Seizures and Movement Disorders in Patients With CLN2 Disease Treated With Cerliponase Alfa in the Real-World Setting

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Conflicts of interest disclosures

- **Angela Schulz** has received consulting fees from Neurogene Inc. and Regenxbio Inc. She received honoraria for speaker fees, research grants, and travel support from and was a Principal Investigator in BMN 190 clinical trials for BioMarin Pharmaceutical Inc.

Background

- CLN2 disease is a rare neurodegenerative disorder caused by deficient TPP1 enzyme activity that typically presents with language delay and/or onset of seizures between 2 and 4 years of age
    - Onset of symptoms is followed by rapid, progressive decline in motor and language function, worsening epilepsy, onset of movement disorders, and vision loss[1–3]
- Cerliponase alfa (recombinant hTPP1) is currently the only disease-modifying therapy approved for the treatment of CLN2 disease
    - Over a period of more than 5 years, ICV administration of cerliponase alfa slowed decline in motor and language function compared with natural history controls[4,5]
- Seizures are a predominant feature of CLN2 disease and present a significant burden throughout disease progression[2,3]
    - In clinical trials, a reduction in the frequency of tonic-clonic seizures was seen over time in patients treated with cerliponase alfa, suggesting that treatment may also have some benefit with respect to seizures[5]

The aim of this retrospective, observational analysis, was to evaluate the incidence and severity of seizures and movement disorders in patients with CLN2 disease treated with cerliponase alfa in a real-world setting

CLN2, ceroid lipofuscinosis type 2; hTPP1, human TPP1; ICV, intracerebroventrical; TPP1, tripeptidyl peptidase 1.

1. Sleat et al. *Am J Hum Genet* 1999; 64: 1511–23. **2.** Schulz et al. *Biochim Biophys Acta* 2013; 1832: 1801–6. **3.** Nickel et al. *Lancet Child Adolesc Health* 2018; 2: 582–90.
4. Schulz et al. *N Engl J Med* 2018; 378: 1898–907. **5.** Schulz et al. *Lancet Neurol* 2024; 23: 60–70.

Methods

Inclusion criteria

- Patients enrolled in the real-world, observational DEM-CHILD database (international NCL patient registry; NCT04613089)
- Diagnosis of CLN2 disease confirmed by genetic and enzyme testing
- Initiated treatment with cerliponase alfa outside a clinical trial setting
- Had ≥6 months of follow-up after treatment initiation

Follow-up

- Patients were followed from date of first cerliponase alfa infusion (index) to the earliest of death, disenrollment, or data cut-off (31 Dec 2022)

Outcomes assessed

- Seizure types, frequency, and complications were derived using the CLN2 Disease Seizure Inventory
- Dystonia and myoclonus were derived using the CLN2 Disease Movement Disorder Inventory
- Numbers and proportion of patients experiencing seizures (primary generalized, atonic, myoclonic) and changes in seizure medications were assessed at 6-month intervals
- Time to onset or worsening of movement disorders was assessed using Kaplan–Meier methods

CLN2, ceroid lipofuscinosis type 2; NCL, neuronal ceroid lipofuscinoses.

Baseline Characteristics

Baseline characteristic	Patients (N=24)
Female, n (%)	14 (58.3)
Age (months), mean (SD)	
At diagnosis	53.1 (25.6)
At genetic analysis	55.3 (26.6)
At cerliponase alfa initiation	61.4 (27.3)
Phenotype, n (%)	
Atypical	4 (16.7)
Presymptomatic	1 (4.2)
Typical	19 (79.2)
Affected sibling (Yes), n (%)	8 (33.3)
Type of kindergarten/school, n (%)[a]	
None	3 (12.5)
Regular kindergarten	4 (16.7)
Special kindergarten/integration group	9 (37.5)
Regular school	2 (8.3)
Special school/integration class	3 (12.5)
Not reported	5 (20.8)

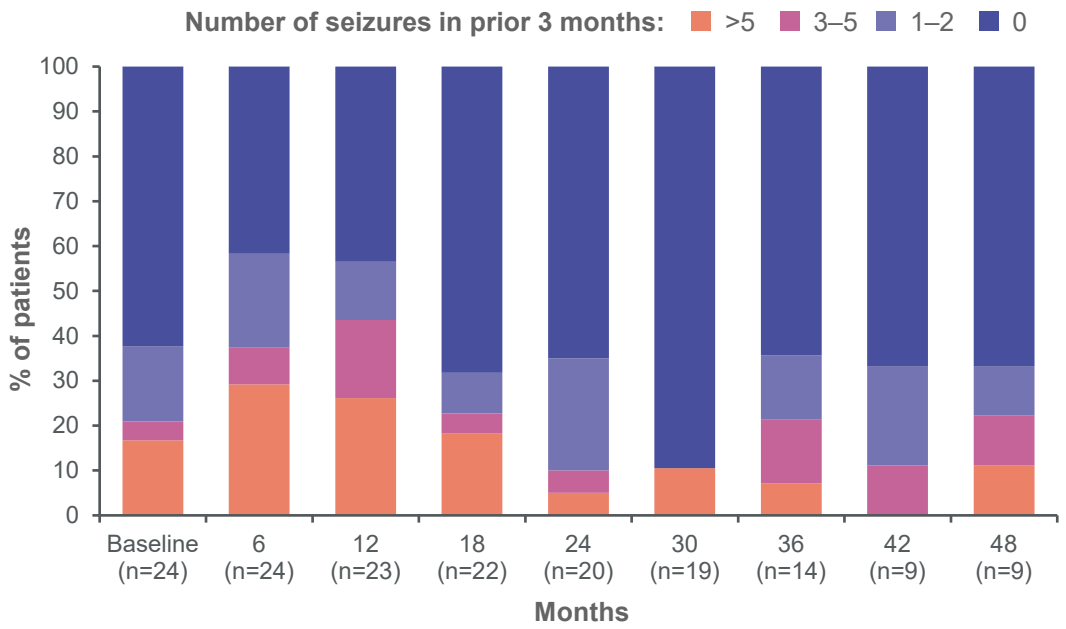
Baseline characteristic	Patients (N=24)
Neurological symptoms, n (%)[a]	
Seizures	20 (83.3)
Ataxia	18 (75.0)
Dystonia	5 (20.8)
Myoclonus	3 (12.5)
Hamburg LINCL motor-language domain score, n (%)	
6	6 (25.0)
5	2 (8.3)
4	7 (29.2)
3	3 (12.5)
2	5 (20.8)
1	1 (4.2)

24 patients were included in the analysis, with a mean (SD) follow-up time of 43.8 (19.0) months

[a]Multiple selection was allowed in the case report form for this variable, so aggregate percentage may exceed 100%.
LINCL, late infantile neuronal ceroid lipofuscinosis; SD, standard deviation.

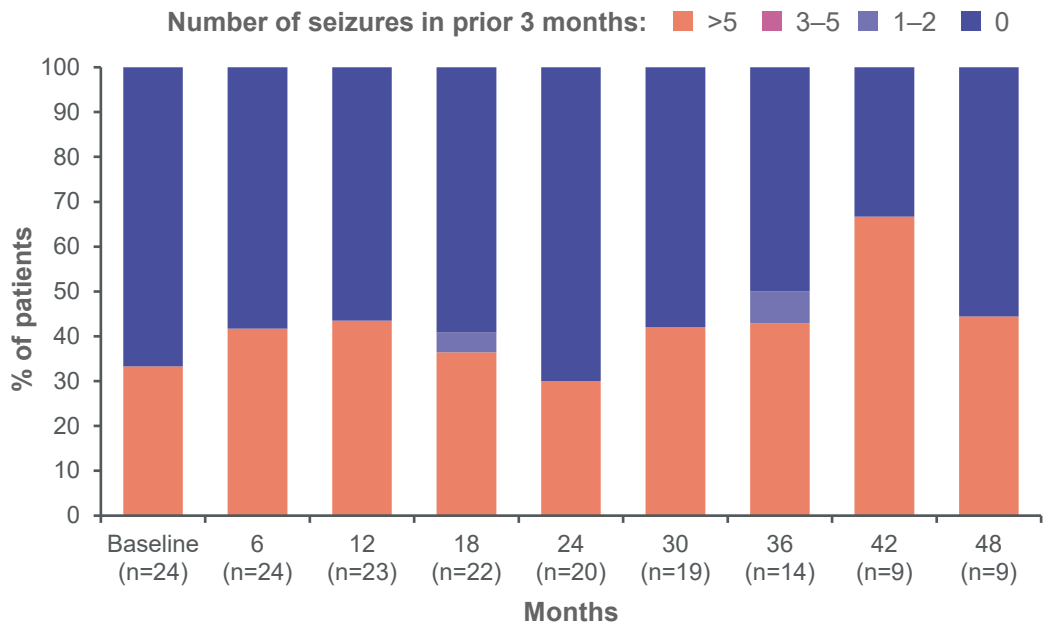
Frequency of Seizures Over Follow-Up (1/2)

Primary Generalised Seizures



- Proportion of patients experiencing >5 seizures increased from baseline to Month 6 and then declined
- No clear correlation between LINCL motor-language score at baseline and frequency of seizures over follow-up (data not shown)

Atonic Seizures

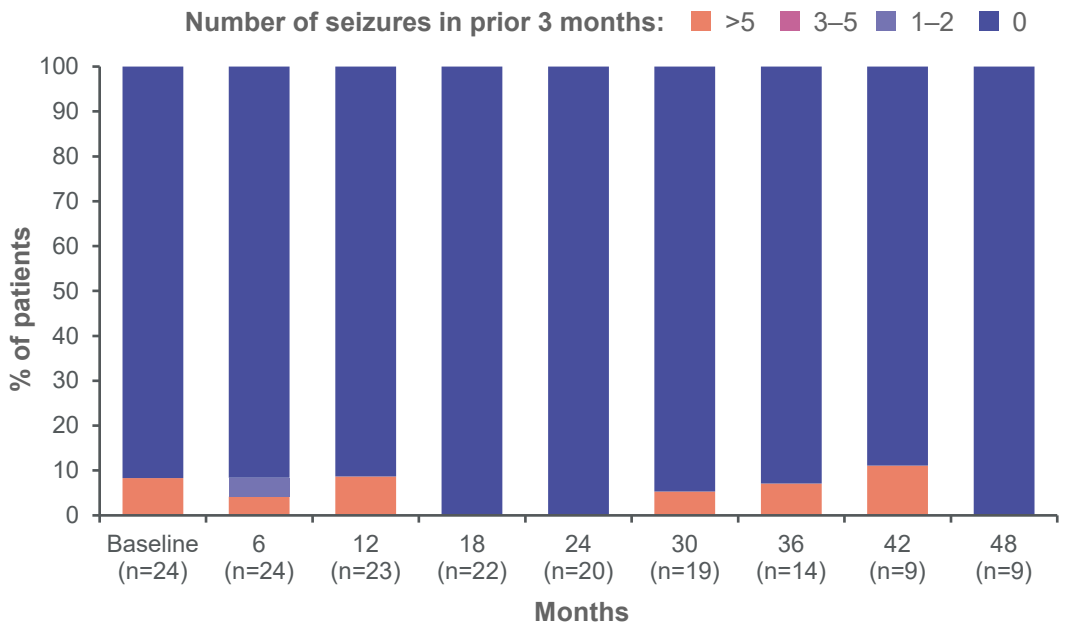


- Relatively stable over follow-up
- Among those with atonic seizures, almost all experienced a frequency of >5 seizures in the prior 3 months

LINCL, late infantile neuronal ceroid lipofuscinosis.

Frequency of Seizures Over Follow-Up (2/2)

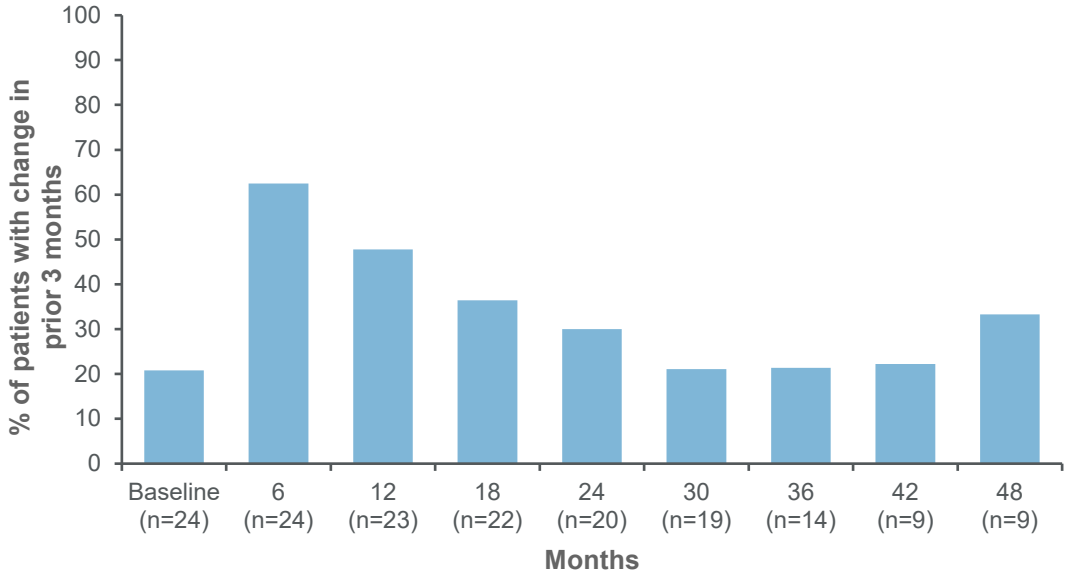
Myoclonic Seizures



- Few patients experienced myoclonic seizures
- Those who did generally reported >5 seizures in the prior 3 months

Anti-Seizure Medication Use

(dose increase/new drug addition)

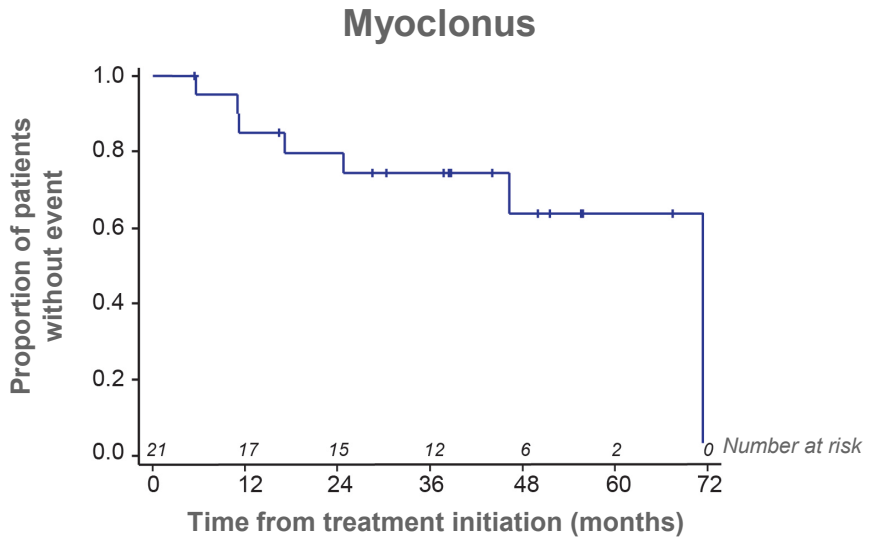


- Proportion of patients with change in medication use in the prior 3 months showed an initial increase, before declining thereafter

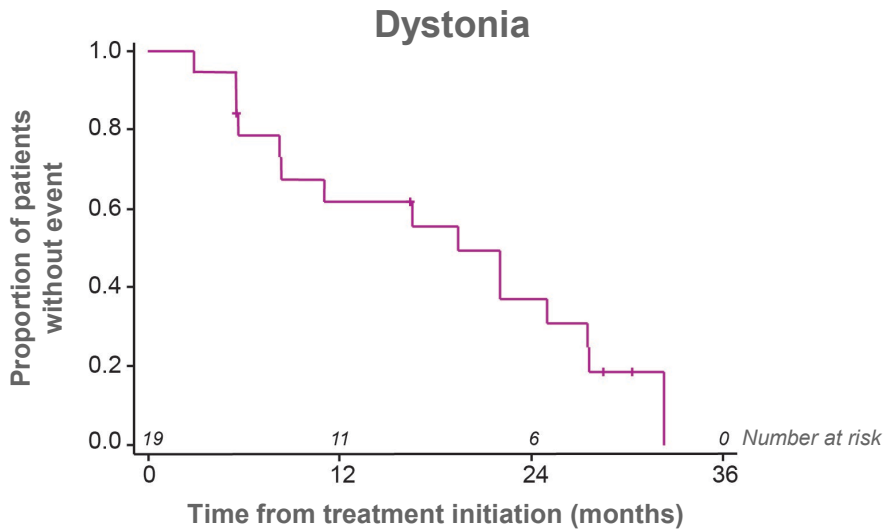
These findings support observations from clinical trials suggesting that cerliponase alfa may have benefit in mitigating the progressive worsening of seizures seen in untreated CLN2 patients

CLN2, ceroid lipofuscinosis type 2.

Incidence and Time to Onset of Myoclonus and Dystonia



Time to first onset of myoclonus	N=21
Patients without event (censored), n (%)	14 (66.7)
Patients with an event, n (%)	7 (33.3)
Age at onset (months), mean (SD)	87.6 (41.8)
Time to onset (months), median (95% CI)	71.4 (24.8–71.4)



Time to first onset of dystonia	N=19
Patients without event (censored), n (%)	4 (21.1)
Patients with an event, n (%)	15 (78.9)
Age at onset (months), mean (SD)	79.6 (26.2)
Time to onset (months), median (95% CI)	19.4 (8.2–27.5)

- Only 33.3% experienced myoclonus onset during follow-up; among those who did, mean age at onset was 87.6 months, suggesting that treatment with cerliponase alfa may delay onset compared with natural history[1]
- Most patients experienced dystonia onset ≤3 years after cerliponase alfa initiation, indicating ongoing burden despite treatment

CI, confidence interval; SD, standard deviation.

1. Worgall et al. *Neurology* 2007; 69: 521–35.

Conclusions

This study provides a comprehensive description of the time course of seizures and movement disorders in patients with CLN2 disease receiving cerliponase alfa in a real-world setting

Findings support observations from clinical trials suggesting that cerliponase alfa may have benefit in mitigating the progressive worsening of seizures seen in untreated patients

Results suggest that treatment with cerliponase alfa may also delay the onset of myoclonus relative to natural history; dystonia remained an ongoing burden despite treatment

CLN2, ceroid lipofuscinosis type 2.

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