Cerliponase alfa (reassessment after the deadline (type 2 neuronal ceroid lipofuscinosis))

Resolution of: 15 December 2022 valid until: unlimited
Entry into force on: 15 December 2022
Federal Gazette, BAnz AT 22 0 2023 B2

Therapeutic indication (according to the marketing authorisation of 30 May 2017):

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

Therapeutic indication of the resolution (resolution of 15 December 2022):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Cerliponase alfa is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Patients with neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.

Extent of the additional benefit and significance of the evidence of cerliponase alfa:

Hint for a major additional benefit

Study results according to endpoints:[1]

Patients with neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival (historical comparison)
Morbidity	↑	Advantages in motor skills and language ability (historical comparison)
Health-related quality of life	n.c.	There are no assessable data.
Side effects	n.c.	There are no assessable data.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.c.: not calculable		

190-201/202 study: single-arm phase I/II intervention study and extension study; final data cut-off: 10.12.2020.

190-203 study: single-arm, phase II intervention study (post-authorisation efficacy study (PAES)); interim data cut-off: 26.04.2020 or interim data cut-off for SAE results: 26.04.2021.

190-504 study: single-arm, non-interventional observational study (post-authorisation safety study (PASS)); interim data cut-off: 26 April 2022.

DEM CHILD RX study: single-arm registry study of subjects treated with cerliponase alfa in Germany; data cut-off: December 2020.

190-901 study: external control for natural history of disease; "Natural History (NH) -Update 2" (data cut-off: August 2016) and "NH Update 3" (data cut-off: February 2021).

[1] Data from the dossier assessment of the G-BA (published on 4. Oktober 2022), and from the amendment to the dossier assessment from 24 November 2022, unless otherwise indicated.

Mortality

Endpoint	Cerliponase alfa		External control		Cerliponase alfa vs control
	N	Patients with event n (%) *Median time to event [95% CI]*	N	Patients with event n (%) *Median time to event [95% CI]*	Hazard ratio [95% CI] p value
Overall survival – Death[a)]					
190-201/202 vs 190-901 NH3[b)]	21[c)]	0 (0) *n.a.*	21[c)]	6 (29) *313 weeks [291; n.a.]*	-[d) e)] 0.0003[f)]
DEM CHILD RX vs 190-901 NH3[g)] *presented additionally*	24	0 (0) *n.a.*	52	25 (48) *10.4 years [9.9; 12.2]*	n.a.[h) i)] 0.017[j)]
Overall survival – Censoring[k)]					
190-201/202 vs 190-901 NH3[b)]	21	21 (100)	21	15 (69)	-
DEM CHILD RX vs 190-901 NH3[g)] *presented additionally*	24	24 (100)	52	27 (52)	-

a) According to module 4, overall survival from baseline to death was collected
b) Results presented post hoc in module 4 for indirect comparison of the 190-201/202 study with external control 190-90 NH3 after 1:1 matching with 2 criteria (same ML/HML score, age difference ≤ 12 months each at baseline)
c) For the matched patient population of the 190-901 NH3 study, the longest follow-up time was chosen that was less than or equal to the follow-up time of the matched patient population of the 190-201/202 study.
d) Calculation of the hazard ratio using the Cox proportional hazards model, adjusted for ML/HML value, age at baseline, genotype (common allele) and sex.
e) In the 190-201/202 study, no event occurred during the observation period. Therefore, no adequate hazard ratio can be determined
f) No detailed information on the calculation of the p value can be found in the study documents. Since 0 events occurred in one of the study groups, a calculation using log-rank test seems likely.
g) Only data for a naïve indirect comparison without matching are available.
h) The hazard ratio was calculated using the Cox proportional hazards model, adjusted for ML/HML value, age at baseline, genotype (common allele) and sex.
i) In the registry study, no event occurred during the observation period. Therefore, no adequate hazard ratio can be determined.
j) While for the indirect comparison of the 190-201/202 intervention study with the 190-901 NH3 external control the likelihood test of the Cox proportional hazards model was used to calculate the p value, data for the indirect comparison of the DEM CHILD RX registry study are missing. Statistical analyses were performed according to Kaplan-Meier curves and Cox proportional hazards model.
k) 190-201/202 vs 190-190 NH3: Subjects for whom no date of death was available were censored at the time of the last measurement of the ML/HML scale.
DEM CHILD RX vs 190-901 NH3: Time from birth to death (event) or until the time of the last CLN2 assessment (censored).

Abbreviations: HML: Hamburg motor/language; CI: confidence interval; ML: motor/language; N = number of patients evaluated; n = number of patients with (at least one) event; n.a.: not applicable; n.a. = not achieved; NH2/NH3: natural history - update 2/ update 3

Morbidity

Endpoint	**Cerliponase alfa**	
	N[a)]	Mean value (SD)
CLN2 rating scale: ML score (0-6 points): 300mg baseline[b)]		
190-201/202	23	3.5 (1.2)
190-203	14	4.6 (1.7)
CLN2 rating scale: ML score (0-6 points): Last evaluable visit Change from baseline		
190-201/202	18	Week 281[c)] -1.2 (0.9)
190-203	10	Week 145 -0.4 (0.9)
Endpoint	N[a)]	Patients with event n (%)
Time to disease progression: *Event* [d) e)]		
190-201/202	23	12 (52)
Time to disease progression: *Censoring* [d) e)]		
190-201/202	23	11 (48)
Endpoint	N[a)]	Median [95% CI]
Time to disease progression: *Median time to event, in weeks*		
190-201/202	23	272 [199; n.a.]
Endpoint	N[a)]	Mean value (SD)
Rate of disease progression[f)]		
190-201/202	23	0.4 (0.5)
190-203	14	0.1 (0.3)
Endpoint	N	Mean value (SD)
EQ-5D-VAS		
DEM CHILD RX: *Baseline*	20	62.0 (22.4)
DEM CHILD RX: *Change from baseline - month 12*	17	3.7 (19.5)

[a)] ITT population
[b)] 190-201/202 study: 300mg baseline corresponds to the last measurement before application of the first 300mg dose of cerliponase alfa. 190-203 study: Baseline corresponds to the last measurement before the first application of cerliponase alfa.
[c)] Week 281 from 300mg baseline of the 190-201 study.

[d] An irreversible loss of ≥ 2 points is any decrease of 2 points or more that has not improved in the last recorded observation. An irreversible value of 0 is a deterioration to 0 points that has not increased to a value > 0 at the last recorded observation.
[e] The naming of events and censoring were adapted for the benefit assessment according to the graphical representation with the Kaplan-Meier curve. An event is defined as the achievement of disease progression. According to the dossier, censoring was originally carried out during the last assessment of the CLN2 score. The event was originally defined as response (no disease progression).
[f] The rate of disease progression is measured by the CLN2 disease scale score loss scaled to 48 weeks. The rate of disease progression is presented as a positive number, with higher values corresponding to faster disease progression.

Abbreviations: CLN2: Ceroid lipofuscinosis type 2; EQ-5D-VAS: European Quality of Life 5 Dimension Visual Analogue Scale; ITT: Intention-To-Treat; ML: motor/language; N = number of patients evaluated; n = number of patients with (at least one) event; n.a. = not achieved; SD: standard deviation

Endpoint	**Cerliponase alfa**		**External control**		**Cerliponase alfa vs control**
	N	Patients with event n (%) *Median time to event [95% CI]*	N	Patients with event n (%) *Median time to event [95% CI]*	Hazard ratio [95% CI] p value
Time to disease progression					
Time to an irreversible loss of ≥ 2 points on the ML/HML scale or a reduction of the ML score to a value of 0-e*vent*					
190-201/202 vs 190-901 NH3[a) b)]	21[c)]	12 (57) *272 weeks [182; n.a.]*	21[c)]	21 (100). *39 weeks [26; 56]*	0.10[d)] [0.03; 0.28] ≤ 0.0001[e)]
190-203 vs 190-901 NH2[f) g)]	12[h) i)]	2 (16.7) *n.a. [1.008; n.a.]*	29[h) i)]	19.7 (67.9) *721 days [601; 811]*	0.11 [0.03; 0.35][j)] n.d.[k)]
DEM CHILD RX vs 190-901 NH3[l) b)]	21	6 (28) *25 months [20; n.c.]*	21	13 (62) *11 months [8; 18]*	0.08[m)] [0.02; 0.28] <0.0001[n)]
Time to an irreversible loss of ≥ 2 points on the ML/HML scale or a reduction of the ML score to a value of 0-*censoring*					
	N	Patients with event n (%)	N	Patients with event n (%)	
190-201/202 vs 190-901 NH3[a) b)]	21[c)]	9 (43)	21[c)]	0 (0)	-
190-203 vs 190-901 NH2[f) g) o)]	12[h) i)]	10 (83.3)	29[h) i)]	9.3 (31.9)	-
DEM CHILD RX vs 190-901 NH3[l) b)]	21	14 (67)		4 (19)	-

[a] Results presented post hoc in Module 4 on 1:1 matching with 2 criteria: Same ML/HML score, age difference ≤ 12 months each at baseline.
[b] The naming of events and censoring were adapted for the benefit assessment according to the graphical representation with the Kaplan-Meier curve. An event is defined as the achievement of disease progression. According to the dossier, censoring was originally carried out during the last assessment of the CLN2 score. Event was originally defined as response (no disease progression).
[c] Baseline was defined for the 190-201/202 study as the last value before the first infusion of cerliponase alfa 300 mg and for the 190-901 NH3 external control was the age (in months at the time of the investigation) at which matching occurred
[d] Hazard ratio and confidence interval were calculated post hoc using the Cox proportional hazards model, adjusted for ML value, age at baseline, genotype (common allele) and sex.
[e] How the p value for the analysis was calculated is not described. Statistical analyses were performed according to Kaplan-Meier curves and Cox proportional hazards model.
[f] The results of the 1:3 matching with 3 criteria (same ML/HML score, age difference ≤ 3 months each at baseline, same number of common alleles (c.622C→T, c.509.1G→C). An evaluation based on a 1:1 matching was not carried out.
[g] An irreversible loss of 2 points is any decrease of 2 points or more that has not improved to a 1-point decrease in the last recorded observation. An irreversible value of 0 is a deterioration to 0 points that had not increased to a value > 0 at the last recorded observation. Supportive analysis for the primary endpoint
[h] According to the pharmaceutical company, due to the different weighting of the control subjects, the number of events may not represent whole numbers. Included in the analysis are all subjects in the 190-203 study who were assigned at least one matching partner.
[i] Baseline was defined for the 190-203 study as the last value before the first infusion of cerliponase alfa and for the 190-901 NH2 external control the age (in months at the time of the study) at which matching occurred
[j] The statistical analysis was planned a priori and carried out using the Cox proportional hazards model without adjustments for specific variables, as the most important variables were included in the matching criteria for the indirect comparison.
[k] No calculation of the p value was planned for the interim analysis.
[l] Results presented post hoc in Module 4 on 1:1 matching with 2 criteria: Same ML/HML score, age difference ≤ 12 months each at baseline.
[m] Hazard ratio and confidence interval were calculated according to pre-specification using the Cox proportional hazards model, adjusted for HML value, age at baseline, genotype (common allele) and sex
[n] While for the indirect comparison of the 190-201/202 intervention study with the 190-901 NH3 external control the likelihood test of the Cox proportional hazards model was used to calculate the p value, data for the indirect comparison of the DEM CHILD RX registry study are missing. Statistical analyses were performed according to Kaplan-Meier curves and Cox proportional hazards model.
[o] It was censored to the last assessment of the CLN2 score. No other reasons for censoring were identified.

Abbreviations: CLN2: Ceroid lipofuscinosis type 2; HML: Hamburg motor-language; n.d.: no data available; CI: confidence interval; ML: motor-language; N = number of patients evaluated; n = number of patients with (at least one) event; n.a. = not achieved; NH2/NH3: natural history - update 2/ update 3

Endpoint	**Cerliponase alfa**		**External control**		**Cerliponase alfa vs control**
	N	Mean value (SD)	N	Mean value (SD)	Difference (control – cerliponase alfa) [95% CI] p value
Progression rate measured by ML/HML scale					
Progression rate (points / 48 weeks)[a]					
190-201/202 vs 190-901 NH3 [b]	21[c]	0.4 (0.5)	21[c]	2.2 (1.1)	1.79 [1.23; 2.35] < 0.0001[d]

190-203 vs 190-901 NH2[e)]	12[c)] [f)]	0.1 (0.3)	29[c)] [f)]	1.2 (1.0)	1.10 [0.69; 1.52] n.d.
DEM CHILD RX vs 190-901 NH3[g)]	21[h)]	0.5 (0.4)	21[h)]	1.9 (1.5)	1.42 [0.74; 2.10] 0.0003[d)]

[a)] The rate of disease progression is measured by the CLN2 disease scale score loss scaled to 48 weeks. The rate of disease progression is presented as a positive number, with higher values corresponding to faster disease progression
[b)] Results presented post hoc in Module 4 for 1:1 matching with 2 criteria, analogous to the ISE analysis of the 190-201/202 study; the following criteria were defined for 2-criteria matching: Same ML/HML score, age difference ≤ 12 months each at baseline
[c)] Baseline was defined for as the last value before the first infusion cerliponase alfa and for the 190-901 NH3 external control the age (in months at the time of the investigation) at which matching occurred
[d)] Two-sided t-test
[e)] Results of 1:3 matching with 3 criteria (same ML/HML score, age difference ≤ 3 months each at baseline, same number of common alleles (c.622C→T, c.509.1G→C)) are presented.
[f)] According to the pharmaceutical company, due to the different weighting of the control subjects, the number of events may not represent whole numbers. Included in the analysis are all subjects in the 190-203 study who were assigned at least one matching partner.
[g)] 1:1 matching, 2 criteria. The following criteria were defined for the 2-criteria matching: Same ML/HML score, age difference ≤ 12 months each at baseline
[h)] Baseline was defined for the DEM CHILD RX registry study as the last value before the first infusion of cerliponase alfa 300 mg and for the 190-901 NH3 external control the age at which matching occurred

Abbreviations: CLN2: Ceroid lipofuscinosis type 2; HML: Hamburg motor-language; ISE: Integrated Summary of Efficacy; n.d.: no data available; CI: confidence interval; ML: motor-language; N = number of patients evaluated; NH2/NH3: natural history - update 2/ update 3; SD: standard deviation.

Health-related quality of life

Endpoint	**Cerliponase alfa**	
	N[a)]	Mean value (SD)
PedsQL[b)] (parent report for toddlers)[c)], baseline[d)]		
<u>190-201/202</u>		
Physical skills	23	63.5 (22.2)
Emotional skills	22	70.2 (20.7)
Social skills	23	49.8 (15.9)
School skills	22	57.0 (19.6)
Psychosocial sum score	23	59.0 (12.4)
Total score	23	60.7 (12.8)
PedsQL[b)] (parent report for toddlers)[c)], *change from baseline at week 243[e)]*		
<u>190-201/202</u>		
Physical skills	19	-30.9 (23.4)
Emotional skills	18	2.2 (20.5)
Social skills	19	-10.3 (15.0)
School skills	18	-13.2 (25.9)
Psychosocial sum score	19	-5.6 (10.6)
Total score	19	-15.2 (12.7)

[a)] ITT population
[b)] For the 190-203 study, no results were submitted for the interim study report.

Endpoint	Cerliponase alfa	
	N[a)]	Mean value (SD)

[c)] In the 190-201/202 study, the parent version was used for children between 2 and 4 years of age, regardless of age. The median age at the time of enrolment in the 190-201/202 study was 4 years, with a range of 3 to 8 years.
[d)] Baseline corresponds to the last measurement before the first infusion of cerliponase alfa, regardless of the dosage ("study baseline").
[e)] Week 243 corresponds to week 193 from the start of the 190-202 study.

Abbreviations: ITT: Intention-To-Treat; N = number of patients evaluated; PedsQL: Paediatric Quality of Life Inventory; SD: standard deviation

Side effects

Endpoint	Cerliponase alfa	
	N	Patients with event n (%)
Adverse events (AEs)		
190-201/202[a)]	24[b)]	24 (100)
190-203 [a)]	14 [b)]	14 (100)
190-504	38[c)]	15 (40)[e)]
DEM CHILD RX	24[d)]	16 (67)[f)]
Serious adverse events (SAE)		
190-201/202[a)]	24[b)]	21 (88)
190-203 [a)]	14 [b)]	12 (86)
190-504	38[c)]	11 (29)
DEM CHILD RX	24[d)]	n.d.[g)]
Severe adverse events (CTCAE grade 3 or 4)		
190-201/202[a)d)]	24[b)]	n.c.[h)]
190-203 [a)]	14 [b)]	9 (64)
190-504	38[c)]	8 (21) [f)]
DEM CHILD RX	24[d)]	n.d.[f) i)]
Therapy discontinuation due to adverse events		
190-201/202	24[b)]	0 (0)
190-203	14 [b)]	0 (0)
190-504	38[c)]	0 (0)
DEM CHILD RX	24[d)]	0 (0)
SAE with incidence ≥ 5%, MedDRA system organ class		

Endpoint	Cerliponase alfa	
	N	Patients with event n (%)
Nervous system disorders		
190-201/202	24[b)]	9 (38)
190-203	14[b)]	2 (14)
190-504	38[c)]	6 (16)
General disorders and administration site conditions		
190-201/202	24[b)]	2 (8)
190-203	14[b)]	7 (50)
Immune system disorders		
190-201/202	24[b)]	7 (29)
190-203	14[b)]	3 (21)
Infections and infestations		
190-201/202	24[b)]	16 (67)
190-203	14[b)]	6 (43)
190-504	38[c)]	5 (13)
Injury, poisoning and procedural complications		
190-201/202	24[b)]	4 (17)
190-203	14[b)]	1 (7)
Product issues		
190-201/202	24[b)]	14 (58)
190-203	14[b)]	1 (7)
Gastrointestinal disorders		
190-201/202	24[b)]	6 (25)
190-203	14[b)]	3 (21)
Respiratory, thoracic and mediastinal disorders		
190-201/202	24[b)]	4 (17)
190-203	14[b)]	3 (17)
Investigations		
190-203	14[b)]	1 (7)
Ear and labyrinth disorders		
190-203	14[b)]	1 (7)

Endpoint	Cerliponase alfa	
	N	Patients with event n (%)

[a] All AEs/SAEs were collected from implantation of ICV access in the 190-201/202 study and from baseline in the 190-203 study. Follow-up of safety events lasted 6 months after administration of the last infusion or early study discontinuation. A follow-up survey was not planned in the case of continued participation in a registry study or a clinical study sponsored by the pharmaceutical company.
[b] Safety population.
[c] Presentation refers to the safety population. 2 subjects were enrolled in the studies but not treated. Therefore, the safety population only includes 38 subjects instead of 40.
[d] Presentation refers to the analysis population (safety) of the DEM-CHILD-RX dataset.
[e] According to Module 4, the TEAE is related to the treatment if the study medication was administered and there is either a meaningful temporal relationship to the TEAE or the possibility that a TEAE was triggered by the treatment and it is not due to any other cause.
[f] According to Module 4, only treatment-related TEAEs were reported that were either related to the study medication or the access device. However, this indication is not found in the study documents.
[g] SAEs were not reported for the DEM CHILD RX study
[h] CTCAE grade 3 AEs occurred in 16 subjects (67%) and CTCAE grade 4 AEs occurred in 3 subjects (13%) according to the study report.
[i] CTCAE grade 3 and 4 AEs were reported separately. One subject (4%) had a grade 3 AE and 3 subjects (13%) a grade 4 AE.

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; n.d.: no data available; MedDRA: Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; n .c.: not calculable; SD: standard deviation; (S)AE: (Serious) Adverse Event.

2. Number of patients or demarcation of patient groups eligible for treatment

Patients with neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.

approx. 40 – 58 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Brineura (active ingredient: cerliponase alfa) at the following publicly accessible link (last access: 5 October 2022):

https://www.ema.europa.eu/en/documents/product-information/brineura-epar-product-information_en.pdf

Initiation and monitoring of treatment with cerliponase alfa should only be carried out by doctors experienced in the intracerebroventricular administration of medicinal products.

This medicinal product was approved under “special conditions”. This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product. The EMA will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

4. Treatment costs

Annual treatment costs:

Patients with neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Cerliponase alfa	€ 616,664.70
Additionally required SHI services	incalculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 November 2022)

5. Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Cerliponase alfa

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis (NCL) type 2 on the basis of the marketing authorisation granted under Medicinal Products Act:

Patients with neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.

- No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.