Interim Results From the First Clinical Gene Therapy Trial for CLN6 Batten Disease

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BACKGROUND

- Mutations in the *CLN6* gene cause lysosomal dysfunction that leads to a variant late-infantile form of neuronal ceroid lipofuscinosis, or Batten disease, a rare and fatal neurodegenerative disorder[1,2]
- The onset of CLN6-type Batten disease is typically between the age of 2-5 years, and affected children experience language delay, motor regression, epilepsy, decline of vision, and premature death, often occurring in late childhood[1,2]
- There is currently no treatment for this rapidly progressive disease
- Current management strategies focus on symptomatic treatment and supportive care[1]

OBJECTIVES

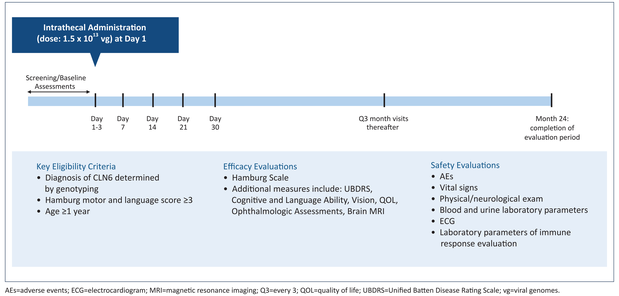
- To evaluate the safety and effectiveness of *CLN6* gene transfer using an adeno-associated virus serotype 9 (AAV9) vector in the first intrathecal gene therapy clinical trial for children with CLN6-type Batten disease

METHODS

Study Design

- This is an open-label, single-site phase 1/2 trial of single-dose *CLN6* gene transfer via intrathecal injection into the lumbar spinal cord region in children with CLN6-type Batten disease (for study design see **Figure 1**)
- *CLN6* gene was delivered using a self-complementary AAV serotype 9 (scAAV9) under the control of a chicken-β-actin promoter
- Efficacy assessments include the Hamburg Scale, which rates motor function and language (HM+L)[3] (Figure 2), as well as vision and seizures[4]

Figure 1. Study Design



AEs=adverse events; ECG=electrocardiogram; MRI=magnetic resonance imaging; Q3=every 3; QOL=quality of life; UBDRS=Unified Batten Disease Rating Scale; vg=viral genomes.

Figure 2. Hamburg Motor and Language Scale[3]

Motor Function	Language Function	In each domain, the rating is structured so that a score of:
3 Normal	3 Normal	3 = normal condition
2 Clumsy, falls	2 Abnormal	2 = slight or just noticeable abnormality
1 Non-walking	1 Minimal	1 = severe abnormality
0 Immobile	0 Unintelligible or no vocalization	0 = complete loss of function

Statistical Analyses

- Safety data were analyzed for all 12 treated patients; efficacy results were presented for 8 patients, including all sibling pairs with ≥1 year of data and non-sibling patients with ≥2 years of data
- HM+L scores of treated patients were compared with their untreated siblings, as well as natural history data derived from an ongoing, retrospective chart review study in CLN6 Batten disease (clinicaltrials.gov: NCT03285425)
- Interim data cutoff was July 31, 2019

RESULTS

Baseline Characteristics

- The study population (n=12) included both male and female patients ranging from 19 to 79 months in age
- Baseline characteristics for the 8 patients evaluated for efficacy are shown in **Table 1**

Table 1. Patient Characteristics

Patient	Sex	Age at Gene Transfer (months)	Exposure Duration (months)*	Hamburg Motor + Language at Baseline	Time Between Baseline and Last Measure (Months)
1	F	63	41	3	25
2	F	30	39	6	23
3	M	36	38	5	24
4	M	67	30	4	24
5	F	79	29	3	24
6	M	56	28	5	24
7	M	19	22	5	22
8	M	61	18	4	16

*Calculated to July 31, 2019. Patients 1-8 were included in the efficacy results.

Safety

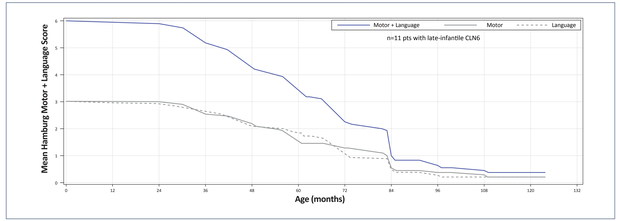
- At interim data cutoff, duration since gene transfer ranged from 8 to 41 months
- 137 adverse events (AEs) were reported among the 12 patients, and most AEs were mild and unrelated to treatment. **Table 2** reports all treatment-emergent AEs [TEAEs] that occurred in >1 patient
- Nine Grade 3 (severe) AEs (SAEs) were reported in 4 patients; 4 of the SAEs were considered possibly related to treatment (2 events of vomiting, 1 event of epigastric pain, and 1 event of fever; all 4 recovered)
- No Grade 4 (life-threatening) AEs or deaths were reported
- No pattern of AEs related to AAV9 or *CLN6* transgene immunogenicity was observed

Table 2. Treatment-Emergent Adverse Events That Occurred in >1 Patient

Adverse event	N=12 n (%)
Upper respiratory tract infection	7 (58.3)
Viral infection	6 (50)
Vomiting	5 (41.7)
Hematuria	4 (33.3)
Back pain	3 (25)
Constipation	3 (25)
Diarrhea	3 (25)
Seizure	3 (25)
Viral gastroenteritis	3 (25)
Abnormal behavior	2 (16.7)
Insomnia	2 (16.7)
Myoclonus	2 (16.7)
Otitis media	2 (16.7)
Procedural pain	2 (16.7)
Pyrexia	2 (16.7)
Urinary tract infection	2 (16.7)

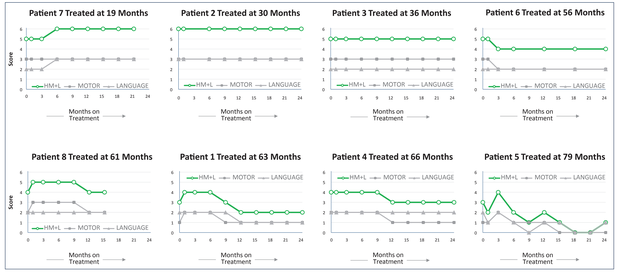
Hamburg Motor and Language Score

Figure 3. Mean Hamburg Motor and Language Aggregate Score, Motor Subscore, and Language Subscore Over Time in CLN6 Natural History Patients



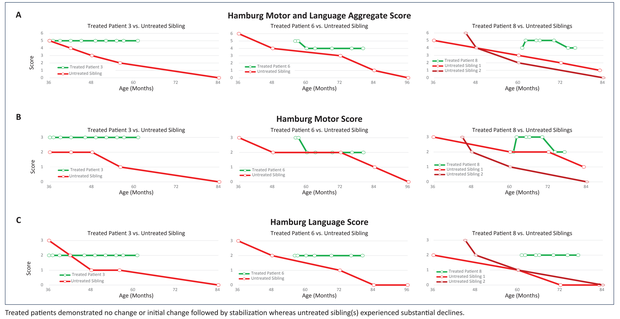
CLN6 natural history shows a progressive decline of approximately one point per year in the Hamburg Motor and Language score from age two onwards with similar decline in motor and language.

Figure 4. Individual Hamburg Motor and Language Aggregate Score, Motor Subscore, and Language Subscore of AAV9-CLN6 Gene Transfer Patients



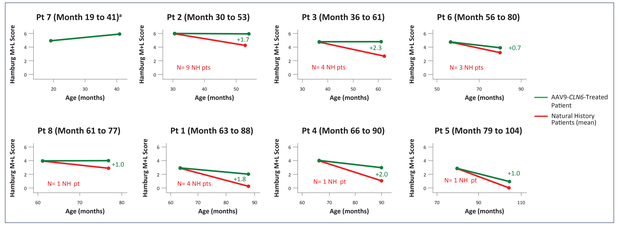
HM+L=Hamburg Motor and Language aggregate score.
Seven of 8 patients with ≥12 months efficacy data maintained the combined Hamburg score or had initial change (+1 to -1 points) followed by stabilization.

Figure 5. Comparison of AAV9-*CLN6* Gene Transfer Patients and Untreated Sibling(s) in (A) Hamburg Motor and Language Aggregate Score, (B) Motor Subscore, and (C) Language Subscore



Treated patients demonstrated no change or initial change followed by stabilization whereas untreated sibling(s) experienced substantial declines.

Figure 6. Comparison of AAV9-*CLN6* Gene Transfer Patients and Natural History Patients Matched Based on Age And Baseline Hamburg Motor and Language Aggregate Scores



HM+L=Hamburg Motor and Language Aggregate Score; NH=natural history; pt=patient.
[a]This patient currently has no age- and baseline HM+L score-matched patients in the natural history cohort.
To facilitate comparison of AAV9-CLN6-treated patients to natural history patients with respect to clinical course over time, HM+L results from the first 8 treated patients in this study were matched with HM+L results from 11 patients in a retrospective CLN6 natural history study (ClinicalTrials.gov Identifier: NCT03285425; PI: Emily de los Reyes, MD).

For each treated patient, all natural history patients who had the same baseline Hamburg M+L score at the same age at which treatment started were "matched." The average Hamburg M+L score for these matched patients was then calculated at the ages corresponding to last observation for each treated patient. Overall, these data indicate that the gene-therapy–treated patients demonstrate stabilization in Hamburg M+L score compared to matched natural history patients.

Hamburg Vision and Seizure SubScores

Table 2. Individual Hamburg Vision and Seizure Subscores of AAV9-*CLN6* Gene Transfer Patients

Patient	Age at Gene Transfer (months)	Hamburg Vison Score			Hamburg Seizure Score		
		Baseline	Month 12	Month 24	Baseline	Month 12	Month 24
1	63	3	2	1	3	3	3
2	30	3	3	3	3	3	3
3	36	3	3	3	3	3	2
4	67	2	1	1	2	3	3
5	79	2	0	0	3	2	0
6	56	3	3	3	3	3	3
7	19	3	3	_	3	3	_
8	61	3	3	_	3	3	_

Hamburg Vision Score is decoded as: 0: no reaction to visual stimuli; 1: reacts to light; 2: grabbing for objects uncoordinated; 3: recognizes desirable object, grabs at it.
Hamburg Seizure Score is decoded as: 0: > 1 seizure per month; 1: 1 seizure per month; 2: 1 - 2 seizures in 3 months; 3: no seizure in 3 months.

CONCLUSIONS

- These interim safety and efficacy data suggest that AAV9-*CLN6* gene therapy has the potential to stabilize disease progression of the variant late-infantile onset CLN6 Batten disease
- Most adverse events were mild and unrelated to treatment; the most common treatment-related adverse events were vomiting and back pain, which were all transient. Therefore, intrathecal administration of AAV9-*CLN6* is generally well tolerated
- Efficacy results demonstrated a meaningful treatment effect in motor and language function
  - AAV9-*CLN6*-treated patients demonstrated stabilization in HM+L score compared with untreated siblings and natural history patients matched for age and HM+L baseline score
  - Comparison of treated younger and older patients further supports the potential benefit of early intervention of gene therapy with AAV9-*CLN6*

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DISCLOSURE

Conflicts of Interest

ER received research grants from Amicus and Biomarin and has been a consultant for Biomarin. KM received a research grant from Audentes and royalties from Amicus. LL attended advisory boards and received consultant fees from Amicus and Biomarin. CA received a research grant from Amicus. JC, HJ, AR and JB are employees of and hold stock in Amicus.

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