First-in-Human Intracisternal Dosing of RGX-181 (Adeno-Associated Virus 9 / Human Tripeptidyl Peptidase 1) for a 5-Year-Old Child With Late Infantile Neuronal Ceroid Lipofuscinosis Type 2 (CLN2): 6-Month Follow-up

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Background

- CLN2 Batten disease is a lysosomal storage disorder caused by biallelic mutations in the *CLN2* gene resulting in deficiency of tripeptidyl peptidase 1 (TPP1)
- Patients with CLN2 have seizures; loss of motor, language, and cognitive skills; vision loss; and premature death[1]
- Treatment involves biweekly intracerebroventricular (ICV) enzyme replacement therapy (ERT) with cerliponase alfa via an indwelling port[2]
- While ERT slows progression of motor loss, it does not stop or reverse most manifestations of the disease[2]
- RGX-181 is a recombinant adeno-associated virus serotype 9 (AAV9) NAV® vector containing a human *CLN2* expression cassette (AAV9.CB7.hCLN2) designed to induce sustained secretion of TPP1 enzyme in the central nervous system
- A recent study in *Cln2R207X* mice demonstrated that treatment with RGX-181 reduced seizures, extended lifespan, and ameliorated many of the CLN2-associated neuropathological changes[3]

Case History

- 5-year-old child with a genetic diagnosis of CLN2 and reduced TPP1 activity in leukocytes
- Refractory epilepsy despite 16 months of biweekly ERT beginning at 4 years, 3 months of age and multiple anti-epileptic medications
- Loss of skills was also observed
- Following baseline volumetric brain imaging, the child received intracisternal RGX-181 at a dose of 1.25×10^{11} genome copies/g brain mass under a single-patient investigator-initiated study
- Prednisone, tacrolimus, and sirolimus were administered per the protocol's immuno-suppressive regimen

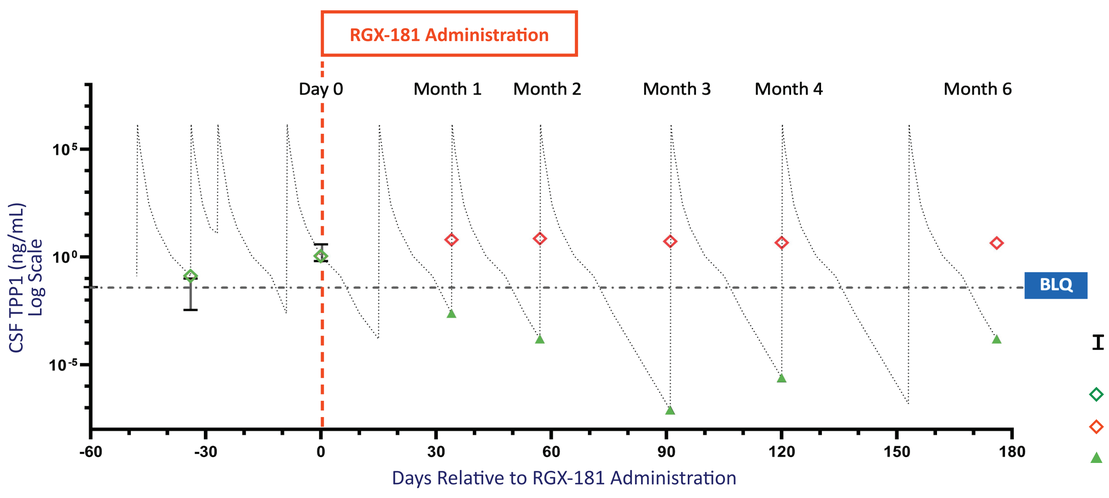
Methods

- Assessments included safety and tolerability, seizure frequency, anti-epileptic medication use, ERT use, CLN2 Clinical Rating Scale Expanded Language and Mobility (CLN2 CRS-LX and -MX) scores, and Mullen Scales of Early Learning (MSEL)
- After receiving instruction from the pediatric neurologist at the time of consent, seizure events were prospectively recorded and categorized as tonic, clonic, tonic clonic, myoclonic, or atonic by the parents
  - The pediatric neurologist subsequently reviewed the parents' report and entered the data into the medical record
- Cerebrospinal fluid (CSF) was collected via indwelling ICV port immediately before ERT infusions at the following timepoints:
  - 34 days prior to RGX-181 administration (Day -34, residual ERT-derived TPP1, 14 days post-ERT infusion)
  - Day 0 prior to RGX-181 administration procedure (residual ERT-derived TPP1, 9 days post-ERT infusion)
  - Days 34, 57, 91, 120, and 176 post–RGX-181 administration (each timepoint ≥19 days post-ERT infusion)
- All CSF samples were measured for TPP1 using electrochemiluminescence immunoassay with lower limit of quantification of 0.0400 ng/mL

Results

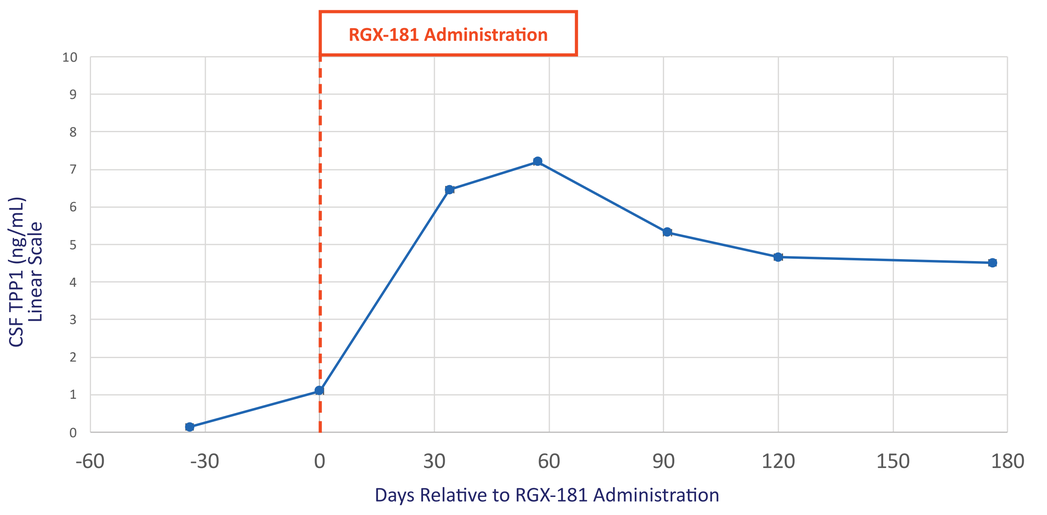
Pharmacokinetic Analysis of ERT-Derived TPP1

TPP1 in CSF Pre– and Post–RGX-181 Administration, Including Predicted Contribution From ERT



- To predict residual ERT-derived TPP1 concentrations in the CSF, nonparametric pharmaco-kinetic analysis was performed. Reported data[4,5] and patient ERT-derived TPP1 concentrations prior to RGX-181 administration were used to predict concentrations from each ERT infusion to trough based on patient's actual ERT infusion dates
- Prior to RGX-181 administration, predicted concentrations were consistent with measured residual ERT-derived TPP1 concentrations at Day -34 (0.1326 ng/mL; 14 days post-ERT infusion) and Day 0 (0.1040 ng/mL; 9 days post-ERT infusion), supporting the predicted residual ERT-derived concentrations
- Predicted residual ERT-derived TPP1 concentrations decreased to below the level of quantification (BLQ, <0.0400 ng/mL) of the assay at ≥15 days post-ERT infusion
- Thus, measured TPP1 concentrations after Day 0 were derived from RGX-181 expression

TPP1 in CSF Pre– and Post–RGX-181 Administration



35- to 55-Fold Increase in TPP1 Concentrations After RGX-181 Administration Through 6 Months

- Following RGX-181 administration, TPP1 concentrations were 35- to 55-fold higher than the measured ERT-derived concentration at Day -34, with peak TPP1 concentration at approximately 60 days and durable TPP1 expression at >4 ng/mL through 6 months
- Predicted ERT-derived TPP1 concentrations were BLQ for all post–RGX-181 administration timepoints (see pharmacokinetic graph of predicted ERT-derived TPP1 concentrations above)

Safety and Tolerability

As of June 30, 2023, 6 months post-RGX-181 administration:

- **No serious adverse events (SAEs)**
- **No adverse events (AEs) related to RGX-181 or its administration**
  - **All AEs were Grade 1 and have resolved**

Neurodevelopmental Measures

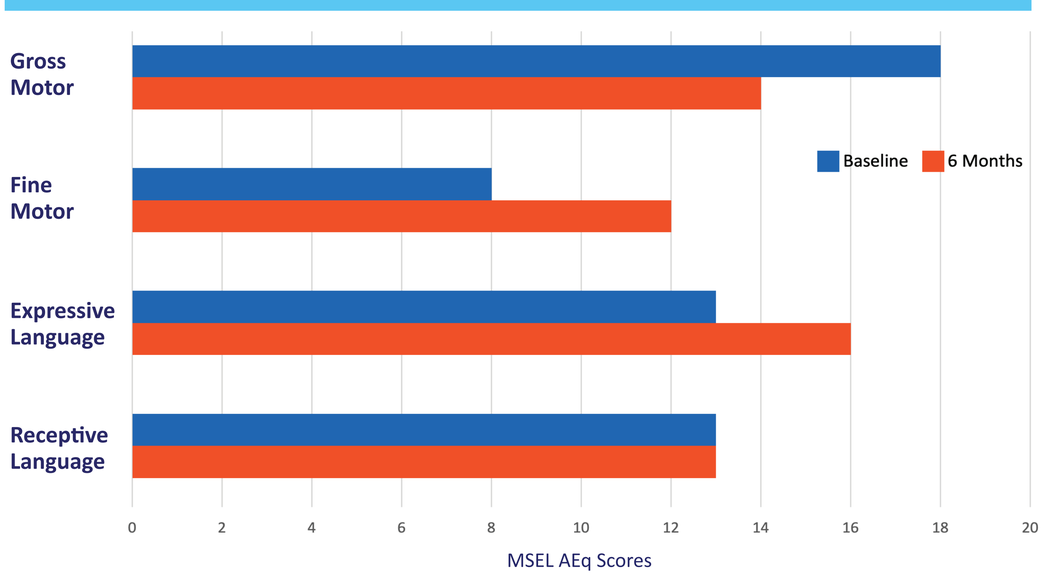
CLN2 CRS-LX and -MX Scores

Stable CLN2 CRS-LX and -MX Scores From Baseline to 6 Months

	Baseline	6 Months	Score Parameters
CLN2 CRS-LX	3	3	• CLN2 CRS-LX Score of 3 - Language limited to 5-9 intelligible words - No 2-word phrases - Single words used to direct attention and request wants and needs
CLN2 CRS-MX	4	4	• CLN2 CRS-MX Score of 4 - Walks 10 steps independently without support, may have some ataxia or instability

MSEL Age Equivalent (AEq) Scores at 6 Months

Skill Acquisition or Stability Present in the Majority of Scales at 6 Months

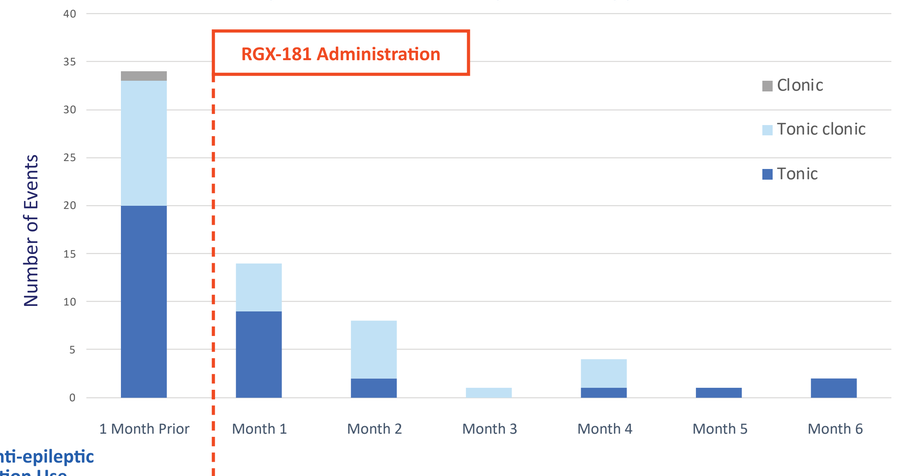


- Baseline chronological age of 6 years but developmental function between <1 and 18 months
- **Small but meaningful skill acquisition in 2 scales:**
  - **Fine Motor: increased from using 2 hands together to finger thumb opposition and pincer grasp**
  - **Expressive Language: increased from saying 1 word to using a 2-word phrase and saying 2-7 words**
- Stable AEq scores in Receptive Language and Visual Reception scales
- Function declined in the Gross Motor scale
- Visual Reception AEq not included in figure because values <1 month

Reductions in Seizure Frequency

86% Reduction in Seizure Frequency After RGX-181 Administration Through 6 Months

Monthy Seizure Count by Event Type



ERT and Anti-epileptic Medication Use	1 Month Prior	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Cerliponase alfa ERT (Brineura®)	▲ ▲	▲	▲	▲	▲	▲	▲
Lamotrigine (Lamictal®)	75 mg BID	75 mg BID	75 mg BID	--	--	--	--
Zonisamide (Zonegran®)	200 mg BID	200 mg BID	200 mg BID	200 mg BID	200 mg BID	200 mg BID	--
Clobazam	5 mg BID	5 mg am 10 mg pm	5 mg am 10 mg pm	5 mg am 10 mg pm	5 mg am 10 mg pm	5 mg am 10 mg pm	5 mg am 10 mg pm
Sodium valproate (Depakote®)	125 mg am 250 mg pm	125 mg am 250 mg pm	250 mg BID	250 mg BID	250 mg BID	250 mg BID	250 mg BID

- **Increased interval between ERT infusions from Q14 days to Q19-34 days after RGX-181 administration**
- **Concomitant withdrawal of 2 anti-epileptic medications**

Conclusions

- First-in-human administration of RGX-181 has been well tolerated without drug- or procedure-related AEs as of 6 months (June 30, 2023)
- RGX-181–derived CSF TPP1 expression:
  - **35- to 55-fold higher than measured ERT-derived concentrations (14 days post-ERT) prior to RGX-181 administration**
  - **Sustained over 6 months**
- Seizure frequency:
  - **86% reduction after RGX-181 administration through 6 months**
  - **Concomitant withdrawal of 2 anti-epileptic medications**
  - **Increased interval between ERT infusions**
- Neurodevelopmental measures:
  - **Stable CLN2 CRS-LX and -MX scores**
  - **Meaningful improvements in fine motor and expressive language skills at 6 months on MSEL**
- Observation and data collection are ongoing

1. Kohlschütter A, et al. *CNS Drugs*. 2019;33(4):315-325.
2. Schulz A, et al. *N Engl J Med*. 2018;378(20):1898-1907.
3. Takahashi K, et al. *J Clin Invest*. 2023;133(12):e165908.
4. Kim A, et al. *Clin Transl Sci*. 2021;14(2):635-644.
5. Hammon K, et al. *Clin Transl Sci*. 2021;14(5):1810-1821.