CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761052Orig1s000

MEDICAL REVIEW(S)

8.1 Safety Results

8.1.1 Deaths

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

8.1.2 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.

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.

8.1.3 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%)

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 (38.7^o 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 ^{o}C). 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 (38^{o} 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 38.8^{o} 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 39.2^{o} 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 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

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.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VICTOR C BAUM
04/26/2017

DRAGOS G ROMAN
04/26/2017
This is the Primary/Secondary Safety Review for the Brineura BLA 761052

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 761052 **Applicant: BioMarin** **Stamp Date:**

Drug Name: BMN 190 (cerliponase alfa, rhTPP1) **NDA/BLA Type: BLA**

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			eCTD in accordance with M4 ICH CTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			Table & figure hyperlinks from clin summary do not work so IR sent to Sponsor
5.	Are all documents submitted in English or are English translations provided when necessary?	X			We agreed that the Sponsor did not need to translate videos at time of submission, but the Agency may request the Sponsor for this during the review process.
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm	X			The proposed labeling does not include secondary clinical endpoints besides CLN2 motor/language scale. The proposed administration advice (b) (4) ," however there is no data regarding benefit (b) (4) (b) (4) (b) (4) so this will require significant discussion if the drug is approved.
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?		X		We previously agreed that this was not needed; There is a Summary of Clinical Safety 2.7.4
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			5.3.5.3
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			2.5.7.3-2.5.7.7
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505b1
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: 190-201 Study Title: A Phase 1/2 Open-Label Dose Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics and Efficacy of Intracerebroventricular BMN 190 in Patients with Late-Infantile CLN2 Disease Sample Size: 9 Treatment Arms: 3 Location in submission: 5.3.5.2	X			MTD approach seems appropriate given the rarity and severity of the disease. Based on non-clinical studies, the Agency determined that the lowest dose used in the dose-ranging study was unlikely to offer prospect of direct benefit but the cohort had already been treated in Europe
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			We agreed that the submitted studies, 190-901 and 190-201/202, were adequate to submit a BLA. Whether the natural history study will serve as an adequate control will be a review issue.
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			It was previously agreed that the submitted studies were adequate for filing a BLA. There was no prior discussion regarding labeling for the entire CLN2 population rather than the narrower population that the drug was tested in.
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	The Agency has not agreed that the Sponsor's endpoints are appropriate for a pivotal trial. During the pre-IND meeting in July 2012, the Division told the Sponsor, "We have concerns regarding the validity and acceptability of these instruments as clinical endpoints in this study (Weill Cornell and Hamburg LINCL scales). Use of patient and observer reported outcome measurements as endpoints in clinical trials must be carefully evaluated so that results can be interpreted ...We recommend standardizing the evaluation procedures…The evaluators must remain blinded to treatment assignment. We also remind you of the importance of adequate study blinding and monitoring especially for investigators who will perform clinical assessments and the investigators should not have access to labs or other data that may lead to

	Content Parameter	Yes	No	NA	Comment
					potential unmasking." This was not done. During subsequent meetings, the Agency informed the Sponsor about challenges in interpreting this data, but concluded during the May 2015 meeting that "although we do not believe the assessments that you included in your study are optimal, they may be acceptable if you clarify and address our concerns." In the end, data interpretation will be a review issue.
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			Submitted on 6/28/16 in response to IR request sent 6/20/16
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Sponsor submitted safety data as agreed upon during pre-BLA meeting
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?		X		The Sponsor did not perform a dedicated QTc study, but provided an explaination on page 14 of 1.11.4. The Sponsor's justification appears consistent with the lack of tQTc studies typically required for other ERTs. The Sponsor collected ECG data in study 201, which they submitted in 2.7.4.4.2.1 and summarized in Table 14.3.6.3.1.
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?	X			The Sponsor provided 48 weeks of data in 23 subjects which we told them was necessary to review BLA. Additional safety information will be required post-marketing if approved & the Sponsor has submitted a registry protocol. The adequacy of this will be a review issue.
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
25.	Has the applicant submitted the coding dictionary[2] used for	X			AE listings in 16.2.7 based

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	mapping investigator verbatim terms to preferred terms?				on MedDRA version 18.1
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Sponsor provided Integrated Subject Narratives for all subjects in 5.3.5.3 that include graphic patient profiles. Based on preliminary review, it appears as though some of the AEs might have been misclassified including subject 1020 (a 3yo) who was classified as having grade 1 vomiting which was associated with significant HTN and mild tachycardia.
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			No special studies were requested; it appears as though requested data was submitted (although only a limited number of additional control subjects were provided)
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			This study was performed in pediatrics. This is an orphan product so PREA does not apply.
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?			X	There is no information. The only subjects exposed to the drug were in study 201/202 and none of the children were of reproductive potential. The Sponsor has planned a post-marketing pregnancy registry.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			Submitted on 6/28/16 in response to IR request sent 6/20/16
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to	X			

(verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	previously by the Division?				
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Provided for study 201/202 but not 901.
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			Provided for study 201/202 but not 901.
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			(b) (6) received $89,879 from BioMarin for consulting between 2012-2016. (b) (6) received $28,851 from BioMarin between 2012-2013 for consulting services.
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			ICD and IRB info was provided 16.1.3.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer Date

Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIZABETH S HART
06/29/2016