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Single-Dose AAV9-CLN6 Gene Transfer Slows the Decline in Motor and Language Function in Variant Late Infantile Neuronal Ceroid Lipofuscinosis 6: Interim Results From a Phase 1/2 Trial

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BACKGROUND

- Variants in the *CLN6* gene cause lysosomal dysfunction, leading to variant late infantile ceroid lipofuscinosis of Batten disease (vLINCL6), a rare and fatal neurodegenerative disorder[1,2]
- *CLN6*-type Batten disease typically presents between 2 and 5 years of age and is associated with language delay, motor regression, intractable epilepsy, vision loss, and premature death in childhood[1,2]
- There is no approved treatment for *CLN6*-type Batten disease, and management is limited to treatment of symptoms and supportive care[1]

OBJECTIVES

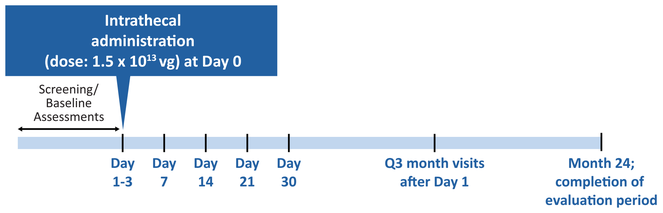
- To evaluate the safety and effectiveness of *CLN6* gene transfer, using an adeno-associated virus serotype 9 (AAV9) vector (AT-GTX-501) administered by intrathecal injection to children with *CLN6*-type Batten disease, an investigational therapy not yet approved by any regulatory agency

METHODS

Study Design

- This is an open-label, single-center, phase 1/2 study of a single dose of AT-GTX-501 administered by intrathecal injection into the lumbar spinal cord region to children with *CLN6*-type Batten disease (clinicaltrials.gov: NCT02725580) (**Figure 1**)
- Human *CLN6* gene was delivered using a self-complementary AAV9 vector under the control of a chicken-β-actin promoter
- Safety and efficacy were evaluated over a 2-year period
  - The primary end point was safety, based on dose-limiting toxicity, which was defined as any unanticipated grade ≥3 adverse event (AE) per the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, considered related to AT-GTX-501
  - The primary efficacy assessment was the rate of decline in Hamburg Motor and Language (HML) aggregate score[3] over 24 months (**Figure 2**)
    - Additional efficacy analyses were
      - Rate of decline in HML scores over 12 months
      - Proportion of patients with an unreversed decline in HML score at month 24
      - Time to an unreversed 2-point decline in HML score

Figure 1. Study Design



Key Eligibility Criteria
- Diagnosis of vLINCL6 as determined by genotyping with a clinical presentation of late infantile NCL
- Hamburg Motor and Language score ≥3
- Age ≥1 year

Efficacy Evaluations
- Hamburg scale
- Additional measures include UBDRS, cognitive and language ability measures, PedsQL™, ophthalmologic assessments, and brain MRI

Safety Evaluations
- AEs
- Vital signs
- Physical/neurological exam
- Blood and urine laboratory parameters
- ECG
- Laboratory parameters of immune response

AE=adverse event; ECG=electrocardiography; MRI=magnetic resonance imaging; NCL=neuronal ceroid lipofuscinosis; PedsQL=Pediatric Quality of Life Inventory; Q3=every 3; UBDRS=Unified Batten Disease Rating Scale; vg=viral genomes.

Figure 2. Hamburg Motor and Language Scale[3]

The Hamburg Motor and Language Scale rates motor and language function of patients with late infantile Batten disease at 3-month intervals to quantify disease progression

Hamburg Motor and Language Scale

Motor Function

3	2	1	0
Normal	Frequent falls, obvious clumsiness	No unaided walking or crawling only	Immobile, mostly bedridden

Language Function

3	2	1	0
Normal (individual best performance)	Recognizably abnormal	Hardly understandable	Unintelligible or no language

In each domain, the rating is structured so that a score of:

3	2	1	0
= normal condition	= slight or just noticeable abnormality	= severe abnormality	= complete loss of function

Statistical Analyses

- The safety population included all patients treated with AT-GTX-501
- The efficacy population included 12 patients for whom ≥1 year of follow-up was available after treatment
- HML scores of treated patients were compared with natural history data derived from an ongoing, retrospective chart review study in *CLN6* Batten disease (clinicaltrials.gov identifier: NCT03285425)
- Time to unreversed 2-point decline in HML score was estimated using the Kaplan-Meier method and was compared between treated patients and untreated natural history subjects by log-rank tests. A Cox proportional hazards model was used to calculate hazard ratio (HR)
- The cutoff date for this interim analysis was March 13, 2020

RESULTS

Baseline Characteristics

- The safety population (n=13) included male and female patients aged 19-79 months at study entry (**Table 1**)
  - Mean (SD) HML score at baseline was 4.2 (0.93), indicating mild-to-moderate disease
- Overall baseline characteristics were comparable between patients receiving AT-GTX-501 and subjects in the natural history cohort (n=17)

Table 1. Patient Characteristics

Patient	Sex	Age at Symptom Onset (months)	Age at Gene Transfer (months)	Duration in the Study (months)[a]	HML Score at Baseline
1	F	24	63	24.9	3
2	F	57	33	23.5	6
3	M	29	30	24.2	5
4	M	36	67	23.7	4
5	F	36	79	24.1	3
6	M	42	56	23.8	5
7	M	16	19	24.7	5
8	M	42	61	24.0	4
9	F	52	71	21.5	4
10	F	42	68	21.5	3
11	F	43	47	14.9	4
12	F	24	66	13.1	4
13	M	6	50	3.0	5

Interim Efficacy Population

[a]Calculated to March 13, 2020. Patients 1-12 years of age were included in the efficacy population, which included all patients for whom ≥1 year of follow-up was available.
F=female; HML=Hamburg Motor and Language; M=male.

Safety

- At interim data cutoff on March 13, 2020, the mean duration of follow-up since gene transfer was 20.5 months (range: 3.0-24.9 months)
- A total of 165 AEs were reported among 13 patients
- The majority of AEs were mild or moderate (grade 1 or 2) and were unrelated to treatment
- The most common treatment-emergent AEs were upper respiratory tract infection, viral infection, vomiting, constipation, and hematuria (**Table 2**)
- Eleven severe (grade 3) AEs were reported in 5 patients
  - All were considered serious AEs
  - Four were considered possibly related to treatment (2 events of vomiting and 1 event each of pyrexia and upper abdominal pain; patients recovered in all cases)
- There were no grade 4 AEs or deaths
- No pattern of AEs related to AAV9 or *CLN6* transgene immunogenicity was observed

Table 2. Adverse Events Occurring in >1 Patient

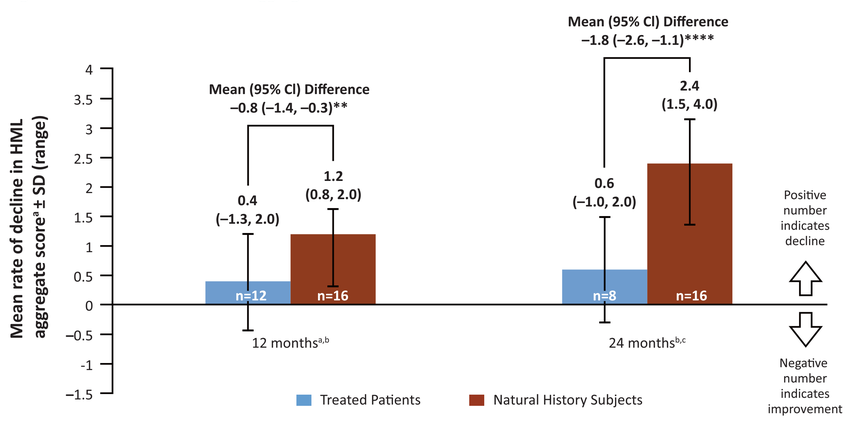
Adverse Event (N=13)	n (%)
Upper respiratory tract infection	8 (61.5)
Viral infection	6 (46.2)
Vomiting	6 (46.2)
Constipation	4 (30.8)
Hematuria	4 (30.8)
Back pain	3 (23.1)
Diarrhea	3 (23.1)
Viral gastroenteritis	3 (23.1)
Myoclonic epilepsy	3 (23.1)
Pyrexia	3 (23.1)
Respiratory disorder	3 (23.1)
Seizure	3 (23.1)
Abnormal behavior	2 (15.4)
Dehydration	2 (15.4)
Insomnia	2 (15.4)
Myoclonus	2 (15.4)
Otitis media	2 (15.4)
Streptococcal pharyngitis	2 (15.4)
Procedural pain	2 (15.4)
Rhinorrhea	2 (15.4)
Skin abrasion	2 (15.4)
Urinary tract infection	2 (15.4)

Efficacy

Rate of Decline in HML Aggregate Score

- *CLN6* gene therapy was associated with a significantly slower rate of decline in HML score among patients with *CLN6*-type Batten disease at 12 and 24 months than among natural history subjects (**Figure 3**)
  - Over 12 months, the mean rate of decline was 0.4 points in patients receiving AT-GTX-501 (n=12) compared with 1.2 points in subjects in the natural history cohort (n=16) (P<0.01)
  - Over 24 months, the mean rate of decline was 0.6 points in patients receiving AT-GTX-501 (n=8) compared with 2.4 points in subjects in the natural history cohort (n=16) (P<0.0001)

Figure 3. Rate of Decline in HML Aggregate Score

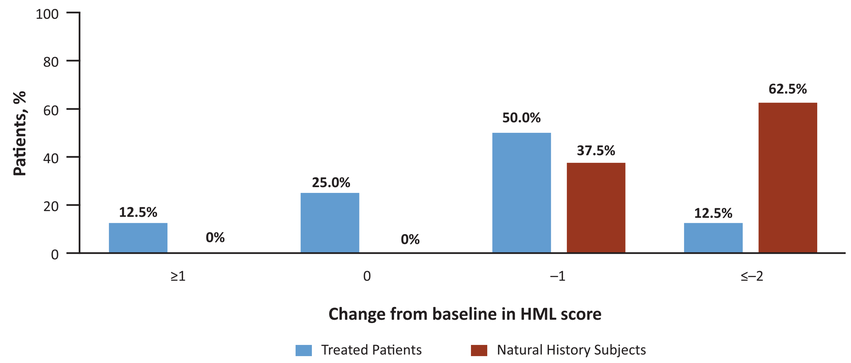


CI=confidence interval; HML=Hamburg Motor and Language; SD=standard deviation.
[a]The efficacy analysis included all patients with 12-month HML data (12 of 13 treated patients in the study). [b]12- and 24-month HML data are available for 16 of 17 subjects in the natural history cohort derived from a retrospective vLINCL6 natural history study conducted by Emily de los Reyes, MD (clinicaltrials.gov ID: NCT03285425). [c]The efficacy analysis included all patients with 24-month HML data (8 of 13 treated patients in the study). Means (ranges) of the absolute values are labeled for each column.
**P<0.001; ****P<0.0001; difference between groups was tested using a 2-sample t-test.

Proportion of Patients With 2-Point Decline in HML Aggregate Score

- Patients treated with *CLN6* gene therapy were less likely than natural history subjects to have an unreversed 2-point decline from baseline in HML score at 24 months (**Figure 4**)
  - One patient (12.5%) who received AT-GTX-501 had a 2-point decline in HML score compared with 10 natural history subjects (62.5%); a risk difference of −50% was observed (95% CI: −77.5%, −3.6%; exact P=0.0335 using the Fisher exact test)

Figure 4. Proportion of Patients With a Change in HML Aggregate Score at Month 24

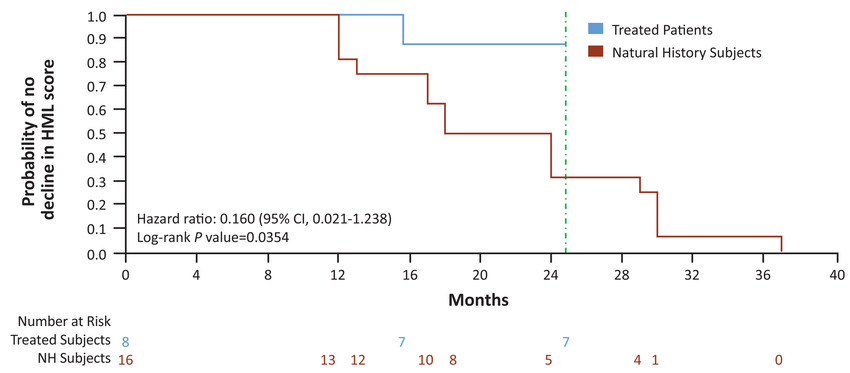


HML=Hamburg Motor and Language.

Time to Unreversed 2-Point Decline in HML Aggregate Score

- Overall, patients receiving AT-GTX-501 reached an unreversed ≥2-point decline in HML score much slower than the natural history subjects (**Figure 5**)

Figure 5. Time to Unreversed 2-Point Decline in the HML Aggregate Score

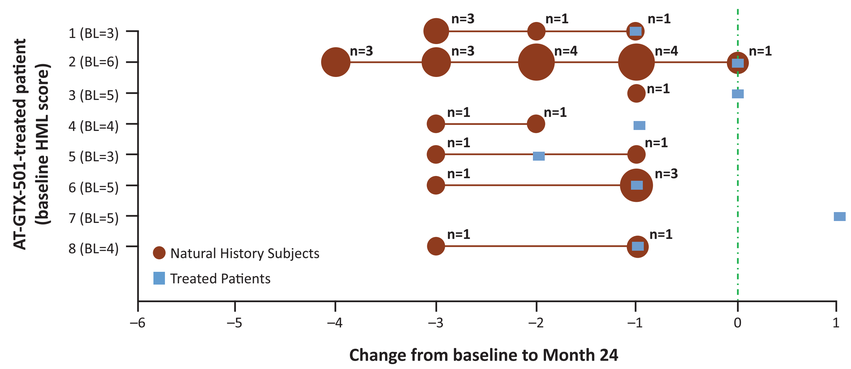


CI=confidence interval; HML=Hamburg Motor and Language; NH=natural history.
Green line indicates length of followup.

Change in HML Aggregate Score for Patients Treated With AT-GTX-501 Versus Matched Natural History Subjects

- Disease progression in patients treated with AT-GTX-501 was slower than in matched natural history subjects who had the same baseline HML score and age (**Figure 6**)

Figure 6. Change From Baseline in HML Aggregate Score at Month 24 Compared With Matched Natural History Subjects



BL=baseline; HML=Hamburg Motor and Language.
In this matched analysis, a treated subject with 24-month HML data (8 of 13 treated patients in the study) was matched with all the natural history subjects who had the same baseline HML aggregate score and age. Treated subject 7 did not have a matching natural history subject.

CONCLUSIONS

- AT-GTX-501 appears to demonstrate a meaningful treatment effect in slowing decline in HML score at 12 and 24 months in pediatric patients with vLINCL6 disease
- Interim safety and efficacy data indicate that AAV9-*CLN6* gene therapy comprising intrathecally administered AT-GTX-501 is generally well tolerated and has the potential to slow or stabilize disease progression of vLINCL6 disease

References

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Disclosure

Conflicts of Interest

ER received research grants and has been a consultant for Amicus and BioMarin. SA received salary support from Amicus and Biomarin. KM received a research grant and honoraria from Alcyone, in which she holds stock options, and received royalties for intellectual properties from Audentes and Amicus. LL attended an advisory board meeting and received a consultant fee from Amicus. CA conducted contracted research for Amicus. DLR received a consultant fee from Amicus. JC, HJ, MG, VJ, and AR are employees of and hold stock in Amicus. JB is a former employee of and holds stock in Amicus.

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