LB-10

An Open-Label, Phase 1/2a, AAV9-*CLN3* Gene Transfer Clinical Trial for Juvenile Neuronal Ceroid Lipofuscinosis

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BACKGROUND

- Pathogenic variants in *CLN3* cause juvenile *CLN3* Batten disease or classic juvenile neuronal ceroid lipofuscinosis (JNCL), a severe neurodegenerative disorder with childhood onset (between 4 and 7 years of age) that leads to blindness, motor impairment, learning difficulties, epilepsy, and ultimately premature death between 20 and 30 years of age[1]
- Currently, there is no therapy for JNCL
- Because pathogenic *CLN3* variants predominantly cause a loss or reduced level of functional protein, a promising therapeutic approach is gene transfer of corrected *CLN3*, leading to production of functional protein[2]

OBJECTIVE

- To report preliminary results from the first clinical gene therapy study (AT-GTX-502; NCT03770572) of classic JNCL currently underway to evaluate the safety and efficacy of *CLN3* gene transfer via an adenovirus-associated virus serotype 9 vector, an investigational therapy

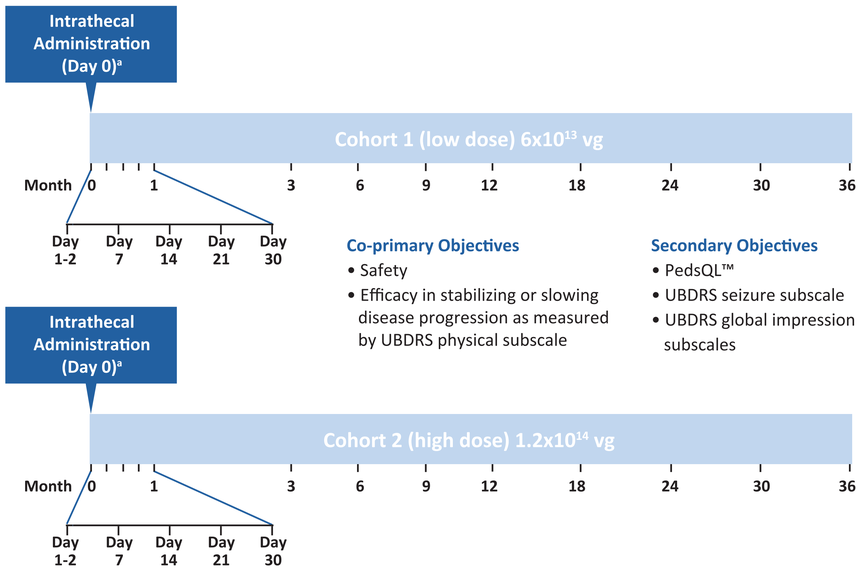
METHODS

- This open-label, dose-escalation, phase 1/2a study included a low-dose and a high-dose cohort (**Figure 1**)
  - The high-dose cohort was dosed ≥6 weeks later than the low-dose cohort to allow a safety review of the low-dose cohort
- Safety assessments included dose-limiting toxicity, adverse events (AEs), vital signs, physical and neurological examination, blood and urine laboratory parameters, electrocardiography, immunologic assessments, and viral shedding
- The Unified Batten Disease Rating Scale (UBDRS) was developed specifically for monitoring disease progression of JNCL and includes physical, behavioral, seizure, and capability subscales.[3] The primary efficacy assessment for this study was the UBDRS physical subscale (**Table 1**)
- The preliminary results are reported as descriptive data; no statistical analysis was conducted for this interim analysis
- The data cutoff date was August 11, 2020

Figure 1. Study Design

Screening
(Up to Day −30)

- Diagnosis of juvenile *CLN3* Batten disease as determined by genotyping
- Aged ≥3 to <11 years
- UBDRS physical score ≤7
- Able to walk independently for ≥50 ft



Co-primary Objectives
- Safety
- Efficacy in stabilizing or slowing disease progression as measured by UBDRS physical subscale

Secondary Objectives
- PedsQL™
- UBDRS seizure subscale
- UBDRS global impression subscales

PedsQL™=Pediatric Quality of Life Inventory; UBDRS=Unified Batten Disease Rating Scale; vg=vector genomes.
[a]Patients were administered prophylactic steroids starting on Day −1.

Table 1. UBDRS Physical Subscale

Category	Item		Scoring
Vision	• Visual acuity		• Each item scored 0-4 0 = normal (or abnormality absent) 4 = severely impaired • Bilateral items scored separately (28 items total) • Maximum total score = 112 • Higher score indicates greater physical impairment
Motor	• Gait • Hand tapping (bilateral) • Heel stomping (bilateral)	• Retropulsion pull test • Finger-to-nose dysmetria	
Speech	• Speech clarity	• Abnormal repetitive speech sounds	
Bulbar function	• Tongue protrusion		
Tone	• Tone of neck • Tone of arms (bilateral) • Tone of legs (bilateral)	• Upper extremity maximal dystonia (bilateral) • Arm strength (bilateral) • Leg strength (bilateral)	
Abnormal movement	• Appendicular chorea • Rest tremor • Action tremor • Myoclonus	• Normal spontaneous movement • Motor tics or stereotypies	

RESULTS

Baseline Characteristics

- Four subjects were enrolled in the study and received a single intrathecal injection of AT-GTX-502: 3 received 6×10[13] vector genomes (vg) (low dose) and 1 received 1.2×10[14] vg (high dose), based on quantitative polymerase chain reaction
- Demographic and baseline characteristics are shown in **Table 2**

Table 2. Demographics and Baseline Characteristics

Dose	Subject	Sex	Genotype	Race	Age at Enrollment, months	Age at Symptom Onset, months	Duration in Study, months
Low	1	M	1-kb deletion in *CLN3* (homozygous)[a]	White	114	72	20.7
Low	2	F	1-kb deletion in *CLN3* (homozygous)[a]	White	71	36	15.6
Low	3	M	1-kb deletion in *CLN3* (homozygous)[a]	White	105	36	16.8
High	4	M	1-kb deletion in *CLN3* (homozygous)[a]	White	120	79	8.7

[a]A 1.02-kb genomic deletion in *CLN3* is the most common variant in JNCL; the deletion covers 2 exons and the flanking intronic sequence and leads to the deletion of 217 base pairs of coding sequence, resulting in a truncated protein.[2,4]

Safety

- AEs that occurred in ≥1 subjects are reported in **Table 3**
- Most AEs were mild or moderate and unrelated to AT-GTX-502
- Four AEs were considered related to AT-GTX-502; all were hepatic enzyme increases that resolved without sequelae
- There were 2 serious AEs, 1 of which was deemed AT-GTX-502-related (elevated alanine aminotransferase, grade 3) and resolved with steroid treatment after 3 months
  - The other serious AE was a grade 2 seizure, which was considered not related to treatment, but rather disease related
- There were no discontinuations in follow-up because of AEs
- There were no grade 4 or 5 (death) AEs

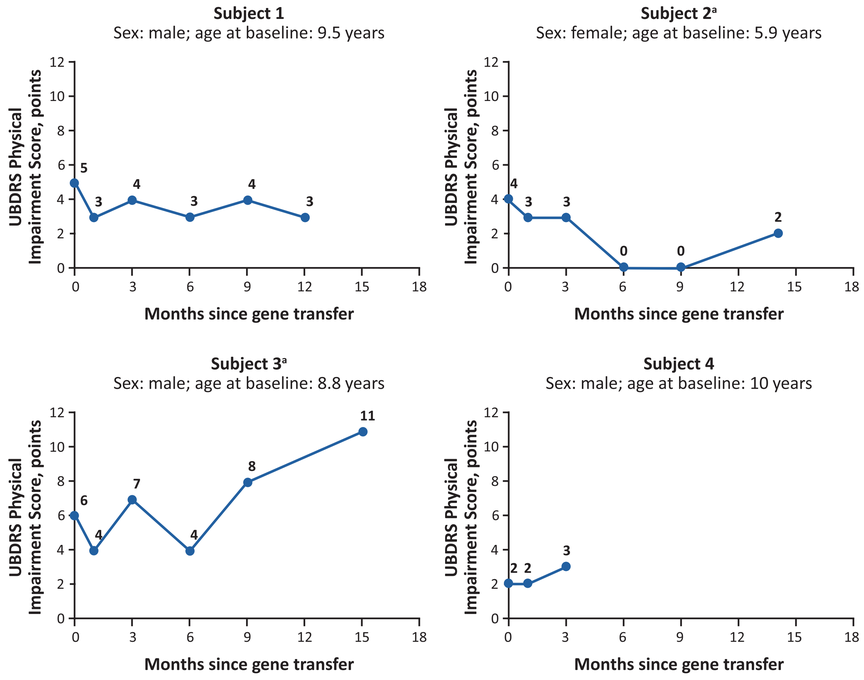
Table 3. Adverse Events Occurring in ≥1 Patient

Adverse Event (preferred term)	Patients, n	Events, n
Vomiting	4	9
Headache	4	6
Nausea	3	3
Respiratory disorder	2	4
Back pain	2	2
Cough	2	2
Hepatic enzyme increased	2	2
Sinus bradycardia	2	2

Preliminary Efficacy

- UBDRS physical impairment scores have been recorded up to month 15 for 3 subjects in the low-dose cohort (**Figure 2**)
  - The only subject in the high-dose cohort had UBDRS evaluations up to month 3

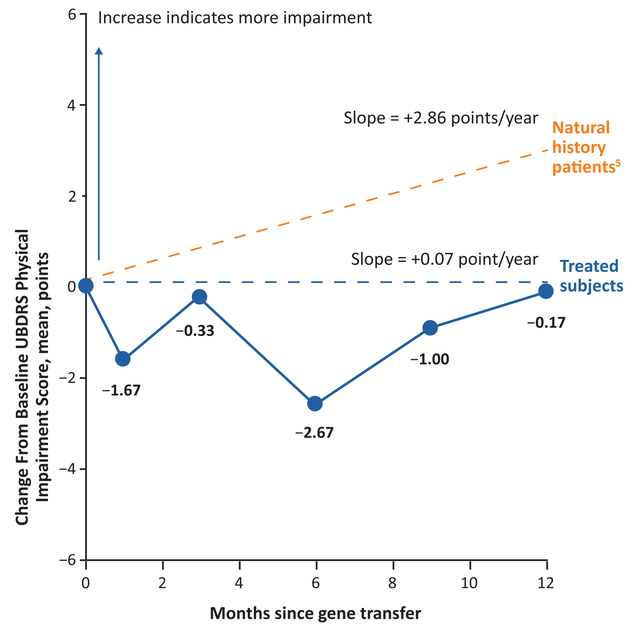
Figure 2. UBDRS Physical Impairment Score Over Time



UBDRS=Unified Batten Disease Rating Scale.
[a]Scheduled month 12 in-person UBDRS assessment was impacted by the COVID-19 pandemic.

- Mean (SD) yearly rate of change in UBDRS Physical Impairment score in the 3 subjects in the low-dose cohort was 0.07 (3.33) (**Figure 3**)
- In comparison, a historical natural history study of 82 patients with JNCL predicted an average increase of 2.86 points per year (95% CI, 2.27-3.45)[5]

Figure 3. Mean Change From Baseline In UBDRS Physical Impairment Score in 3 Subjects in the Low-Dose Cohort Compared With Patients in the Natural History Study



UBDRS=Unified Batten Disease Rating Scale.
The solid blue line shows the mean change from baseline in UBDRS Physical Impairment score in treated subjects. The dotted regression lines show the slopes of change from baseline for patients in the natural history study (orange) and treated subjects (blue), respectively.

CONCLUSIONS

- The mean yearly rate of change in UBDRS Physical Impairment score in the 3 subjects with *CLN3* Batten disease receiving 6×10[13] vg of AT-GTX-502 was substantially lower than that expected for untreated patients based on historical natural history studies (0.07 vs 2.86 points/year), suggesting potentially early signs of disease stabilization
- Preliminary results suggest that AT-GTX-502 was generally well tolerated and support further evaluation

References

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Disclosures

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