21 April 2017
EMA/31226/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Brineura

International non-proprietary name: cerliponase alfa

Procedure No. EMEA/H/C/004065/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug antibodies
ADE	Acceptable daily exposure
AE	Adverse event
API	Active pharmaceutical ingredient
BBB	Blood brain barrier
BMN 190	Recombinant human tripeptidyl peptidase-1
CE-LIF	Capillary electrophoresis with laser induced fluorescence
CFS	Cerebrospinal fluid
CHO	Chinese Hamster Ovary
CHOP	CHO proteins, host cell proteins
CI-M6PR	Cation-independent mannose-6-phosphate receptor
CLN2	Classical late infantile CLN2, cLINCL, or Jansky-Bielschowsky disease
CQA	Critical quality attributes
CRF	Case report form
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CZE-LIF	Capillary Zone Electrophoresis/Laser-Induced Fluorescence Detection
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
DP	Drug product
DS	Drug substance
EOPC	End of Production Cells
ERT	Enzyme replacement therapy
FBDS	Formulated bulk drug substance
FS	Flushing solution
HCCF	Harvested cell culture fluid
HIC	Hydrophobic interaction chromatography
HIPAA	Health Insurance Portability and Accountability Act
HTST	High-Temperature-Short-Time
ICF	Informed consent form
ICV	Intracerebroventricular
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-OES	Inductively coupled plasma optical emission spectrometry
IM	Intramuscular
IND	Investigational New Drug (application)
IRB	Institutional Review Board
cIEF	Capillary Isoelectric Focusing
IT-C	Intrathecal-cisternal
IT-L	Intrathecal-lumbar
ITT	Intent-to-treat
IVC	Intracerebroventricularly
LCA	Limit of in vitro cell age

MALLs	Multi angle laser light scattering
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NAA	N-acetylaspartate
Nab	Neutralizing anti-TPP1 antibody
NCI	National Cancer Institute
NCL	Neuronal ceroid lipofuscinosis
NOR	Normal operating ranges
PAR	Proven acceptable ranges
PDE	Permitted Daily Exposure
PLR	Pupillary light reflex
PQ	Process qualification
PV	Process validation
QOL	Quality of life
rhTPP1	Recombinant form of the human serine tripeptidyl peptidase 1
RP-HPLC	Reverse Phase High-Performance Liquid Chromatography
SAE	Serious adverse event
SAP	Statistical analysis plan
SAX	Strong ion exchange
SBP	Systolic blood pressure
SC	Subcutaneous
SCMAS	Mitochondrial ATP synthase subunit c
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SEC	Size exclusion chromatography
SMQ	Standardized MedDRA query
STD	Standard deviation
SVAUC	Sedimentation velocity analytical ultracentrifugation
TAb	Total anti-TPP1 antibody
TEAE	Treatment emergent adverse event
TPP1	Tripeptidyl peptidase-1
TRE	Temporally related event
WBV	Whole Brain Volume
WCB	Working Cell Bank
WT	Wildtype

1. Background information on the procedure

1.1. Submission of the dossier

The applicant BioMarin International Limited submitted on 27 May 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Brineura, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 August 2014.

Brineura was designated as an orphan medicinal product EU/3/13/1118 on 13 March 2013 in the following condition: Treatment of neuronal ceroid lipofuscinosis type 2.

The applicant applied for the following indication:

Brineura is indicated for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase- 1 (TPP1) deficiency.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Brineura as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that cerliponase alfa was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0260/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0260/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's requests for consideration

Marketing authorisation under Exceptional circumstances and Accelerated assessment

The applicant requested consideration of its application for a marketing authorisation under exceptional circumstances in accordance with Article 14(8) of the above mentioned Regulation.

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance cerliponase alfa (recombinant human tripeptidyl peptidase-1, rhTPP1) contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 19 September 2013 and 24 July 2014. The Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Concepcion Prieto Yerro

- The application was received by the EMA on 27 May 2016.
- Accelerated Assessment procedure was agreed-upon by CHMP on 28 April 2016.
- The procedure started on 15 September 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 November 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 22 November 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 November 2016. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 1 December 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 5 December 2016.
- During the meeting on 13 December 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 15 December 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 January 2017.

The following GMP and GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:

- A GCP inspection at 2 investigator sites in Germany and Italy between 02 December 2016 and 09 December 2016. The outcome of the inspection carried out was issued on 02 January 2017.
- A GMP inspection at one site responsible for the manufacture of the finished product, located in the United States of America, on 24, 25, 26, 27 and 28 October 2016. Based on this inspection, GMP compliance of the site could not be confirmed.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 9 February 2017.
- During the CHMP meeting on 21 February 2017, the CHMP agreed on a list of outstanding issues to be addressed in writing the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 February 2017.
- During a meeting of an Ad hoc Expert group on 07 March 2017, experts were convened to address questions raised by the CHMP.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 12 April 2017.
- During the meeting on 21 April 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Brineura under exceptional circumstances.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Neuronal ceroid lipofuscinoses are a genetically heterogeneous group of inherited neurodegenerative lysosomal storage disorders, which are characterised by accumulations of intracellular lipofuscin-like material in multiple organs leading to functional impairments and ultimately death (Mole *et al*., 2005). The different neuronal ceroid lipofuscinoses are distinguished by the genetic origin, ultrastructural composition of the lysosomal storage material, clinical symptoms, age at disease onset and course of disease.

Late Infantile Neuronal Ceroid Lipofuscinosis Type 2 (CLN2) disorder, formerly also known as Jansky-Bielschowsky disease or classical late infantile onset neuronal ceroid lipofuscinosis (cLINCL), is a rare, paediatric-onset neurodegenerative lysosomal storage disorder caused by TPP1 enzyme deficiency as a consequence of loss-of-function mutation in the CLN 2 gene.

2.1.2. Epidemiology

Late infantile neuronal ceroid lipofuscinosis type 2 occurs with an estimated incidence between 0.22 to 9.0 per 100,000 live births worldwide (Mole and Williams, 2013; Fietz *et al*., 2016). The estimated worldwide prevalence of CLN2 is 0.6 to 0.7 per million population in northern Europe (Claussen *et al*.,1992; Uvebrant and Hagberg, 1997). Recent estimates based solely on genetically diagnosed cases suggest a prevalence of 0.75 per million with 15-20 new patients born each year (0.22 per 100.000 live births) in Germany. Since the epidemiology estimates are based on identified cases, and since access to paediatric neurologists and medical genetics is limited, it is likely that there are additional cases that remain undiagnosed. However, even assuming that the true prevalence is several folds higher than the current estimates, CLN2 is still a very rare disorder.

2.1.3. Biologic features, aetiology and pathogenesis

So far, 89 different recessive mutations in the autosomal CLN2 gene encoding TPP1 have been identified. The mutations mainly result in reduction or loss of TPP1 activity due to impaired lysosomal transport and cleavage of the truncated or misfolded pro-enzyme (Kousi *et al*., 2012). The two most common mutations in the Northern European and US populations are the splice site mutation IV5-1G>C and the nonsense R208X. Whichever of the common mutations are present, the clinical phenotype is broadly similar. However, considerable inter- and intra-familial variation in disease severity has been described in the literature (Mole*et al*., 2005).

TPP1 deficiency causes progressive intracellular accumulation of lysosomal storage material with characteristic autofluorescence under the light microscope and mitochondrial ATP synthase subunit c (SCMAS) as its major component. This lysosomal storage material shows a *"curvilinear profile"* during electron microscopy.

The connection between the storage process and neurodegeneration remains unknown. Organ damage has been described to be restricted to the central nervous system, although pathologic intracellular storage occurs in almost any tissue, including muscle, skin and peripheral blood lymphocytes (Kohlschütter and Schulz, 2016).

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Patients with Late Infantile Neuronal Ceroid Lipofuscinosis Type 2 (CLN2 disease) typically present with slowing of development and psychomotor regression, usually in the second or third year of life. The diagnosis is on average confirmed at 4 years of age. Epilepsy typically develops early, between 2 and 4 years of age, usually presents with variable seizure types and is often refractory to treatment. Patients further develop ataxia, myoclonus, impaired speech and cognition as well as developmental regression. The visual, cognitive and motor skills decline rapidly. The general decay of psychomotor function is rapid and uniform between the third and fourth birthday, however atypical patients with later onset, tending to have a milder course with more prominent ataxia and less prominent epilepsy have also been described (Kohlschütter and Schulz, 2016; Schulz *et al*., 2013; Steinfeld *et al*., 2002). Some children become extremely irritable and distressed. Limb spasticity may become prominent with truncal hypotonia and loss of head control (Mole *et al*., 2005).

In general, patients loose vision, are wheelchair-bound and require gastrostomy feeding at approximately 6 years of age. They subsequently enter a vegetative state with death occurring between 10 and 16 years of age.

Diagnosis is based on demonstration of TPP1 enzymatic deficiency in dried blood spots, leukocytes or fibroblasts. The residual TPP1 activity in fibroblasts is <2%. The last step for confirmation of the diagnosis is mutation analysis of the TPP1 gene.

2.1.5. Management

Currently, no curative treatment for late infantile neuronal ceroid lipofuscinosis type 2 exists and the diagnosis is invariably fatal. Symptomatic treatments are focused on the treatment of seizures (anticonvulsants), motor control loss (bracing or wheelchairs) and feeding/control of aspiration risk (gastrostomy tube). Disease management further includes physical and speech therapy, different medications aiming at alleviating symptoms like myoclonus, spasticity, dystonia and pain as well as end-of-life care at advanced disease stage.

2.2. About the product

Brineura (cerliponase alfa, also referred to as BMN 190 in this report) is an unmodified recombinant form of the human serine tripeptidyl peptidase-1 (rhTPP1) that is expressed as inactive 563 amino acid pro-enzyme (zymogen) in Chinese Hamster Ovary (CHO) cells.

The enzyme replacement therapy with the BMN 190 exopeptidase is expected to reduce the inclusions of lysosomal storage material in the CNS and attenuate progression of the disease. In order to allow passage of the macromolecule across the blood-brain-barrier, BMN 190 is administered intracerebroventricularly (ICV) into the cerebrospinal fluid (CSF) as an inactive pro-drug by a catheter that is implanted into the lateral cerebral ventricle of the non-dominant hemisphere. The post-translational glycosylation of the inactive 563 amino acid pro-enzyme BMN 190 with N-linked oligosaccharides is critical for the lysosomal uptake of the enzyme by the cation-independent mannose-6-phosphate receptor (CI-M6PR). During secretion into lysosomes, a 195 amino acid fragment is then cleaved from the 66 kDa zymogen to release the active 46 kDa TPP1. Thus, the activity of BMN 190 is confined to the lysosome.

Brineura has been formulated as 30 mg/ml solution for ICV infusion in 5 ml vials.

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the unmet medical need as currently there are no approved treatments for CLN2. The data available from the development programme have demonstrated that Brineura as an enzyme replacement therapy delivered via ICV application has a potential to address this unmet medical need.

The Applicant requested marketing authorisation under exceptional circumstances. The applicant argued that comprehensive data on the efficacy and safety under normal conditions of use could not be provided. As outlined in section 2.1.2 of this report, CLN2 is an ultra-rare disease and is encountered so rarely that it cannot reasonably be expected that comprehensive evidence will be obtained. The CHMP agreed with this argumentation.

2.3. Quality aspects

2.3.1. Introduction

The finished product, also referred as 'drug product' (DP) by the applicant, is presented as a sterile solution for ICV infusion containing cerliponase alfa, an unmodified recombinant form of rhTPP1, as active substance, also referred as drug substance (DS) by the applicant, formulated at a concentration of 30 mg/mL. Cerliponase alfa and rhTPP1 are used interchangeably throughout the dossier and report.

Other ingredients are: sodium phosphate dibasic heptahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride, potassium chloride, magnesium chloride hexahydrate, calcium chloride dihydrate, and water for injection.

The formulation is packaged in a container closure system consisting of a 10 mL Type 1 clear borosilicate glass vial closed with a fluoropolymer coated butyl rubber stopper and a flip-off cap and aluminium crimp seal. Each vial is supplied as a 150 mg dosage strength vial.

The pack size consists of 3 vials (two vials with 5 mL solution for ICV infusion of Brineura and one vial with 5 mL flushing solution for ICV infusion). The contents of two vials of the finished product are combined for a volume of 10 mL and are administered to patients for a dose of 300 mg. Following administration the infusion set, port needle and ICV device are flushed with 5 mL Flushing Solution (ICV solution) in order to fully administer the finished product and maintain patency of the ICV access device.

The DP is supplied frozen and stored at a temperature of -20 ± 5°C.

2.4. Active Substance

Cerliponase alfa is secreted by recombinant CHO cells as an enzymatically-inactive, 544 amino acid zymogen (pro-enzyme), rhTPP1. rhTPP1 has identical primary amino acid sequence to the human tripeptidyl peptidase-1 (hTPP1) zymogen

The zymogen can be further processed to form the mature, active protease (amino acids 177 to 544). This processing is autocatalytic *in vitro* upon exposure of the pro-enzyme to low pH, while the *in vivo* activation upon uptake to the lysosome may involve additional proteases. rhTPP1 contains 7 cysteine residues, 6 of which are involved in intramolecular disulphide bridges (C92–C103, C346–C507, and C503–C518). One

cysteine residue on the mature enzyme (C208) is unpaired. There are 5 N-glycosylation sites on rhTPP1, decorated with high mannose, phosphorylated high mannose and complex glycosylation structures.

The primary activity of the mature rhTPP is as a tripeptidyl exopeptidase with a broad substrate specificity. rhTPP1 is taken up and translocated to the lysosomes by target cells through the Cation Independent Mannose-6-Phosphate receptor (CI-MPR, also known as M6P/IGF2 receptor).

Manufacture, process controls and characterisation

BioMarin Pharmaceutical Inc., Novato Campus/Galli Drive, CA, USA, performs manufacture of rhTPP1 formulated bulk drug substance (FBDS).

Description of manufacturing process and process controls

The manufacture of cerliponase alfa active substance has been adequately described. rhTPP1 is produced by CHO cells that over-express the rhTPP1 transgene**.** The rhTPP1 manufacturing process consists of fed-batch cell culture, harvest recovery, and purification processes, including viral filtration, resulting in FBDS, which is a process hold point preceding manufacture of the finished product.

The FBDS manufacturing process description and the control of critical steps provided in sections S.2.2 and S.2.4 has been updated to meet the requirements of a sound regulatory commitment.

During the procedure, deficiencies were addressed with respect to the upstream process: The process parameters that have been defined as critical are adequately reflected in the dossier sections S.2.2 and 2.4. Several issues were updated with regard to process description of the downstream process as well. Regarding the viral inactivation/ virus reduction steps, the mixing conditions applied are stated and the filter types and sizes of the filters used for virus reduction have been defined.

The active substance manufacturing process is considered acceptable and the in-process controls are adequately set.

BioMarin has assessed the suitability of the container closure system for use in the rhTPP1 manufacturing process. Studies to evaluate extractables and leachables have been performed. This container closure format is used for the stability program for rhTPP1 FBDS using scaled-down versions of the FBDS bottles. Stability studies indicate FBDS stability and compatibility with the container closure materials.

Control of materials

rhTPP1 is expressed in CHO cells; a two tiered banking system consisting of a master cell bank (MCB) and a working cell bank (WCB) has been established for the production cell line. Full and comprehensible information regarding the preparation and testing of MCB and WCB has been provided. All test results were satisfactory and the cell banks have been released for production use by Quality Assurance. In addition, preparation of cells at the limit of in vitro cell age (LCA) has been also included in the dossier. Results for cell culture samples obtained at the end of production demonstrate that cells at the LCA are genetically stable, and that under the cell culture conditions, no new viral or infectious retroviral particles are expressed or introduced that were not detected during screening of the MCB and WCB. Finally, the results of the studies performed on cells from the MCB and End of Production Cells (EOPC) to determine genetic identity and stability following ICH guidelines confirm the expected genetic characteristics of the cell line.

The raw materials used for cell culture and purification are listed in the dossier. Where applicable, reference is made to compendial monographs. No raw materials derived from animal sources are used in the process. Information on the qualitative composition of the cell culture media has been provided.

Control of critical steps and intermediates

BioMarin utilises a control system in the manufacture of rhTPP1 through monitoring of in-process conditions, characteristics and release specifications. In-process testing is performed on each lot of rhTPP1. Action limits have been defined for bioburden and endotoxin. In case a deviation is encountered, an investigation is initiated and corrective actions will be defined and implemented. The hold times stated in this section are supported by the process validation (PV) data provided.

A proper justification for CQAs selection and their related CPPs has been presented. The information provided in section S.2.4 comprises critical in-process tests and critical process parameters. Process step yield and purity will be monitored on an ongoing basis and defined as critical controls once sufficient manufacturing experience is gained. This is considered acceptable.

Process validation

Three consecutive FBDS batches were manufactured at commercial scale by the intended commercial process. Overall, the consistency of the FBDS manufacturing process has been adequately confirmed.

Column resin re-use studies and hold time studies have been performed the results of which are adequately reflected in the process description/control of critical steps.

The overall shipping strategy performed by the Applicant is adequate.

Characterisation

For the characterisation exercise, the three process qualification (PQ) lots, manufactured using the final commercial process, three clinical FBDS lots and the reference material BMN190-0313-001 were analyzed head-to-head by the tests included in the specification and additional tests. These studies were also intended to establish comparability between clinical batches and batches manufactured by the final commercial process.

In general, the active substance has been comprehensively characterised by orthogonal methods. The characterisation studies comprise studies of the primary, secondary and tertiary structure, post-translational modifications as well as functional analysis. The extent and the sites of glycosylation of rhTPP1 have been adequately investigated. The amino acid sequence of rhTPP1 has been sufficiently confirmed. Disulfide linkage determination confirmed the existence of the three disulfide bridges. Charge heterogeneity has been determined. The molecular weight of the protein has been determined. Profiling of N-linked glycans has been analysed. Overall, glycosylation has been appropriately investigated.

Cellular uptake of rhTPP1 through the M6P receptor was measured. Enzyme activity was determined with and without prior activation of rhTPP1 zymogen. The potency assays are considered adequate to demonstrate biological functionality of rhTTP1 comprising receptor binding, cellular uptake and enzymatic activity.

Samples of rhTPP1 lots were subjected to a set of forced degradation conditions chosen for their expected impact on the protein structure. The studies demonstrate that rhTPP1 is sensitive to acid and base hydrolysis, oxidation, thermal stress and extreme prolonged exposure to light.

To characterise the product-related impurities, a panel of analytical methods including release tests as well as additional characterization tests have been used.

Specification

The active substance specification includes test parameters on identity, potency and content, purity and impurities and microbiological safety. The list of parameters tested at release is considered comprehensive.

During the procedure, the proposed specification for release and shelf-life was updated and the limits of several relevant parameters were tightened.

Analytical methods

The appearance, pH, and osmolality assays are performed per Pharmacopoeia, and were qualified for their intended use. The in-house analytical methods used for DS release testing have been linked with respective SOPs which are also provided. Non-compendial methods are adequately described. Detailed information has been provided with regard to the validation of the proposed analytical procedures included in the DS specification. All in-house analytical procedures were demonstrated to meet the defined validation requirements and have been shown to be suitable for their intended use. Potency is determined using different methods.

Batch analysis

Batch data have been provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

Three primary reference standards have been used through the development of the product. The current standard is derived from one batch obtained by the commercial process and is used as primary and secondary reference standard.

Stability

Stability data are provided. Stability batches have been stored at the proposed long-term storage condition and at accelerated conditions which is in accordance with ICH requirements. The proposed stability protocols are considered appropriate.

2.4.1. Finished Medicinal Product

The finished product consists of 3 vials: two vials of Brineura and one vial of the flushing solution. These are described separately here below.

2.4.1.1. Finished Medicinal Product: Brineura

Description of the product and Pharmaceutical development

The finished product, also referred to as BMN 190 in the submission, is a sterile solution for intracerebroventricular infusion. It is a clear and colourless to pale yellow liquid containing rhTPP1 protein formulated at a concentration of 30 mg/mL.

The finished product formulation was developed to present the active substance in a simulated cerebrospinal fluid (CSF) without protein stabilisers as there is insufficient knowledge on adverse effects associated with foreign substances in the brain. The formulation is finalised at FBDS stage, further formulation steps are not applied during finished product manufacturing. In addition to the active substance, the formulation contains buffering agents (Sodium phosphate dibasic heptahydrate and Sodium dihydrogen phosphate monohydrate),

an isotonicity agent (sodium chloride), excipients to maintain the level of CSF electrolytes (potassium chloride, magnesium chloride hexahydrate and calcium chloride dihydrate), and water for injection as diluent. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur and/or USP standards. There are no novel excipients used in the finished product formulation. As the formulation does not contain stabilisers to mitigate protein aggregation, measures to avoid and remove potential particulates have been implemented, including using an in-line filter during administration, gentle handling of rhTPP1, and appropriate freeze-thaw instructions.

The container closure system for the DP consists of type 1 glass vials, butyl rubber stoppers with fluoropolymer coating and an aluminium seal with color-coded flip caps. The material complies with Ph.Eur. and EC requirements. Compatibility of the formulation with the container closure system as well as container closure integrity of the frozen product was demonstrated by stability studies.

The finished product is shipped frozen on dry ice.

Leachable studies were performed with the container closures system using finished product and flushing solution as extraction fluids. All found leachables were evaluated to be of no toxicological concern. Furthermore, the vials filled with finished product and flushing solution were not found to be susceptible to glass delamination for the proposed shelf life period of 24 months. Studies demonstrated that finished product and flushing solution are compatible with the infusion system components which have been used for the administration to date. For sterile, drug contacting infusion system components, this consisted of testing the components for adverse impact on the quality or potency of the DP, using multiple assays. Studies were completed under simulated clinical use conditions for the longest anticipated infusion and contact time. An in-line, 0.2 µm filter will be required for administration of the finished product to remove proteinaceous particulates which are formed in the absence of stabilizing agents in the DP as mentioned above. It has been demonstrated that the filter delivers a solution that complies with the requirements for the sub-visible particles test in accordance with Ph. Eur. 2.9.19. Studies also show that in-line filtration does not have a detectable effect on the purity or strength of the finished product.

The infusion system components used to date are considered sufficiently evaluated for use with the DP and FS. The results of compatibility studies of the finished product and flushing solution with application systems are reflected in the SmPC, the compatible application systems are included.

No changes to the formulation have been made between the clinical and commercial manufacturing campaigns.

Manufacture of the product and process controls

A GMP Certificate issued by an EEA authority for the proposed finished product manufacturer originally included in the MAA is not available. A pre-approval GMP inspection as prerequisite for a GMP Certificate resulted in major deficiencies. The deficiencies could not be solved and a GMP Certificate was not provided during the ongoing authorisation procedure. Therefore, the original site has been removed from the application dossier as required in the respective Major Objection.

Due to the unmet medical need of Brineura, CHMP agreed to replace the proposed finished product manufacturer, during the on-going authorisation procedure. The minimum conditions for the introduction the replacement site were discussed and agreed on.

To support the replacement of the manufacturing site, a detailed description of changes, a full risk assessment of the transfer, data supporting analytical methods transfer validation, previous relevant experience the applicant has at this site and process validation plans were required and in general provided.

For approval, satisfactory validation and comparability data had been provided. The process validation protocol has been provided as requested. Furthermore, the proposed submissions timelines are detailed and are accepted. The applicant has provided acceptable data and documentation concerning the introduction of the replacement site.

The manufacturing process of the finished product is a common fill-finish procedure.

Process validation data have been provided. The process parameters have been verified, in process controls met defined criteria and the final drug product met release specifications. The release results have been found to be in line with historical results.

Product specification

The finished product specification comprises tests for identity, quality, potency, strength, purity, safety, and composition. The specification includes all necessary quality attributes to control the finished product.

Analytical methods

Most of the analytical methods are identical to the methods used for the release of the active substance which is accepted as FBDS and DP are identical in composition. The descriptions of the additional analytical procedures specific for the DP are acceptable and the methods are suitable for their intended use.

Batch analysis

Finished product batch analysis data for batches used in clinical, stability and process validation studies were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

The reference material used to test the finished product is the same as that used for testing of FBDS. Refer to Section 3.2.S.5 for information regarding reference materials.

Stability of the product

The proposed drug product shelf-life of 24 months at -20±5°C is considered acceptable.

In section 6.3 of the SmPC storage of the unopened vials at 2-8°C is limited to 24 hours. This is accepted based on the stability testing results at accelerated storage conditions (5 ± 3°C).

The applicant demonstrated physico-chemical in-use stability for 12 hours which covers the maximum infusion time. In addition, in-use storage of open vials or product held in syringes of 4 hours at 2-8°C prior to infusion was claimed based on a microbial challenge study on FBDS. Given the sensitive application way for Brineura in-use storage prior to infusion is not considered acceptable. The applicant was requested to revise section 6.3 of the SmPC accordingly. Hence, in-use storage of open vials or product held in syringes of not more than 4 hours at 2-8°C prior to infusion has been deleted. The requirement that the drug product should be withdrawn from the unopened vials only immediately prior to use has been added instead.

Photostability studies were conducted on the FBDS placed in the same container closure system as the drug product demonstrating that the drug product is light sensitive. The photo sensitivity is reflected in labelling and SPC: “Store in the original package to protect from light.”

2.4.1.2. Finished Medicinal Product: Flushing solution

The flushing solution (FS) is a sterile solution for infusion for ICV administration that will be supplied in a Type 1 clear borosilicate glass vial, closed with a fluoropolymer coated butyl rubber stopper and capped with an aluminium seal. The FS is clear and colourless. Each vial is filled to a target volume of 5.4 mL to enable the withdrawal and delivery of 5 mL of solution. The composition of the FS is the same as of the finished product, except the FS does not contain the active substance, rhTPP1. The manufacturing process corresponds to that described for the finished product, only the volume filtered and filled is different.

Validation of the manufacturing process has been performed. The provided information is sufficient. The specification for the flushing solution covers all necessary tests for identity, quality, safety and composition.

Formal stability study data for FS stored at -20 ± 5 ºC combined with those generated with storage at 25 ± 2 ºC / 60 ± 5% RH support a cumulative shelf life of 24 months, which may include up to a year at room temperature prior to being frozen.

Adventitious agents

The finished product does not contain any animal-derived ingredients. Prior to release of the MCB and WCB of the production cell line testing was performed to ensure the cell line is free of endogenous infective viral particles or other adventitious agents.

The ability of the rhTPP1 manufacturing process to remove or inactivate potential viruses has been validated. The overall inactivation/removal capacity is regarded as sufficient for eliminating potential viral contamination. The risk with TSE is considered negligible.

2.4.2. Discussion on chemical, pharmaceutical and biological aspects

A GMP Certificate issued by an EEA authority for the originally proposed finished product manufacturer is not available (Major Objection). A pre-approval GMP inspection as prerequisite for a GMP Certificate resulted in major deficiencies. The deficiencies could not be solved and a GMP Certificate was not provided during the ongoing authorisation procedure. Therefore, the site was removed from the application dossier as required.

Due to the unmet medical need of Brineura, the CHMP agreed to replace the proposed finished medicinal manufacturer during the on-going authorisation procedure. The replacement site is appropriately authorised for the proposed manufacturing activities and holds a valid MIA. The minimum conditions for the introduction of the replacement site were discussed and agreed on. Comparability data and process validation data were requested (Major Objection) and satisfactory data was provided. The updated information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Two recommendations have been included.

2.4.3. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.4. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends points for investigation.

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical program consisted of one *in vitro* study in TPP1-deficient human fibroblasts, and 8 *in vivo* studies; 3 single-dose studies in Beagle dogs and Cynomolgus monkeys, and 5 repeat-dose studies in TPP1 KO mice, and juvenile TPP1-null and WT dachshund dogs.

2.5.2. Pharmacology

Primary pharmacodynamic studies

The primary pharmacodynamic properties of BMN 190 were investigated in TPP1-deficient human fibroblasts *in vitro* and in two animal models of human late infantile neuronal ceroid lipofuscinosis type 2, TPP1 knockout mice and TPP1-null longhaired dachshund dogs.

BMN 190 was taken up into TPP1-deficient human fibroblasts with an average half maximum rate (K_{uptake}) of 3.1 nM, which is considerably lower than the c_{max} of BMN 190 in human CSF. This uptake of BMN 190 was effectively inhibited by either the lysosomal enzyme N-acetyl-galactosamine-4-sulfate sulfatase, or high levels of mannose-6-phosphate, hence confirming the expected role of the cation-independent mannose-6-phosphate receptor (CI-M6PR) in the lysosomal uptake of the substance.

In adult TPP1 knockout mice, three consecutive IT-L infusions of 0.8 mg/day BMN 190 effectively reduced the brain levels of SCMAS, a surrogate marker of lysosomal storage material, which is known to accumulate in late infantile neuronal ceroid lipofuscinosis type 2. When the three consecutive IT-L infusions of up to 0.4 mg/day (~30 mg/kg) were started at an earlier age of 4 weeks, BMN 190 dose-dependently prolonged the survival of the TPP1 knockout mice compared to vehicle-treated TPP1 mutant controls from 16 to 23 weeks. In addition, BMN 190 clearly delayed the impairments in locomotor function, which already declined in vehicle-treated TPP1 mutant controls from 14 weeks of age.

In four investigations in juvenile TPP1-null longhaired dachshund dogs aged 9 weeks to approximately 4 months, BMN 190 was repeatedly administered by either IT-C bolus injection or as infusions via the ICV and IT-L routes, because administration sites had to be changed depending on the patency of the catheter and its dislocation due to growth of the animals.

Three consecutive BMN 190 doses of up to 32 mg effectively reduced the autofluorescent lysosomal storage material throughout the brain and spinal cord of one TPP1-null dachshund dog, albeit with variable levels of TPP1 activity. After repetitive infusion of 4 to 48 mg BMN 190 at rates of 0.3 to 0.6 ml/h, BMN 190 dose-dependently attenuated neurological deficits, improved cognitive learning functions in a T-maze apparatus and prolonged the lifespan of TPP1-null dachshund dogs in a single case for up 88 weeks of age. Moreover, quantitative MRI demonstrated that BMN 190 delayed ventricular enlargement and brain atrophy until approximately 16.5 months of age.

Secondary pharmacodynamic studies

No investigation of the secondary pharmacodynamic properties of BMN 190 was performed, which was justified by its administration as a pharmacologically inactive pro-drug that requires activation in the acidic environment of the lysosome. This has been accepted by the CHMP.

Safety pharmacology programme

No stand-alone safety pharmacology studies were performed with BMN 190, but parameters of cardiovascular safety and CNS function were integrated into one single-dose toxicity study in Cynomolgus monkeys and following repetitive administration in TPP1-null and WT dachshund dogs in line with the pertinent ICH S6(R1) guideline (EMA/CHMP/ICH/731268/1998).

BMN 190 did not adversely affect safety pharmacological parameters of cardiovascular and CNS function, in these studies. The absence of the evaluation of respiratory function is accepted given the lack of adverse respiratory findings in monkeys, after repeated administration in dachshund dogs and during clinical development.

Pharmacodynamic drug interactions

As BMN 190 is an inactive pro-drug of a recombinant human protein that requires activation in the acidic environment of the lysosome, no pharmacodynamic interaction with other drugs can be reasonably expected.

2.5.3. Pharmacokinetics

Pharmacokinetic/toxicokinetic parameters of BMN 190 in CSF and plasma were evaluated in single dose toxicity studies in Cynomolgus monkeys and following repeated dosing in the four pharmacodynamic investigations in TPP1-null and WT dachshund dogs. In addition, the CNS distribution of BMN 190 was analysed as part of the studies in dachshund dogs and also after single administration in Beagle dogs. In these investigations, BMN 190 concentrations were determined in the different matrices using non-validated ELISA assays.

Maximum BMN 190 concentrations in the CSF of Cynomolgus monkeys and dachshund dogs were achieved shortly after the end of ICV infusions and remained above the K_{uptake} (~3.1 nM or ~183 ng/ml) determined in TPP1-deficient human fibroblasts. The intracellular trafficking of BMN 190 to lysosomes has not been investigated. The t_{max} was prolonged with the extension of the infusion duration from 2 to 4 h. The AUC increased dose-dependently in the CSF of dachshund dogs after the first dose. There was no difference in the CSF exposure between TPP1-null and WT dachshund dogs following multiple administrations. In addition, no influence of the age of the animals at study initiation was apparent.

Despite the macromolecular size of BMN 190, systemic exposure was evident in both Cynomolgus monkeys and dachshund dogs after ICV, IT-L or IT-C administration, although C_{max} and AUC values were comparably about 230 to 1000-fold lower in plasma than in CSF of both species. Accordingly, BMN 190 not only passed the presumably compromised blood-brain-barrier (BBB) in TPP1-null dachshund dogs and human CLN2 patients, but also crossed the intact BBB in healthy monkeys. In contrast, BMN 190 apparently does not enter the eye to ameliorate the retinopathies in TPP1-null dachshund dogs.

BMN 190 was extensively distributed into various brain and spinal cord regions in Beagle and dachshund dogs as well as Cynomolgus monkeys and was commonly found to be enriched in superficial brain regions in proximity to CSF flow compared to deep brain layers. In Cynomolgus monkeys, highest BMN 190

concentrations were determined in superficial occipital cortex, cerebral cortex and cerebellum as well as in deep regions of the medulla, whereas in dachshund dogs, BMN 190 levels were particularly increased in hypothalamus, pons, cerebral cortex and cerebellum. The majority of BMN 190 in dachshund dogs was eliminated from CSF within 168 h and from plasma within 80 h post infusion.

CHMP accepted the lack of any investigation of the metabolism and excretion of BMN 190 in line with the prevailing the ICH S6(R1) guideline (EMA/CHMP/ICH/731268/1998). CHMP also considered that pharmacokinetic drug interaction studies are not required, because no interference with potentially co-administered small molecule drugs is reasonably expected for the unmodified recombinant human BMN 190 protein.

2.5.4. Toxicology

Single dose toxicity

Two single dose distribution, toxicity and TK studies were conducted in Cynomolgus monkeys given BMN 190 via either by ICV or IT-L infusion. Both single dose toxicity studies did not reveal any BMN 190-related findings in the CNS or other organs. Only catheter-related inflammation was observed in all animals, including vehicle controls, and this was an expected finding due to the route and method of administration. After IT-L infusion, mononuclear cell infiltrates were additionally identified in the meninges of the brain and spinal cord, which represent common non-adverse findings of CSF-administered drugs.

Repeat dose toxicity

Instead of performing stand-alone repeated-dose toxicity studies, the safety of multiple doses of BMN 190 administered either monthly or biweekly for 3 to 18 months was evaluated as part of the abovementioned four investigations in juvenile TPP1-null mutant and WT longhaired dachshund dogs. This approach was endorsed, because this animal model replicates disease-related aspects of human CLN2 disease, which would not be reflected by standard toxicity investigations in healthy species. Moreover, dachshund dogs were approximately 2 to 2.5 or 4 months old at study initiation and correspond to the age range of the envisaged paediatric patient population.

Anaphylactoid reactions/hypersensitivity reactions (facial oedema, erythema of the ears and face, urticaria, pale mucous membrane, vomiting, diarrhoea, tachycardia and hypotension) emerged shortly after the second or third administration of BMN 190 doses greater than 4 mg in TPP1-null and WT dachshund dogs, but not in vehicle-treated animals. Inflammatory reactions attributable to the catheter administration procedure (pleocytosis, infections, astrocytosis, microgliosis) developed after prolonged infusion in all dachshund dogs independent of the genotype or treatment with BMN 190 or vehicle. The serum levels of cardiac troponin I, a marker for cardiomyopathy, were found to be elevated in the surviving BMN 190-treated male and female TPP1-null dachshund dogs from 36, 40 and 43 weeks of age, respectively, whereas cardiac troponin I remained within normal ranges in BMN 190-treated WT dogs.

Genotoxicity

No genotoxicity studies were conducted with BMN 190. BMN 190 is not anticipated to be genotoxic due to its molecular structure and its mechanism of action. BMN 190 is an unmodified recombinant variant of the human TPP1 pro-enzyme. BMN 190 is not anticipated to enter the nucleus or interact with DNA, thus the genotoxicity risk is negligible.

Carcinogenicity

No carcinogenicity studies were conducted for BMN 190 as it is not anticipated to be carcinogenic based on its mechanism of action. BMN 190 is not an immunomodulator and is not expected to bind to DNA or influence cell proliferation. BMN 190 is administered as an inactive proenzyme, and activated following lysosomal uptake. Enzymatic activity is restricted to the lysosome where BMN 190 degrades accumulated storage materials.

Reproduction Toxicity

No reproduction toxicity studies were conducted. Reproductive organs were supposed to be analysed in the multiple dose dachshund dog studies, but limited histopathological data were only available from two studies. Overall, one testis, 4 cervices, 3 ovaries and uteri of 1 male and 4 female TPP1-null dachshund dogs were compared with 2 testes and 1 cervix, ovary and uterus of 2 male and 1 female WT dachshund dogs indicating lack of any adverse effect of BMN 190.

Local Tolerance

Local tolerance studies were not conducted. In agreement with current ICH S6(R1) recommendations (EMA/CHMP/ICH/731268/1998), the tolerability of the catheter-mediated drug delivery has been evaluated after single administration in Cynomolgus monkeys and following repeated dosing in TPP1-null and WT dachshund dogs. Histopathological assessment revealed no BMN 190-related effects, but neuronal necrosis and inflammation directly associated with mechanical damage from the ICV catheter, that were present in all groups including vehicle controls.

2.5.5. Ecotoxicity / environmental risk assessment

BMN 190 is an unmodified recombinant human protein, which is metabolised to endogenous amino acids. For this reason, BMN 190 is not expected to pose a risk to the environment in line with the pertinent European guideline (EMEA/CHMP/SWP/4447/00 corr. 1).

2.5.6. Discussion on non-clinical aspects

The pharmacodynamic rationale for clinical therapy of human CLN2 disease with BMN190 has been adequately demonstrated in two non-clinical *in vivo* models of CLN 2, TPP1 knockout mice and juvenile TPP1-null longhaired dachshund dogs. In these investigations, BMN 190 administered by the ICV, IT-L or IT-C routes effectively ameliorated the disease symptoms. BMN 190 reduced the lysosomal storage material, dose-dependently prolonged the survival and attenuated the impairments in cognitive learning and locomotor function of the animals. In TPP1-null dachshund dogs, BMN 190 also delayed ventricular enlargement and brain atrophy. Given the demonstration of lysosomal uptake of BMN 190 by TPP1-deficient human fibroblasts *in vitro* and the undoubted efficacy of BMN 190 in two different animal models of human late infantile neuronal ceroid lipofuscinosis type 2 *in vivo*, further *in vitro* investigation of the uptake of BMN 190 in neuronal cells of dachshund dogs and humans is not necessary.

It was noted that the TPP1 activity assay used to determine the effective BMN 190 dose revealed a high variability between TPP1 knockout mice that had received the same BMN 190 regimen, probably due to the technical difficulties in administering BMN 190 to the intrathecal space of TPP1 KO mice.

The results have also shown that BMN 190 did not reduce lysosomal storage material in the retina of TPP1-null dachshund dogs and, hence, did not interfere with progressive multifocal retinal detachment lesions in these animals. This lack of efficacy has been ascribed to the restricted CSF supply of the eye compared to other part of the CNS. BMN 190 is not expected to reach therapeutic concentration in the eye.

The investigations in juvenile TPP1-null and WT dachshund dogs were also used to evaluate the repeated-dose toxicity of BMN 190. This was endorsed as the animals covered the age range of the intended paediatric patient population. In addition, non-compliance with GLP regulations was also accepted, because this animal model better reflects the disease-related symptoms of CLN2 than healthy species in standard toxicity studies. However, the investigations in dachshund dogs are afflicted by several deficiencies in the design, the performance and documentation, which clearly limit the interpretation of the results. Specifically, the overall low number of animals, the lack of appropriate controls including historical data as well as the different doses and variable number of infusions within studies due to prominent hypersensitivity reactions clearly limit the interpretation of the findings. The remarkably different pharmacokinetic results even at the same BMN 190 doses are most likely attributable to the frequent changes of the CSF administration routes in dachshund dog studies due to complications with the catheter device, to the infusion duration, the generally low and variable numbers of CSF samples with high inter-individual variability and the use of non-validated ELISA assays. For these reasons, the results of the studies in juvenile dachshund dogs are inconclusive.

As the clinical dose of 300 mg BMN 190 was justified based on the tolerability of the 16 mg dose in dachshund dogs, clarification of the different hypersensitivity reactions observed in two dachshund dog studies after ICV infusion of 16 mg BMN 190 had been requested. The drug batches used in both studies had comparable specifications for endotoxins and high molecular weight species and differed only in low contents of polysorbate-80. However, a possible influence of CHOP contaminants and also of the vehicle could not be excluded, because hypersensitivity reactions even continued in the absence of BMN 190. As the hypersensitivities observed during clinical BMN 190 therapy only partially resemble those noted in animals and are also included in the proposed SmPC, the lack of further clarification on the inconsistent tolerability of the 16 mg BMN 190 dose is accepted.

The increased levels of cardiac troponin I, a marker for cardiomyopathy, which were determined in four BMN 190-treated TPP1-null dachshund dogs starting between 36 and 43 weeks of age, were attributed to the disease progression in these animals. This is agreed, because cardiac myofibre degeneration was additionally found only in the BMN 190-treated TPP1-null dachshund dog, which survived for the longest time period of 88 weeks. Moreover, autofluorescent lipopigments had been previously detected in the heart of another dog model of neuronal ceroid lipofuscinosis (Armstrong *et al.*, 1986) and cardiac hypertrophy was identified in human patients (Hofman *et al*., 2001; Gilbert-Barness, 2004) including also one case of cardiac death of an adult CLN2 disease patient (Fukumura *et al*., 2012). Based on available ECG measurements from therapeutic use of BMN 190, the need for routine ECG monitoring will be further pursued clinically.

The reproduction toxicity of BMN 190 was not investigated, although the drug might potentially be able to prolong the survival and quality of life of paediatric CLN2 disease patients. Accordingly, CHMP had recommended during scientific advice to perform a fertility assessment. So far, very limited histopathological data from male and female reproductive organs of BMN 190-treated TPP1-null dachshund dogs did not indicate any adverse effect of BMN 190. The absence of the relevant non-clinical data has been adequately labelled in the Product Information.

2.5.7. Conclusion on the non-clinical aspects

The CHMP considers the non-clinical data sufficient to support a positive opinion concerning this Marketing Authorisation Application.

2.6. Clinical aspects

2.6.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- **Tabular overview of clinical studies**

Study	Description	Objective	Number of Subjects	Dose
Study 190-201	First-in-human Phase 1/2 open-label dose-escalation study in CLN2 disease subjects followed by at least 48 weeks of treatment with a stable dose of BMN 190 every other week	Safety, Efficacy, PK, Immunogenicity	24 (23 completed)	30, 100, and 300 mg ICV, Q2W
Study 190-202	Extension study for subjects who complete treatment in 190-201. Subjects who enroll in 190-202 will continue to receive every other week treatment with BMN 190 for up to 5 years.	Safety, Efficacy, PK, Immunogenicity	18 of 23 subjects who completed 190-201 were enrolled in 190-202 until interim cut-off date (15th October 2015) All enrolled patients, except the one patient who received a single dose of study drug in study 201 and then withdrew from the study (n = 23) continued in study 202 until 03 June 2016.	300 mg ICV, Q2W

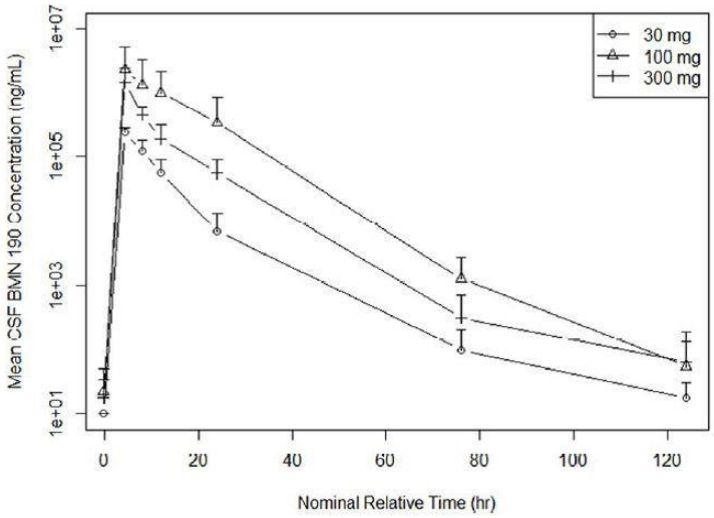
2.6.2. Pharmacokinetics

Absorption

BMN 190 is applied as aqueous solution directly into the CSF therefore absolute or relative bioavailability and food effect studies were not conducted. The formulation used in the clinical trials has been declared to be identical with the marketed formulation. A rapid increase in CSF concentration was observed with Cmax occurring after the end of infusion. T_{max} was reached at ~4-5 hours in CSF and ~12 hours in plasma after start of infusion.

After the first ICV administration of 30 mg dose, 100 mg dose and 300 mg dose, Cmax was $0.22 \cdot 10^6$ ng/ml, $2.32 \cdot 10^6$ ng/ml and $1.49 \cdot 10^6$ ng/ml, respectively. AUC was $1.60 \cdot 10^6$ ng/ml, $24.0 \cdot 10^6$ ng/ml and $9.5 \cdot 10^6$ ng/ml after the first ICV administration of 30 mg dose, 100 mg dose and 300 mg dose, respectively.

Figure 1. Mean Single Dose BMN 190 CSF Concentration-Time Profile by Dose



Mean BMN 190 concentration-time profiles by dose level in CSF following the initial ICV infusion in patients with CLN2. Error bars represent the standard deviation. Mean representations of the CSF PK profiles are based on between 2 and 3 samples per time point from 3 patients for the 30 mg and 100 mg dose level, and between 14 and 18 samples per time point from 18 patients for the 300 mg dose level. BQL values were set to one-half the LLOQ of the bioanalytical assay (10 ng/ml).

Peak BMN 190 concentrations in the plasma were approximately 1000-fold lower than concentrations in the CSF, with no apparent correlation between CSF and plasma exposure within patients following ICV administration.

Multiple dose CSF and plasma PK data suggest no apparent accumulation of BMN 190, or time-dependence in BMN 190 PK in CSF or plasma with ICV administration of 300 mg every two weeks. This is line with the results of the half-life is about 7 hours in CSF. Based on results of in vitro studies the lysosomal half-life of rhTPP1 was estimated to 11.5 days. Consequently steady state can be expected after 8 weeks. In most cases there were no quantifiable trough levels in CSF, indicating that no accumulation occur in this compartment.

Distribution

The distribution volumes are up to ~400 ml and support the assumption that BMN190 is absorbed by CNS tissue.

Elimination

BMN 190 is a recombinant human protein which is metabolised to endogen components (amino acids), therefore neither metabolic or excretion studies nor studies in special populations have been conducted. For the same reason, the interaction potential with small chemical molecules is considered negligible and no DDI studies have been conducted.

Dose proportionality and time dependencies

In general, BMN 190 single dose CSF exposure increased less than proportionally with dose across the 30 to 300 mg dose level following the initial ICV infusion. Comparing the 30 mg to 300 mg dose level, mean CSF C_{max} and $AUC_{0-\infty}$ increased 6.74-fold and 5.27-fold, respectively, with the 10-fold increase in dose. However the results are partially inconclusive as the 100m strength showed higher exposure as the 300 mg. This has been attributed to the low number of patients treated with the 100 mg strength (n=3) so that a single outlier could affect the result.

Variability

The intra individual variability was moderate to high in CSF and very high in plasma. There was no apparent effect of patient baseline sex, age, race, bodyweight, BMI or CLN2 score on the PK of BMN 190 in CSF or plasma with 300 mg Q2W ICV infusions.

Immunogenicity

ADAs were detected in the CSF of 5/24 subjects (21%) and in the serum of 19/24 subjects (79%) treated with BMN 190 for 49-107 weeks. The presence of ADA in the CSF and serum did not appear to have an impact on the PK of BMN 190 in CSF or plasma, respectively. The magnitude of BMN 190 CSF exposure, within the range of exposure obtained with 300 mg Q2W administration, did not correlate with the development of ADA in CSF.

There was no apparent correlation between the magnitude of BMN 190 plasma exposure, within the range evaluated with 300 mg Q2W dosing, and magnitude of ADA response or the time to ADA development in the serum.

The validity of the analytical method for the determination of IgE used in the clinical study is questionable. A new method has been developed by the applicant which is considered reliable and will be used in the future.

2.6.3. Pharmacodynamics

Mechanism of action

CLN2 disease is autosomal recessively inherited, characterized by the deficiency of TPP1 that is caused by mutations in the CLN2 gene. The active pharmaceutical ingredient (API) in Brineura is a recombinant

proenzyme form of human lysosomal serine protease tripeptidyl peptidase-1 (TPP1) which is intended as an enzyme replacement therapy for CNL2 patients with insufficient TPP1 activity.

Primary pharmacology

TPP1 cleaves the N-terminal tripeptide from polypeptides imported into the lysosome, without any known substrate specificity. The pro-enzyme BMN190 is taken up into the lysosome via the cation independent mannose 6-phosphate receptor (CI-M6PR) where a 176 amino acid pro-peptide fragment is cleaved in the acidic environment, yielding the 368 amino acid active enzyme.

Response to treatment, as described in the Clinical Efficacy section, does not appear to correlate with BMN 190 exposure in the CSF, within the range of exposures obtained with 300 mg Q2W ICV administration.

Up to date no predictive biomarkers have been described.

2.6.4. Discussion on clinical pharmacology

The applicant presented a much reduced PK program. This was justified in regard to the absolute and relative bioavailability as the drug product is an aqueous solution directly administered to the CSF. As the drug substance is a protein which is expected to be metabolised to endogenous amino acids the lack of excretion, interaction studies and data in special populations is considered acceptable.

Only one clinical study plus an extension was conducted in a small number of patients and therefore pharmacokinetic data are limited. There are several uncertainties due to the small number of patients (e.g. CSF PK measurements for 100mg strength was highly affected by one patient receiving this dose), so that results are partially inconclusive (e.g. dose proportionality, effect of race). However these are considered minor deficiencies given the high medical need and the rarity and severity of the disorder to be treated.

The data derived from study 201 including the extension allow a basic description of the pharmacokinetic profile of BMN 190 but are of limited value. No correlation between the exposure in CSF and clinical response could be established and provided data in plasma is incomplete and highly variable.

The immunogenicity has been investigated and the results so far indicate that ADAs occur but have no significant effect on PK.

2.6.5. Conclusions on clinical pharmacology

The limited data derived from study 201 including the extension allow a basic description of the pharmacokinetic profile of BMN 190 but are of limited value. No correlation between the exposure in CSF and clinical response could be established and provided data in plasma is incomplete and highly variable.

The immunogenicity has been investigated and the results so far indicate that ADAs occur but have no significant effect on PK. A fully validated analytical method for the determination of IgE ADA has been established in order to evaluate a possible relationship of severe hypersensitivity reactions with drug-specific IgE in the future.

2.7. Clinical efficacy

A Phase 1/2 dose escalation study (Study 190-201) and its open label extension (Study 190-202) form the basis to support the efficacy of BMN 190 (cerliponase alfa) in the treatment of Neuronal Ceroid Lipofuscinosis type 2 (CLN2).

Additionally, a Natural History non interventional study has been conducted and submitted to provide a comparator group. A Phase 2 study (Study 190-203) conducted in siblings of subjects enrolled in the other two studies is ongoing as agreed in a Paediatric Investigation Plan. Given the very limited exposure (as of 15 May 2016 only 3 subjects have been enrolled) no data from this study is included in the efficacy assessment.

2.7.1. Dose response study

No dose response study in CLN2 patients has been submitted. All information with respect to starting dose, timing of dose as well as infusion volume and rate has been derived from the nonclinical programme.

Findings from the nonclinical program were originally used to support a clinical dose regimen of 300 mg every other week by ICV infusion approximately 4 hours in duration. Chronic administration of 16 mg every other week BMN 190 by ~4 hour infusion to juvenile TPP1-null dogs resulted in significant attenuation of the disease progression.

BMN 190 concentrations in the CSF remained above the K_{uptake} (~3.1 nM or 183 ng/mL) for 48-72 hours following ICV infusion in monkeys and dogs, enabling the widespread distribution to most superficial and deep brain tissues in both species by likely maintaining a concentration gradient across the CSF tissue barrier. The CNS tissue half-life of BMN 190 assumed to be between 3-15 days in monkeys, together with the 11.5 day lysosomal half-life of BMN 190 characterized previously (Lin, 2001, Biochem.J.), was used to support ICV administration once every other week.

As indicated in section 2.4.6 above, however, a No Observed Effect Level (NOAEL) could not be reliably determined after repeated administration in the investigations in juvenile TPP1-null and WT dachshund dogs, due to the overall low number of animals, the lack of appropriate controls and the different doses and variable number of drug infusions. An interspecies comparison of BMN 190 exposure levels (C_{max} and AUC_{0-t}) in monkeys, juvenile dachshund dogs and human patients further indicated that no relevant safety margin between maximum CSF and plasma exposure of animals with respect to the proposed therapeutic regimen of human patients exists. For this reason, the proposed clinical dose is not supported by the inconclusive non-clinical data. Although the proposed dose may not be optimal for the whole target population, it was found to be effective in the main clinical study and is thus acceptable.

2.7.2. Main study

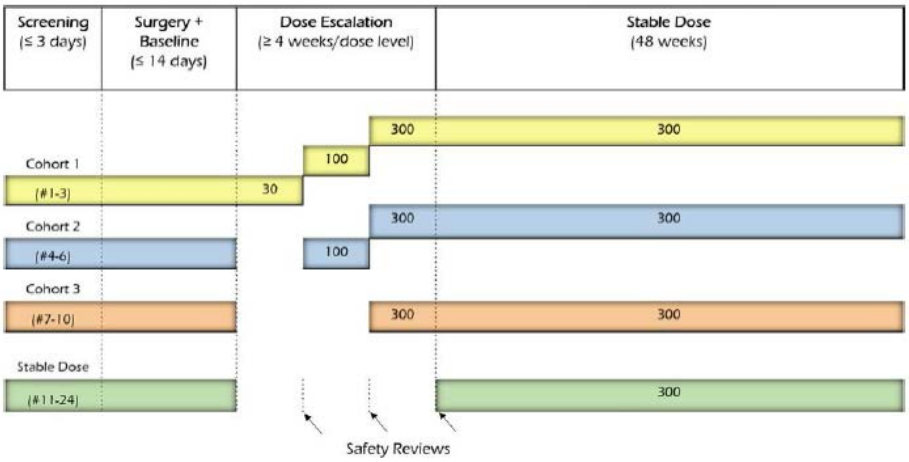
A Phase 1/2 Open-Label Dose-Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Intracerebroventricular BMN 190 in Patients with Late-Infantile Neuronal Ceroid Lipofuscinosis (CLN2) Disease

Methods

This was a single-arm open label study, designed to assess safety and tolerability of Brineura starting at low doses (30 mg and 100 mg). All subjects escalated to the therapeutic dose (300 mg) when the lower doses

were deemed to be safe by an independent data monitoring committee (DMC). The study duration for all enrolled subjects was 48 weeks of treatment at the therapeutic dose of 300 mg every other week.

Figure 2. Dose Escalation Scheme (190-201)



Study Participants

Inclusion Criteria

Patients were recruited in the trial if they complied with the following:

- Had a diagnosis of CLN2 disease determined by TPP1 enzyme activity (dried blood spot) available at study entry.
- Had early-to-moderate disease progression documented by a score of 3-6 on the ML scale, with a score of at least 1 in each of the motor and language domains
- Seizures and concomitant seizure medications were stable in the judgment of the investigator

Exclusion Criteria

Patients who met any of the following exclusion criteria were not eligible to participate in the study:

- Were less than 3 years old at enrolment
- Were 16 years old or older at enrolment
- Had another inherited neurologic disease,
- Had another neurological illness that may have caused cognitive decline (e.g., trauma, meningitis, haemorrhage) before study entry
- Required ventilation support, except for non-invasive support at night
- Had received stem cell, gene therapy, or ERT for CLN2 disease
- Had contraindications for neurosurgery or MRI scans

- Had generalized motor status epilepticus within 4 weeks before the First Dose visit, taking care that status epilepticus was on clinical examination and not only EEG (enrollment could be postponed)
- Had severe infection (e.g., pneumonia, pyelonephritis, or meningitis) within 4 weeks before the First Dose visit (enrolment may be postponed)
- Were prone to complications from intraventricular drug administration, including patients with hydrocephalus or ventricular shunts
- Had known hypersensitivity to any of the components of BMN 190
- Had received any investigational medication within 30 days before the first infusion of study drug or was scheduled to receive any investigational drug other than BMN 190 during the course of the study
- Had a medical condition or extenuating circumstance that, in the opinion of the investigator, might compromise the subject's ability to comply with the protocol required testing or procedures or compromise the subject's well-being, safety, or clinical interpretability

Treatments

Subject participation involved surgical implantation of the ICV access device (reservoir and cannula) followed by no more than 14 days of post-operative recovery prior to any dosing with BMN 190.

BMN 190 was administered every other week by ICV infusion in the morning after a minimum fast of 2 hours. BMN 190 was diluted to 10 mL prior to administration of doses lower than 300 mg. The study drug was infused ICV at a rate of 2.5 mL/hour to deliver the entire volume over approximately 4 hours. Subjects were pretreated with an age-appropriate dose of antihistamine (and antipyretic, if appropriate) medication ~30 minutes before infusion. Subjects could be pretreated, at the discretion of the Investigator, with age-appropriate sedative medication approximately 30 minutes before BMN 190 infusion according to institution's standard practices.

The planned dose levels were 30, 100, and 300 mg. Subjects 1-10 were assigned to the Dose Escalation Period and placed in 1 of 3 dose level cohorts to receive dosing at 30 mg, 100 mg, and/or 300 mg. Subjects in the Dose Escalation Period received between 4-22 weeks of treatment at 30 mg, 100 mg, and/or 300 mg, prior to the start of the Stable Dose Period. Once the Dose Escalation Period was completed, all subjects graduating from the Dose Escalation Period, in addition to 14 new subjects who had not yet received treatment, were administered a stable dose of BMN 190 (300 mg, the highest tolerated dose) every other week for 48 weeks. At the end of the 48-week treatment period, all subjects were eligible to enrol in the ongoing extension study (190-202).

Medications (prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days before informed consent were recorded. At each subsequent visit change in any medication was recorded.

Objectives

The *primary objectives* of this study were to:

- Evaluate safety and tolerability of BMN 190 administered to subjects with CLN2 disease by an implanted intracerebroventricular (ICV) access device
- Evaluate effectiveness using an adapted CLN2 disease-specific rating scale in comparison with natural history data after 48 weeks of treatment

Secondary objectives of this study were to:

- Evaluate the impact of treatment on measurement of brain atrophy in comparison with CLN2 disease natural history data after 48 weeks of treatment
- Characterize single- and repeated-dose pharmacokinetic (PK) in cerebrospinal fluid (CSF) and plasma
- Determine immunogenicity in CSF and serum

Exploratory objectives of this study were to:

- Evaluate impact of treatment on disease-related CSF/plasma biomarkers
- Assess age-appropriate developmental milestones
- Assess CLN2 disease-specific quality of life (QOL)

Outcomes / endpoints

The primary endpoint was the score on the 6-point adapted CLN2 motor-language scale (abbreviated as “ML scale” throughout this document)

Primary efficacy analysis: a responder analysis performed to examine the population of responders during the 300 mg dosing period on the ML scale

The following subsets of this scale were also measured for analysis:

- 9-point adapted CLN2 motor-language-vision scale (MLV scale)
- 12-point adapted CLN2 motor-language-vision-seizure scale (total CLN2 scale)

Key secondary endpoint was brain atrophy. Changes in brain structure and anatomy related to disease progression were assessed by MRI measuring specific parameters:

- Whole brain volume (WBV) (in mm3)
- Volume of cerebrospinal fluid (in mm3 and as a percentage of WBV)
- Volume of total cortical grey matter (in mm3 and as a percentage of WBV)
- Total white matter volume (in mm3 and as a percentage of WBV)
- Whole brain apparent diffusion coefficient (mm2/s)

Exploratory endpoints were as follows:

- CSF/plasma biomarkers
- Developmental Milestones (measured by the Denver II Development Scale)
- Quality of Life (assessed with the following survey instruments: PedsQL- Parent Report for Toddlers, PedsQL- Parent Family Impact, CLN2 Disease-based Quality of Life)

Sample size

The sample size estimate was derived from analysis of a natural history database from Hamburg, Germany that includes the longitudinal analysis of 29 genotype-proven CLN2 disease patients.

The primary endpoint was assumed to be the within-subject estimate of slope reflecting the rate of decline in the ML scale over time. Based on a review of subjects from the natural history database referenced above, it was assumed that untreated patients would decline a mean of 2.0 points per 48 weeks. The actual slopes for rate of change estimates using two different modelling methods were both greater than 2 (2.18 and 2.89 per year), but 2.0 per 48 weeks was chosen as a conservative estimate for purposes of comparison for the 190-201 analysis).

The primary analysis was assumed to be a one-sample t-test against a fixed point alternative:

H0: μBMN-190 = 2.0

H1: μBMN-190 $\neq$ 2.0

where μBMN-190 represents the population mean rate of decline with treatment with BMN 190.

If treatment resulted in a mean rate of decline of 0.5, with a standard deviation of 1.8, then 18 evaluable subjects were required to achieve 90% power to reject H0 in favour of H1, assuming a 2-sided test with significance level α=0.05. This was increased to 22 subjects to allow for a discontinuation rate of ~20%.

Randomisation

This was a single-arm study. Eligible subjects were enrolled sequentially into 3 dosing cohorts (and later into a stable dosing period) in this single arm study.

Blinding (masking)

This was an open-label study. Oversight of MRI evaluation was performed by independent radiologists at a central imaging facility. The interpreting radiologists and software analysis were blinded to subject and time on study.

Statistical methods

Analysis Populations:

ITT Population (n=23): all subjects who received BMN 190 and reported any efficacy results excluding one subject who withdrew from the study after a single infusion of study drug during the Dose Escalation Period due to inability to continue with study procedures.

Per Protocol Population: Because the ITT and PP populations were determined to be identical, no separate PP analysis was performed.

Populations for Sensitivity Analyses:

- *Efficacy Population (n=21):* ITT subjects, but excluding 2 subjects who enrolled with a baseline ML scale score of 6 (the maximum score) and who showed no decline in their ML scale score at the end of 48 weeks of Stable Dose Period treatment with 300 mg BMN 190. These two subjects were

excluded because the analysis of the rate of decline presupposes that the subject has, in fact, entered the period of clinical decline; subjects who achieve the maximum score on the ML scale and do not decline from that score during the study are assumed not to yet be in the period of clinical decline.

Subset of Efficacy population (n=18): includes only subjects with a 300-mg baseline ML scale of 3, 4, or 5.

- *Enrolled Population (n=24):* all subjects who provided informed consent for 190-201

  Subset of enrolled population (n=22): includes the single dose subject (with imputed 4-point loss), but excludes the 2 subjects with stable ML scores of 6.

- *Safety Population (n=24): all subjects who had an ICV access device implanted*

Baselines:

Two different baselines are defined, depending on the analysis:

- For evaluation of efficacy of the 300 mg dose of BMN 190 with respect to adapted CLN2 scale ratings and MRI measurements, baseline is the last observation preceding the first 300 mg infusion. This is referred to as "300 mg baseline" and is used for primary efficacy analyses and the majority of sensitivity analyses in this report. As a result of this definition, the 48-week treatment period for efficacy evaluation can extend beyond 48 weeks for subjects enrolled in the dose escalation cohorts.
- For evaluation of efficacy of BMN 190 at any dose, baseline is the last observation preceding the first infusion of BMN 190. This is referred to as "study baseline". Efficacy results that were analyzed over the entire dosing period include full Hamburg and WC CLN2 scores versus analysis day (sensitivity analysis), PedsQL Generic Core Scale and Family Impact Module, and the CLN2 disease-based QoL instrument.

Primary Efficacy Endpoints

The primary analysis was a responder analysis based on the ITT population. Response was defined as the absence of an unreversed two-point decline or score of zero in CLN2 score by Week 48 (Study Day 340 relative to first 300 mg infusion). An unreversed 2-point decline was defined as a decline that had not returned to within 1-point of baseline at the time of the final study ML assessment.

The proportion of subjects responding by Week 48 was tested against a fixed-point alternative using a 1-sample exact binomial test. The null and alternative hypotheses to be tested were:

H0: $p_{BMN\text{-}190} \leq 0.5$

H1: $p_{BMN\text{-}190} > 0.5$

where $p_{BMN\text{-}190}$ represents the percent responding in the BMN 190-treated population.

As a sensitivity analysis, the analysis was repeated with response defined as the absence of an unreversed one-point decline in CLN2 by Week 48. The percent of subjects responding by this definition were tested against a fixed proportion of 0.25 using the exact binomial test.

The boundary values for hypothesis testing, 0.50 and 0.25, were determined as follows: The mean estimated rate of decline within natural history patients was approximately 2 units/48 weeks with standard deviation 1. Assuming that the rates of decline are normally distributed, one would expect 50%

of untreated patients to have rates of decline less than 2 units, and 16% of untreated patients to have rates of decline less than 1 unit. Consequently, the null hypotheses for testing 2- and 1-point responder rates (RR), namely H0: RR ≤0.50, and H0: RR ≤0.25, respectively, is reasonable.

The response criterion, a two-point decline in ML score by Week 48, coincides with the population rate of decline for natural history patients (2.0 points per 48 weeks). For subjects with a 300 mg baseline score of 1 (n = 1), a responder is defined as a subject who did not progress to a 0 in the treatment period. For individual motor and language domains, responders were identified as subjects who did not lose a point on that domain at time of last assessment. Responder rates were presented as binomial proportions and Kaplan-Meier estimates.

Another important measure of treatment effect was the rate of decline of the subject's score on the ML scale, reported as a point loss per 48-week 300-mg dosing period. Slopes analysis was a comparison of the observed rate of decline to a population rate of decline in untreated natural history patients of 2.0 points per 48 weeks. The rate of decline was estimated for each treated subject, based on comparing the last adapted CLN2 rating scale assessment to the baseline assessment and scaling that change to a 48-week time period.

In addition to analysis of the ML scale score, analyses of the rate of decline were also performed for the MLV scale and the total CLN2 scale scores.

Analyses of the change in scale scores from the 300 mg baseline to the last recorded observation were conducted on the ML, MLV, and total CLN2 scale scores.

Secondary Efficacy Endpoints:

The secondary outcome measure was brain MRI parameter assessments. Results were presented descriptively over time and summarized in tabular format by nominal timepoint.

Exploratory Endpoints:

a) The Denver II Development Scale was administered to assess development milestones and summarized in tabular format by nominal timepoint.

b) Quality of life was assessed using 3 different instruments:

- PedsQL Parent Report for Toddlers
- Parent Family Impact
- CLN2 disease-based Quality of Life

These 3 QoL instruments include multiple modules, which were scored separately and then added for an overall score. Results were presented descriptively over time and summarized in tabular format by nominal timepoint.

Results

Participant flow

Twenty-four subjects were enrolled. Subjects 1-10 were assigned to three 3-subject cohorts to participate in a Dose Escalation Period. Subsequent to completion of the Dose Escalation Period, all subjects (including

Subjects 11 through 24) were administered a stable dose of BMN 190 (300 mg) every 14 days for 48 weeks. A single subject enrolled in Cohort 3 (1287-1007) withdrew consent from the study after ICV access device placement and a single infusion because of inability to continue with study procedures. All other subjects (n = 23) who enrolled in 190-201 remained on treatment through the end of the study.

Table 1. Subject Disposition

Category	C1 (n = 3)	C2 (n = 3)	C3 (n = 4)	SDO (n = 14)	Overall (n = 24)
Overall[a]					
Subjects Enrolled	3 (100%)	3 (100%)	4 (100%)	14 (100%)	24 (100%)
Subjects Treated	3 (100%)	3 (100%)	4 (100%)	14 (100%)	24 (100%)
Subjects who Completed the Study	3 (100%)	3 (100%)	3 (75%)	14 (100%)	23 (96%)
Subjects who Discontinued from the Study	0	0	1 (25%)	0	1 (4%)
Subjects Evaluable for Safety[b]	3 (100%)	3 (100%)	4 (100%)	14 (100%)	24 (100%)
Subjects Evaluable for ITT Analysis[c]	3 (100%)	3 (100%)	3 (75%)	14 (100%)	23 (96%)

Cohort: C1, C2, C3=Cohorts 1, 2, and 3; SDO=Stable dose only
a The total number of subjects enrolled in each cohort and overall was used as the denominator for each cohort, dose group, and overall.
b The safety evaluable population included all subjects who had an ICV access device implanted..
c The ITT population included all subjects who received at least one dose of BMN 190 and reported any efficacy results, but excluded subject 1287-1007 who withdrew from Cohort 3 after a single infusion.

Recruitment

First patient randomized: 13 September 2013

Last patient completed: 30 November 2015 (last dose given)

Conduct of the study

Five protocol amendments were issued for this study. None of the changes negatively impacted subject safety or integrity of the data collected during the course of the study.

Based on clinical review of the protocol deviation listing, there have been no important protocol deviations that were considered to meaningfully impact the welfare of the subjects or the integrity of the data. Additional protocol deviations were observed across all subjects. The most frequent of these deviations were attributed to procedures which were not done or which were completed outside of the protocol-specified windows.

A total of 616 infusions were performed during the course of the study. Compliance, as measured by (infusions given)/(infusions planned), was 99.8%. Of the 616 infusions started during the study, 16 (in 9 subjects) were interrupted and 8 (in 6 subjects) were not completed. Compliance, as measured by (infusions completed)/(infusions planned), was 98.7%. Most incomplete infusions were due to device-related problems (such as leaking or dislodgement of the needle).

Baseline data

Twenty-four subjects were enrolled at 5 clinic sites: University of Hamburg (Germany), Bambino Gesu Children's Hospital (Italy), Evelina Children's Hospital (United Kingdom), Great Ormond Street Hospital (United Kingdom), and Nationwide Children's Hospital (United States).

Overall, the treatment group included 9 (38%) males and 15 (63%) females. The mean (SD) age of the subjects at enrolment was 4.3 (1.24) years. Twenty-three subjects (96%) were white and 1 (4%) was Asian.

Table 2. Demographic Characteristics (Analysis Population: Enrolled Population)

Demographic	C1 (n = 3)	C2 (n = 3)	C3 (n = 4)	SDO (n = 14)	Overall (n = 24)
Age at Enrollment (yrs)					
Mean (SD)	4.3 (1.53)	4.7 (1.15)	5.5 (1.91)	3.9 (0.83)	4.3 (1.24)
Median	4.0	4.0	5.0	4.0	4.0
Min , Max	3.0 , 6.0	4.0 , 6.0	4.0 , 8.0	3.0 , 5.0	3.0 , 8.0
Sex					
F	1 (33%)	2 (67%)	3 (75%)	9 (64%)	15 (63%)
M	2 (67%)	1 (33%)	1 (25%)	5 (36%)	9 (38%)
Childbearing Potential (females only)					
No	1 (100%)	2 (100%)	3 (100%)	9 (100%)	15 (100%)
Race					
Asian	0	1 (33%)	0	0	1 (4%)
Black or African American	0	0	0	0	0
White	3 (100%)	2 (67%)	4 (100%)	14 (100%)	23 (96%)
Other	0	0	0	0	0
Ethnicity					
Hispanic or Latino	0	0	0	1 (7%)	1 (4%)
Not Hispanic or Latino	3 (100%)	3 (100%)	4 (100%)	13 (93%)	23 (96%)

Overall, the mean (SD) age of disease onset was 3.4 (1.07) years. One or both of the two most common alleles (c.622C>T and c.509-1G>C) were present in 17 subjects (71%), and other mutations were present in 7 (29%) of subjects.

The baseline characteristics of the population are presented in the Table below.

Table 3. Baseline Characteristics (Enrolled Population)

	C1 (n = 3)	C2 (n = 3)	C3 (n = 4)	SDO (n = 14)	Overall (n = 24)
Age at Disease Onset (yr)					
< 3	0	1 (33%)	0	6 (43%)	7 (29%)
3- < 5	1 (33%)	1 (33%)	2 (50%)	8 (57%)	12 (50%)
≥ 5	1 (33%)	1 (33%)	2 (50%)	0	4 (17%)
Pre-symptomatic	1 (33%)	0	0	0	1 (4%)
n	2	3	4	14	23
Mean (SD)	4.0 (1.36)	3.6 (1.42)	4.7 (1.59)	3.0 (0.29)	3.4 (1.07)
Median	4.0	3.0	4.7	3.0	3.0
Min , Max	3.1 , 5.0	2.5 , 5.2	3.2 , 6.3	2.6 , 3.6	2.5 , 6.3
Genotype					
c.622C>T	0	1 (33%)	1 (25%)	3 (21%)	5 (21%)
c.509-1G>C	0	1 (33%)	0	1 (7%)	2 (8%)
c.622C>T and c.509-1G>C	0	0	0	2 (14%)	2 (8%)
c.622C>T and Other	1 (33%)	0	2 (50%)	1 (7%)	4 (17%)
c.509-1G>C and Other	2 (67%)	0	1 (25%)	1 (7%)	4 (17%)
Other	0	1 (33%)	0	6 (43%)	7 (29%)
Screening ML Scale Score					
6	1 (33%)	0	1 (25%)	0	2 (8%)
5	0	0	0	2 (14%)	2 (8%)
4	0	0	1 (25%)	6 (43%)	7 (29%)
3	2 (67%)	3 (100%)	2 (50%)	6 (43%)	13 (54%)
n	3	3	4	14	24

	C1 (n = 3)	C2 (n = 3)	C3 (n = 4)	SDO (n = 14)	Overall (n = 24)
Mean (SD)	4.0 (1.73)	3.0 (0.00)	4.0 (1.41)	3.7 (0.73)	3.7 (0.95)
Median	3.0	3.0	3.5	4.0	3.0
Min , Max	3 , 6	3 , 3	3 , 6	3 , 5	3 , 6
Baseline ML Scale Score					
6	1 (33%)	0	1 (25%)	0	2 (8%)
5	0	0	0	2 (14%)	2 (8%)
4	0	0	1 (25%)	5 (36%)	6 (25%)
3	2 (67%)	3 (100%)	1 (25%)	6 (43%)	12 (50%)
2	0	0	1 (25%)	1 (7%)	2 (8%)
n	3	3	4	14	24
Mean (SD)	4.0 (1.73)	3.0 (0.00)	3.8 (1.71)	3.6 (0.85)	3.6 (1.06)
Median	3.0	3.0	3.5	3.5	3.0
Min , Max	3, 6	3, 3	2, 6	2, 5	2, 6
300 mg Baseline ML Scale Score					
6	1 (33%)	0	1 (33%)	0	2 (9%)
5	0	0	0	2 (14%)	2 (9%)
4	0	0	0	5 (36%)	5 (22%)
3	2 (67%)	2 (67%)	1 (33%)	6 (43%)	11 (48%)
2	0	0	1 (33%)	1 (7%)	2 (9%)
1	0	1 (33%)	0	0	1 (4%)
0	0	0	0	0	0
n	3	3	3	14	23
Mean (SD)	4.0 (1.73)	2.3 (1.15)	3.7 (2.08)	3.6 (0.85)	3.5 (1.20)
Median	3.0	3.0	3.0	3.5	3.0
Min , Max	3, 6	1, 3	2, 6	2, 5	1, 6

Concomitant medications and/or nutritional supplements were taken by 100% of the subjects. All subjects were taking anticonvulsants. Subjects could also be taking medications for myoclonus, tremor, agitation, and pain.

Numbers analysed

24 subjects have signed the informed consent. Intent-to-Treat (ITT) Population included 23 patients as one patient withdrew from the study after a single infusion of study drug.

Outcomes and estimation

The clinical severity of CLN2 disease has been quantified by two related clinical scales, the Hamburg scale (Steinfeld, 2002, Am.J.Med.Genet.); (Worgall, 2008, Hum.Gene Ther.) and the Weill Cornell Scale (WC scale)

(Dyke, 2012, AJNR Am.J Neuroradiol.); (Worgall, 2007, Neurology). Both scales are 0-12 point inventories of disease-based clinical assessments that measure function in children older than 2 years through the course of the disease. Each scale consists of four domains: Hamburg (motor, language, vision, and seizures) and WC (gait, language, myoclonus, and feeding). Within each domain of both scales, a score from 0 to 3 represents age-appropriate best function (3) to essentially no function (0). Overall scores are calculated by summing the 4 domain scores for a final rating of 0 (severely impaired) to 12 (normal). The scales use similar gradations to measure major clinical domains of gross motor and language. These domains are the hallmarks of neurological loss of function, are predictive of disease severity, and are scales on which a potential therapeutic benefit may be measured.

However, the total Hamburg and WC scores have limitations that affect interpretation of disease progression. Of the 8 domains for the 2 clinical scales, 4 have therefore been excluded for assessment of the primary efficacy analysis: Hamburg ‘seizure’ and ‘vision’ domain, WC ‘feeding’ and ‘myoclonus’ domain.

The primary metric used to quantify disease progression was the aggregate of the Hamburg ‘motor’ and ‘language’ domains (the ML scale), which was a 0 to 6-point scale in which each point measured a major inflection point in the decline of motor and language function from age-defined normal to minimal or no function.

In order to ensure consistency across sites and throughout the 190-201 study, the CLN2 motor-language scale was adapted by the Hamburg investigators to include anchor point definitions that would allow consistent ratings within the study conduct. These anchor point definitions were minimal, and they were proposed by Hamburg investigators to be consistent with those used in the collection of the clinical information used in the natural history analysis. The adapted CLN2 ML scale was intended to respect the historical application of the Hamburg scale, and allow consistent and harmonized ratings in a multi-national, multi-site clinical efficacy study. Differences between the original Hamburg scale and the adapted CLN2 rating scale used in 190-201 are outlined in the table below:

Table 4. Differences between Hamburg and Adapted CLN2 Rating Scales

Domain	Score	Hamburg Scale (natural history)	Adapted CLN2 Rating (190-201)	Rationale for Modifications
Motor	3	Walks normally[a]	Grossly normal gait.	Clarification
	2	Frequent falls, obvious clumsiness	Abnormal gait; independent≥10 steps[c] Frequent falls, obvious clumsiness	Added "step" criteria to clarify and harmonize the definition of gait changes across sites/investigators
	1	No unaided walking or crawling only	No unaided walking or crawling only. Cannot walk 10 unassisted steps.	Clarification
	0	Immobile, mostly bedridden	Immobile, mostly bedridden	No changes
Language	3	Normal[b]	Grosslynormal[d]	Clarification
	2	Recognizably abnormal	Has become recognizably abnormal (worse than the individual maximum)[e]	Added the language baseline definition to loss of function
	1	Hardly understandable	Hardly understandable[f]	No changes
	0	Unintelligible or no language	Unintelligible or no language	No changes

[a] In some children, motor development was never really normal.

[b] In some children, normal language development was never present. In such cases, the best performance ever achieved was taken as a starting point and rated 3; when language then became recognizably worse, it was rated 2.

[c] May have obvious instability and intermittent falls.

[d] Intelligible and grossly age appropriate.

[e] Language has become recognizably abnormal.

[f] Few intelligible words in the context of unintelligible vocalizations.

Primary endpoint

The mean score was 3.5 points at 300 mg baseline and declined by 0.4 points to a score of 3.1 points over a 48 week stable treatment period with BMN 190 300 mg every 14 days. When compared to the expected rate of decline based on natural history (2 points per 48 weeks), the study results are statistically significant ($p < 0.0001$).

Table 5. 0 to 6 Point Motor-Language CLN2 Clinical Rating Scale: Rate of Decline over 48 weeks (Intent to Treat (ITT) population)

Rate of Decline (points/48 weeks)[a]	Overall (n = 23)	p-value[b]
Mean (SD)	0.40 (0.809)[c]	<0.0001
Median	0.00	
Min, Max	-0.88, 2.02	
95% CI Limits	0.05, 0.75	

[a] Patient rate of decline per 48 weeks: (baseline CLN2 score - last CLN2 score) / (time elapsed in units of 48 weeks)

[b] p-value based on 1-sample T-test comparing rate of decline to the value 2

c Positive estimates indicate clinical decline; negative estimates indicate clinical improvement

Primary endpoint analysis

20 of 23 (87%) patients responded as they did not have a 2-point decline on the ML scale at week 48 of treatment. The responder population for the ML score in the 300 mg dosing period significantly exceeded the predicted untreated responder rate of 50% (p = 0.0002).

Table 6. Responder Analysis: Proportion of Subjects without an Unreversed 2-point Decline or Score of 0 in ML Scale Score at 48 Weeks (ITT Population, 300 mg Dosing Period)

Outcome	190-201 (n=23)	95% Confidence Interval	1-sided p-value
Response(Absence of decline)	20(87%)	(66%,97%)	0.0002
Non-Response(Presence of decline)	3 (13%)		

A 'response' is defined as the absence of an unreversed two-point decline in the 0-to-6 point ML score at 48 weeks.

Inference is by an exact binomial test of the null hypothesis H_0: Prob (response) <= 0.50 vs. the alternative hypothesis H_1: Prob (response) > 0.50, where Prob (response) denotes the population probability of a response. The confidence interval is an exact interval.

Responder rates for the separate motor and language domain scores for the ITT population during the 300 mg dosing period showed that eighteen subjects (78%) and 16 subjects (70%) met the definition of a responder on the language and motor domains, respectively.

Fifteen (65%) of the 23 treated patients had no unreversed single point loss. These patients were stable or improved over the full duration of 300 mg treatment as measured by the ML scale. As the responder rate for the untreated population that has an unreversed single point drop is assumed to be 25%, the estimated treated responder rate of 65% significantly exceeds the expected untreated responder rate of 25% (p < 0.0001). The 8 non-responders include 3 patients with an unreversed 2-point decline and 5 patients with an unreserved 1-point decline.

Table 7. Responder Analysis: Proportion of Subjects without an Unreversed 1-point Decline in ML Scale Score at 48 Weeks (ITT Population, 300 mg Dosing Period)

Outcome	190-201 (n=23)	95% Confidence Interval	1-sided p-value
Response (Absence of decline)	15 (65%)	(43%, 84%)	<0.0001
Non-Response (Presence of decline)	8 (35%)		

A 'response' is defined as the absence of an unreversed one-point decline in the 0-to-6 point CLN2 score at 48 weeks.

Inference is by an exact binomial test of the null hypothesis H0: Prob(response) <= 0.25 vs. the alternative hypothesis H1: Prob(response) > 0.25, where Prob(response) denotes the population probability of a response. The confidence interval is an exact interval.

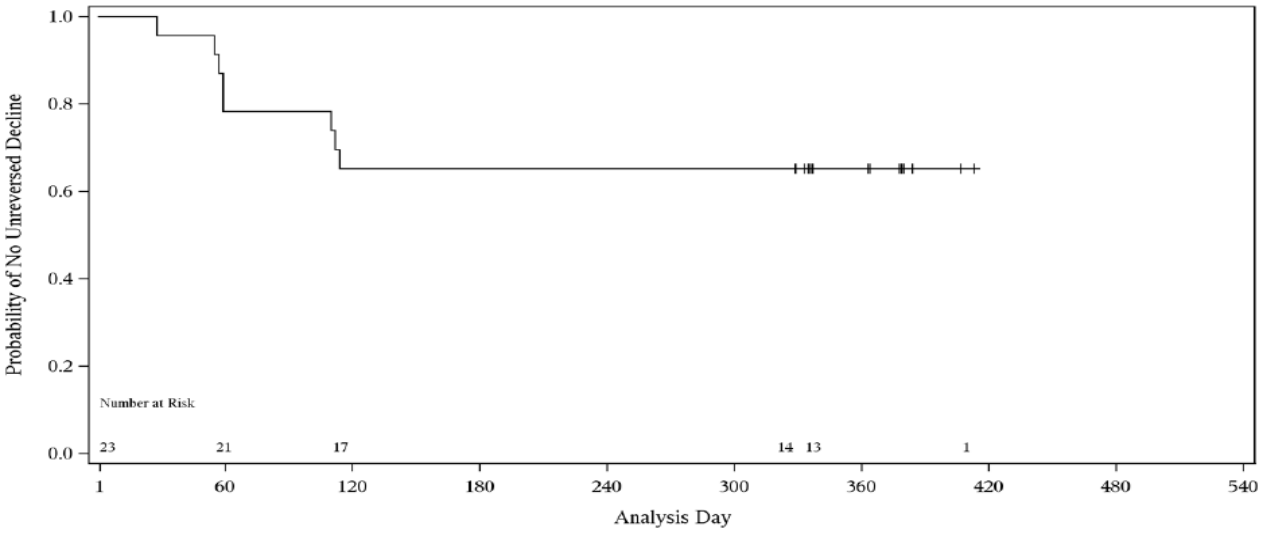
The table considers CLN2 assessments through Day 340 (relative to first 300 mg infusion).

Source: Table 14.2.8.2.1.

All 8 subjects who experienced an unreversed point drop did so during the first 16 weeks on study; after that time point, only 3 of the 8 subjects experienced a second unreversed point decline. The remaining 5 subjects stabilized after losing a first point on the ML scale.

The Kaplan-Meier analysis performed on the total dosing period from study baseline for the ITT population and for the primary efficacy population showed similar results.

Figure 3. Time to First Unreversed Decline in ML Scale: Kaplan-Meier Estimation (ITT Population, 300 mg Dosing Period)



Note: An unreversed decline is any decline that had not reverted to the baseline value (or better) as of the last recorded observation. Analysis Day 1 is the date of the first 300 mg infusion.

Source: 190-201 CSR, Figure 14.2.4.4.1

Analysis of 9-point adapted CLN2 motor-language-vision scale (MLV scale) has shown that no benefit was received in the vision domain during the 48 week period.

Secondary endpoints

The results observed in Magnetic Resonance Imaging are as follows:

- Over 48 weeks of 300 mg dosing, there were some changes across the population in the proportion of whole brain volume (WBV) occupied by CSF and by cortical grey matter: the percent total volume occupied by CSF increased by 2.1%, while a mean decline of 2.2% (1.89) was shown in the proportion of WBV occupied by cortical grey volume.
- Whole brain volume (WBV) decreased by 4.4%
- Cerebrospinal fluid (CSF) increased by 3.6%
- A loss in volume was shown for the cortical grey matter (9.7%)
- A loss in volume was shown for the white matter (4.2%)

Overall, when these results were compared to the clinical response, MRI results did not change in the same direction over the 48 weeks of 300 mg stable treatment.

Scatter plots compared the change from 300 mg baseline ML scale score at week 49 with MRI changes at Week 49. Overall, the provided analysis did not show a very obvious correlation between ML score and total cortical grey matter volume (r = 0.20), total white matter absolute volume (r = 0.27), total white matter percentage (r = -0.17), or whole brain ADC (r = 0.12). There was a modest correlation between ML score and absolute CSF fluid volume (r = 0.61), percent total cortical grey matter (r = -0.48) and whole brain volume (r=0.52).

The Quality of Life outcomes were as follows:

- PedsQL Generic Core Scale, Parent Report for Toddlers: Overall, between study baseline (mean score: 60.7) and Stable Dose Period Week 49 (mean score: 63.3) there was a mean increase of 2.6 (12.16) points in the ITT population, demonstrating an improvement of approximately 4.3%.
- PedsQL Family Impact Module:Overall, between study baseline (mean score: 61.4) and Stable Dose Period Week 49 (mean score: 65.1) there was a mean increase of 3.7 (19.04) points in the ITT, demonstrating an improvement of approximately 6.0%.
- CLN2 Disease-based QoL: Overall, between study baseline (mean score: 74.2) and Stable Dose Period Week 49 (mean score: 81.9) there was a mean (SD) increase of 8.1 (14.33) points in the ITT population, demonstrating an improvement of approximately 10.9%.

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 8. Summary of efficacy for trial 190-201

Title: A Phase I/II Open-Label Dose-Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Intracerebroventricular BMN 190 in Patients with Late-Infantile Neuronal Ceroid Lipofuscinosis (CLN2) Disease			
Study identifier	190-201		
Design	Phase I/II, open-label, dose-escalation study (stable dose: 300 mg) to evaluate safety, tolerability, PK, and efficacy of Intracerebroventricular BMN 190 in Patients with Late-Infantile Neuronal Ceroid Lipofuscinosis (CLN2) Disease		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks Study 190-202: ongoing
Hypothesis	Superiority		
Treatments groups	Active treatment		BMN 190 300 mg every 14 days
Endpoints and definitions	Primary endpoint	Responder analysis on the 6-point adapted CLN motor-language scale (ML scale)	Response: absence of an unreversed 2-point decline or score of zero in CLN2 score by week 48 relative to 300 mg baseline Response : absence of an unreversed 1-point decline (sensitivity analysis)

	Secondary endpoint	Brain atrophy	Changes from 300 mg baseline at week 49 in brain structure and anatomy related to disease progression measured by specific MRI parameters: whole brain volume, volume of cerebrospinal fluid, volume of total cortical grey matter, total white matter volume, whole brain apparent diffusion coefficient
Database lock	30 November 2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT: all enrolled patients with the exception of one patient who withdraw after first dose After 48 weeks of stable dose (300 mg) - treatment		
Descriptive statistics and estimate variability	Treatment group	BMN 190 300 mg every 14 days	
	Number of subject	23	
		Responder (Absence of decline)	Non-Responder (Presence of decline)
	Primary endpoint: (Absence of unreversed 2-point decline)	20 (87%)	3 (13%)
	Sensitivity analysis: Absence of unreversed 1-point decline	15 (65%)	8 (35%)
	MRI parameter: Whole brain volume Cortical grey matter White matter Cerebrospinal fluid Whole brain ADC	Baseline Vol (cm^3) 1104.9 (188.94) 452.0 (87.70) 342.6 (54.57) 310.3 (72.19) 0.88 (0.040) (mm^2/s)	Week 49 Vol (cm^3) 1054.5 (191.27) (408.3 (88.53) 328. (63.70) 317.4 (70.17) 0.90 (0.039) (mm^2/s)
Effect estimate per comparison	Primary endpoint	Single arm	BMN 190 300 mg
		Rate difference (fixed comparison to 50%)	37%=87%-50%
		95% CI	(66%, 97%) for responder rate
		P-value	0.0002
	Sensitivity analysis	Rate difference (fixed comparison to 25%)	40%=65%-25%
		95% CI	(43%,84%) for responder rate
		P-value	<0.0001
	Additional analysis: Rate of Decline	0.4 (p <0.0001) p-value computed as a two-sided t-test for the hypothesis H_0: Rate =2.0 points lost/48 weeks vs. H_1:Rate not equal 2.0 points lost/48 weeks	

	MRI parameter:	Changes from baseline (cm^3)	% change	Correlation MRI/ML scale
	Whole brain volume	-50.5 (74.88)	-4.4 (8.46)	r = 0.52
	Cortical grey matter	-43.8 (30.70)	-9.7 (8.08)	r = 0.20
	White matter	-13.8 (30.81)	-4.2 (9.58)	r = 0.27
	Cerebrospinal fluid	7.1 (40.18)	3.6 (15.30)	r = 0.61
	Whole brain ADC	0.02 (0.023) (mm^2/s)		r = 0.12
Notes	ITT population: all enrolled patients with the exception of one patient who withdraw after first dose Results were confirmed by several sensitivity analyses			

Analysis description	**Primary comparison across studies**		
Treatments groups	Active treatment (BMN 190) (Study 201 population)	BMN 190 300 mg every 14 days	
	Natural history data (available from study 901 supplemental report)	Treatment naïve subjects	
Endpoints and definitions	Primary endpoint	Responder analysis based on close 1-1 matching using Method # 1 (Baseline ML score equal, baseline age close)	Response: Rate of decline <2 points per 48 weeks
Descriptive statistics and estimate variability	Treatment group	BMN 190 300 mg every 14 days (study 201)	treatment naïve patients (study 901 supplemental)
	Number of subject	22	22
	Primary endpoint:	20 (91%)	10 (45%)
Effect estimate per comparison	Primary endpoint	Comparison groups	BMN 190 300 mg every 14 days vs. treatment naïve patients
		Rate difference	46%
		95% CI	N/A
		2-sided P-value	0.0028
Notes	For 1:1 matching, 1 patient in study 201 could not be matched and was omitted from ITT population (besides the patient who withdraw after first dose)		

Supportive studies

Long-term extension Study 202

Study 190-202 is an ongoing Phase 1/2 open-label, multi-centre, extension study to evaluate the safety and efficacy of BMN 190 treatment in subjects with CLN2 who completed study 190-201. All subjects who enrolled in study 202 continued dosing at 300 mg every other week for up to 240 additional weeks. The analyses for the provided interim report include data up to 03 June 2016. All patients were treated with the 300 mg dose for a minimum of 72 weeks, thus complete data were available up to 72 weeks. Thereafter, the maximum time of exposure until the new data cut-off ended individually.

Efficacy measurement tools used in study 202 are similar to those from study 201. CLN2 rating scale assessments were performed every 8 weeks (videotaping every 24 weeks). MRI assessments were also performed every 24 weeks. The Denver II instrument and QoL tests were done every 24 weeks; in addition to the PedsQL and CLN2-specific QoL instruments used in study 201, subjects in study 202 were also assessed by the EQ-5D-5L QoL test. In addition, adapted motor-language CLN2 score and MRI correlation analyses (week 49 change from baseline) have been performed.

Primary endpoint

Overall, there was no change in the responder rates with regard to the primary analysis defined (i.e. the proportion of subjects without a 2-point decline in ML scale score, 1-point decline in motor domain score or 1-point decline in language domain score).

As of the data cut-off date, the responder population for the ML score in the 300 mg dosing period significantly exceeded the predicted untreated responder rate of 50% for an unreversed 2-point decline ($p = 0.0002$) with 87% responders and 13% non-responders.

Responder rates for the individual motor and language domains were comparable to those seen in study 201, with 65% responders on motor and 70% responders on language.

A Kaplan-Meier analysis was performed on the ITT population to examine the timing at which subjects had unreversed declines of 2 points or ML score of 0 (unresponsive to treatment). The graph was flat beyond Study Week 48, indicating that there were no additional unreversed 2-point declines or score of 0 after Week 48.

Eight subjects had unreversed 1-point declines in CLN2 score within 120 days of first 300 mg dose. After 120 days, the curve remained flat over the first year and then 3 additional subjects had unreversed 1-point declines in CLN2 score after the first year of therapy. Three of the 8 subjects with 1-point unreversed decline within the first 120 days experienced a second unreversed point decline.

The slopes analysis of the ITT population ($n = 23$) ML endpoint showed that treatment with BMN 190 300 mg every other week for over 1 year demonstrated a statistically significant improvement in the mean rate of decline on the ML scale when compared with a population rate of decline in untreated subjects of 2.0 points per 48 weeks ($p < 0.0001$). The mean rate of decline was 0.32 points per 48 weeks. These preliminary results are better than the mean rate of decline seen in study 201 (0.40 points/48 weeks).

This result was supported by multiple sensitivity analyses (all $p<.0001$).

Secondary endpoints

MRI measurements from baseline till Last recorded observation prior to the 03 June 2016 data cut off were as follows:

- The percent total volume occupied by CSF increased by 3.2%, while a mean decline of 3.2% was shown in the proportion of WBV occupied by cortical grey volume over the 300 mg treatment period.
- Whole brain volume (WBV) decreased by 3.7%
- Cerebrospinal fluid (CSF): Mean absolute increase of 8.6%
- A loss in volume was shown for the cortical grey matter (11.4%)

- A loss in volume was shown for the white matter (3.8%)

Results at 72 weeks positively compare to those estimated by Lobel et al (2016) from a group of 13 patients from a prospective natural disease cohort of patients. Whereas no differences were seen during the first year of treatment, data suggest a slower loss of cortical grey matter at Week 72. This means that anatomical changes may be noticeable only after 18 months of treatment.

Exploratory Efficacy Endpoints

The Quality of Life outcomes were as follows:

PedsQL Parent Report for Toddlers: All subjects had reached Week 25 in Study 202; 21 subjects (91.3%) with a PedsQL score at Week 25 showed a mean (SD) change of -1.7(13.69) points from study baseline to Week 25. Only 12 subjects (52.2%) had a PedsQL score assessed at Week 49 in Study 190-202; these12 subjects showed a mean (SD) change of -14.1 (13.08) points from study baseline to Week 49.

PedsQL Family Impact Module: 22 subjects (95.6%) with a PedsQL score at Week 25 in Study 202 showed a mean (SD) increase of 4.1 (19.52) points from study baseline to Week 25. Only 12 subjects (52.2%) had a PedsQL score assessed at Week 49 in Study202; these 12 subjects showed a mean (SD) change of -1.3 (18.09) points from study baseline to Week 49.

CLN2 Disease-based QoL Instrument: 21 subjects (91.3%) with a CLN2 Disease-based QoL score at Week 25 in Study 202 showed a mean (SD) increase of 6.5 (14.75) points from study baseline to Week 25. Twelve subjects (52.2%) with a PedsQL score at Week 49 in Study 202 showed a mean (SD) change of 1.9 (15.15) points from study baseline to Week 49.

As of the 03 June 2016 data cut, only a subgroup of 12 subjects (52%) had a Denver II test when they reached the Week 49 time point in Study 202. All 12 subjects had no change in classification from study 201 assessments (baseline and end of study).

Natural History Studies

Study 190-901:

The original 190-901 natural history analysis included 78 patients from cohorts in Hamburg, Germany (n=29) and at Weill Cornell Medical College (WCMC) in New York, USA (n=49) and was started prior to the initiation of the 190-201 treatment study.

The intention of the natural history analyses was to examine disease onset, symptoms and rate of progression in the context of genotype and imaging biomarkers. Both cohorts had been administered reliable clinical scales to quantify disease severity.

Hamburg cohort

Hamburg cohort included patients with longitudinal assessment of clinical severity using the HML scale. The clinical course prior to diagnosis was constructed retrospectively from family interviews and integrated with prospectively gathered data from the time of diagnosis from clinical rater assessments. This dataset was evaluated to determine rate of progression, age of onset, and first clinical symptom.

Table 9. Rate of Decline (Units per Year) in Motor/Language Aggregate Score (Method of Estimation: Linear Regression)

	Hamburg Cohort N=29
Annualized slope	
Mean (SD)	-2.18 (1.07)
Range (min, max)	-4.8, -0.2
Quartiles (25^{th}, median, 75^{th})	-2.7, -2.0, -1.5

Hamburg profiles

The mean rate of decline was 2.18 units per year and the middle 50% of the distribution had rates of progression ranging from only -1.5 to -2.7 units per year.

Analyses confirm that the large majority of patients decline rapidly in a predictable manner in terms of age of onset and rate of decline. This population has only a few outliers for each parameter. Based on these findings, an estimate of a 2.0-point loss per 48 weeks was used as the basis for comparison for treated patients in the ML scale analysis for study 201.

WCMC cohort

WCMC cohort originated from screening data for two clinical trials (Cohort 1 and Cohort 2) and included 49 CLN2-confirmed patients with clinical and MRI data. The cohort was cross-sectional; all patients had just one or two clinical ratings in a relatively short time frame, and therefore did not contribute to the longitudinal analysis. For patients with two clinical ratings, the analysis used the first assessment by convention. The WCMC rating scale quantified clinical severity and was used in correlations with patient age and with MRI findings.

The Weill Cornell group collected a number of MRI parameters that were compared to clinical severity and patient age. For each of the parameters, e.g. intracranial cerebrospinal fluid, subcortical white matter and N-Acetyl Aspartate, a good correlation between worsening MRI/MRS findings and increased clinical severity (as measured by the WCMC gait-language scale) was noted (r2 values ranged from 0.49 to 0.65). Similar results were obtained when these measurements were compared to patient age and to the total WCMC scores.

A composite MRI score, including contributions from all of the parameters listed above (percent CSF, MRS and normalized NAA concentrations), showed a strong relationship (r2=0.71) to clinical severity. However, this has to be interpreted carefully, given the fact that the MRI composite was developed on the same data set and external validation would be needed for robust conclusions on the correlation.

Study 190-901 supplement

A new collaborative database (DEM-CHILD) has been formed from a consortium of investigators of expert clinical sites organized by a charter intended to collect and analyse clinical, genetic, and biomarker data in patients with neuronal ceroid lipofuscinosis (NCL) diseases (including CLN2). This new database has expanded the number of patients that was available at the time of the original 190-901 report.

The DEM-CHILD database included 74 CLN2 patients, 63 evaluated at Hamburg and 11 from Verona. Of the 74 patients available in the DEM-CHILD database as of February 2015, 41 were ultimately included in the evaluable population for the 901 supplemental analysis.

In order to be included in the untreated comparison group, patients needed to have HML scale score ratings at least 6 months apart. Furthermore, to match the study inclusion criteria to the population, the patients must have had at least two HML scale ratings at age ≥ 36 months and have at least one rating score of 3 or better. The eligibility criteria as presented excluded 30 patients from the Hamburg cohort and 3 patients from the Verona cohort. Of the 33 excluded patients, 32 were excluded for failing one or more of the HML scale score filters (the remaining excluded patient was an identical twin of a patient also in the DEM-CHILD database). Patients from the Verona site were assessed by the HML scale.

The original 901 analysis report included 29 patients from the Hamburg site. 26 of the original 29 Hamburg patients were included in the evaluable population for the 901 supplemental report. The 3 excluded patients from the original 901 analyses did not meet the eligibility criteria for inclusion in the evaluable population: 2 patients did not have an otherwise evaluable post-baseline HML scale assessment that was at least 6 months after the baseline assessment; and 1 Patient had no otherwise evaluable HML scale assessments ≥ 3.

Thus, of the 41 patients in the evaluable population, 26 were included in the original 901 analysis and 15 (7 from the Hamburg site and 8 from the Verona site) are new patients that contribute to this supplemental analysis.

Table 10. Rate of Decline of the HML Scale Score (Evaluable Population)

Estimation by First Point/Last Point Algorithm	Hamburg (n= 33)	Verona (n= 8)	Overall (n= 41)
Rate of Decline(points/48weeks)			
Mean(SD)	2.23(0.973)	1.54(0.758)	2.09(0.966)
Median	2.17	1.36	1.87
25^{th},75^{th}percentile	1.66,2.80	1.03,1.77	1.36,2.80
Min,Max	0.45,4.27	0.80,3.20	0.45,4.27
95%ConfidenceIntervals	1.88,2.57	0.91,2.17	1.79,2.40

Source: Table 14.2.1

Analyses on the 901 supplement population, confirmed a similar rate of decline of 2.09 points per 48 weeks as seen for the original study 901 patient population.

Updated 190-901 supplemental report

The updated data included additional 8 evaluable subjects for Study 901 (n=49), based on an updated data transfer from the DEM-CHILD collaborative natural history database as of 11 August 2016.

Since the previous data transfer summarized in the 901 supplement report (March 2015), the total CLN2 patient population has decreased from 74 to 69. This change is based on the removal of 9 patients previously in the Hamburg database and the addition of 4 patients new to the database. Of the 9 patients removed, only 1 was in the evaluable population (the patient was removed after withdrawing consent to be included).

Evaluable Population

Table 11. Patient Evaluability (DEM-CHILD Population)

	Overall[a] (n=74)	Overall[b] (n = 69)
Patients in the DEM-CHILD Population	74 (100%)	69 (100%)
Patients after exclusion of second twin	73 (99%)	68 (99%)
Patients with at least two HML scale scores	51 (69%)	57 (83%)
Two HML scale scores at age ≥ 36 months	51 (69%)	57 (83%)
With a HML scale score ≥ 3	49 (66%)	56 (81%)
With two HML scale scores between 1 and 5, inclusive	48 (65%)	55 (80%)
With at least one score ≥ 6 months after the first HML scale score	41 (55%)	49 (71%)

a: Data from Study 190-901 supplement report dataset (MA)
b: Data from DEM-CHILD registry updated dataset
Source: Table 14.1.2

The total evaluable patients increased from 41 to 49 based on the removal of one previously evaluable patient who withdrew informed consent, the addition of 3 new, evaluable patients and the conversion of 6 patients previously unevaluable to evaluable based on the availability of additional data.

Results (Disease progression)

Table 12. Rate of Decline of the HML Scale Score (Evaluable Population)

Estimation by First Point/Last Point Algorithm	Overall[a] (n=41)	Overall[b] (n = 40)	Overall[c] (n = 49)
Rate of Decline (points/ 48 weeks)			
Mean (SD)	2.09 (0.966)	2.11 (0.970)	2.02 (0.971)
Median	1.87	1.91	1.95
25th, 75th percentile	1.36, 2.80	1.38, 2.80	1.36, 2.64
Min, Max	0.45, 4.27	0.45, 4.27	0.00, 4.27
95% Confidence Intervals	1.79, 2.40	1.80, 2.42	1.74, 2.30

a: Data from Study 190-901 supplement report dataset (MA)
b: Data from Study 190-901 registry updated dataset (removing one patient who withdrew consent)
c: Data from DEM-CHILD registry updated dataset
Source: Table 14.2.1.1; Table 14.2.1.2

Compared to the previous natural history dataset (n=41 evaluable population), the mean (SD) rate has changed from 2.09 (0.966) points/48 weeks to 2.02(0.971) points/48 weeks. Removing the patient who withdrew consent, the rate of decline of the remaining patients from the Study 901 supplement population (n=40) is 2.11 (0.970) points/48 weeks.

Taken together, these results demonstrate that the most current natural history dataset, generated after the addition of more contemporaneous data, comprises a similar patient cohort with similar clinical characteristics compared to the natural history dataset described in the original 901 report.

Analysis performed across trials

Integrated summary of effectiveness (ISE):

To evaluate the effectiveness of BMN 190 300 mg every other week, outcomes of treated subjects in studies 190-201/202 were compared with the outcomes of the untreated patients in the evaluable population of the study 901 supplemental report.

Study 201/202: 23 patients of 24 patients who completed study 201 and continued into study 202. The one subject who discontinued did so after a single dose. There were no drop outs or discontinued subjects due to safety reasons or lack of efficacy.

901 supplement: the total population of possible natural history subjects (n=74) was reduced to an evaluable population (n=41) by removing patients in whom the rate of decline could not be robustly estimated.

Primary Analysis: HML/ML score is the primary endpoint and the primary analysis is a responder analysis based on the 1-1 matching using Method #1. Response was defined as a rate of decline < 2 points per 48 weeks. The rate of decline is estimated as the change in HML/ML score from baseline assessed at the last visit and scaled to a 48 week period.

22/23 subjects in the 190-201/202 ITT population were matched; one subject could not be matched because the subject's closest match had an age difference of 21 months. That subject has been omitted from these analyses; thus, the ITT population for these 1:1 matching analyses has an n=22.

Sensitivity analyses relating to the primary analysis: As the primary analysis is a single 1-1 matching analysis using Method #1, and as there may be other potential matchings that achieve similar quality of matching, a supportive simulation was performed. 1000 simulated matchings were performed using a simpler variation of matching Method #1. The responder analysis was repeated for each of the 1000 simulated matchings and described by summary statistics for the realized treatment effects and p-values.

For sensitivity analyses subjects with a baseline value of 6 that does not decline during the course of the study and subjects with a baseline HML value <3 (that was ≥3 at screening) were excluded.

1:1 Matching:

The primary responder analysis showed a relevant and statistically significantly higher proportion of responders with a decrease in the rate of disease progression (rate < 2/48 weeks) under active treatment (91%) as measured by the ML scale compared to untreated patients (historical data) (45%).

Table 13. ML/HML Scale: Estimated Response Rate Using 1:1 Matching
(201/202 ITT Population, 901 Matched Population, 300 mg Dosing Period)

Response	190-901 (n=22)	190-201/202 (n=22)	Rate Difference	2-sidedp-value
Positive(rate< 2)	10(45%)	20(91%)	46%	0.0028
Negative(rate≥ 2)	12(55%)	2 (9%)		

Estimation: Within-subject Slope Estimation Categorized <2, ≥2;

Testing: Fisher-exact Test

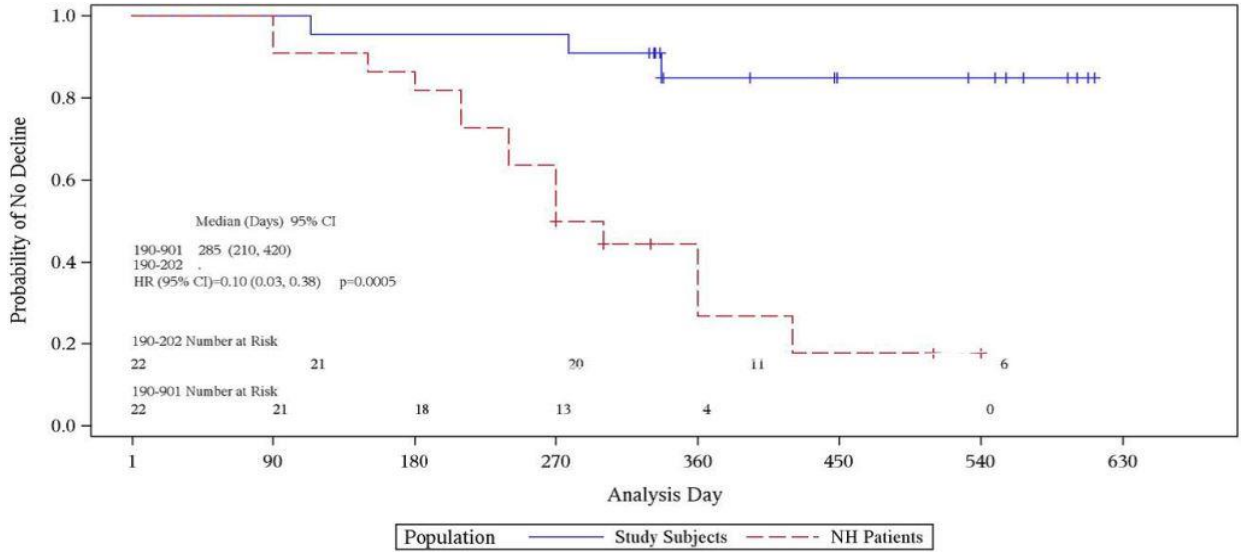
Matching was performed based on equal baseline ML/HML scale score and age within 12 months.

Source: ISE Table 3.1.1

The mean of the estimated difference in response rates over 1000 matchings in a simulation study was 41.7% with test of statistical significance ranging (1-sided) from p < 0.0001 - 0.033. Further, all 1000/1000 matchings showed at least a 90.0% response rate in the treated subjects, while the maximum response rate (out of 1000 matchings) for the untreated patients was only 61.9%.

Sensitivity analyses support the findings from the primary analysis of a statistically significant difference in response between treated subjects and natural history patients (p=0.0031 to 0.0074).

Figure 4. Kaplan-Meier Estimation: Time to First Unreversed 2-point ML/HML Scale Score Decline Using 1:1 Matching (201/202 ITT Population, 901 Matched Population, 300 mg Dosing Period)



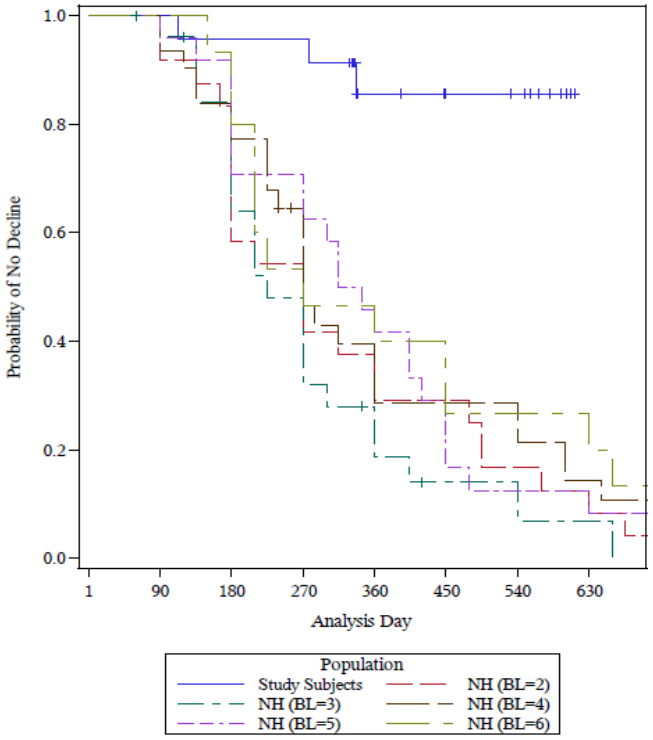
HR: hazard ratio

Note: an unreversed decline is any decline that had not reverted to the baseline value (or better) as of the last recorded observation.

Source: ISE Figure 3.2.2

Unmatched Kaplan-Meier Estimations of Time to Unreversed Decline

Figure 5. Kaplan-Meier Estimation: Time to First Unreversed 2-point Decline in ML Scale Score (201/202 ITT Population, 901 Evaluable Population, 300 mg Dosing Period)



190-901 baseline was calculated using the set of contiguous visits with an ML scale score equal to the earliest ML scale score (< 6); 190-901 baseline was defined as the midpoint between the first and last of these contiguous visits.

Source: ISE Figure 3.2.7

Regardless of the baseline ML scale starting point in unmatched 901 population, all patients declined at a fast rate with very similar trajectories (in comparison to the treated 190-201/202 subjects who show few unreversed 2-point declines). This leads to the conclusion that the relative efficacy under treatment is independent from baseline ML scale at start of the treatment.

The estimated mean (SD) rate of decline in the ML/HML scale score (in points/48 weeks) was 2.06 (1.379) for the 901 supplement patients and 0.53 (0.737) for the 190-201/202 subjects, a difference of 1.53 points/48 weeks (p<.0001). There was no overlap for the 95% CI for the estimated rate of decline for the 190-201/202 (0.20, 0.86) and 901 supplement (1.45, 2.68) patients.

Sensitivity analyses support the findings from slopes analysis on the ITT 1:1 matched population.

The rate of decline on the individual domains showed a treatment difference in favour of the 190-201/202 treated subjects. The mean treatment difference for the motor domain was 0.72 (0.240) points/48 weeks (p=0.0055) and the mean treatment difference for the language domain was 1.01 (0.200) points/48 weeks (p<.0001).

Integrated Efficacy Analyses Addendum:

Following DEM-CHILD registry update, two different natural history evaluable populations were examined:

- The n=49 population described above
- The n=42 population, which excludes 7 subjects from the n=49 population who later entered a BMN 190 study for treatment.

The focus of the integrated efficacy analysis is on the n=42 history population; however, the n=49 data results were also provided. A comparison of the results of matching using each of the two different populations revealed no substantial differences for the various matching analyses.

As in study 201/202, the primary integrated efficacy analysis is a responder analysis, here based on the ITT population for 190-201/202 and the updated natural history population, using a 1:1 matching method based on age as closely as possible (but no more than 12 months apart) and baseline ML scale scores (for 190-201/202subjects)/HML scale scores (for natural history patients). The method is designed to allocate, to a maximal number of 190-201/202 subjects, a unique DEM-CHILD patient (no sharing). Using this method, 21/23 subjects in the 201/202 ITT population were matched; two subjects could not be matched to a natural history comparator as for the ISE update, matching based on stricter age definition for 12 patients .

Primary Analysis

Responder analysis

Table 14. ML/HML Scale: Estimated Response Rate Using 1:1 Matching (201/202 ITT Population, DEM-CHILD Matched Population, 300 mg Dosing Period)

Response	DEM-CHILD (n=21)	190-201/202 (n=21)	Rate Difference	2-sided p-value
Positive (rate < 2)	9 (43%)	21 (100%)	57%	<0.0001
Negative (rate ≥ 2)	12 (57%)	0		

Estimation: Within-subject Slope Estimation Categorized <2, ≥2;

Testing: Fisher-exact Test

Matching was performed based on equal baseline ML/HML scale score and age within 12 months.

Source: ISE Table 3.1.1b

The estimated response rate for the 201/202 ITT population was 100%. The estimated response rate for the matched DEM-CHILD population was 43% (9/21). The estimated difference in response rates was 57% (p<0.0001). These results are similar to those seen at the time of the original marketing application, where 45% of DEM-CHILD patients and 91% of 190-201/202 subjects met the responder definition (p=0.0028).

Sensitivity Analyses

Table 15. Summary of 1:1 Matched Responder Analysis and Sensitivity Analyses

Analysis	n	Population Description	DEM-CHILD		190-201/202		Treatment Effect	p-value
			Responder	Non-Responder	Responder	Non-Responder		
Primary Analysis	21	ITT Population	9 (43%)	12 (57%)	21 (100%)	0	57%	<0.0001
Sensitivity Analysis	19	Excludes 2 subjects with ML scale scores of 6 with no decline	8 (42%)	11 (58%)	19 (100%)	0	58%	0.0001
Sensitivity Analysis	18	Excludes 2 subjects with ML scale scores of 6 with no decline Excludes 1 matched pair with baseline ML scale score = 1	7 (39%)	11 (61%)	18 (100%)	0	61%	0.0001
Sensitivity Analysis	22	Matching age ≤ 6 months	10 (45%)	12 (55%)	22 (100%)	0	55%	<0.0001

The pre-specified sensitivity analyses support the findings from the primary analysis of a statistically significant difference in response between treated subjects and natural history patients (p=0.0001 to <0.0001).

Responder Analysis: Individual Domain Contributions

Table 16. Motor and Language Individual Domains: Estimated Response Rate Using 1:1 Matching (201/202 ITT Population, DEM-CHILD Matched Population, 300mg Dosing Period)

	DEM-CHILD		190-201/202		p-value
	Responder	Non-Responder	Responder	Non-Responder	
Motor Domain (n=21)	11 (52%)	10 (48%)	21 (100%)	0	0.0005
Language Domain (n=20)	8 (40%)	12 (60%)	20 (100%)	0	<.0001

Estimation: Within-subject Slope Estimation Categorized <1, ≥1

Testing: Fisher-exact Test

Matching was performed based on equal baseline ML/HML scale score and age within 12 months.

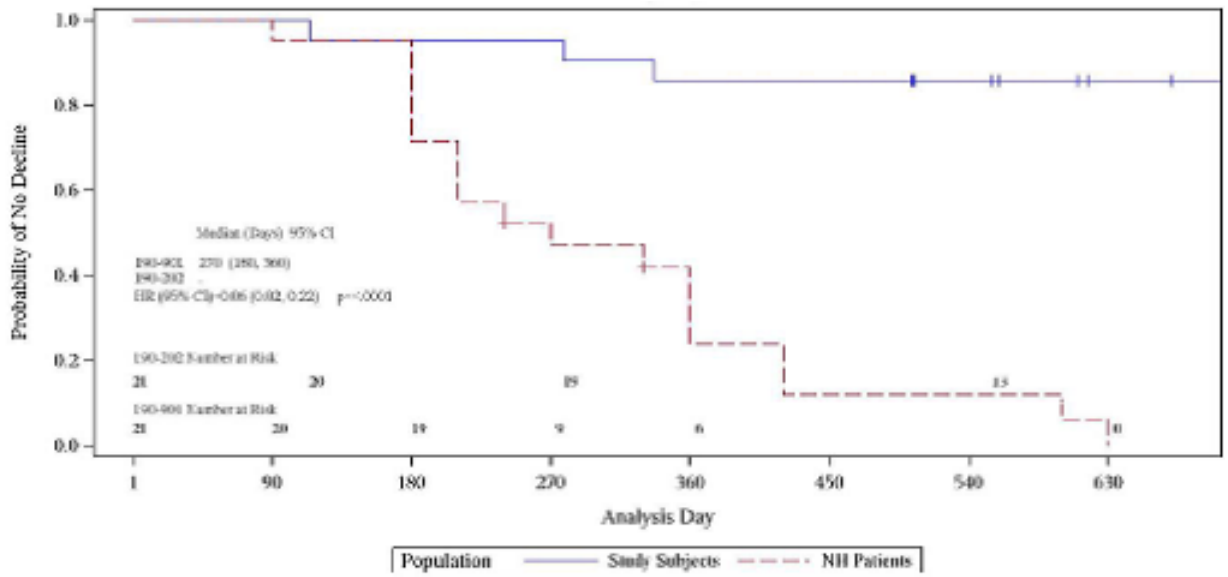
One pair for language was deleted because the baseline language score = 0 for at least one member of the pair.

Source: ISE Table 3.1.4b, Table 3.1.5b

For language, one matched pair was not used because one member of the pair had a baseline language score of 0.The estimated difference in response rate for the motor domain was 48% (p=0.0005), and for the language domain was 60% (p<.0001). These results were similar to those seen at the time of the marketing application (41% difference in response rate for the motor domain, 66% difference for the language domain).

Time to Unreversed ML/HML Scale Score

Figure 6. Kaplan-Meier Estimation: Time to First Unreversed 2-point ML/HML Scale Score Decline Using 1:1 Matching (201/202 ITT Population, DEM-CHILD Matched Population, 300 mg Dosing Period)

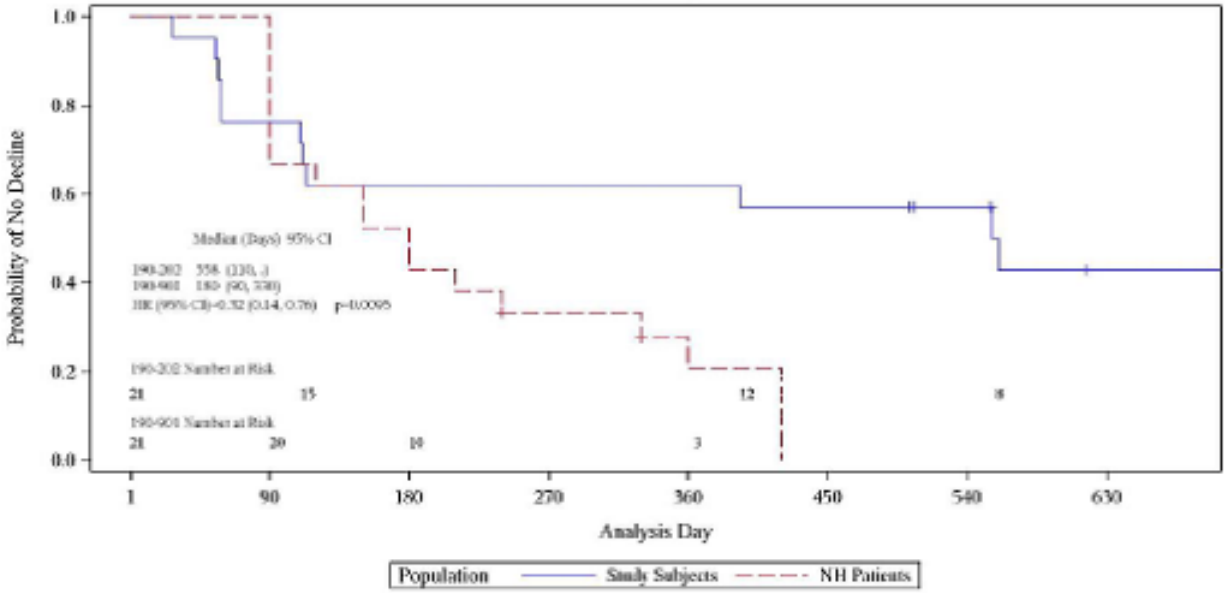


Note: an unreversed decline is any decline that had not reverted to the baseline value (or better) as of the last recorded observation.

Source: ISE Figure 3.2.2b

The Kaplan-Meier figure shows the significantly lower likelihood in developing an unreversed 2-point decline in the treated subjects when compared with the natural history patients over a course of time approximating the 300 mg treatment time in 201/202. No subjects in 201/202 have experienced an additional unreversed 2-point decline during the update period for this analysis, whereas all matching DEM-CHILD subjects have reached at least a 2-point unreversed decline.

Figure 7. Kaplan-Meier Estimation: Time to First Unreversed 1-point ML/HML Scale Score Decline Using 1:1 Matching (201/202 ITT Population, DEM-CHILD Matched Population, 300 mg Dosing Period)



Note: an unreversed decline is any decline that had not reverted to the baseline value (or better) as of the last recorded observation.
Source: ISE Figure 3.2.1b

Table 17. Summary of Analysis by Time Change from Baseline Results

	ML Scale (0-6)		MLV Scale (0-9)		Total CLN2 Scale (0-12)	
	DEM-CHILD	190-201/202	DEM-CHILD	190-201/202	DEM-CHILD	190-201/202
Baseline						
n	42	23	42	23	42	23
Mean (SD)	4.5 (0.77)	3.5 (1.20)	7.2 (1.12)	6.3 (1.34)	9.3 (1.80)	8.0 (1.83)
Week 49						
n	39	23	39	23	39	23
Mean (SD)	2.3 (1.11)	3.0 (1.33)	4.7 (1.47)	5.7 (1.56)	7.0 (2.38)	7.9 (2.07)
Mean (SD) Change from Baseline	-2.2 (1.09)	-0.4 (0.79)	-2.6 (1.29)	-0.6 (1.03)	-2.3 (1.89)	-0.1 (1.93)
Week 81						
n	37	18	37	18	36	18
Mean (SD)	1.2 (1.97)	2.8 (1.58)	3.0 (1.51)	5.3 (2.03)	5.1 (2.37)	7.6 (2.52)
Mean (SD) Change from Baseline	-3.4 (1.12)	-0.5 (0.86)	-4.4 (1.59)	-0.8 (1.29)	-4.3 (2.10)	-0.1 (2.49)

Source: ISE Table 2.1.1b, Table 2.2.1b, Table 2.3.1b

2.7.3. Discussion on clinical efficacy

Design and conduct of clinical studies

No specific dose finding studies were performed. Dose selection was based on results from nonclinical studies, which were originally used to support the dose of 300 mg to be tested in the clinical study. Two additional doses of 30 mg and 100 mg were administered only for safety (tolerability) purposes.

Study 190-201 is considered pivotal in this clinical programme. This study was extended in 190-202 with a very similar design and study objectives. In addition, a natural history study 190-901 (with a supplement) was performed to facilitate comparisons of untreated patients with treated patients in study 201.

Study 190-201

Study 201 was a single-arm, open-label study which cannot generate evidence at the usually expected level with regard to potential bias and a confirmatory approach with control of type I error for the primary analysis. This is acceptable considering CLN2 is a very rare disease, with fast and debilitating progression leading to death and no available treatment options. Therefore, the important evidence of efficacy comes from comparisons with untreated natural history patients performed for the Integrated Summary of Effectiveness (ISE).

Included CLN2 patients were aged 3-15 years. Most of patients (79%) had symptom onset below 5 years (7 patients below 3 years, 12 patients 3-5 years of age). Mean age at enrolment was 4.3 years. Of note, at recruitment one of the patients was 8 years old and three other patients were aged 6 years. The age of disease onset (symptoms) was over age 5 years in these four cases. It is described in the literature that, by the age of 6 years, the affected children are usually unable to walk and sit unsupported (Worgall 2007). Several clinical variants of LINCL have been reported. In some of them, the symptoms are similar to those of the classical type but tend to occur somewhat later. Their overall course may be more protracted. One additional patient was enrolled during the pre-symptomatic phase of his condition.

Although a few patients (n = 4) with a rather late onset of the disease and a potentially protracted disease course may have been included in the study, the one-to-one matching in the comparative analysis reduces potential bias and the sensitivity analyses suggest that the results are robust.

Three patients, two with a baseline ML score of 3 and one with a baseline ML score of 6 were detected of which all three patients had no change in the ML score at week 72 compared to baseline. As these three patients only comprise 12.5 percent out of 24 patients, they have a limited impact on the overall positive results.

According to the selection criteria, mild to moderate patients were to be recruited (ML Scale Score from 3 to 6). Two patients entered the study with a baseline ML score of 6, which in principle corresponds to normal function. Disease was detected early because both had affected siblings. However, exclusion of these patients in a sensitivity analysis did not affect the study results.

The evaluation of efficacy mainly relies on the effect on two main clinical features of the disease (motor function and language). The main variable of the study was expressed as a responder rate (the proportion of patients without an unreversed two-point decline or score of zero in Motor/Language scale by Week 48). This was an ad-hoc developed scale based on two already existing clinical rating scores: the Hamburg Late Infantile Neuronal Ceroid Lipofuscinosis Scale (4 functional domains: motor function, seizure activity, language skills and vision) and the Weill Cornell Late Infantile Neuronal Ceroid Lipofuscinosis Scale (4 functional domains: swallowing dysfunction, gait, motor and language abnormalities). The selected Adapted

CLN2 disease rating scale included the motor (gait in the WCMC Scale) and language scales, present in both primary scales. The experts consulted by the CHMP considered the scale acceptable and stated that the mean decline of 2 points per year is the expected deterioration rate in CLN2 disease.

Study 190-202

Study 190-202 is the extension study for 190-201. Subjects who completed 48 weeks of dosing in the Stable Dose Period of 190-201 are eligible to enrol in 190-202. All subjects who enrolled in 190-202 continued dosing at 300 mg every other week for up to 240 additional weeks. Objectives of the study as well as efficacy outcome measures were very similar to those of the pivotal study 201 and considered adequate to evaluate the long-term treatment effect.

Until June 2016 the mean exposure at any dose over the total studies 201/202 dosing period was 96.4 weeks. Subjects were treated at the 300 mg dose for a minimum of 72 weeks and a maximum of 124.4 weeks.

Natural History Studies

Study 190-901

Study 901 included 2 cohorts that had been administered reliable clinical scales to quantify disease severity: Hamburg cohort: included 30 CLN2 genotype-confirmed patients with longitudinal assessment of clinical severity using the HML scale. The clinical course prior to diagnosis was constructed retrospectively from family interviews and integrated with prospectively gathered data from the time of diagnosis from clinical rater assessments. This dataset was evaluated to determine rate of progression, age of onset, and first clinical symptom.

WCMC cohort (originated from screening data for two clinical trials (Cohort 1 and Cohort 2):
49 CLN2-confirmed patients with clinical and MRI data. The cohort was cross-sectional; all patients had just one or two clinical ratings in a relatively short time frame, and therefore did not contribute to the longitudinal analysis. For patients with two clinical ratings, the analysis used the first assessment by convention. The WCMC rating scale quantified clinical severity and was used in correlations with patient age and with MRI findings.

Overall, the clinical course determined by the analysis of the Hamburg cohort confirms published information.

Study 190-901 supplement

Study 901 supplement included 2 Study Sites: University Medical Center Hamburg-Eppendorf (Hamburg, Germany) and Universita degli Studi di Verona (Verona, Italy). A total of 7 patients took part in both, the natural history study and study 201/202.

The updated data included additional 8 evaluable subjects for Study 901 (n=49), based on a data transfer from the DEM-CHILD collaborative natural history database. Unfortunately, recently included patients had no longitudinal MRI analyses that could be compared to the data derived from study 201.

For purpose of the ISE analyses, two different natural history evaluable populations were examined:

- The n=49 population described above

- The n=42 population, which excludes 7 subjects from the n=49 population who later entered a BMN 190 study for treatment.

It is considered acceptable that the new integrated efficacy analyses focuses on analyses including 42 patients of the natural history population, excluding 7 patients from the natural history cohort later treated in study 201/202. Excluding these patients is a logical step, as the resulting analyses are pure between-groups comparisons, avoiding a component of intra-individual comparisons and using individual patient data twice.

Efficacy data and additional analyses

The applicant demonstrated statistically significant (p = 0.0002) and clinically relevant effects for the primary outcome measure of the pivotal study. 20 of 23 (87%) patients responded as they did not have a 2-point decline on the adapted motor-language scale (ML scale) at week 48 of treatment. This responder population for the ML score in the 300 mg dosing period significantly exceeded the predicted untreated responder rate of 50% and therefore strongly favour treatment in comparison to no treatment based on the untreated decline of natural history CLN2 children. Several sensitivity and supportive analyses confirmed these results.

The rate of decline was 0.40 points/48 weeks (95% CI Limit 0.05, 0.75). After 1 year (48 weeks) 15 of 23 patients treated experienced a stabilisation (no change) and in two cases improvement of the studied functions.

The Kaplan Meier analysis showed that 8 of 23 patients experienced a decline of at least one point during the 48 weeks dosing period. This deterioration took place in the first part of the study followed by an apparent stabilisation until the end of the observation period.

Although vision deterioration is a relevant component of the disease no specific examination (OCT, electro retinogram, visual evoked responses) was conducted. This was justified by the Applicant by the fact that the ICV administration does not allow reaching therapeutic drug concentrations to eye (retina) tissues. This is in line with the findings in the animal models. Since very low systemic exposure to BMN 190 has been detected after each administration, an effect cannot be totally excluded. When the vision function was recorded as part of the Hamburg LINCL Scale some effect was observed: -0.7 points of difference in the 9-point Motor/Language/Vision Scale compared to -0.4 points in the 6-point Motor/Languaje Scale). A close correlation between ophthalmic manifestations of CLN2 disease with the degree of neurological function and the age of the patient has been described in literature (Orlin, 2013). Ophthalmological evaluations have been suggested as an objective marker of disease severity and disease progression. A positive trend in an ophthalmic functional endpoint (e.g. OCT) would have given additional plausibility to the changes detected in the clinical evaluation; however, it is not clear whether drug concentrations in the retina are high enough to elicit a beneficial effect. Study 203 (currently ongoing as a PIP measure) will include ophthalmic evaluation, including optical coherence tomography.

MRI parameters can support the clinical efficacy outcome, especially if those patients showing better apparent clinical response are also those showing better MRI results. However, changes in brain volume parameters and clinical response were not observed consistently in the same direction over the 48 weeks of 300 mg stable treatment. It has been suggested that this discrepancy in relation to data derived from natural history data (which suggest a good correlation between clinical disease severity and several MRI outcome parameters) may be potentially explained by not yet understood re-modelling effects of the treatment (e.g. debulking of lysosomal storage material in the early phase of treatment). However, for successfully treated

patients, overall changes from baseline to endpoint are expected to be smaller than in untreated patients, as shown in the natural history analyses where all of the patients were untreated and declined rapidly.

Brain volume measurements in treated patients showed a progressive decline of brain volumes in both grey and white matter, and an increase of ventricular volumes. Changes of -5.3% at 24 weeks, -9.7% at 48 weeks, and -10.6% at 72 weeks in cortical grey matter have been estimated. However, whereas a clear reduction in cortical grey matter was observed during the first year of treatment the loss of cortical grey matter appeared to slow down at Week 72. This means that anatomical stabilisation under treatment may only become obvious beyond 12 months of treatment. Overall, the assessment of the anatomical parameters (MRI brain volumes) suggest a reduction of the rate of volume loss in treated vs. untreated patients and therefore further support the benefit (stabilisation) observed in motor and language function compared to untreated controls (Lobel, 2016).

Conclusions on quality of life parameter assessments are difficult on the basis of small changes and lack of an untreated comparator arm. Overall, the results can be interpreted as stabilisation of QoL. However, as also pointed out by the ad hoc expert group meeting, QoL results were not surprising: as the treatment appears to largely halt disease progression but is not curative, it is not expected that QoL measurements will considerably improve compared to baseline. The consulted experts considered this stabilisation as benefit compared to the considerable QoL deterioration regularly experienced with disease progression.

The results of extension study 202 show for the majority of treated subjects overall stability of ML scores, indicating continued durability of treatment effect. The decline rate estimates showed lower values compared to the earlier interim results, indicating a further slowing of the disease.

The supplementary information provided by the DEM-CHILD database was consistent with those reported by Hamburg/WCMC cohorts. A total of 41 out of 74 patients met the inclusion criteria, with 15 new patients in the cohort in comparison with the original one. The estimated rate of decline was 2.09 points per 48 weeks although differences were detected between participating centres: Verona (rate of 1.54 points/48 wk) and Hamburg (rate of 2.23 points/48 wk). These differences have been justified by the low number of patients (n=8) and the relative paucity of data available from the Verona site.

Comparisons of untreated patients (901 supplement) with treated patients from study 201 in the initial ISE showed a clinically relevant and statistically significantly higher proportion of responders with a decrease in the rate of disease progression (rate < 2/48 weeks) under active treatment (91%) as measured by the ML scale compared to untreated patients (historical data) (45%) (primary responder analysis). Additionally, a high number of sensitivity and supportive analyses showed that the effect was not dependent on the analysis method.

The focus of the updated integrated efficacy analysis was on the n=42 history population; however, the n=49 data results were also provided. A review comparing the results of matching using each of the two different populations revealed no substantial differences for the various matching analyses.

With regards to responder analysis, the estimated response rate for the 201/202 ITT population was 100%. The estimated response rate for the matched DEM-CHILD population was 43% (9/21). The estimated difference in response rates was 57% ($p<0.0001$). Analyses of the estimated rate of disease progression, analyses of time to unreversed declines, and simple analyses of change from baseline all yield similar results confirming the improvement in disease progression seen in the treated population versus untreated patients.

Subjects of less than 3 years of age were not included in 201/202 study since certain degree of deterioration was required at entry in order to demonstrate a detectable change. This was deemed acceptable in the

context of the clinical study, especially as the diagnosis is usually made in the symptomatic phase of the disease. However, it can be expected that patients diagnosed at presymptomatic stage (e.g. when there is already a known, affected family member) and those with an earlier onset of the disease may require treatment when they are younger than 3 years. In these cases and given the nature of the product (aimed to restore the enzymatic defect) the treatment would be expected to have better outcome (as work in animal model suggests). The proposed dose in these patients is based on brain mass and was found to be sufficiently justified. Therefore, the CHMP has agreed to grant Brineura an unrestricted indication. Further data on efficacy, PK and dose selection for the 0-3 population will be collected post-approval.

Additional expert consultation

The discussions from the convened Ad-hoc Experts meeting are summarised below.

1. In the experts' experience, is the natural history of CLN2 disease as homogeneous as it has been described in the Natural History Study 190-901?

Based on the experts' experience and data from the parents' association database, the CLN2 disease is fairly homogeneous. The usual age of onset and progression rates are comparable to those described in the Natural History Study.

2. The Applicant has presented an adapted CLN2 rating scale (covering language and motor functions) as a valid reference to assess the clinical effect of Brineura. In the experts' view, are these two functions relevant enough in the clinical picture of the disease to serve as the primary endpoint for efficacy?

Majority of the experts were of the opinion that the adapted ML scale is appropriate as a primary endpoint and can be used to assess the course of the disease. Omitting vision and seizures as criteria prevented a complete description of the clinical situation. However, since treatment effects on vision were not expected and there is no evidence for it, and since effects on seizure were beneficial (if any) the data set was considered suitable to measure treatment effects.

Some of the scores were defined differently in active and historical control group but as the changes were only minor no significant impact was expected on the overall results.

The patients' representatives emphasized that the motor and language aspects that were assessed are the most important ones in the daily life of the children and their families.

Some of the experts thought that the scale is not appropriate as it does not cover cognition and developmental aspects. Nevertheless, the scale results seem adequate to capture changes in relation to disease regression (decline from maximum stage of development) but not on progression to new milestones; prior to the trial the company assumed that it won't be possible to observe any development improvement . It was also noted that in several of the children it is not possible to assess cognition at the time of diagnosis.

The experts also stated that although the short term effect is clear, there is a need to generate long term data post-approval with appropriate endpoints.

3. If the adapted scale is considered acceptable by the experts, is a mean decline of 2-points per year the expected deterioration rate in CLN2 disease? What range of decline might be expected in this population?

The experts who found the scale acceptable thought that the mean decline of 2 points per year is the expected deterioration rate in CLN2 disease.

It was noted that, on rare occasions, some children can be stable for a few months without any intervention. However, the duration of stabilisation is never as long as the stabilization effect observed in the clinical trial in some children.

4. In the experts' view, can the reduction in rate of decline observed in study 190-201 vs. the natural history study 190-901 (estimated difference (with 1:1 matching) of 1.56 points/48 weeks) be considered clinically relevant in the whole clinical picture of the disease?

The experts concluded that the observed effect size is clinically relevant.

5. How is the (lack of) effect on MRI parameters or QoL scales interpreted by the experts?

The experts believed that the value of the MRI measurements is not as high as the clinical outcomes observed in the trials.

The experts also stated that although there was no improvement in MRI measurements as compared to the individual baseline, stabilisation was still observed. Moreover, the usual rate of cortical grey matter loss was significantly greater in the untreated cohort (as measured at the Hamburg site).

One of the experts also noted that PET scan would have been preferable as imaging technique as it allows assessing brain metabolism.

With regards to Quality of Life outcomes, the results were not seen as surprising. The CLN2 diagnosis is a major challenge for a family and the participation in a trial was expected to bring additional burden e.g. necessity to move to a different country. As the treatment is not curative and stabilises the clinical situation, it is not expected that the drug effect will bring significant improvements compared to the baseline QoL measurements. However, if the progression of disease is halted, the QoL is likely to be better in comparison to untreated control group.

The experts discussed the potential stopping criteria in the case of apparently ineffective treatment and possible QoL consequences in cases when stabilisation was achieved in a patient with a low score. It was acknowledged that any decision to continue or discontinue treatment would have to be made on an individual case by case basis by the affected family supported by their physicians.

6. In the experts' view, what are the biological, pharmacological and clinical considerations for drawing inferences from these trial results to children younger than 3 years of age?

The experts were unanimous in their opinion that presymptomatic young children with confirmed genetic diagnosis (e.g. siblings of index cases) should be eligible for treatment. It is assumed that earlier treatment initiation will limit the development of the disease. This preference was confirmed by patients' representatives.

With regards to posology, the experts discussed possible dose adjustments. The dose used in clinical trial for patients older than 3 years old was extrapolated from the preclinical data and adjusted for the average brain weight. Similar approach could be used for the younger population. One of the experts has also raised the possibility to increase administration frequency as the younger children's brains grow at a higher rate. Experience with other lysosomal diseases could also be taken into account. The experts concluded that the company is best placed to propose alternative dose schedule, as they already developed them for the 203 study.

The experts also reported that the neurosurgeons at their sites do not perceive changes of the catheters, which would be necessary in the younger population, as a problem. Similarly, the required volume of infusion is not expected to cause safety or tolerability problems.

Additional efficacy data needed in the context of a MA under exceptional circumstances

As a specific obligation the applicant will conduct and submit results of the Phase 2 study (190-203) in order to further evaluate the treatment effectiveness as a delay in progression of CLN2 motor-language clinical sale and to further evaluate the safety and tolerability of cerliponase alfa. This study will include at least 5 patients below the age of 2 years.

2.7.4. Conclusions on the clinical efficacy

Overall, BMN 190 treatment over 48 weeks demonstrated a significant therapeutic effect on disease progression as measured by response rate and rate of decline in the ML score. Results observed for the majority of treated subjects represent overall stability of ML scores. Based on the results derived from the long-term extension study, efficacy results after prolonged treatment confirm the findings from study 201. Sustained treatment effect was observed for more than 1 year and occurred even when there was significant pre-existing burden of disease.

Overall, the available data on the effect of Brineura in CLN2 children show a sufficiently convincing beneficial effect. Further long-term efficacy and safety data will be provided post-approval. Particularly relevant will be the study intended to assess the effect of Brineura in children that are pre-symptomatic or at very early stages of the disease (Study 190-203).

The CHMP considers the following measures necessary to address the missing efficacy data and to be considered a specific obligation in the context of a MA under exceptional circumstances:

The Applicant will conduct and submit the results of the Phase 2 study (190-203) in order to further evaluate the treatment effectiveness as a delay in progression of CLN2 motor-language clinical sale and to further evaluate the safety and tolerability of cerliponase alfa. This study will include at least 5 patients below the age of 2 years.

2.8. Clinical safety

Patient exposure

24 subjects with CLN2 were exposed to BMN 190. All of them received at least one 300 mg dose of BMN 190. 1 subject has received only 1 single infusion of ICV BMN 190 and 23 subjects have received at least 72 weeks of treatment with 300 mg ICV BMN every other week during study 201/202.

Over the total 201/202 dosing period median time of exposure at any dose as well as at the 300 mg dose was 95.1 weeks, with a maximum of 141 weeks at any dose and a maximum of 124.4 weeks at the 300 mg dose.

All 23 subjects who completed study 201 entered study 202 and were continuing it as of 3 Jun 2016.

Baseline data

The most commonly reported medical history findings by PT for nervous system disorders were epilepsy (75%), ataxia (58%), language disorder (46%), and psychomotor skills impaired (42%). Either epilepsy or seizures was reported in 22/24 (92%) of subjects.

Severity of Disease

All subjects enrolled in study 201 had early-to-moderate CLN2 disease at Screening, as defined by a score of 3-6 on the ML scale (with at least 1 point in both the motor and language domains).

Concomitant medication

Concomitant medications were reported for all 24 subjects (100%) in 201/202. The most common concomitant medications were acetaminophen (92%), propofol (79%), midazolam (75%), valproate sodium (75%), diazepam (71%), cetirizine (67%), ibuprofen (67%), levetiracetam (50%), prednisolone (50%), sevoflurane (46%), and valproic acid (46%).

Adverse events

In studies 201/202, an MRI-compatible ICV reservoir and cannula leading to the lateral ventricle of the right hemisphere were implanted surgically. Following informed consent, but prior to ICV access device implantation, only SAEs related to study-mandated procedures were reported. Treatment emergent Adverse Events (TEAEs) were defined as any events occurring after the placement of the ICV access device, i.e. following the surgery for ICV access device implantation.

Overall summary of adverse events

All subjects experienced at least one treatment-emergent AE, 23 (96%) of subjects experienced at least one drug-related AE (ADR) and 19 (79%) of subjects experienced at least one SAE.

The majority of subjects (N=14; 58%) had ADR with moderate severity as highest severity level, 6 (25%) subjects had ADRs with only mild severity, at least 1 severe ADR occurred in 3 (13%) subjects. Drug related SAE occurred in 8 (13%) subjects.

The most common AEs were pyrexia (71%), seizure (58%), vomiting (58%) and upper respiratory tract infection (50%). Other common events included epilepsy and generalized tonic-clonic seizures (46% each), rhinitis (42%) and hypersensitivity and nasopharyngitis (38% each).

Related Adverse Events / Adverse Drug Reactions

Twenty-three subjects (96%) experienced an AE assessed as related to BMN 190 treatment by the investigator. The most common related AEs included pyrexia (46%), hypersensitivity (38%), seizure (38%), epilepsy (17%), vomiting (13%), and headache (13%); feeling jittery and myoclonus were reported in 2 subjects (8%) each, and the following PT for related AEs were reported in 1 subject (4%) each: bradycardia, abdominal pain, gastrointestinal disorder, nausea, oral mucosal blistering, tongue blistering, device leakage, needle issue, gait disturbance, pain, conjunctivitis, upper respiratory tract infection, infusion related reaction, body temperature increased, CSF test abnormal, atonic seizures, dropped head syndrome, dyskinesia, dystonia, generalised-tonic clonic seizures, partial seizures, pleocytosis, tremor, irritability, staring, rash and urticaria.

A total of 15 events with the PT of hypersensitivity were reported, including 5 events with Grade 3 severity. 86 of the 175 (49%) total treatment-related events reported had the PT of pyrexia.

Adverse Events of Special Interest (AEOSI)

Prospective selection of adverse events of special interest (AEOSI) was based on nonclinical findings, known effects of enzyme replacement therapies (ERTs), and literature review of AEs associated with ICV delivery systems.

AEOSI - Hypersensitivity Adverse Events (HAEs):

Hypersensitivity reactions, including anaphylaxis and less severe allergic reactions, are an identified risk for enzyme replacement therapy and investigators were instructed to pre-treat subjects with an age-appropriate dose of antihistamines (and antipyretics, if appropriate) ~30 minutes before infusion.

A hypersensitivity adverse event (HAE) was defined as any AE that maps into either:

- The broad “hypersensitivity” Medical Dictionary for Regulatory Activities (MedDRA) standardized MedDRA query (SMQ), or
- the broad algorithmic “anaphylactic reaction” SMQ with onset within 24 hours of start of a study drug infusion, as defined by MedDRA.

No HAEs were identified by the broad algorithmic anaphylactic reaction SMQ.

Fourteen of 24 subjects (58%) had a total of 36 HAEs in 201/202 identified by the hypersensitivity SMQ. It was the most common PT reported, occurring in 9 of the 14 subjects and accounting for 15 of 36 total events. The broad hypersensitivity SMQ also identified the following preferred terms: conjunctivitis (experienced by 4 subjects), contact dermatitis, rash, and urticaria (experienced by 2 subjects each) and stomatitis, dermatitis, and seasonal allergy (experienced by 1 subject each). Of the 36 hypersensitivity events, 9 (25%) (all events with the PT of hypersensitivity) were reported as SAEs.

Fourteen of the 15 events with the PT of hypersensitivity (including all events with Grade 3 severity) occurred during 201, no new events with the PT of hypersensitivity were reported in 202.

For reports of hypersensitivity, the most common manifestations were pyrexia, vomiting, pleocytosis, or irritability. According to the presented narratives, symptoms reported in the context of serious hypersensitivity AEs or infusion related reactions, respectively or grade 3 hypersensitivity AEs included: fever, nausea, vomiting, tiredness, motor agitation, increased heart rate, leucocytosis, increase in CRP,

increase in serum total IgE (but no drug specific IgE positivity), CSF pleocytosis, increased protein in CSF, increase in IL-6 in CSF. HAEs were observed during or within 24 hours after completion of the BMN 190 infusion.

AEOSI - Temporally Related Events (TREs) (as of 03 Jun 2016):

A TRE was defined as any AE with onset after initiation of BMN 190 infusion and within 24 hours after start or restart of infusion, regardless of the investigator's assessment of relatedness to study drug administration. The most common TREs (incidence > 10%) by PT were pyrexia (46%), hypersensitivity (38%), seizure (33%), vomiting (29%), tremor (25%), needle issue (21%), constipation, gait disturbance, upper respiratory tract infection, headache, myoclonus (17% each), diarrhoea, gastroenteritis, fall, and generalised tonic clonic seizure (13% each).

Most TREs were mild to moderate in severity (CTCAE Grade 1 to 2). Seven subjects (29%) had at least one grade 3 TRE over the total dosing period. Grade 3 TREs included acidosis (1 subject), anaemia (1 subject), thrombocytopenia (1 subject), hypersensitivity (5 events in 3 subjects), pharyngitis bacterial (1 subject), Propionibacterium infection (2 events in 1 subject), and skin infection (1 subject). Of the grade 3 TREs, only hypersensitivity events were considered related to the study drug itself. The events of Propionibacterium infection were device related events.

AEOSI - Device Related Events

Eleven subjects (46%) in 201/202 experienced a total of 30 device-related AEs over the total dosing period. Needle issue (5 events in 4 subjects), device leakage (5 events in 1 subject), and pleocytosis (3 events in 3 subjects), device malfunction (2 events in 2 subjects), and Propionibacterium infection (2 events in 1 subject) are the only device-related AEs to occurred more than once.

2 subjects had 3 ICV access device infections, both serious. All device infectious events resolved after treatment with antibiotics and removal/replacement of the ICV access device. Neither subject required discontinuation from study participation as a result of the events.

As of now, 4 device replacements in 2 subjects became necessary: Apart from 3 device replacements due to infectious events, one non-infectious device-related SAE (i.e. incorrect positioning/malfunctioning) required surgical device revision.

All other device-related AEs were grade 1 in severity.

12 infusions were interrupted and not completed. 7 of these cases were secondary to device-related AEs (3 events of needle issue, 1 with multiple events reported (needle issue and device malfunction), and 1 event each of device infusion issue, complication associated with device, and Propionibacterium infection). Two additional incomplete infusions were secondary to device problems that were not reported as AEs (1 instance of the needle being dislodged, and 1 instance of problem with the port). The remaining 3 instances of incomplete infusions were secondary to non-device related reasons.

Additional operation-related findings of study 201/202:

Of the 3 SAEs that occurred before the first BMN 190 infusion, 2 occurred in close temporal relationship with the device implantation:

- Subject 1287-1007 experienced a grade 3 peri-operative intracranial hemorrhage from Day -11 to Day -9 (at the time of ICV access device surgery).
- Subject 1323-1018 experienced two grade 2 pre-dosing events: epilepsy (Day -33 to Day -32, i.e. before device implantation) and pyrexia without evidence of device infection (Day -17 to Day -13; starting 1 day after device implantation).

Further AEs described after ICV surgery and before first BMN 190 infusion included vomiting, seizure/atypical focal seizure, agitation, peri-/post-operative pain, fever, minor head injury, mild cough, granulocytic pleocytosis [CSF], myoclonus, (grade 1 and reversible) alteration of venous flow detected at the level of the superior sagittal sinus. These AEs are largely compatible with the known risks of device implantation and CLN2 disease characteristics.

AEOSI -Convulsion/Status Epilepticus:

Seven subjects (29%) experienced 14 AEs meeting the AE of special interest definition of status epilepticus (includes MedDRA PTs petit mal epilepsy and status epilepticus). 13 of the 14 reported events had the PT of petit mal epilepsy, were non-serious and Grade 1 in severity, and were reported as not related to study treatment. The remaining event was reported as a serious Grade 4 event of status epilepticus. No events required dose modification.

Overall, 23 (96%) subjects experienced 362 AEs that map to the Convulsions Standardized MedDRA Query. The majority of convulsion AEs (>90%) were grade 1 or 2 in severity, and 94 % were considered unrelated to study drug. There was no clear pattern of reporting of convulsion events as drug related; the most commonly reported drug-related convulsion events included seizure (14 events in 9 subjects) and epilepsy (4 events in 4 subjects). Six subjects (25%) experienced 7 convulsion AEs that occurred after ICV implantation but before first dose of BMN 190.

Four subjects (17%) experienced 4 convulsion SAEs: a Grade 4 event of status epilepticus, a Grade 3 event of seizure, and 2 Grade 2 events of epilepsy. None of the SAEs were judged to be related to study drug. No further convulsion SAEs were reported during the update period.

59 out of 362 overall reported convulsion AE occurred temporally related to BMN 190 infusion (within 24 hours of start of infusion).

AEOSI – Hydrocephalus

No events meeting the pre-specified definition of hydrocephalus have been reported.

AEOSI – Meningitis:

No events meeting the pre-specified definition of meningitis have been reported.

Serious adverse event and deaths

A total of 19 subjects (79%) had at least 1 reported SAE during 201/202. A total of 51 SAEs were reported over the total dosing period, including 31 SAEs during 201 and 20 SAEs during 202. The most commonly reported SAEs were hypersensitivity (9 events in 7 subjects), upper respiratory tract infection (4 events in 4subjects), epilepsy (3 events in 3 subjects), bacterial pharyngitis (3 events in 2 subjects), gastroenteritis (3 events in 2 subjects), pyrexia (2 events in 2 subjects), Propionibacterium infection (2 events in 1 subject), and infusion related reaction (2 events in 1 subject). No other SAE was reported more than once.
The most common SOCs with SAEs were Infections and Infestations (22 events in13 subjects), Immune System Disorders (9 events in 7 subjects), and Nervous System Disorders (7 events in 6 subjects).

Eleven subjects (46%) had Grade 3 SAEs. Four subjects (17%) reported multiple Grade 3 SAEs:

• Subject 1244-1006 experienced 5 Grade 3 SAEs (1 event of pneumonia in 201, and events of bacterial pharyngitis, dysphagia, skin infection, and tonsillar hypertrophy in 202).

• Subject 1323-1015 experienced 4 Grade 3 SAEs: events of motor dysfunction, pharyngitis, and Propionibacterium infection during 190-201, and an additional Grade 3 event of Propionibacterium infection during 190-202.

• Subject 1287-1005 experienced a Grade 3 SAE of vaginal discharge during 201 and a Grade 3 SAE of seizure during 202.

• Subject 1244-1002 experienced a Grade 3 SAE of hypersensitivity during 201 and a Grade 3 SAE of upper respiratory tract infection during 202.

One subject (4%) had a Grade 4 SAE of status epilepticus, assessed by the investigator as unrelated to study treatment and not temporally related to BMN 190 infusion.

Eleven SAEs in 8 subjects were assessed by the investigator as related to treatment with BMN 190 - 9 SAEs of hypersensitivity and 2 SAEs of infusion related reaction. All 11 drug-related SAEs resolved with appropriate medical management, and all subjects with drug-related SAEs tolerated subsequent dosing and remained in the study.

No deaths were reported during study drug treatment or during follow-up in either study 201 or 202.

Laboratory findings

Hematology

Treatment-emergent abnormal hematology test results occurred in 100% of subjects. The most common abnormalities were low lymphocyte (71%) and low leukocyte (67%) level, low hematocrit (50%) and low platelet count (46%).

Nine abnormal laboratory reports were reported as Grade 1 AEs (2 anemia, hemolysis, 2 thrombocytopenia, platelet count decreased, RBC count decreased, hemoglobin decreased, hematocrit decreased), and 2 abnormalities were reported as Grade 3 AEs (anemia, thrombocytopenia). None of these events were

reported as study drug related and no action was taken with BMN 190 treatment. The nature of these changes is also not consistent with immunologically-induced effects on red blood cells or platelets.

Overall, mean changes in median, maximum and minimum hematology values from baseline did not reveal any clinically significant trends. However, in the safety population as a whole, there was a trend towards a decrease in the platelet count over the study duration. The change from study baseline to within value was -63 (10^9 cells/L). There were no similar changes in other hematology labs as the mean change for hemoglobin, hematocrit and red blood cells were overall stable.

Hematology shift tables revealed > 25% of subjects had post-baseline thrombocytopenia, leucopenia, or lymphopenia. However, platelet clinical laboratory results were variable over the course of the study and six of the 11 subjects who had low platelet laboratory, had a single low platelet value during 201 / 202, preceded and followed by normal value. Bleeding events were noted in 11 subjects and included bone contusion, contusion, hematoma, epistaxis, post procedural hematoma, traumatic hematoma, subdural hematoma, coagulopathy wound haemorrhage (all grade 1) and peri-operative intracranial haemorrhage (grade 3). All of them appear not to be associated with decreased platelet counts.

Hemoglobin levels were abnormally low in 6/24 subjects, and abnormally high in 7/24 subjects.

Clinical chemistry

Treatment-emergent abnormal chemistry test results occurred in 100% of subjects. Common abnormalities included low urate (74%), high chloride (63%), high AST (63%), high carbon dioxide (61%), high blood urea nitrogen (58%), low cholesterol (58%), low bilirubin (54%), and high lactate dehydrogenase (52%). Two abnormal laboratory reports were reported as AEs: blood alkaline phosphatase increased (Grade 2) and liver function test increased (Grade 1). None of these events were reported as study drug related and no action was taken with BMN 190 treatment.

Mean changes in median, mean, maximum, and minimum values from baseline did not reveal any clinically significant trends.

Urine-analysis

Treatment-emergent abnormal urinalysis test results occurred in 92% of subjects; the majority (75%) were high pH values. None of these abnormalities were reported as AEs.

Mean changes in median, mean, maximum, and minimum values from baseline did not reveal any clinically significant trends.

Cerebrospinal fluid

Treatment-emergent abnormal CSF test results occurred in 83% of subjects. For the 5 CSF parameters (cell count, protein, glucose, lymphocytes/leukocytes (%), monocytes/leukocytes (%)), 4%-71% of subjects had abnormal values. The most common treatment-emergent abnormalities were low CSF protein (71%) and

high CSF cell count (75%). Four subjects (17%) were noted to have CSF pleocytosis prior to first infusion, with a cell count ranging from 8 to 739 cells/µL. Of these subjects, the cell counts of 2 subjects remained elevated in the treatment period, while 14 subjects developed new CSF pleocytosis during the treatment period. These post-infusion abnormalities in CSF cell count were typically mild elevations, peaking between 7 and 25 cells/µL. The cell type was variable, but (where differentials were collected) was usually neutrophil predominant.

Vital sings/physical findings

AEs related to vital signs included Grade 1 pyrexia (9 subjects [38%]), Grade 2 pyrexia (8 subjects [33%]), Grade 1 bradycardia (2 subjects [8%]), Grade 1 sinus bradycardia (1 [4%]), Grade 2 postoperative fever (1 [4%]), Grade 1 oxygen saturation decreased (1 [4%]), Grade 2 oxygen saturation decreased (1 [4%]), Grade 1 hypotension (1 [4%]), and Grade 2 hypotension (1 [4%]). Of these, the Grade 1 bradycardia (1 [4%]), Grade 1 pyrexia (8 [33%]), and Grade 2 pyrexia (3 [13%]) were the only AEs reported to be study drug related. Sporadic transient changes in systolic and diastolic blood pressure have been observed during periods of frequent monitoring during and following infusions of BMN-190, but were non-progressive, non-sustained, and not associated with clinical sequelae.

Electrocardiograms (ECGs)

At baseline, 18 subjects (75%) had normal and 4 subjects (17%) had abnormal ECG results. Post-baseline, 16 subjects (67%) had 1 or more abnormal ECG, and 8 subjects (33%) had all normal ECGs. In the change from baseline to post-baseline, 6 subjects (25%) retained normal ECGs, 12 subjects (50%) were reported to shift from normal to one or more abnormal ECG. One subject (4%) had an abnormal baseline ECG that was normal post-baseline, and 3 subjects (13%) had an abnormal baseline ECG that shifted to 1 or more abnormal post-baseline.

Mean changes in ECG heart rate and RR, PR, QRS, and QT intervals and QTcF intervals did not reveal any clinically meaningful trends. There was a single patient with a QTcF interval > 450 msec, which was a 50 msec increase compared to the baseline measurement.

From the details of reported ECG abnormalities no clear patterns suggesting myocardial damage are seen. However, in one subject ECG signs of a possible left ventricular (LV) hypertrophy were reported during study 202 but not during the preceding study 201. In this subject grade 2 hypotension was reported 8 hrs after BMN 190 infusion and was reportedly resolved.

As of now, 9 cardiac AEs occurred in 5 subjects, one of which was considered related to study drug, i.e. bradycardia during infusion in one subject with a history of bradycardia and hypotension.

Electroencephalograms (EEGs)

Compared with baseline, there were changes in epileptiform activity and frequency slowing. Three subjects (13%) showed new focal epileptiform activity, while 6 subjects (25%) showed new generalized epileptiform activity and 6 subjects (25%) showed both new focal and generalized activity.

Eight subjects (33%) showed new focal frequency slowing. Three subjects (13%) showed new generalized frequency slowing, and 4 subjects (17%) showed both new focal and generalized frequency slowing.

Safety in special populations

Age of study subjects at enrolment in study 201 ranged from 3-8 years, with a median age of 4. From the presented analysis of AEs categorized by < 4 years and ≥ 4 years of age, no clear difference in the reported AE frequency can be derived. Vomiting occurred approx. twice as often in older compared to younger subjects, however, as the subgroup of subjects < 4 years was low (N=6), these data must be interpreted with caution.

There was no apparent gender difference in the severity of AEs or the occurrence of drug-related AEs, device-related AEs, or hypersensitivity AEs. Differential incidences of AEs by race/ethnicity could not be ascertained because 23/24 subjects were in the same racial and ethnic groups.

Studies 201/202 were conducted in 4 countries, with exposure in subject years being 18.4 in Germany, 6.3 in Italy, and 2.7 each in the UK and US, respectively. No apparent regional differences can be derived from the provided safety data by country.

Immunological events

Immunogenicity assessment included characterizing the anti-drug antibody (ADA) response and assessing the impact of ADA on safety, exposure and efficacy. Routine immunogenicity tests included TAb in the serum and CSF and neutralizing antibody (NAb) in the CSF. NAb testing was not performed if the CSF TAb was negative.

ADAs were detected in the serum of 9/24 subjects (79%) by 73-133 weeks of treatment. ADA were first detected between Weeks 5-13, and in subjects who developed an ADA response, the response was either sustained (12/19, 63%) or declined (7/19, 37%), of which 5/19 (26%) reverted to undetectable by week 133.

ADAs were detected in the CSF of 6/24 subjects (25%) treated with BMN 190 for 73-133 weeks. The ADA titres were sustained in 2/6 (33%) and declined to undetectable in 4/6 (66%) of the subjects that developed antibodies by Week 133. The earliest time to onset of ADA development in the CSF was Week 13. Anti-BMN 190 neutralizing antibodies (NAb) were not detected in the CSF of any BMN 190-treated subjects (0/24) for up to 133 weeks.

No association was found between serum ADA titre and incidence or severity of hypersensitivity AEs. All subjects who experienced a serious or grade 3 hypersensitivity adverse event were reported to be negative for drug-specific IgE, however, the test used for evaluation of drug-specific IgE was not considered reliable. During the marketing authorization procedure the applicant submitted a valid test method which will be used for further evaluation of immunogenicity post-marketing.

A comparison of CSF and serum ADA negative and positive subjects showed no association between ADA titre and treatment outcome as measured by the ML scale.

Safety related to drug-drug interactions and other interactions

No formal studies of drug-drug or drug-disease interactions were performed. The catabolism of BMN 190 is not expected to be affected by another drug or disease.

Discontinuation due to adverse events

There were no discontinuations due to adverse events.

Post marketing experience

N/A

2.8.1. Discussion on clinical safety

From the safety database all the adverse reactions identified in clinical trials have been included in the Summary of Product Characteristics.

The clinical dossier submitted in support of Brineura MAA contained safety data of the completed uncontrolled study 201 conducted in 24 subjects and the ongoing extension study 202. As of 3 June 2016, all 23 subjects who completed study 201 entered study 202 and were continuing participation.

The clinical safety database is very limited. During the course of the evaluation, the applicant has informed CHMP that 4 subjects have additionally been enrolled in the sibling study 203, and that 16 subjects have been treated since 12 Aug 2016 in compassionate use programs. Although additional information is very limited, no new safety issues have been reported.

All 24 subjects experienced TEAEs. The most frequent TEAEs were pyrexia (71%), seizure (58%), vomiting (58%), and upper respiratory tract infections (50%). Other common events included epilepsy and tonic-clonic seizures (46% each), rhinitis (42%) and hypersensitivity and nasopharyngitis (38% each).

Causality assessment of the reported AEs is made difficult by the fact that studies 201/202 were uncontrolled and that several AEs may have multiple causes, e.g. can be related to the drug, device, device implantation, ICV infusion, underlying disease and/or concomitant medication. Furthermore, BM190 is a first in class compound and the pre-clinical data package is very limited and with restricted transferability to humans.

Hypersensitivity AEs (HAEs) are currently considered the most relevant safety concern related to the drug itself. The majority of study subjects (58%) had hypersensitivity AEs (HAEs) identified by the broad “hypersensitivity” SMQ, 5 HAEs in 3 subjects were rated as grade 3. All 9 AEs (in 7 subjects) with the PT hypersensitivity were reported as SAEs. It is currently reassuring, that all hypersensitivity reactions were manageable (mainly with antihistamines, antipyretics and/or steroids) and did not lead to dose reduction or withdrawal from treatment with BMN 190, and that no anaphylactic/anaphylactoid reactions have been reported. However, the occurrence of life threatening anaphylactic reactions due to ICV BMN 190 can currently not be excluded. Therefore, precautionary measures during drug administration have been included in the SmPC.

Further evaluation revealed no increase of hypersensitivity AEs over time, with a trend towards decreasing severity of hypersensitivity reactions. From the provided data, it appears that the results regarding ADA development and risk of hypersensitivity are also valid for subjects without residual TPP1 (who may be at

potentially higher risk of hypersensitivity). In order to reduce the risks of hypersensitivity reactions, pre-treatment with antihistamines with or without antipyretics 30-60 minutes before each BMN 190 infusion is recommended in the SmPC.

30 device-related AEs occurred in 11 (46%) subjects and were generally in line with known risks of ICV devices. The presented data and available literature indicate that infection appears to be the most significant device-related safety risk. ICV drug delivery is an effective route of administration into the CNS but stringent measures are necessary to prevent complications. The Applicant will develop educational materials for Health Care Professionals (HCPs), describing the correct infusion preparation, the intracerebroventricular (ICV) drug administration and the monitoring of the patients in order to reduce the risk of device-related infections. Besides the 3 infection-related device replacements, a 4th device replacement was necessary due to an event of incorrect positioning/malfunctioning. All other non-infectious device-related complications were reported as mild. During an acute device-related infection, ICV administration of Brineura is considered to pose an unacceptably high risk. Device malfunction and leakage may further lead to reduced availability of BMN 190 in the targeted areas or lead to increased risk of hypersensitivity due to increased off-target exposure. Therefore, Brineura is contraindicated in case of signs of acute ICV access device leakage, failure or device-related infection.

In addition to AEs classified as device-related, 2 SAEs occurred in close temporal relationship with device implantation but before first study drug administration, i.e. intracranial hemorrhage (associated with the reversible symptoms of fever, lethargy, vomiting and seizure) and pyrexia without evidence of device infection. These SAEs as well as further non-serious AEs reported after device implantation were generally compatible with the known risks of ICV device implantation. In order to reduce device related risks, instructions and precautionary measures have been included in the SmPC.

Seizures and epilepsy were among the most common TEAEs. However, seizures and/or epilepsy occur in the vast majority of CLN2 patients, often as the first symptom, and were reported in 92% of subjects at screening. Besides being related to the underlying disease, seizures could potentially also be caused by the ICV device, ICV drug administration or protein administration. Therefore, interpretability of the results of the uncontrolled study 201/202 is very limited. Whereas seizures were not counted with seizure diaries during study 201/202, it is generally reassuring that the mean change in total CLN2 score suggests improvement in the seizure domain and that the majority (>90%) of convulsion AEs were graded as mild or moderate. Of the 14 AEs that met the AEOSI definition of status epilepticus, only 1 AE was coded with the PT status epilepticus considered unrelated to study drug, the other 13 AEOSI were related to absence type seizures. On the other hand, in analyses presented as of cut off of 15 Oct 2015, compared to baseline, new (focal and/or generalised) epileptiform EEG activity was reported in 62.5% of subjects. Further (and in contrast to the applicant's argumentation that only "few" subjects experienced convulsion events within 24 hours of study drug administration), 18.5% of all convulsion AEs were temporally related to BMN 190 infusion (i.e. 48 out of 260 convulsion AEs), which is considerably above the overall average of convulsion AEs expected, i.e. 1 in 14 days (approx. 18.6 out of 260; 7.1%). The updated data still revealed a clearly increased rate of temporally related convulsion AEs (59/362, 16.3% of all convulsion AEs) and 6% out of 362 seizures (N > 20) were considered treatment related by the investigator.

Although interpretability of convulsion AEs reported in studies 201/202 is difficult and there appears to be an overall beneficial effect of BMN 190 with regard to seizures, general plausibility of a causal relationship with BMN 190 treatment as well as a considerably increased rate of convulsion AEs reported to be temporally related with BMN 190 infusion, strongly point to the possibility that some seizures may also be provoked by BMN 190 treatment. Adequate information has been presented in section 4.8 of the SmPC.

Currently, due to the limited number of treated patients as well as time of exposure, the risk for hydrocephalus due to treatment with BMN (i.e. protein administration via ICV device) cannot be quantified. However, it is reassuring that so far no cases of hydrocephalus have occurred. Subjects prone to complications from ICV drug administration (e.g. with ventricular shunts) were excluded from participation in studies 201/202. As ventricular shunts which bypass CSF to the body system are presumed to reduce exposure to BMN 190 in the CSF and in the targeted brain areas while increasing the systemic exposure to BMN 190, which may reduce efficacy and increase hypersensitivity risk at the same time, treatment with BMN 190 has been contraindicated in subjects with these shunts.

CSF pleocytosis was seen in 75% of subjects and emerged as isolated finding which was often rather mild and could be related to the placement of the ICV device; however, in some subjects higher CSF cell counts (up to 4646.6/ µL) were also reported during treatment without any associated AEs reported. In 8 (33%) subjects, CSF pleocytosis was persistent with > 20% of their follow-up labs also demonstrating CSF pleocytosis. Predominantly more pronounced CSF pleocytosis occurred in association with hypersensitivity, fever and device-related infection. Elevated CSF protein, reported in 4 (17%) subjects may be indicative of a device related infection but appears also to occur as isolated finding. Low CSF protein was reported in 71% of subjects and could be caused by loss of CSF, either by CSF sampling or by device related CSF leakage. However, the AE of device leakage has been reported in only 1 subject (5 events), no case of low CSF protein was reported as AE and the exact reason for decreased CSF protein is currently not clarified.

Immunogenicity evaluations revealed a very high percentage (79%) subjects who developed anti-drug antibodies (ADA) in serum, and the ADA response was sustained in approx. 2/3 of subjects. A lower proportion of subjects (25%) developed ADAs in CSF. Descriptive as well as graphical correlation analyses showed no apparent correlation between the serum ADA titres and the incidence or severity of hypersensitivity AEs or treatment effect. The clinical relevance of sustained ADA response in serum and CSF remains unclear. Until further elucidation of the potential role of antibodies in serum/CSF, the routine monitoring does not appear to be necessary. However, further data regarding ADA should be collected in the ongoing clinical studies.

There appears to be no relationship of thrombocytopenia observed in 11 out of 24 treated children and the trend towards a decrease in platelet count in the overall study population over the study period. Thrombocytopenia was mostly mild and without clear pattern and occurred in a patient group with potential confounders. There were only 2 observed thrombocyte values below 100 (10^9 cells/L) and none of the 4 AEs (3 grade 1 and 1 grade 3) was reported as drug related. There are potential confounders to a possible mechanism-based effect on platelets, including concomitant medications and a patient population of chronically ill pediatric patients with inter-current illnesses, polypharmacy, and potential nutrition issues during the study period which may affect platelet count.

The type of the 11 bleeding events observed in the 201/202 (bone contusion, contusion, hematoma, epistaxis, hemorrhage intracranial grade 3, post procedural hematoma, traumatic hematoma, subdural hematoma, epistaxis, coagulopathy, and wound hemorrhage) is not typical for bleeding events associated with thrombocytopenia but seems to be rater related to surgery and CLN2 associated symptoms like seizures and gait disturbance. Inclusion of thrombocytopenia in the RMP is therefore not considered warranted.

In non-clinical studies, increased Troponin I was found in dogs after intrathecal BMN 190 application. Although this finding may be a symptom of the CLN2-model (i.e. due to lysosomal storage in heart tissue) and although systemic exposure to BMN190 is very low, a causal relationship with BMN 190 administration cannot be excluded based on limitations of the respective study data. Cardiotoxicity has not been particularly addressed and troponin has not been measured in the clinical studies. From the presented details of reported

ECG abnormalities, no clear patterns suggesting myocardial damage are seen. However, one subject developed a possible left-ventricular hypertrophy during the course of study 202. In another subject, a cardiac AE of bradycardia during BMN 190 infusion was considered related to treatment. As currently no clear safety signal regarding cardiotoxicity can be derived from the pre-/clinical data, 12-lead ECG evaluations every 6 months as routine monitoring in cardiac normal subjects are considered sufficient. However, since some of these CLN2 patients may develop conduction disorders or heart disease, ECG monitoring during infusion is recommended in patients with present or past bradycardia, conduction disorders, or with structural heart disease. Cardiac AEs will be monitored as AEs of special interest and further evaluation of potential acute cardiac effects will be implemented in the ongoing clinical studies.

As only one dosing regimen has been tested, it remains unclear whether the evaluated dose and infusion rate could have been further optimized. From the safety point of view, a lower dose and infusion rate might be associated with a lower hypersensitivity risk as the systemic exposure of BMN 190 would be anticipated to be lower. On the other hand, a longer infusion procedure might increase the infection risk as well as the discomfort for the patients.

No AEs of increased intracranial pressure have been reported. However, as intracranial pressure has not been measured during the study, it cannot be excluded that in some cases symptoms such as headache, nausea, vomiting or seizures may have been caused by a temporary increase in intracranial pressure. As a precautionary measure, which is of particular importance with regard to children below 3 years of age, the CHMP advised that appropriate information should be added to section 4.2 of the SmPC: the infusion should be interrupted and/or the infusion rate slowed, in case symptoms would occur, which in the judgment of the treating physician are considered caused by an increase in intracranial pressure.

During the MAA evaluation, concerns were raised with regards to the safety of ICV devices in very young children (in particular < 1 year of age) compared to children ≥ 3 years which also concerned differences in diagnosis and prognosis of device related infections, need for catheter changes due to brain growth as well as vulnerability of the very fast developing brain.

As of now, two subjects aged 2 years have been included in the ongoing study 203 and have received 8 BMN 190 infusions (at the same posology as studied and proposed for older children). They appeared to tolerate the treatment well so far. The applicant has provided some reassurance that the infusion of BMN 190 in these young children would not be expected to bear an unacceptably high risk of increased intracranial pressure as the Brineura infusion rate of 2.5 mL/h is still below the CSF production rate of 3.1 mL/h calculated for a 2-year old female at the 3rd percentile according to the formula developed by Yasuda et al. (2002).

The applicant has also proposed a posology for treatment of children < 2 years (which is in line with the posology scheduled for evaluation in study 203) and provided argumentation that this dose is anticipated to provide an acceptable safety profile in very young children: BMN 190 should be infused ICV every 14 days at the same infusion rate but at a reduced dose of 100 mg in children from birth up to < 0.5 years and of 150 mg in children from 0.5 to 1 year of age, as well as at a reduced dose of 200 mg for the first 4 infusion in children from > 1 to 2 years. These reduced dosages are calculated based on lower brain mass in younger children. Further argumentation supporting a low risk of increased intracranial pressure due to the proposed infusion volume referring to total CSF volume and turnover rate has been found reassuring.

In the absence of clinical data with BMN 190 in these age groups, this approach to posology currently appears reasonable with regard to safety. However, further PK data will need to be collected in the ongoing study 203, in order to allow for confirmation of the appropriateness of this approach or lead to further

optimization of posology and for comparison of PK parameters in CSF and plasma between children < 2 y and children > 2y. Of these latter Cmax is considered particularly important with regard to safety (as e.g. an immature blood-brain-barrier in newborns and very young infants might lead to disproportionately high BMN 190 exposure in plasma).

As all subjects enrolled in study 201 had early-to-moderate CLN2 disease at screening (defined by a score of 3-6 on the ML scale), safety data in subjects with advanced CLN2 disease is missing. It can currently not be excluded that the risk of hypersensitivity/immunogenicity increases in these patients. Disturbance of the blood brain barrier, which is commonly described in advanced neurodegenerative disease, might occur in these patients and would be anticipated to be associated with higher plasma exposure of BMN 190. Therefore, SmPC includes caution that no clinical data is available in subjects with advanced CLN2 disease.

Although Brineura is intended for chronic treatment, long-term safety data is currently limited. An ongoing benefit/risk evaluation is necessary in individual patients.

Additional safety data needed in the context of a MA under exceptional circumstances

In the context of a MA under exceptional circumstances, specific obligations are included in the terms of the Marketing Authorisation. The applicant will conduct as a specific obligation a Phase 2 study (190-203) in order to further evaluate the safety and tolerability of cerliponase alfa. The applicant will also monitor the long term safety in patients treated with Brineura from a patient registry for which details are reflected in the risk management plan. Reports on recruitment progress of the registry will be reported at the time of PSURs and Annual Re-assessments. Progress and results from the registry will form an important element of the annual reassessments of the benefit/risk profile of Brineura. The CHMP is of the opinion that the value of the registry data would be increased if the Applicant established a formal cooperation with a well-established international disease registry.

2.8.2. Conclusions on the clinical safety

The clinical safety database derived from studies 201/202 is considered limited. Causality assessment of reported AEs is difficult as the clinical studies were uncontrolled and several AEs may have different causes including active substance, device and underlying disease, respectively. Further, BMN 190 is a first in class compound and the pre-clinical safety data package is very limited and with restricted transferability to humans. Although ICV treatment with Brineura is associated with potentially serious adverse drug reactions and device-related issues, these were so far manageable.

Given the rarity, as well as the rapidly progressive and invariably fatal character of CLN2 disease and the absence of disease specific treatment options, the uncontrolled and limited safety data base is considered sufficient in order to grant approval under exceptional circumstances.

The CHMP considers the following measures necessary to address the missing safety data in the context of a MA under exceptional circumstances:

The Applicant will monitor the long term safety of Brineura in the treatment of CLN2 on the basis of the registry. Additional data collected this way will help broaden knowledge of identified and potential risks of cerliponase alfa, as well as provide new information on long-term safety and tolerability.

2.9. Risk Management Plan

Table 18. Summary of the Safety Concerns

Important identified risks	• Hypersensitivity Reactions • Device Issues: device infection/blockage/dislocation • Convulsion related adverse drug reactions
Important potential risks	• Immunogenicity • Cardiac events/bradycardia • Hydrocephalus • Meningitis
Missing information	• Long Term Safety and Tolerability • Use in Pregnancy and during Lactation • Use in patients below 2 years of age • Use in patients above 8 years of age • Use in patients with advanced CLN2 disease

Pharmacovigilance plan

Table 19. Ongoing and planned studies / activities in the Pharmacovigilance plan

Study / activity	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
190-501 Neuronal Ceroid Lipofuscinosis Type 2 (CLN2) Registry Study [**Category 2**]	The safety objectives of this CLN2 Disease Registry are: • To evaluate the long term safety of cerliponase alfa, including, but not limited to, the occurrence of serious hypersensitivity reactions, and anaphylaxis.	Additional data collected will help broaden knowledge of identified and potential risks of cerliponase alfa, as well as provide new information on long-term safety and tolerability.	Planned	Study protocol to be submitted for PRAC evaluation and approval within 1 month from the EC decision Reports to be submitted annually

Risk minimisation measures

Table 20. Summary table of the Risk Minimisation Measures

Safety Concern	Routine risk minimisation Measures	Additional risk minimisation measures
Important identified risks		
Hypersensitivity Reactions	Wording in SmPC Section 4.2, 4.4, and 4.8	None
Device issues	Wording in SmPC Section 4.2, 4.3, and 4.4	Healthcare provider educational materials
Convulsion related adverse drug reactions	Wording in SmPC Section 4.8	None
Important potential risks		
Immunogenicity	Wording in SmPC Section 4.8	None
Cardiac events/bradycardia	Wording in SmPC Section 4.4 and 4.8	None
Hydrocephalus	Wording in SmPC Section 4.4	None
Meningitis	None	None
Missing information		
Long Term Safety and Tolerability	Wording in SmPC Section 4.8	None
Use in Pregnancy and during Lactation	Wording in SmPC Section 4.6	None
Use in patients under 2 years of age	Wording in SmPC Section 4.2 and 4.8	None
Use in patients above 8 years of age	Wording in SmPC Section 4.2	None
Use in patients with advanced CLN2 disease	Wording in SmPC Section 4.2	None

The CHMP and PRAC considered that the risk management plan version 1.4 (dated 24 April 2017) is acceptable.

2.10. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.11. New Active Substance

The applicant declared that cerliponase alfa has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers cerliponase alfa to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.12. Product information

2.12.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.12.2. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.12.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Brineura (cerliponase alfa) is included in the additional monitoring list as it contains new active substance and has been approved under exceptional circumstances.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Neuronal ceroid lipofuscinoses are a genetically heterogeneous group of inherited neurodegenerative lysosomal storage disorders, which are characterised by accumulations of intracellular lipofuscin-like material in multiple organs leading to functional impairments and ultimately death (Mole *et al*., 2005). The different neuronal ceroid lipofuscinoses are distinguished by the genetic origin, ultrastructural composition of the lysosomal storage material, clinical symptoms, age at onset and course of disease.

Late Infantile Neuronal Ceroid Lipofuscinosis Type 2 (CLN2) disorder, formerly also known as Jansky-Bielschowsky disease or classical late infantile onset neuronal ceroid lipofuscinosis (cLINCL), is a rare, paediatric-onset neurodegenerative lysosomal storage disorder caused by TPP1 enzyme deficiency as a consequence of loss-of-function mutation in the CLN 2 gene.

Affected patients usually become symptomatic in the second or third year of life and present with slowing of development and with psychomotor regression. Epilepsy typically develops early and is often refractory to medical treatment. The visual, cognitive and motor skills decline rapidly. In general, patients lose vision, are wheelchair-bound and require gastrostomy feeding at approximately 6 years of age and subsequently enter a vegetative state with death between 10 and 16 years of age.

3.1.2. Available therapies and unmet medical need

No curative treatment for classic late infantile neuronal ceroid lipofuscinosis type 2 exists and the diagnosis is invariably fatal. Clinical management guidelines for CLN2 disease have not been developed yet. Symptomatic treatments are focused on the treatment of seizures (anticonvulsants), motor control loss (bracing or wheelchairs) and feeding/ control of aspiration risk (gastrostomy tube). Disease management includes physical and speech therapy, different medications aiming at alleviating symptoms such as myoclonus, spasticity, dystonia and pain as well as end-of-life care at advanced disease stage. Therefore, there is currently a high unmet medical need.

3.1.3. Main clinical studies

The evidence of the efficacy of BMN 190 in the treatment of CLN2 is mainly based on data from two studies: a Phase 1/2 open-label dose escalation study (Study 190-201) and its extension (Study 190-202).

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

Included patients had a confirmed diagnosis of CLN2 disease by TPP1 enzyme activity and genotype information, mild-to-moderate progression of CLN2 disease, as measured by a 2-domain (motor/gait and language) score (ML scale score) of 3-6 on the adapted CLN2 disease rating scale, including a score of at least 1 in each of the two domains and were 3-15 years of age at study enrolment.

Additionally, a Natural History non interventional study (study 190-901) has been conducted and submitted to provide a comparator group. A Phase 2 study (Study 190-203) in siblings of subjects enrolled in 201/202 studies is ongoing. Given the very limited exposure (as of 15 May 2016 only 3 subjects have been enrolled) no data from this study is included in the efficacy evaluation of Brineura.

3.2. Favourable effects

In study 190-201, 20 of 23 (87%) patients responded to treatment as they did not have a 2-point Decline on the ML scale at week 48. The responder population for the ML score in the 300 mg dosing period significantly exceeded the predicted untreated responder rate of 50% ($p = 0.0002$).

Responder rates for the separate motor and language domain scores for the ITT population during dosing period showed that eighteen subjects (78%) and 16 subjects (70%), respectively, met the definition of a responder.

Fifteen (65%) of the 23 treated patients had no unreversed single point loss. These patients were stable or improved over the full duration of 300 mg treatment as measured by the ML scale. The estimated responder rate of 65% in treated patients significantly exceeds the expected responder rate of 25% in untreated patients ($p < 0.0001$).

As shown by the Kaplan-Meier analysis, all patients with an unreversed single point decline lost function early under active treatment and were stable afterwards. Thus, the disease-modifying effect of Brineura may not become obvious immediately.

In comparison to untreated patients (Integrated summary of effectiveness, *1:1 Matching* based on age and baseline ML scale scores (for 190-201/202 subjects)/HML scale scores (for natural history patients*),* the primary responder analysis showed a relevant and statistically significantly higher proportion of responders with a decrease in the rate of disease progression (rate < 2 points/48 weeks) under active treatment (91%) as measured by the ML scale compared to untreated patients (historical data) (45%).

During the procedure, the applicant identified 7 children that had participated in the natural history study 190-901 before having been recruited into study 190-201. Excluding these patients from the comparative analyses did however not change the overall study results. In addition, the decline in ML score of these patients showed a clear favourable deflection during treatment compared to the previous untreated phase.

With respect to results derived from the long-term extension study 202 (cut-off date 03 June 2016), the observed effect was stable, and seemed to be independent from baseline ML scale score at the start of the treatment. In comparison to untreated patients (updated Integrated summary of effectiveness; 1:1 Matching), the primary responder analysis showed a statistically significantly higher proportion of responders with a decrease in the rate of disease progression (rate < 2/48 weeks) under active treatment (100%) as measured by the ML scale compared to untreated patients (historical data) (43%).

With regards to MRI findings, the assessment of the anatomical parameters (MRI brain volumes) suggest a reduction of the rate of volume loss after 72-week treatment compared to untreated patients and therefore further support the stabilisation observed in motor and language function compared to untreated controls. However, as also confirmed by the ad hoc expert group, the value of the MRI measurements is not as relevant as the clinical outcomes.

Scatter plots compared the change from 300 mg baseline ML scale score at week 49 with MRI changes at Week 49. Overall, the provided analysis showed no clear correlation between ML score and total cortical grey

matter volume (r = 0.20), total white matter absolute volume (r = 0.27), total white matter percentage (r = -0.17), or whole brain ADC (r = 0.12). There was a modest correlation between ML score and absolute CSF fluid volume (r = 0.61), percent total cortical grey matter (r = -0.48) and whole brain volume (r=0.52).

3.3. Uncertainties and limitations about favourable effects

Dose selection was based on results from non-clinical studies and no specific dose finding studies were performed. Only one dose was studied and no dose adjustment is proposed according to age, severity of the condition or relative volume of the CSF/brain (brain atrophy). Although the proposed dose may not be optimal for the whole target population, it was found to be effective and is thus acceptable.

Study 201 was a small single-arm open-label study which cannot generate evidence at the usually expected level with regard to potential bias and a confirmatory approach with control of type I error for the primary analysis. However, this is acceptable considering that CLN2 is a very rare paediatric disease, with fast debilitating progression until death and no available treatment options. The important evidence of efficacy comes from comparisons with a longitudinal untreated historical control group. The applicant has applied acceptable methods (most importantly the 1:1 matching) to account for potential bias and provided several sensitivity analyses that support the robustness of the findings.

Three patients recruited into the study 201 showed a presumably atypical protracted progression course compared to that described for the classic form: these patients were 5.0-5.8 years old at disease onset, while usually first symptoms are noticed in the second or third year of life. One additional patient was enrolled during the pre-symptomatic phase of his condition. Two patients, 3 and 6 years old, entered the study with a baseline ML score of 6, which in principle corresponds to normal function. In these cases, disease was detected early because both had affected siblings.

The applicant has addressed the concerns of bias that may arise from the inclusion of such patients with a potentially “milder” disease course. Most importantly, the relevant comparison between treated and untreated patients was based on a 1:1 matching for age and baseline disease scores. In this analysis, one treated patient could not be included due to the lack of a matching control. Further sensitivity analyses were provided (e.g. one to many matching, or excluding the two patients with a baseline score of 6) all of which supported the primary comparison. The 3 patients with first disease symptom onset ≥ 5 years of age, two with a baseline ML score of 3 and one with a baseline ML score of 6, had no change in the ML score at week 72 compared to baseline. As these three patients only comprise 12.5 percent out of 24 patients, they have a limited impact on the overall positive results.

Given the absence of a concurrent control arm, the effect of the treatment on the natural course of the disease in comparison to the untreated period before entering the study would have been of help. In this respect, data on 7 patients who participated in both study 901 and 201 are available and show a clear amelioration of disease progression with BMN190 treatment.

No benefit was observed for the vision domain during the 48 week 300 mg period. There was even a small addition to the clinical decline when the vision domain was added to the ML score (-0.7 vs -0.4 points). Although vision deterioration is a relevant component of the disease, no specific examination (OCT, electro-retinogram, visual evoked responses) was conducted as Brineura was not expected to reach therapeutic drug concentrations in the eye. However, more information with respect to potential effects on the vision domain

is expected from study 203 that will include ophthalmic evaluation, including optical coherence tomography, and preclinical (animal) studies.

Changes in MRI parameters and clinical response were not consistently in the same direction over the 48 weeks of 300 mg stable treatment. However, this discrepancy in relation to data derived from natural history data (which suggest a good correlation between clinical disease severity and several MRI outcome parameters) may be potentially explained by not yet understood re-modelling effects of the treatment (e.g. debulking of lysosomal storage material in the early phase of treatment). Overall, for successfully treated patients, changes from baseline to endpoint are expected to be smaller than in untreated patients, as observed in the natural history study where all of the patients declined rapidly.

Achievement of developmental milestones was assessed by the Denver II Development Scale. While 22 patients showed no change in their overall interpretation of development, one subject was categorised as untestable at 201 study completion (week 48). Quality of life assessments showed only a small increase and can overall be interpreted as stabilisation. As in principle and confirmed by the patient representatives, QoL deteriorates with disease progression, a clear decline would have been expected in case of insufficient/lack of efficacy of Brineura.

No quality of life measurements of untreated patients exist in CLN2 disease, neither from the natural history cohorts nor from the published literature. As also pointed out by the ad hoc expert group, study results with regard to quality of life were not surprising: as the treatment appears to largely halt the disease progression but is not curative, it is not expected that QoL measurements will relevantly improve compared to baseline. The experts considered this stabilisation as benefit compared to the considerable QoL deterioration regularly experienced with disease progression.

An external control arm comprised by untreated patients from a cohort from Hamburg and a cohort from New York was intended to solve the main issue of lack of placebo/active comparator. These databases provided valuable information of reference although with several limitation. They were non concurrent, the information was partially retrospective and different patient information was gathered in each cohort so that only a restricted number of items reflect the data from the pooled cohort. The longitudinal analysis (progression of the condition) was based on the Hamburg cohort whereas cross-sectional information from the WCMC cohort was mainly considered for demographics and brain imaging analysis. Some differences between the two natural history cohorts have been observed with respect to demographic characteristics. WCMC Cohort included 38% of males vs 63% in Hamburg cohort, which is likely not relevant. Similarly, a relevant percentage of children from the Hamburg cohort were born before the year 2000. However, the applicant could show that improvements in standard of care did not affect the functional decline in patients recruited earlier vs later. The Applicant has justified the differences in the reported rate of decline between the Hamburg (-2.09) and the Verona cohort (-1.54). The difference in the density of the data between cohorts (at the Verona site, 5 of the 8 included patients had only two measurements) and the existing variability in the clinical phenotype may explain these variations. However, it is also possible that the expected decline per 48 weeks could be more variable than that initially estimated.

3.4. Unfavourable effects

The majority of study subjects (58%) have experienced hypersensitivity AEs (HAEs), 5 HAEs in 3 subjects were rated as grade 3. The most common manifestations of hypersensitivity were: pyrexia, vomiting, pleocytosis, or irritability. In addition, symptoms reported in the context of serious hypersensitivity AEs, infusion related reactions, or grade 3 hypersensitivity AEs included: nausea, tiredness, motor agitation,

increased heart rate, leucocytosis, increase in CRP, increase in serum total IgE (but no drug specific IgE positivity), increased protein in CSF, increase in IL-6 in CSF. All hypersensitivity reactions were manageable (mainly with antihistamines, antipyretics and/or steroids) and did not lead to dose reduction or withdrawal from treatment.

Seizures or epilepsy were reported in 22 (92%) of study subjects at screening. 23 (96%) subjects experienced 362 AEs that map to the Convulsions SMQ, the majority of convulsion AEs (>90%) were grade 1 or 2 in severity. 6% of 362 overall convulsion events were considered related to treatment. A considerably increased rate of convulsion AEs was found to be temporally related to BMN 190 infusion (more than twice the overall average rate). In EEG examinations during study 201/202 new (focal and/or generalised) epileptiform activity was seen in 62.5% of subjects.

Treatment with BMN 190 requires surgical implantation of an ICV reservoir and cannula leading to the lateral ventricle of the non-dominant hemisphere. Known risks associated with ICV devices (including device implantation) involve infections, intracerebral hemorrhage, device/CSF leakage, disconnection of ventricular catheter, catheter malpositioning, wound dehiscence, and seizures as well as risks associated with anaesthesia.

In studies 201/202, 30 device-related AEs occurred in 11 (46%) of subjects. In 2 subjects, a total of 3 serious cases of device infection and 1 serious event of device malfunction due to incorrect positioning occurred, each requiring explantation of the device. Other device related AEs were rated grade 1 events. The needle issue, device leakage, CSF pleocytosis, device malfunction and Propionibacterium infection, were reported more than once. 7 of 12 incomplete BMN 190 infusions were attributable to device related AEs.

In addition, 1 SAE of intracranial haemorrhage (without significant mass effect) was attributed to the implantation of the device.

CSF pleocytosis occurred in 75% of subjects, in 4 (17%) subjects, CSF pleocytosis occurred after device implantation prior to first infusion. CSF pleocytosis could be an isolated finding which was often mild, however, in some subjects, higher CSF cell counts (up to 4646.6/µL) were also reported during treatment with BMN 190 without associated AEs reported. In 8 (33%) subjects CSF pleocytosis was persistent with > 20% of their follow-up labs also demonstrating CSF pleocytosis. Predominantly more pronounced CSF pleocytosis occurred also in association with hypersensitivity, fever and device-related infection.

Immunogenicity evaluations revealed positive anti-drug antibodies (ADA) in serum in 19 (79%) and in CSF in 6 (25%) subjects. ADA response in serum was sustained in approx. 2/3, in CSF in approx. 1/3 of subjects. Incidence or severity of hypersensitivity AEs appeared not to be associated with serum ADA titres. Anti-BMN 190 neutralizing antibody (NAb) was not detected in the CSF in any treated subject so far.

3.5. Uncertainties and limitations about unfavourable effects

General uncertainties regarding the unfavourable effects result from the limited clinical safety data base (24 subjects exposed for a median time of 95.1 weeks, maximum 141 weeks in studies 201/202), the fact that clinical studies were uncontrolled, and that several AEs may have multiple causes, e.g. can be related to the drug, device, including device implantation, ICV infusion, underlying disease and/or concomitant medication. Furthermore, BMN 190 is a first in class compound and the preclinical safety data package is very limited with restricted transferability to human patients.

So far, no anaphylactic reactions have been identified. However, the occurrence of more severe hypersensitivity reactions including anaphylactic reactions can currently not be excluded. The overall study

results regarding risk of hypersensitivity appear to be also valid in subjects without residual TPP1 protein. It can further not be excluded that the risk of hypersensitivity is increased in subjects with advanced CLN2 disease, as disturbance of the blood brain barrier, which is commonly described in advanced neurodegenerative disease, might occur in these patients and would be anticipated to be associated with higher plasma exposure of BMN 190.

Up to now, no cases of hydrocephalus or septic/aseptic meningitis have been reported in studies 201/202. However, ICV treatment has been associated with these risks (e.g. via intraventricular haemorrhage, device infection). As ventricular shunts which bypass CSF to the body system (e.g. ventriculo-peritoneal shunts) are presumed to reduce exposure to BMN 190 in the CSF and in the targeted brain areas while increasing the systemic exposure to BMN 190, which may reduce efficacy and increase hypersensitivity risk at the same time, treatment with BMN 190 has been contraindicated in subjects with these shunts.

A possible causal relationship of temporally related AEs like headache, vomiting and seizures, respectively with a possible transient increase in intracranial pressure due to the total infusion volume cannot be fully excluded.

The reason for the high incidence of low CSF protein (71%) remains unclear.

Whereas in non-clinical studies increased troponin I was found in dogs after intrathecal BMN 190 application, cardiotoxicity has not been particularly addressed in clinical studies. From the presented ECG evaluations, no clear patterns suggesting myocardial damage are seen, however, cardiac findings of studies 201/202 included possible left-ventricular hypertrophy and related bradycardia during infusion. The potential risk of cardiotoxicity of Brineura will be further evaluated post-marketing.

No clinical data is available in patients below 2 as well as in subjects with advanced CLN2 disease and limited experience is available in subjects above 8 years of age. Long-term safety data for ICV BMN 190 treatment is limited.

3.6. Effects Table

Table 21. Effects Table for Brineura 150 mg solution for ICV infusion; CLN2 disease (data cut-off: 03 Jun 2016)

Effect	Short Description	Unit	Treatment		Uncertainties/ Strength of evidence	Ref
Favourable Effects						
Responder rate	Absence of unreserved 2-point decline after 48 weeks of stable dose (300 mg) treatment	%	Responder 87% (20 patients)	Non-Responder 13% (3 patients)	95%-CI (66%, 97%) P 0.0002	Study 201

Effect	Short Description	Unit	Treatment		Uncertainties / Strength of evidence	Ref
Responder rate	Absence of unreversed 1-point decline after 48 weeks of stable dose (300 mg) treatment	%	Responder 65% (15 patients)	Non-Responder 35% (8 patients)	95%-CI (43%, 84%) P <0.0001	Study 201
Rate of decline	Change from baseline to 300 mg baseline to week 48	Mean	0.40 p-value computed as a two-sided t-test for the hypothesis H_0:Rate =2.0 points lost/48 weeks vs H_1:Rate not equal 2.0 points lost/48 weeks		P <0.0001	Study 201
Whole brain volume	Change from baseline to 300 mg baseline to week 48	Vol (cm^3) % Change	-50.5 (74.88) -4.4		Correlation MRI/ ML scale: r = 0.52	Study 201
Cortical grey matter	Change from baseline to 300 mg baseline to week 48	Vol (cm^3) % Change	43.8 (30.70) -9.7		Correlation MRI/ ML scale: r = 0.20	Study 201
White matter	Change from baseline to 300 mg baseline to week 48	Vol (cm^3) % Change	-13.8 (30.81) -4.2		Correlation MRI/ ML scale: r = 0.27	Study 201
Effect	**Short Description**	**Unit**	**Treatment** **BMN 190 300 mg every 14 days**	**Control** **Natural history data**	**Uncertainties / Strength of evidence**	**References**
Responder rate	Response: Rate of decline <2 points per 48 weeks	%	100% 21 patients	43% 9 patients	Responder analysis based on close 1-1 matching using Method # 1 (Baseline ML score equal, baseline age close) 2-sided P-value 0.0001	ISE
For 1:1 matching, 2 patient in study 201 could not be matched and was omitted from ITT population (besides the patient who withdraw after first dose) For ISE analyses, the following natural history evaluable population was used: n =42 (excluded 7 patients from n = 49 who later entered a BMN 190 study for treatment)						
Unfavourable Effects						

Effect	Short Description	Unit	Treatment		Uncertainties / Strength of evidence	Ref
Hyper-sensitivity reactions	Incidence of hypersensitivity reactions (frequent symptoms included fever, vomiting, irritability, CSF pleocytosis)	%	58	N/A	Possibly increased risk: - in advanced CLN2 disease? - in newborns due to immature blood-brain barrier? no apparent increase over time; overall study results appear valid for subjects without residual TPP1 So far no anaphylactic reaction (risk not excluded), no reliable test for drug specific IgE	S1
Convulsion /status epilepticus	Incidence of convulsion AEs	%	96	N/A	Increased rate of temporally related convulsion AEs; EEG: new epileptiform activity in 62.5% subjects during studies; prevalence of seizures/epilepsy at screening: 92%; 6% of 362 convulsion AEs considered related;	S1
	Grade 4 status epilepticus	Number of AEs	1	N/A		
Device-related events	Incidence of device-related events	%	46	N/A	Generally in line with known risks of ICV devices/implantation 2 subjects with 3 severe device-related infections and 1 malfunction required device replacement. In addition, 1 subject with intracranial haemorrhage attributed to device implantation	S1

Effect	Short Description	Unit	Treatment		Uncertainties/ Strength of evidence	Ref
CSF pleocytosis	Incidence of CSF pleocytosis	%	75	N/A	- isolated findings (often mild, however up to 4646.6/µL reported) or - associated with AEs (hypersensitivity, device infection; predominantly more pronounced pleocytosis); -in 33% of subjects persistent pleocytosis (seen in > 20% follow-up measures)	S1
Immunogenicity	Incidence of -ADA in Serum -ADA in CSF	 % %	 79 25	N/A	- so far no apparent correlation with hypersensitivity - Hitherto no neutralizing AB in CSF	S1
Cardiotoxicity	Incidence of related cardiac AEs Incidence of post-baseline ECG abnormalities Incidence of significant ECG abnormalities	% % %	0 67 0	N/A	- Troponin I increase in pre-clinical studies (dogs) - Troponin/cardiotoxicity not particularly evaluated in clinical study - 1 possible left-ventricular hypertrophy - 1 AE of related Bradycardia during infusion	S1

Abbreviations: Whole brain ADC: whole brain apparent diffusion coefficient; ML scale = adapted 0-6 point Hamburg motor language rating scale; ADA: anti-drug antibodies, ICV: intra-cerebroventricular, TPP1: tripeptidyl peptidase 1

Notes: 300 mg baseline: starting from first 300 mg infusion; Estimated decline of 2 points over 1 year was derived from natural history data; MRI assessments: Presented descriptively over time; ISE: Integrated summary of effectiveness from Study 201 and 901 supplement; (S1) Integrated data from the uncontrolled studies 201 and 202

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

CLN2 disease is a rare, debilitating, fast progressing and invariably deadly lysosomal storage disease caused by mutated or absent TPP1 enzyme. Currently no disease-modifying treatment is available. Therefore, a high medical need exists that can, at least partially, be addressed by enzyme replacement therapy with Brineura. This treatment is expected to slow or even halt the psychomotor decline caused by loss of brain tissue of affected children but not necessarily to restore functions. Therefore, early treatment initiation is considered important.

The mechanism of action of cerliponase alfa in the treatment of CNL2 disease is clear and undisputed and has been confirmed in two animal CLN2 disease models. In the human study 201, treatment with Brineura demonstrated statistically significant (p = 0.0002) and clinically relevant effects for the primary outcome measure of the pivotal study 201: 20 of 23 (87%) patients responded as they did not have a 2-point decline on the adapted motor-language scale (ML scale) at week 48 of treatment.

The clinical relevance of a two-point decline in the ML scale was accepted by the ad hoc expert group as a mean decline of 2 points per year is the expected deterioration rate in CLN2 patients. Already a 1-point decline can be considered clinically relevant as it reflects the loss of a developmental milestone in the respective domain.

Outcomes of treated patients in study 201 and from the long-term extension study 202 were also compared with the outcomes of the untreated patients in the evaluable population of the study 901 supplemental report. The primary responder analysis showed a relevant and statistically significantly higher proportion of responders with a decrease in the rate of disease progression (rate < 2-point decline/48 weeks) under active treatment (91%) as measured by the ML scale compared to untreated patients (study 901) (45%).

Overall, BMN 190 treatment demonstrated a significant therapeutic effect over 48 weeks of stable treatment on disease progression as measured by response rate and rate of decline in the ML CLN2 score. The trend observed for the majority of treated subjects is overall stability of ML scores. On the other hand, no improvement from baseline was observed on vision, seizures, MRI parameters and QoL. However, during the ad hoc expert meeting, it was emphasized that the motor and language aspects of the disease are the most important ones in the daily life of the children and their families. Moreover, the treatment with Brineura cannot be expected to regain brain tissue and lost functions, and therefore no improvement of MRI parameters, developmental scores or QoL should be anticipated. Stabilisation could already be considered a major success. Therefore, the lack of clear effects on these parameters does not invalidate the positive clinical results found in comparison to untreated patients from the natural history group.

The clinical safety data base for Brineura is still limited, owing to the small target population in this rare disorder, restricted time of exposure, uncontrolled study design, difficulties in interpretability of AE causality as well as the limited informational value of the pre-clinical study program regarding safety. As of data cut-off (03 Jun 2016) only 1 out of 24 subjects withdrew from studies 201/202 and AEs were not given as direct reason for withdrawal in this case.

A clinical study without lower age limit is currently ongoing (203) and two subjects aged 2 years included in this study appeared to tolerate BMN 190 treatment well.

As of now, no clinical data is available in patients below 2 years of age. However, the applicant has provided a rationale for an efficacious and safe dose of BMN 190 for children below 2 years of age, based on reduced

dose scaled by brain mass. Further argumentation referring to total CSF volume and turnover rate has been presented by the applicant which supports a low risk of increased intracranial pressure due to the proposed infusion volume. In addition, as a precautionary measure slowing/interruption of BMN 190 infusion is recommended in the SmPC in case symptoms occur which are interpreted as indicative of increased intracranial pressure by the treating physician. There is further clear indication that earliest possible treatment with BMN 190 in confirmed CLN2 may provide a maximum benefit. Accordingly, the consulted experts were unanimous in their opinion that pre-symptomatic children should be eligible for treatment without age restriction. Based on these considerations, the proposed posology is currently regarded sufficiently justified and expected to provide a positive benefit/risk balance of Brineura also in children below 2 years. However, further post marketing data collection is mandatory in order to substantiate or optimize the dose in the youngest age group. The applicant has therefore committed to include at least 5 subjects < 2 years in study 203.

Adequate information has been included in the SmPC that limited clinical data is available in patients above 8 years, that no clinical data is available in subjects with advanced CLN2 disease (including the fact, that it can currently not be excluded that the hypersensitivity risk may be increased in these patients), and that regular assessment during long-term treatment is recommended, whether the benefit is considered to outweigh adverse effects and potential harms in individual patients.

As an obligation to the approval under exceptional circumstances, the safety concerns regarding hypersensitivity/anaphylaxia, immunogenicity, hydrocephalus, meningitis, cardiotoxicity as well as general uncertainties regarding safety resulting from the small safety population, limited time of exposure and uncertainties regarding posology in children below 2 years of age will be addressed by post-marketing data collection as well as by continuation of ongoing clinical studies 202 and 203.

3.7.2. Balance of benefits and risks

The B/R balance for Brineura in the treatment of CLN2 disease is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Although the data base is limited, the safety profile resulting from studies 201/202 did not unveil unacceptable safety concerns which would preclude authorisation of Brineura. Given the rarity as well as the rapidly progressive and invariably fatal character of CLN2 disease and the absence of disease specific treatment options, the uncontrolled and limited data base is considered sufficient in order to grant approval under exceptional circumstances, subject to the conditions:

- that the ongoing study 203 (scheduled study population: subjects from birth to less than 18 years of age; not less than 10 patients; proposed completion date: July 2020) will be completed and resulting data will be reported regularly. The 203 study will include at least 5 subjects < 2 years.
- That further data collection and analysis will be performed post-marketing by conducting a registry-based PASS in order to address the safety concerns regarding hypersensitivity/anaphylaxia, immunogenicity, hydrocephalus, meningitis, cardiotoxicity as well as general uncertainties regarding safety resulting from the small safety population, limited time of exposure and uncertainties regarding posology in children below 2 years of age.

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances was requested by the applicant in the initial submission.

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because the applied for indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence. Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

3.8. Conclusions

The overall B/R of Brineura is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority that the risk-benefit balance of Brineura is favourable in the following indication:

"Brineura is indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency."

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP

presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to the launch of BRINEURA in each Member State (MS), the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each MS where BRINEURA is marketed, all HCPs who are expected to handle / administer the product are provided with an educational programme (i.e. a dosing and administration guide), aiming at preventing and/or minimising the important identified risk of Device issues (infection/blockage/dislocation), containing information about:

- How to store BRINEURA;

- The device-related complications (i.e. infections, device's leakage and/or failure; the integrity of the device should be confirmed by a neurosurgeon);

- How to prepare BRINEURA and the flushing solution;

- A detailed step-by step description of BRINEURA intra-cerebro-ventricular infusion and the administration of the flushing solution (provided after BRINEURA infusion is complete)

- How to monitor the patients receiving BRINEURA.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	**Due date**
Non-interventional post-authorisation safety study (PASS): Study 190-501. In order to evaluate the long-term safety of cerliponase alfa, including the occurrence of serious hypersensitivity reactions and anaphylaxis, the MAH should submit the results of a study based on adequate source of data deriving from a registry of patients with neuronal ceroid lipfuscinosis Type 2 (CLN2).	Annual reports to be submitted as part of the annual re-assessment
Post-authorisation efficacy study (PAES): Study 190-203. In order to further evaluate the treatment effectiveness as a delay in progression of CLN2 motor-language clinical scale and to further evaluate the safety and tolerability of cerliponase alfa, the MAH	July 2020

Description	Due date
will submit the results of study 190-203 including at least 5 patients below the age of 2 years.	

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that cerliponase alfa is considered to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union has not been authorised previously in the European Union.

APPENDIX 1

DIVERGENT POSITION DATED 21 April 2017

Divergent position

The undersigned member(s) of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of cerliponase alfa indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.

The reason for the divergent opinion was as follows:

As the submitted studies do not clearly demonstrated an increased degradation of ceroid lipofuscin (i.e. no increase in degradation products or a clear indisputable decrease in the brain volume due to the decrease in accumulation of ceroid lipofuscin is observed) it cannot be concluded that, using the studied dosing regimens, cerliponase alfa has a pharmacological effect in men. Given the absence of a clear pharmacodynamic effect the positive findings in the motor and language scale cannot be directly related to the treatment. The effect of cerliponase alfa on quality-of-life is considered an important aspect for patients and parents/caretakers and is unclear. Cerliponase alfa does not show any effect on epileptic insults (myoclonic epilepsy due to the disease) or on the development of blindness. The appearance of pleocytosis, irritability as well as the new focal and generalised epileptiform activity during treatment with cerliponase alfa are of major concern. The procedural burden (e.g. invasive surgery, biweekly infusions) is associated with further severe safety concerns (among others epileptic insults). Finally, the consequences of the administration of cerliponase alfa in the long-term, in terms of safety and efficacy, are unknown as the duration of exposure is limited. Therefore the results are difficult to translate into a clinical meaningful benefit for the patient/caregiver. Optimal dose selection is questioned because it was only based on findings from nonclinical studies. No data is available in patients in the lower age ranges and the risks associated with cerliponase alfa treatment are considered especially high in the very young patient population. Based on the uncertain benefit for the patient/parents/caregiver and the evident risks associated with treatment, the benefit risk balance of cerliponase alfa is considered negative.

London, 21 April 2017

Hans Hillege (The Netherlands)