Seizures in Children with CLN2 Disease Receiving Cerliponase Alfa for >5 Years

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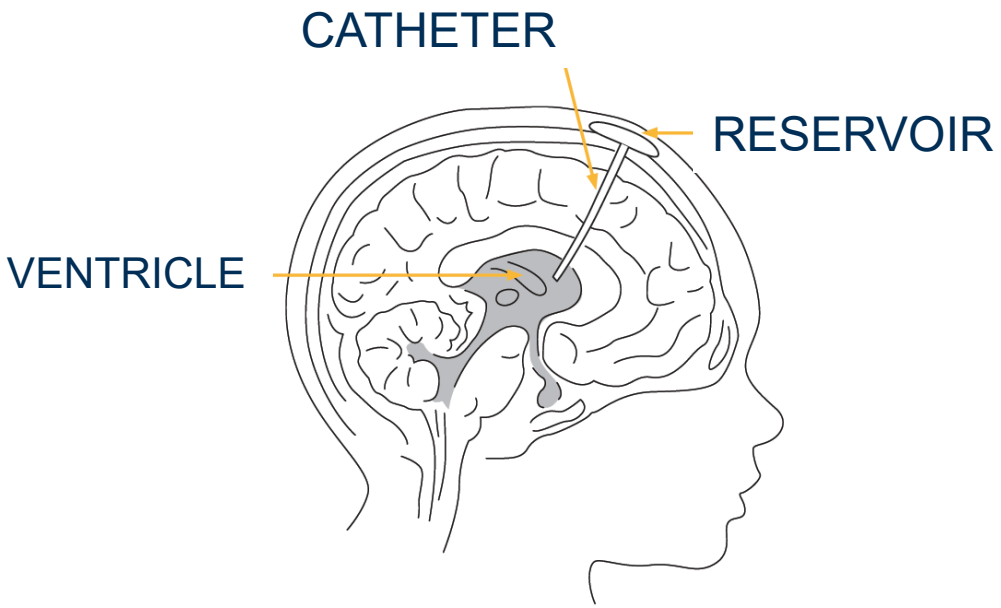
Cerliponase Alfa for the Treatment of CLN2 Disease

- Cerliponase alfa is a recombinant human form of TPP1 enzyme (rhTPP1)[1] approved for the treatment of CLN2 disease in the US and EU in 2017, and subsequently in a number of other countries worldwide



- Administered through an implanted Rickham or Ommaya device into the lateral cerebral ventricle
- 300 mg dose* every 14 days via intracerebroventricular (ICV) infusion over ~4 hours

[1]Schulz et al. Study of intraventricular cerliponase alfa for CLN2 disease. *N Engl J Med* 2018; 378:1898-1907.
*Age adjusted dosing may be indicated for patients <2 years of age

Cerliponase Alfa: 190-201/202 Study Design

190-201: Phase 1/2 study

N=24 (age ≥3 years)
Dose escalation phase followed by
48-week stable dose period (300 mg qow)

(Clinicaltrials.gov: NCT01907087)

190-202: Open-label extension

N=23 (enrolled from 190-201)
Up to 240 weeks (300 mg qow)
6-month safety follow up period

(Clinicaltrials.gov: NCT02485899)

Combined data from both primary and extension studies used to assess long-term safety and efficacy

- Safety was assessed in all subjects who had an ICV access device implanted (N=24)
- Efficacy analyses included all subjects who received >1 dose of cerliponase alfa (N=23)

Efficacy Assessment: CLN2 Disease Clinical Rating Scale

Motor	Score
Walks normally	3
Frequent falls, ataxia, independent walk >10 steps	2
No unaided gait	1
Immobile, mostly bedridden	0

Language	Score
Normal	3
Loss of words, intelligible but abnormal speech	2
Some comprehension, mostly unintelligible speech	1
Unintelligible or no language	0

Vision	Score
Recognizes and coordinated reach to objects	3
Uncoordinated reach to objects	2
React to light	1
No reaction to visual stimuli	0

Seizures (Grand Mal)	Score
No seizures in 3 months	3
1–2 seizures in 3 months	2
1 seizure per month	1
>1 seizure per month	0

CLN2 Disease Clinical Rating Scale: Combined Motor-Language Score as Primary Outcome

Motor	Score
Walks normally	3
Frequent falls, ataxia, independent walk >10 steps	2
No unaided gait	1
Immobile, mostly bedridden	0

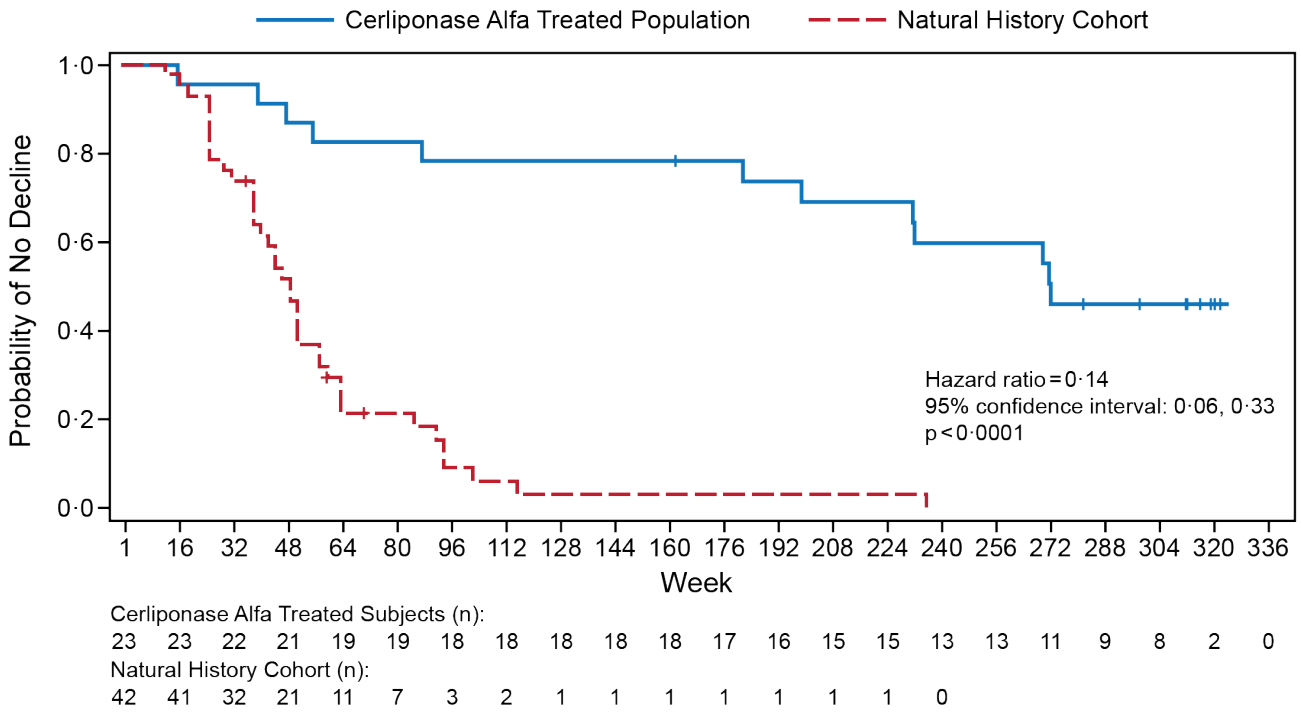
Language	Score
Normal	3
Loss of words, intelligible but abnormal speech	2
Some comprehension, mostly unintelligible speech	1
Unintelligible or no language	0

Vis	re
Rec	
Un	
React to light	1
No reaction to visual stimuli	0

1 seizure per month	1
>1 seizure per month	0

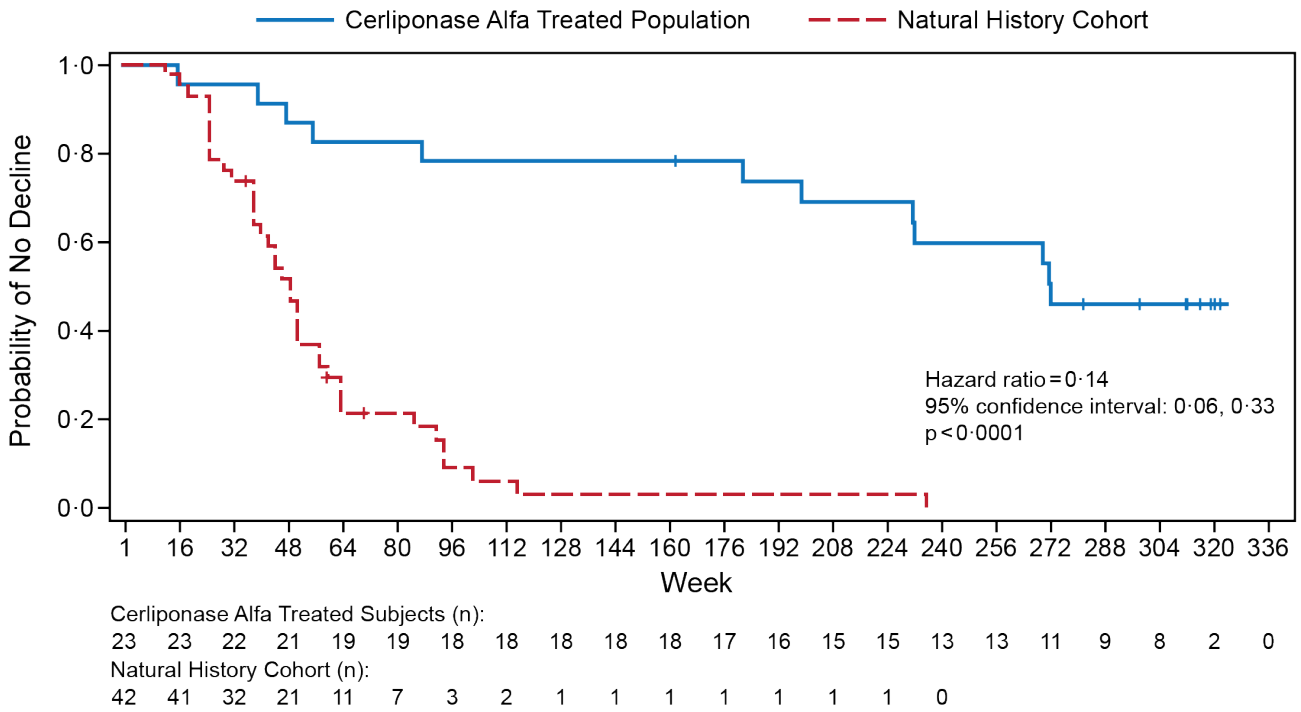
- Motor and language loss are central to disease morbidity
- Combined **motor-language score** was used as the **primary outcome measure** in clinical trials of cerliponase alfa

190-201/202 Primary Efficacy: Decline in Motor-Language Score



Treated subjects were significantly less likely than natural history controls to have an unreversed 2-point decline or a score of 0 in the combined motor-language domains

190-201/202 Primary Efficacy: Decline in Motor-Language Score



Rate of Decline in ML Score (points per 48 weeks)	Natural History (N=42)	190-201/202 (N=23)	Difference
Mean (SD)	2.13 (0.95)	0.38 (0.50)	1.75
Median (IQR)	2.08 (1.40, 2.80)	0.30 (0.15, 0.37)	
95% Confidence Interval	1.84, 2.43	0.16, 0.59	0.39, 2.11

Treated subjects were significantly less likely than natural history controls to have an unreversed 2-point decline or a score of 0 in the combined motor-language domains

Rate of decline in motor-language score was significantly reduced among treated subjects compared to natural history controls

CLN2 Disease Clinical Rating Scale: Seizure Domain as Exploratory Outcome

Motor	Score
Walks normally	3
Frequent falls, ataxia, independent walk >10 steps	2
No	
Imm	

Language	Score
Normal	3
Loss of words, intelligible but abnormal speech	2

- Seizures present a significant burden throughout CLN2 disease progression
- **Seizure domain score** was assessed as an **exploratory outcome** in clinical trials of cerliponase alfa

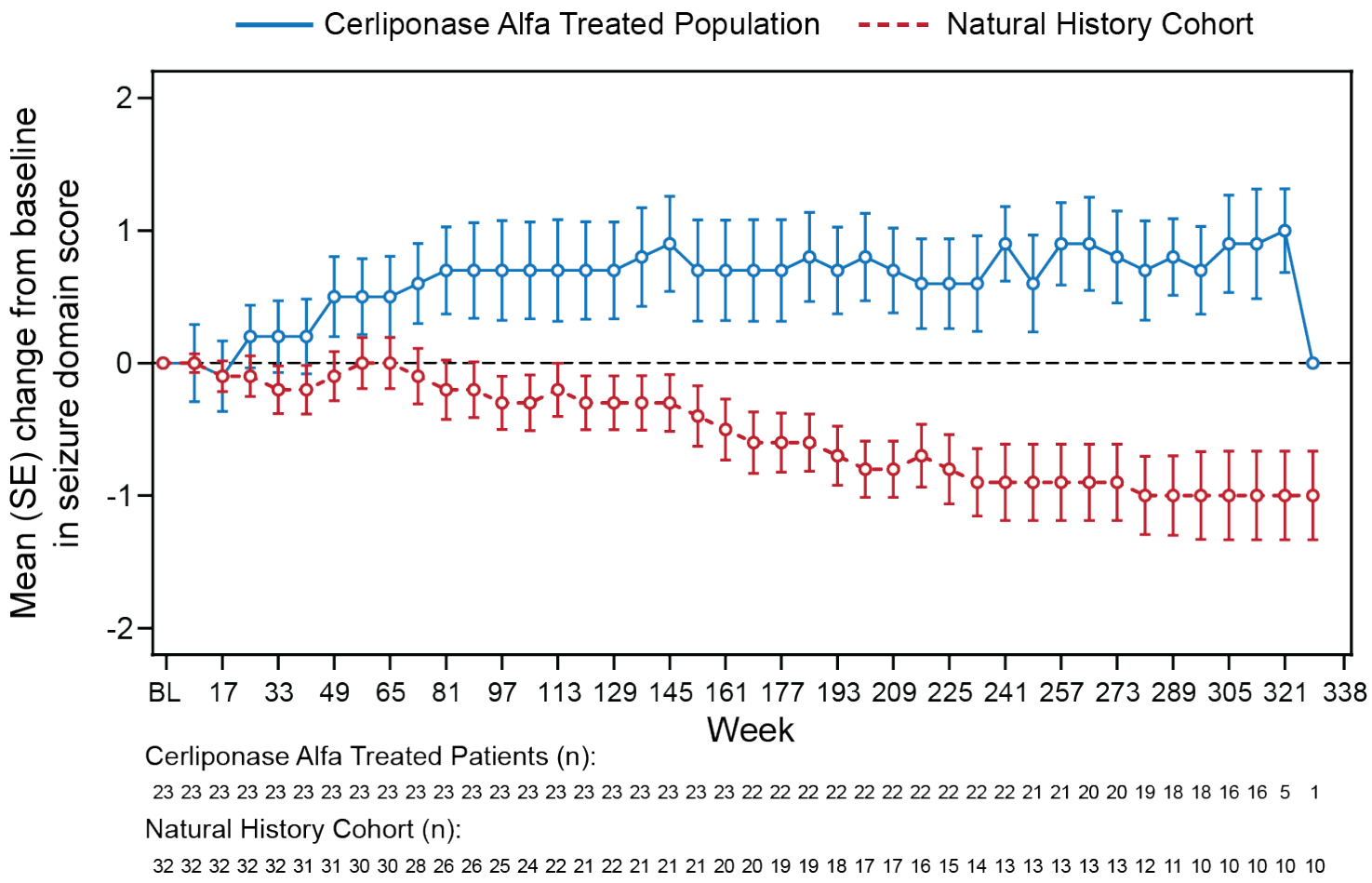
Vision	Score
Recognizes and coordinated reach to objects	3
Uncoordinated reach to objects	2
React to light	1
No reaction to visual stimuli	0

Seizures (Grand Mal)	Score
No seizures in 3 months	3
1–2 seizures in 3 months	2
1 seizure per month	1
>1 seizure per month	0

190-201/202: Seizure Assessments

- Incidence of seizures in subjects treated with cerliponase alfa in 190-201/202 was assessed as follows:
  - Change from baseline in seizure domain score of CLN2 clinical rating scale compared to natural history controls
  - Number of treated subjects reporting ≥1 adverse event (AE) mapping to the Convulsions Standardized MedDRA Query for each 24-week period of follow-up

190-201/202: Change from Baseline in Seizure Domain Score



Mean (SD) seizure score increased* from 1.7 (1.2) at baseline to 2.4 (0.8) at week 289 in treated subjects and decreased from 1.7 (1.1) to 0.7 (1.2) in natural history controls.

*Increase in seizure domain score represents decrease in seizure burden

190-201/202: Change from Baseline in Seizure Domain Score

Change in Seizure Domain Score (Baseline to Last Assessment), n (%)	(N=23)
+3 (improvement)	4 (17.4)
+2	4 (17.4)
+1	4 (17.4)
0 (no change)	5 (21.7)
-1	4 (17.4)
-2	1 (4.3)
-3 (decline)	1 (4.3)

At the last assessment of the 300 mg dosing period, 12 subjects (52.2%) showed improvement in seizure score compared to baseline, 5 (21.7%) showed no change, and 6 (26.1%) showed decline

190-201/202: Overall Summary of Adverse Events

Summary of AEs	Subjects (N=24), n (%)
Any AE	24 (100)
Any AE considered related to study drug	23 (96)
Any AE leading to:	
Dose interruption	15 (63)
Dose reduction	0 (0)
Discontinuation	0 (0)
Deaths	0 (0)

Most common AEs (occurring in ≥50% of subjects), n (%)

URTI	21 (88)	Device end of service	13 (54)
Pyrexia	20 (83)	Dysphasia	13 (54)
Viral URTI	19 (79)	Epilepsy	13 (54)
Vomiting	19 (79)	Rhinitis	13 (54)
Generalized tonic-clonic seizure	16 (67)	Body temp. increased	12 (50)
Seizure	14 (58)	Gait disturbance	12 (50)
Constipation	13 (54)		

- Most AEs were Grade 1 or 2 in severity
- All AEs resolved spontaneously or with appropriate medical management

- Seizures were among the most common AEs

190-201/202: Convulsions Adverse Events

Summary of Convulsions AEs [a]	**Subjects (N=24),** n (%)
Any convulsions AE	23 (96)
Any convulsions AE considered related to study drug	12 (50)
Any convulsions SAE	5 (21)
Any convulsions SAE considered related to study drug	0 (0)

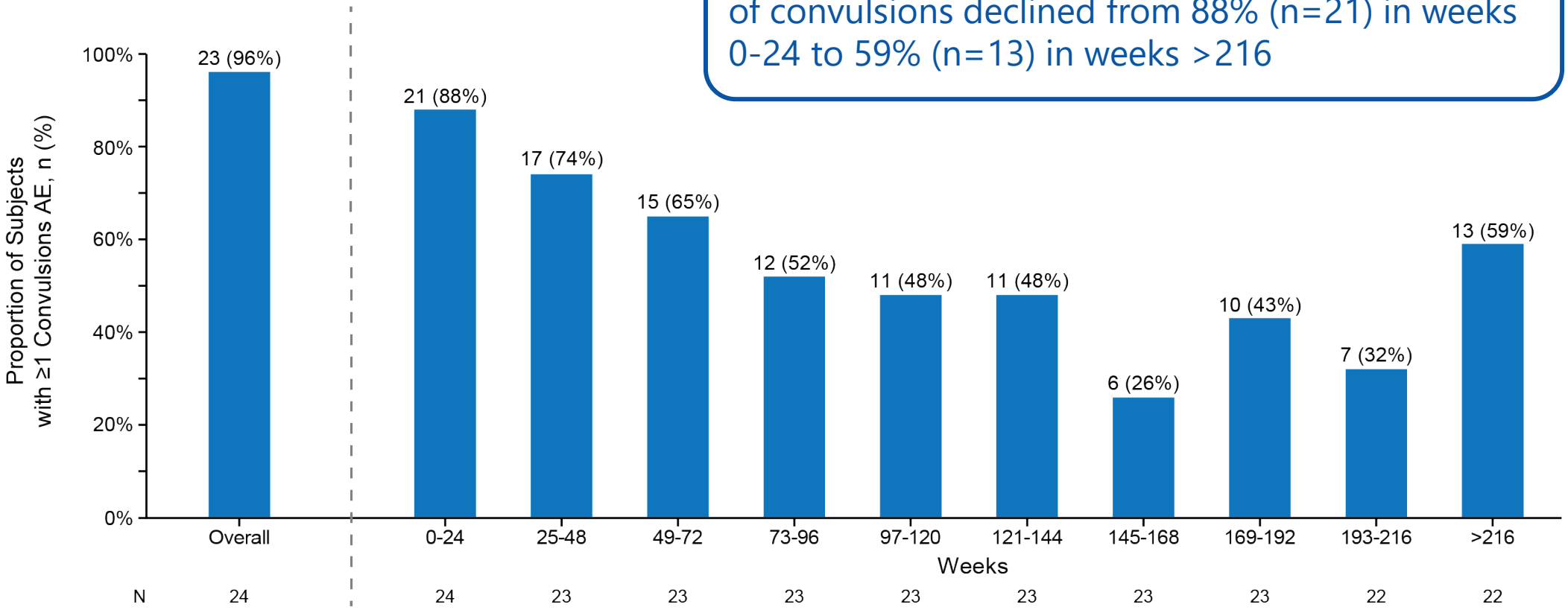
Convulsions AEs, n (%)			
Generalized tonic-clonic seizure	16 (67)	Myoclonic epilepsy	3 (13)
Seizure	14 (58)	Seizure cluster	3 (13)
Epilepsy	13 (54)	Drop attacks	2 (8)
Petit mal epilepsy	8 (33)	Status epilepticus	2 (8)
Partial seizures	7 (29)	Clonic convulsion	1 (4)
Atonic seizures	3 (13)	Tonic convulsion	1 (4)

- 23 subjects experienced a total of 693 convulsions AEs: most were Grade 1 or 2 in severity
- 12 subjects experienced 27 convulsions AEs that were considered related to study drug

[a] Represents AEs mapping to the Convulsions Standardized MedDRA Query

190-201/202: Convulsions Adverse Events over Study Follow-Up

The proportion of treated subjects reporting ≥1 AE of convulsions declined from 88% (n=21) in weeks 0-24 to 59% (n=13) in weeks >216



Represents AEs mapping to the Convulsions Standardized MedDRA Query

Conclusions

- These results suggest that there may be a reduction in the incidence of seizures over time in subjects receiving cerliponase alfa treatment
- Further evaluation will be needed to assess the impact of disease progression, concurrent illness, and anti-seizure medication use, and to delineate the impact on specific seizure types and seizure duration/severity

Acknowledgements

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- Authors: Angela Schulz[1], Emily de los Reyes[2], Nicola Specchio[3], Paul Gissen[4], Peter Slasor[5], Shailesh Bondade[5], Sara Dosenovic[5], Jessica Cohen-Pfeffer[5]

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