs and treatment-related AEs. All subjects who had seizures had additional anti-seizure medications or increases in anti-seizure medications during the trial that could have masked the impact of the drug/device on seizure incidence.

Multiple children were premedicated prior to drug infusions. This could have masked the true incidence of hypersensitivity reactions.

8.3.2 Categorization of Adverse Events

The Applicant defined AE as "any untoward medical occurrence (e.g. sign, symptom, illness, disease or injury) in a subject administered study drug or other protocol intervention, regardless of attribution." AEs were recorded following ICV implantation and up to 6 months following the last administration of study drug or early termination visit. AEs were followed until they resolved, stabilized, it was determined that the study treatment or participation was not the cause of the AE or the subject was lost to follow-up. Severity of AEs was defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events v.4 (CTCAE) and events without a corresponding CTCAE term were defined by the following guidelines:

Grade	Description
1	Mild; asymptomatic or mild symptoms; intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate ADL
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization; disabling/limiting self care ADL
4	Life threatening or debilitating; urgent intervention required
5	Death related to AE

The Investigator assessed whether the AEs appeared to be related to the study drug or study device. The Applicant defined "related" as being reasonably related in time and with a reasonable possibility that the event may have been caused by exposure to the study drug/device.

The Applicant defined serious adverse events (SAE) as a medical occurrence that is fatal, life threatening (placing the patient at immediate risk of death), requires or prolongs inpatient hospitalization, results in persistent or significant disability or incapacity or a congenital anomaly or birth defect (in a child or fetus exposed to the study drug before pregnancy or conception), or an important medical event or reaction (status epilepticus, hydrocephalus, meningitis, hypersensitivity, IAR and rapid decline on CLN2 scale not attributed to other causes) deemed to

be serious by the Investigators. Hospitalizations required to perform study procedures were not considered SAE. All SAE were reported following implantation of the ICV until 6 months after the final dose of study drug or early termination visit, and if a SAE was associated with a protocol imposed intervention it was reported between informed consent and implantation of the ICV device.

All AEs prior to the 120 day safety update were coded using the MedDRA, version 18.1. The data from the 120-day safety update is based on MedDRA, version 19.0. Hypersensitivity AEs were defined by "hypersensitivity" standardized MedDRA query SMQ or "anaphylactic reaction" SMQ. IAR were defined as AE occurring within 24 hours of start or restart of study drug infusion.

8.3.3 Routine Clinical Tests

Safety assessments included vital sign assessments, physical examinations, electrocardiograms (ECGs), electroencephalograms (EEGs), laboratory testing, and immunogenicity testing. The 190-201 and 190-202 protocols specified that vital signs should be collected 30 minutes prior to drug infusion, every 15 minutes during infusion and then every 30 minutes for an hour after the infusion. Following the first dose and after a dose escalation vital signs were also collected every hour for hours 2-4 following infusion and every 4 hours until 24 hours following infusion. The protocols specified that a complete physical examination should be performed at baseline, end of study 190-201 and then every 12 weeks; when a complete physical examination was not performed, a limited physical examination focused on general appearance, cardiovascular, respiratory, gastrointestinal and neurologic systems would be performed every 2 weeks. The protocols specified that awake EEGs should be performed at baseline and then every 24 weeks and 12-lead ECGs should be performed at baseline and then every 24 weeks for the first 48 weeks and then every 12 weeks. Chemistry, hematology and urinalyses should be performed in all subjects prior to first infusion, 24 hours after infusion, and when applicable before and 24 hours after dose modification, and then approximately every 4 weeks. The protocols also specified that serum total anti-TPP1 antibody (TAb) and CSF TAb and neutralizing anti-TPP1 antibody (NAb) should be collected prior to the first infusion and then approximately every 4 weeks during study 190-201. CSF TAb would then be collected every 12 weeks and CSF NAb only be collected every 12 weeks in subjects who have positive CSF TAb. Drug-specific IgE levels, serum C4, and serum tryptase should be measured at the end of study 190-201 and at any time-point during the study within 1 hour of a suspected serious hypersensitivity event, a grade 3-5 severe hypersensitivity event, or a suspected anaphylaxis reaction. Following a potential hypersensitivity reaction, 8 hours afterwards to 2 weeks later, serum C4, serum tryptase and IgE levels should be measured should be collected from blood 8 hours after the event and prior to the next infusion. The schedule of assessments is summarized below in Table 2.

Table 2. Schedule of Assessments

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Assessments and Events	Screening [a] (≤ 3 days prior to ICV Surgery)		Baseline visit Prior to First Dose	First Infusion (Days 1-6) Week 1 Study Day						During Dose Escalation Period (prior to next escalation)	Dose Modification Infusion (Days 1-6) Week 1 of Each Escalation Study Day						Stable Dose Period (Procedures repeated at the start of the Stable Dose Period)	Study Completion / Early Termination	Safety Follow-Up
			≤2 Days	1	2	3	4	5	6	Visit every 2 weeks	1	2	3	4	5	6	Visit every 2 weeks (±3 days)	Proximity to last dose (±3 days)	6 months after last dose ±1week
Informed consent/assent [a]	X	ICV Surgery and Recovery (≤14 days) [w]																	
Diagnosis [b]	X																		
Genotype [b]			X [b]																
TPP1 Activity (dried blood spot) [c]			X																
CLN2 disease rating scales with videotaping [d]	X		X				X			Q4W				X			W1 then Q8W	X	
Criteria for study entry	X																		
ECG, 12-lead [e]			X	X							X						W1 then Q24W	X	X
EEG, standard awake [f]			X								X						W1 then Q24W	X	X
MRI [g]	X		X							Q8W							W1, W9, W25, W49	X	
CSF (cell count, protein, glucose) [n]				X					X	X	X					X	X	X	X
Administer study drug				X						X	X						X		
Phone follow-up [i]										X							X		
CSF/plasma for Serial PK [j]				X [j]							X [j]						Weeks 5, 13		
CSF/Plasma for Trough PK [k]																	W1 then Q4W	X	X
CSF/plasma for biomarkers [l]				X						Q12W							W1 then Q12W	X	
CSF/serum for immunogenicity [m]			X							Q4W							W1 then Q4W	X	X
Vital signs [n]				X	X					X	X	X					X	X	X
Complete physical examination [o]	X		X								X						Week 1	X	X
Brief physical examination [p]				X						X		X					X		
Blood/urine for clinical lab tests [q]			X		X					Q4W	X	X					W1 then Q4W	X	X
QOL survey [r]			X														W1 then Q12W	X	
Denver II Developmental Scale [s]			X														W1 then Q24W	X	
Pregnancy testing [t]	X																		
Adverse events [u, v]	X		continuous monitoring																
Concomitant medications	X		continuous monitoring																

QOL, Quality of Life

Source: BLA 761052 Study Report Body Study 190-201, Table 9.5.1.1, page 72/1800.

For full definitions of superscripts see original table

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Reviewer Comment: We do not believe that the EEGs are fully interpretable as there were no videos, so clinical correlation is not possible. This conclusion is supported by the consult from Dr. Buracchio in the Division of Neurology.

8.4 Safety Results

8.4.1 Deaths

No subjects died during the course of the clinical development program.

8.4.2 Adverse Events (AE)

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%). The most common AEs are listed in Table 3.

Table 3. Adverse Events Occurring in ≥ 20% of Subjects by System Organ Class and Preferred Term (Safety Population, Total Dosing Period) in Studies 190-201 and 190-202

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System Organ Class/Preferred Term	Overall (n = 24)
Subjects with at Least 1 Reported AE	**24 (100%)**
Gastrointestinal disorders	**19 (79%)**
Vomiting	13 (54%)
Constipation	8 (33%)
Diarrhea	5 (21%)
General disorders and administration site conditions	**20 (83%)**
Pyrexia	16 (67%)
Gait disturbance	7 (29%)
Immune system disorders	**10 (42%)**
Hypersensitivity	9 (38%)
Infections and infestations	**24 (100%)**
Upper respiratory tract infection	12 (50%)
Nasopharyngitis	7 (29%)
Gastroenteritis	6 (25%)
Pharyngitis	6 (25%)
Rhinitis	6 (25%)
Viral infection	6 (25%)
Injury, poisoning, and procedural complications	**19 (79%)**
Fall	7 (29%)
Nervous system disorders	**24 (100%)**
Seizure	14 (58%)
Epilepsy	11 (46%)
Myoclonus	7 (29%)
Tremor	6 (25%)
Dystonia	5 (21%)
Generalised tonic-clonic seizure	5 (21%)
Respiratory, thoracic, and mediastinal disorders	**8 (33%)**
Cough	6 (25%)

Subjects experiencing more than one AE within a given MedDRA system organ class or preferred term were counted only a single time within that organ class or preferred term.
Source: BLA 761052 Summary of Clinical Safety, Table 2.7.4.2.1.1.1, page 11 of 42

Twenty-three subjects (96%) had treatment-related AEs as assessed by the Investigator. The most common were pyrexia (46%), hypersensitivity (38%), seizure (38%) and epilepsy (17%). According to the Applicant's analysis, all subjects experienced at least one treatment emergent adverse event (TEAE) during the study, but only 96% of subjects had a treatment related adverse event (TRAE). TRAE are listed by in Table 2. Treatment-related AEs are shown in Table 4.

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Table 4. Treatment-related AEs

System Organ Class/Preferred Term	190-201/202 (n=24)		190-203 (n=3)	
	Events	Incidence	Events	Incidence
Subjects with at Least 1 Reported Treatment-Related AE[a]	**175**	**23 (96%)**	**2**	**2 (67%)**
Cardiac disorders	**1**	**1 (4%)**		
Bradycardia	1	1 (4%)		
Gastrointestinal disorders	**17**	**6 (25%)**		
Vomiting	10	3 (13%)		
Abdominal pain	2	1 (4%)		
Gastrointestinal disorder	1	1 (4%)		
Nausea	1	1 (4%)		
Oral mucosal blistering	2	1 (4%)		
Tongue blistering	1	1 (4%)		
General disorders and administration site conditions	**92**	**12 (50%)**	**1**	**1 (33%)**
Pyrexia	86	11 (46%)	1	1 (33%)
Feeling jittery	4	2 (8%)		
Gait disturbance	1	1 (4%)		
Pain	1	1 (4%)		

Immune system disorders	**15**	**9 (38%)**	**1**	**1 (33%)**
Hypersensitivity	15	9 (38%)	1	1 (33%)
Infections and infestations	**2**	**2 (8%)**		
Conjunctivitis	1	1 (4%)		
Upper respiratory tract infection	1	1 (4%)		
Injury, poisoning and procedural complications	**3**	**1 (4%)**		
Infusion related reaction	3	1 (4%)		
Investigations	**1**	**1 (4%)**		
CSF test abnormal	1	1 (4%)		
Nervous system disorders	**36**	**18 (75%)**		
Seizure	14	9 (38%)		
Epilepsy	4	4 (17%)		
Headache	6	3 (13%)		
Myoclonus	2	2 (8%)		
Atonic seizures	2	1 (4%)		
Dropped head syndrome	1	1 (4%)		
Dyskinesia	2	1 (4%)		
Dystonia	1	1 (4%)		
Generalised tonic-clonic seizure	1	1 (4%)		
Partial seizures	1	1 (4%)		
Pleocytosis	1	1 (4%)		
Tremor	1	1 (4%)		
Product issues	**2**	**2 (8%)**		
Device leakage	1	1 (4%)		
Needle issue	1	1 (4%)		
Psychiatric disorders	**3**	**2 (8%)**		
Irritability	1	1 (4%)		
Staring	2	1 (4%)		
Skin and subcutaneous tissue disorders	**3**	**2 (8%)**		
Rash	2	1 (4%)		
Urticaria	1	1 (4%)		

Subjects experiencing more than one AE within a given MedDRA system organ class or preferred term were counted only a single time within that organ class or preferred term
Source: BLA 761052 120 day Safety Update Table 5.2.3.1., page 57 of 2556

Reviewer Comment: Categorization of events as either seizure or epilepsy was inconsistent among investigational centers.

8.4.3 Serious Adverse Events (SAE)

At the time of BLA submission, based on the Applicant's classification of AEs, there were 45 SAEs reported in 19 (79%) of subjects during studies 190-201 and 190-202, including 32 SAEs during study 190-201 and 13 SAEs during study 190-202. Nine patients experienced a single SAE and 10 patients experienced > 1 SAE. The largest number of SAEs in a single patient was eight. The number of reported SAEs increased to 52 in the 120 day Safety Update (32 SAEs for study 190-201 and 20 for 190-202).

Only 11 of the SAEs (in 8 subjects) were assessed as related to Brineura by the study investigators. These SAE were all classified as hypersensitivity or infusion related reactions; (9 were mapped to the immune system disorder and 2 were mapped to procedural complications). The distribution of SAEs (prior to the 120 day Safety Update) are shown in Table 5, below.

Table 5:SAEs

System Organ Class/Preferred Term	Overall (n = 24)	
	Events	Incidence
Subjects with at Least 1 Reported SAE	**45**	**19 (79%)**
Infections and Infestations	**17**	**12 (50%)**
Pharyngitis bacterial	3	2 (8%)
Gastroenteritis	2	2 (8%)
Adenoviral upper respiratory infection	1	1 (4%)
Clostridium difficile colitis	1	1 (4%)
Corona virus infection	1	1 (4%)
Device related infection	1	1 (4%)
Influenza	1	1 (4%)
Pharyngitis	1	1 (4%)
Pneumonia	1	1 (4%)
Propionibacterium infection	1	1 (4%)
Rhinovirus infection	1	1 (4%)
Skin infection	1	1 (4%)
Upper respiratory tract infection	1	1 (4%)
Viral pharyngitis	1	1 (4%)
Immune System Disorders	**9**	**7 (29%)**
Hypersensitivity	9	7 (29%)
Nervous System Disorders	**8**	**6 (25%)**
Epilepsy	3	2 (8%)
Haemorrhage intracranial	1	1 (4%)
Hemiparesis	1	1 (4%)
Motor dysfunction	1	1 (4%)
Seizure	1	1 (4%)
Status epilepticus	1	1 (4%)
Respiratory, Thoracic and Mediastinal Disorders	**3**	**2 (8%)**
Adenoidal hypertrophy	1	1 (4%)
Sleep apnoea syndrome	1	1 (4%)
Tonsillar hypertrophy	1	1 (4%)
Injury, Poisoning and Procedural Complications	**3**	**2 (8%)**
Infusion related reaction	2	1 (4%)
Subdural haematoma	1	1 (4%)

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Gastrointestinal Disorders	**2**	**2 (8%)**
Dental caries	1	1 (4%)
Dysphagia	1	1 (4%)
General Disorders and Administration Site Conditions	**2**	**2 (8%)**
Pyrexia	2	2 (8%)
Reproductive System and Breast Disorders	**1**	**1 (4%)**
Vaginal discharge	1	1 (4%)

Subjects who experience more than 1 AE within a given MedDRA system organ class or preferred term were counted once in the incidence column within that system organ class or preferred term.
Source: BLA 761052 Summary of Clinical Safety, Table 2.7.4.2.2.2.1, page 17 of 42

The 120-day safety update included 9 additional SAEs in 8 subjects; 6 from study 190-202 and 2 from study 190-203. These events are summarized in Table 6.

Table 6. Additional SAEs in by Preferred Term in the 120 day Safety Update

SOC/PT for SAE	Study 190-202 (n=23)		Study 190-203 (n=3)	
	Number of SAE	**Incidence of Subjects with SAEs**	**Number of SAE**	**Incidence of subjects with SAEs**
At least 1 SAE	7	6 (27%)	2	2 (67%)
Infections and Infestations	5	5(22%)	0	0
Gastroenteritis	1	1 (4%)	0	0
Propionibacterium infection	1	1 (4%)	0	0
URI	3	3 (13%)	0	0
Immune System Disorders	0	0	1	1 (33%)
Hypersensitivity	0	0	1	1(33%)
General Disorders & Administration Site Conditions	0	0	1	1 (33%)
pyrexia	0	0	1	1 (33%)
Metabolism & Nutritional Disorders	1	1 (4%)	0	0
Acidosis	1	1 (4%)	0	0
Product Issues	1	1 (4%)	0	0
Device deployment issue	1	1 (4%)	0	0

SOC, System Organ Class; PT, Preferred Term. Mapping based on MedDRA v. 19.0
Source: BLA 760152 120 day Safety Report Table 5.2.4.1, page 60 of 2556

All SAEs in study 190-202 were assessed by the investigators as not related to the study drug. However, the Applicant classified two of the events, propionibacterium infection and a device

deployment issue, as being device related. These events occurred at different times in the same patient, who experienced the ICV infection with propionibacterium discussed above. The narratives of these events are included below.

- Subject 1323-1015, a 3 yo Caucasian non-Hispanic female: On day 395 a device culture was positive for *Propionibacterium acnes* and the subject was hospitalized and the device was removed the following day. The device had most recently been replaced 6 months prior due to a *Propionibacterium acnes* infection. The current infection was detected on routine surveillance (CSF protein 11.3 and WBC 32) [the submitted data are not clear whether this reflects CSF or blood WBC] that was conducted prior to administration of study drug on day 394. She was hospitalized and treated with a several week course of antibiotics. A new ICV access device was placed. She missed one dose of study drug due to this event.

- Subject 1323-1015: On day 424, a new ICV access device was placed as the previous device was removed on day 396 for a Propionibacterium infection. Following placement of this new device, a CT scan showed that the ICV device was not properly positioned and the catheter was too short to extract a sample. On day 426, the ICV device was removed and a new ICV device was placed. There were no further complications, and the event was considered resolved on day 429. Infusion of study drug was delayed due to this event.

The investigators attributed 2 SAEs (pyrexia and hypersensitivity) to the study drug for subjects in 190-203. Both of these subjects began the study drug during this reporting period. The narratives for these events are below.

- Subject 1244-3002, a 2 yo Caucasian non-Hispanic female: On day 18, the subject developed pyrexia during infusion of the study-drug. Prior to the infusion, she received cetirizine. One hour into the infusion, she developed a temperature of 37.8^{o} C. She was treated with acetaminophen and prednisone. There were no clinical signs of infection and serum WBC was normal. She had no problems during the remainder of the infusion, but was admitted to the hospital for observation. For subsequent infusions, she was pre-medicated with acetaminophen and prednisone.

- Subject 1244-3003, a 2 yo Caucasian non-Hispanic male: On day 1, less than an hour after the infusion of study drug ended, he had a temperature of 37.9^{o} C. Prior to the infusion, he was pre-medicated with cetirizine. Following the fever he was treated with acetaminophen and prednisone and admitted to the hospitalization for observation. The investigator stated that there were no other obvious reasons for fever besides an immune response to the study drug. For subsequent infusions, he was premedicated with acetaminophen and prednisone.

Reviewer Comment: Prior to reclassifying SAEs, the Applicant's analysis was confirmed using MedDRA Adverse Event Diagnosis Service (MAED). We agree with the investigators, and believe that the ICV infections were device-related. We agree that the hypersensitivity reactions attributed to Brineura by the investigators may be due to the drug.

The neurologic SAEs reported by the Applicant included five seizures, motor dysfunction, hemiparesis and intracranial hemorrhage. We believe that the intracranial hemorrhage and hemiparesis were complications from the ICV device. We believe that the SAEs of motor dysfunction could represent worsening of underling cLINCL or could be related to Brineura, but there are inadequate data to determine causality. With respect to seizures reported as SAEs, they might be due to progression of underlying cLINCL or they might be due to Brineura exacerbating the underlying seizure disorder of these subjects. One of the grand mal seizures occurred 4 hours after the infusion and therefore might have been related to a hypersensitivity reaction or culture-negative meningitis.

We agree with the Applicant that two of the seizures reported as SAE are unlikely related to Brineura; one SAE seizure was associated with missed anti-epileptic medication and one SAE seizure occurred prior to initiation of Brineura.

The SAE infections that the Sponsor did not attribute to Brineura or the ICV device were primarily respiratory infections (pharyngitis, upper respiratory tract, influenza, and pneumonia) and gastrointestinal disorders. It has not been reported that patients with CLN2 who are not end-stage are at increased risk of serious infections. However, isolated and even recurrent serious morbidities in children with significant, though not end-stage, neurologic and metabolic disorders, are often observed. While infections are common in children, the SAE infections reported in the safety database may be more severe than those that commonly occur in children. For example, one subject was ill for over 2 months and hospitalized for over 2 weeks with C. difficile colitis. In another instance, a subject who was diagnosed with bacterial pharyngitis had a C reactive protein of 72mg/L (normal <2), which suggests that this patient was more ill then is typical for this type of infection. Also, seven of the fifteen (47%) SAE infections that the Applicant did not attribute to Brineura were diagnosed within 24 hours of study drug infusion. Thus, one cannot formally rule out an immunosuppressive effect, but this remains unlikely in absence of a more convincing pattern of infections.

With regards to the other SAE, severe constipation (classified as gynecologic as there was concern for a recto-vaginal fistula), dental carries, tonsillar hypertrophy, adenoidal hypertrophy, and sleep apnea from hypertrophic tonsils, and dysphagia) we agree with the Applicant that these events are unlikely to be related to Brineura or the ICV device. Dysphagia is likely related to underling worsening of the CLN2 disease.

8.4.4 Hypersensitivity AEs

Hypersensitivity AEs were defined as any AE that mapped to either the broad hypersensitivity standardized MedDRA query (SMQ) or the broad algorithmic anaphylactic reaction SMQ. Thirty six hypersensitivity AEs were identified. The majority occurred within 24 hours of drug administration. Nine were classified as SAEs due to prolongation of hospitalization. Most were

CTCAE grade 1-2; 1 was CTCAE grade 3. No AEs that mapped to the anaphylaxis SMQ were identified.

Patient narratives for hypersensitivity/infusion related reactions are provided below. Unless otherwise indicated, symptoms did not recur with additional doses (although symptoms could have been modulated by the addition of premedication).

- Subject 1244-1001, a 4 yo Caucasian, non-Hispanic female: On day 538, 6 hours after completion of the infusion, subject developed a fever to 38 C, without any other symptoms. Subject was treated with acetaminophen and prednisone and the hypersensitivity event resolved the next day.

- Subject 1244-1002, a 6 yo Caucasian, non-Hispanic female: On day 156, during the final 30 minutes of the infusion (5.75 hours after infusion started due to problems with the infusion pump), the subject became "unusually tired." At the end of the infusion (6.25 hours after started) the patient vomited profusely. An hour later the subject developed a fever to 38.9 C. He had systolic hypertension with a widened pulse pressure (120/53). The subject developed CSF pleocytosis (CSF leukocytes 207/μL, CSF protein 544 mg/L, CSF glucose 760 mg/L) and elevated serum WBC (16 $x10^9$ /L). He had a self-limited grand mal seizure lasting < 1 minute, 6 hours after the infusion ended. He was treated with methylprednisolone, antihistamine, acetaminophen, metamizole, vancomycin and cefotaxime. He was hospitalized for 3 days following this event. At the time of discharge, CSF cultures were negative, CSF pleocytosis was improving, and IgE and C4 complement levels were normal. He received pre-medications prior to subsequent infusions.

- Subject 1244-1002 (as above): On day 350, the subject had a rise in temperature 2.5 hours into the infusion (tmax=38.9^{o}C). He was apparently otherwise asymptomatic. At the end of the infusion he had a widened pulse pressure (120/62); no BPs during infusion were provided. He received cetirizine, prednisolone and acetaminophen as pre-medications. He was treated with prednisolone and kept in the hospital for an additional 24 hours of monitoring. His IgE level, C4 complement level and serum tryptase were all normal.

- Subject 1244-1004, a 6 yo Asian, non-Hispanic female: On day 101, 10 minutes prior to the end of the infusion, she developed nausea and "motor agitation". Her temperature rose to 37.7C . Vital signs were reported to have "worsened"; her heart rate rose from 75 bpm to 127 bpm and her respiratory rate rose from 14 to 22. She treated with lorazepam, prednisolone and clemastine. She was hospitalized for observation and follow-up of CSF cultures for 3 days. Her IgE, complement C4 and tryptase levels were normal. She received pre-medications for subsequent infusions.

- Subject 1244-1006: On day 239, 5 hours after completion of infusion, he developed an elevated temperature to 37.9 C. He had no other symptoms. He had been pre-treated with cetirizine. IgE, C4 complement and tryptase were all normal.

- Subject 1244-1006, a 4 yo Caucasian non-Hispanic male: On day 312, during the infusion, he had an elevated HR (max 146). Then 15 hours after the infusion, he developed a

fever (38.7º C). He had no other symptoms. He had received pre-treatment with cetirizine, acetaminophen and prednisolone. At the time of the fever, he was treated with prednisolone and acetaminophen. At this time he had an elevated WBC (17.9 umol/L) and CRP (5mg/L), but CSF cultures were negative. IgE, complement C4 and tryptase levels were normal.

- Subject 1244-1010, a 6 yo Caucasian non-Hispanic male: On day 170, five hours after the infusion ended, he developed a fever, 38.5 C. He had been pre-treated with cetirizine, and was treated with acetaminophen and prednisolone. His IgE level was elevated to 475.2ug/L (ULN 240); C4 complement and tryptase were normal.

- Subject 1244-1012, a 3 yo Caucasian non-Hispanic female: On day 265, 4 hours after the infusion started, she developed an elevated temperature (37.8 ºC). At this time her diastolic blood pressure was low, and there was a widened pulse pressure (117/52); the diastolic pressure dropped 10 mmHg from pre-infusion. She was pre-treated with cetirizine, and the reaction was treated with acetaminophen and prednisolone. Her C-reactive protein was elevated at 8mg/dL, but IgE, complement C4 and serum tryptase were not elevated. She was hospitalized for 24 hours for observation.

- Subject 1244-1024, a 3 yo Caucasian non-Hispanic female: On day 211, 17 hours after the infusion ended, she developed a fever (38º C). She had been pre-medicated with cetirizine and was treated with acetaminophen and prednisolone. Her serum WBC, IgE, complement C4 and tryptase levels were within the normal range. She subsequently received cetirizine, acetaminophen and prednisolone as pre-medications.

- Subject 1287-1005, a 4 yo Caucasian non-Hispanic female: On day 130, less than 24 hours after her infusion, she developed a fever to 38.8º C. She was sleepy during and after the infusion, but otherwise asymptomatic. She had elevated temperatures with prior infusions, and received alimemazine and ibuprofen as pre-medications, and her fever was treated with acetaminophen. Complement C4 levels were normal.

- Subject 1287-1005 (as above): On day 144, less than 24 hours after her infusion, she had a fever to 38 C. Later in the day, her temperature rose to 39.2º C, which was associated with a tremor, lethargy and decreased appetite. Her blood WBC was 1.8 (absolute neutrophil count not reported), her CSF had 7 RBC and 19 WBC/µL and scant "pus cells." Three days later, her CSF WBC was 32/µL and the CSF RBC 4/µL. She received pre-medication with alimemazine and ibuprofen, and her fever was treated with acetaminophen and ibuprofen. The event was considered resolved day 148, but she continued to have non-serious frequent events of pyrexia during and immediately following infusions.

Reviewer Comment: The presenting sign for most of these SAE was pyrexia, which is nonspecific and not necessarily due to a hypersensitivity reaction. The normal C4, IgE and tryptase levels indicate these were not hypersensitivity reactions. A rapid increase in temperature could have caused a febrile convulsion. Although pleocytosis in culture negative CSF can be a marker for aseptic (viral) meningitis, some degree of pleocytosis can also be seen in patients who have foreign implanted materials, such as ICV devices.

8.4.5 Device-related AEs

Nine subjects had a total of 20 device-related AEs: needle issues (4 events in 3 subjects), pleocytosis (3 events in 3 subjects) and device leakage (2 events in 1 subject). There were 2 SAEs (in 2 subjects) that were assessed as device related by the investigators. Both events were ICV infections, propionibacterium (1) and staphylococcus epidermidis (1), both skin commensals, which required hospitalization, IV antibiotics, and removal/replacement of the ICV access device. Further details of these events are provided in the following narratives.

- Subject 1244-1009, a 4 yo Caucasian non-Hispanic female: On day 457, she began complaining of headache and nausea, and vomited repeatedly. She was taken to the ED [emergency department] where she was reported to be "pale and tired," but without new neurologic findings. CSF showed 1292 cells/μL (predominately neutrophils), which was an increase from 1.3 cells/μL on day 455 at the time of her last BMN 190 infusion. Her serum WBC was 15, and she was admitted to the PICU and treated with vancomycin, cefotaxime and prednisolone. CSF cultures were positive for staphylococcus epidermis, and her antibiotics were switched to flucloxacillin and fosfomycin. Her Rickham device was removed on day 459; the device membrane showed "frequent puncturing" and was "brittle at the edges." She was continued on IV antibiotics until day 466 and then oral antibiotics until day 469. She was re-hospitalized on day 475 for re-implantation of Rickham ICV and resumed study drug on day 479, 10 days late.

- Subject 1323-1015, a 3 yo Caucasian non-Hispanic female: On day 199, per-protocol CSF was noted to be "very cloudy", CSF WBC was 707 cells/μL and protein was elevated at 0.736 g/L. She received 1.5 hours of the infusion, before it was stopped. Six hours after the infusion was stopped, she was febrile. CT scan with contrast was normal. She was treated with IV ceftriaxone and amikacin, and antibiotics were switched to amikacin and vancomycin on day 201. Her CSF WBC rose to 940 cells/μL. Her CSF cultures remained negative until antibiotics were stopped on day 205; on day 206 CSF cultures were positive for *Probionibacterium acnes*. The Rickham device was removed on SD 207. A new ICV device was placed on day 224, and she resumed study-drug on day 228, 15 days later than scheduled, having missed one dose.

Reviewer comment: In addition there were three device-related SAEs that were not attributed to a device by the Investigator, but appear to be probably device-related as per our assessment.

Subject 1287-1007, an 8 yo Caucasian non-Hispanic female: On day 11, less than 24 hours after the ICV device was placed, she had a fever (tmax=38.7^{o}C), vomiting, and a generalized tonic-seizure. She "appeared unwell and lethargic" and had involuntary shaking for 10 minutes. On day 2, it was determined that she had an intracranial hemorrhage and edema in the frontal lobe along the shunt track without any significant mass effect, and the ventricular catheter had its tip at the foramen of Monro. Her fever and lethargy were attributed by the Investigator to the hemorrhage.

Subject 1287-1007, an 8 yo Caucasian non-Hispanic female: On day 21, 20 days after her dose of Brineura, she developed acute right hemiparesis. She was dragging her right foot, had dropping face on the right, was leaning to the right and had general right-sided weakness. Symptoms persisted and on day 24, and an MRI was performed that showed that the Ommaya

reservoir catheter tip had advanced and was at the right foramen on Monro. Her symptoms spontaneously resolved on day 25.

Subject 0146-1023, a 5 yo Caucasian non-Hispanic female: On day 168 she developed a right parietal subdural hematoma. The event was considered to have been resolved by day 337. No other details are provided. The Applicant attributed this to brain shrinkage and rupture of superficial vessels. However, subdural hematomas are not routinely described as a consequence of the natural history of CLN2.

8.4.6 Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant reports that no subjects discontinued the trial due to adverse events. One subject withdrew from the trial after a single 300mg dose of the study drug. The explanation for this withdrawal was that the subject had concerns related to ability to comply with study procedures.

However, it is interesting to note that this subject had a postoperative grade 3 intracranial hemorrhage that required prolongation of her hospitalization. Following withdrawal from the study, 21 days after her dose of study drug and prior to removal of the ICV device, she developed grade 2 acute right sided hemiparesis that on MRI was determined to be due to the advancement of the Ommaya reservoir catheter tip into the right foramen of Monro.

Reviewer's Comment: One subject (4%) withdrew from the study. Although the Applicant did not attribute the withdrawal due to an AE, we believe that complications associated with the ICV device may have contributed to this subject's decision to withdraw from the study.
As there are no narratives provided for most AEs (not required for TEAEs), we are unable to independently concur with the Investigators' determinations that only these events are related to treatment.

8.4.7 Laboratory Findings

Overall, 96% of subjects had at least one treatment-emergent abnormal laboratory test result. Clinically significant findings were reported by the Applicant as occurring in CSF laboratory results. Laboratory findings reported as AEs included pleocytosis (3 subjects [13%]), anemia (2 [8%]), thrombocytopenia (1 [4%]), CSF RBC positive (1 [4%]), platelet count decreased (1 [4%]), and RBC count decreased (1 [4%])]. Treatment-emergent abnormal CSF test results occurred in 83% of subjects. The most common abnormality in the CSF was increased cell count.

Reviewer Comment: Although elevated CF white cell count can be seen with CSF infection, some degree of pleocytosis can also be observed solely from inflammation related to an ICV device.

8.4.8 Vital Signs

AEs related to vital signs and physical findings included bradycardia (2 subjects [8%]), sinus bradycardia (1 [4%]), postoperative fever (1 [4%]), body temperature increased (1 [4%]),

grip strength decreased (1 [4%]), and oxygen saturation decreased (1 [4%]).

Twenty-four subjects developed some degree of hypotension during an infusion; 21 subjects had at least one episode post-infusion. All subjects developed diastolic hypotension during an infusion at least once, whether this was defined as decrease of at least 20% (82% of infusions), <45 mmHg (74% of infusions), <40 mmHg (49% of infusions), or <5th percentile for age, sex and height (39% of infusions). There were no reports of symptomatic hypotension and no AEs were assigned by the Applicant to hypotension.

Reviewer Comment: During the review process there was some discussion of the methodology. A substantial number of measurements were obtained via a leg (rather than arm) cuff. However, we believe that any artifact introduced would not have resulted in significant measurement errors. In addition, we note that when blood pressure is measured oscillometrically, as here, the diastolic measure is the least reliable (of systolic, mean and diastolic).

Electrocardiograms (ECGs)

ECGs were supposed to be performed at baseline, on day 1 and prior to dose escalation for those subjects in the dose escalation cohort and then every 24 weeks during study 190-201 and every 12 weeks during study 190-202. Despite the ECG specifications in the protocol, two subjects did not have baseline ECGs; for those subjects day 1 ECGs are imputed for analysis. Of those with baseline ECGs, 4 subjects (17%) had abnormal baseline ECGs (2 abnormal rhythm, 1 nonspecific depolarization, 1 biphasic T waves). A single subject had an abnormal baseline ECG that normalized post-baseline. During the course of the study 16 subjects (67%) had at least one abnormal ECG finding, including 50% of subjects who had normal ECGs at baseline. Of subjects with baseline normal ECGs who had abnormal ECGs at the end of study 190-201 and had ECGs prior to the data-cut during study 190-202, 88% (7 out of 8 subjects) had persistence of their ECG abnormalities. None of the ECG abnormalities that occurred represented prolonged QTc. The clinical significance of ECG abnormalities was based on the medical judgment of the clinical investigators, who are neurologists, or consultations provided by a cardiologist. All ECG abnormalities were deemed to be not clinically significant. Similarly, no pathologic rhythm abnormalities were observed during a repeat dose study in TPP-1-null Dachshund dogs (study BMN190-12-027).

Clinical Reviewer Comment: Given the high frequency of reported abnormalities and that children with JNCL and older patients with cLINCL are at risk from their underlying disease of conduction abnormalities, the ECG tracings were reviewed. Although the quality of the ECG tracings submitted for review was poor, there was no discernable pattern to suggest a drug effect. This is a small study which may not adequately capture less common effects of the study drug on conduction abnormalities. Also, drug induced conduction abnormalities can only occur in older children and young adults due to the underlying disease, and these children were not evaluated during the clinical development program. Therefore, we recommend that cardiac conduction abnormalities be monitored in any post-marketing studies.

QT

A thorough QT study was not performed. The Applicant claims that a thorough QT study is not

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necessary for Brineura since the drug has highly localized distribution to the CNS, the enzyme's activity is limited to the lysosome and would not impact cardiac repolarization, and no adverse cardiovascular findings were noted in animals.

Reviewer Comment: The Agency has not required thorough QT studies for other ERTs, and based on the Applicant's rationale, it is unlikely that a thorough QT study is needed. However, based on the large number of ECG abnormalities and that patients with JNCL and older patients with CLN2 are at risk for underlying cardiac conduction abnormalities, it is important to ensure that Brineura does not exacerbate cardiac conduction abnormalities. We believe that the ECG findings in 190-201/202, this can be evaluated in the post-marketing setting.

8.4.9 Immunogenicity

CSF for anti-drug and neutralizing antibodies was obtained during each drug administration. In the event of a suspected anaphylactic reaction, serious hypersensitivity event, or severe hypersensitivity (defined as a hypersensitivity event of Grade 3 or higher), blood samples were collected within 1 hour of the event to assess C4, serum tryptase, and total IgE; to assess drug-specific IgE, a blood sample would be collected no sooner than 8 hours after the event (or before the next infusion). As submitted in the 120 day Safety Report, anti-drug antibodies (ADA) were detected in the serum of 19/24 subjects (79%) by 73 to 133 weeks of assessment. In subjects who developed an ADA response, the response was either sustained (12/19, 63%) or declining (7/19, 37%), of which 5/19 (26%) reverted to undetectable by Week 133. Time to antibody development varied across subjects and did not appear dose dependent.

ADA were detected in the CSF of 5 (21%) subjects treated with Brineura by the end of the study. and were first detected between weeks 9 and 73. The response was sustained in 3/5 while it declined in 2/5 subjects by week 69 or earlier. NAb to Brineura was not detected in CSF for 24/24 (100%) of subjects at up to 107 weeks.

All subjects who experienced a serious or grade 3 hypersensitivity AE were tested for drug-specific IgE and found to be negative. No association was found between serum ADA titer and incidence or severity of hypersensitivity adverse events. A comparison of CSF ADA negative and positive subjects showed no association between ADA and treatment outcome as measured by the motor + language scales.

Analysis of Submission-Specific Safety Issues

8.4.10 ICV device longevity

Intracerobroventricular devices have a long clinical history, particularly in young children, as ventricular drains or as ventriculoperitoneal shunts. Even in the best of centers, these devices can require revision or replacement, often multiple times, due to infection or malfunction. Not only will these children require these devices for the remainder of their lives, but the devices will require multiple access punctures of the reservoir, and with a larger needle than is recommended by the manufacturer (due to the "gripper" nature of the needle, making it more stable). The Applicant, in response to an Information Request, submitted the results of an in vitro multiple

puncture study (BLA 761052 amendment 105, February 28, 2017). The results of this study were reviewed by the clinical reviewers and the CDRH consultant. CDRH concluded that there could be a need to replace the intraventricular access device after approximately 105 perforations, equal to approximately 4.3 years of use of the device under the labeled treatment plan. However, these children could potentially require the device for longer than this, and this study did not assess additional potential complications such as other device malfunction or infection. The clinical trials used a specified intracerebroventricular access device. Long term complications with other marketed devices is unknown.

8.5 Safety Analyses by Demographic Subgroups

The population is too small to allow any meaningful sub-group analyses.

8.6 Specific Safety Studies/Clinical Trials

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No additional safety studies were performed.

8.7 Additional Safety Explorations

8.7.7 Human Carcinogenicity or Tumor Development

No human carcinogenicity studies were performed. During the clinical development program no tumors were reported in any subject. ERT has not been associated with an increased incidence of neoplasms. Based on the mechanism of action of Brineura there does not appear to be an increased risk of malignancies.

8.7.8 Human Reproduction and Pregnancy

There was no Brineura exposure during pregnancy or lactation; all patients were pre-pubertal.

8.7.3 Pediatrics and Assessment of Effects on Growth

All subjects were children. The proposed indication is for children 3 years of age and older. Brineura was granted orphan drug status (April 1, 2013, orphan designation 13-3919) and therefore is exempt from the Pediatric Research Equity Act (PREA) required assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients.

8.7.9 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No drug overdoses occurred during the clinical trials.

Reviewer Comment: We believe that there is no abuse potential as the drug's site of action is limited to the lysosome, so there would not be expected to be any increase in neurotransmitters which might lead to euphoria and abuse. In addition, this drug is only administered via an intracerebroventricular access device by healthcare professionals, which should further limit the availability of this drug and potential for abuse.

8.8 Safety in the Postmarket Setting

8.8.7 Safety Concerns Identified Through Postmarket Experience

Brineura is not currently marketed in any jurisdiction therefore there are no postmarketing data

8.8.8 Expectations on Safety in the Postmarket Setting

As indicated above, questions remain about the long term integrity and functioning of the intracerebroventricular delivery devices. The draft label indicates that Brineura is intended to be administered via Codman® Holter Rickham Reservoirs with the Codman® Ventricular Catheter, the same device that was used in the clinical trials. In addition, data are currently lacking on use in children <3 yo and use in children who are diagnosed but currently asymptomatic. It is expected that these can be assessed by the proposed Postmarketing requirement (PMR) 3207-5 and that additional risk evaluation and mitigation strategies (REMS) will not be required.

8.9 Additional Safety Issues From Other Disciplines

None.

Safety Conclusion
The safety database consists of all treated children and is assessed as adequate relative to the size of the estimated total patient population. It is, however, limited to the ages of the treated subjects, 3 to 8 years of age, and the duration of the trials. Additional safety data on younger children will be obtained via PMR 3207-5 and safety information on longer use in PMR 3207-1. The indication for use will be limited to use in children 3 years of age and older. Only a single child discontinued prematurely, possibly related to a device insertion complication.

All children experienced at least one AE. Most were assessed as drug and device-unrelated. Hypersensitivity reactions were noted but were limited in severity and duration. Device-related SAEs (infection, intracranial bleed) occurred and were severe. In this small group all neurologic AEs could not be adequately assessed as drug-related or disease-related.

In conclusion, although SAEs have been associated with this drug and device, given the uniformly poor prognosis of this disease, leading to a vegetative state and death, the safety profile is considered adequate for licensure.

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Reference ID: 4089891

Appendix 2

Financial Disclosures

Covered clinical study (name and/or number): 190-201		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 67		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation

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		from applicant)
Covered clinical study (name and/or number):190-202		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 51		
Number of investigators who are applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in applicant of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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/s/

DRAGOS G ROMAN
04/26/2017