# RGX-381: First-in-human clinical trial of an investigational AAV9 gene therapy encoding TPP1 for the treatment of ocular manifestations of CLN2 Batten disease

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## Purpose

- RGX-381 (AAV9.CB7.hCLN2) is an investigational one-time gene therapy comprising a recombinant NAV AAV9 vector that delivers a human tripeptidyl peptidase 1 (TPP1) transgene directly to the retina, potentially providing an ongoing source of secreted TPP1 to prevent progressive photoreceptor (PR) degeneration.
- A human recombinant form of this enzyme, cerliponase alfa, is approved to slow the loss of ambulation in children with CLN2 disease, although intracerebro-ventricular (ICV) delivery has been shown not to affect the ocular manifestations of the disease.[1,2]
- In preclinical studies in human CLN2-derived retinal organoids (ROs) and retina-on-a-chip (RoC), RGX-381 restored TPP1 expression and prevented or reduced accumulation of lysosomal storage material (subunit C of mitochondrial adenosine triphosphate synthase, or SCMAS) in a dose-dependent manner.[3,4]
- In nonhuman primate (NHP) studies, a single subretinal (SR) dose of RGX-381 led to elevated and sustained TPP1 concentrations in vitreous humor at multiples over wild-type over 3 months, showing no observed adverse effects at 1x10$^{10}$ genome copies (GC)/eye.[5,6]
- A human starting dose of 2×10$^{10}$ GC/eye (200 µL of 1×10$^{11}$ GC/mL concentration) was selected based on: (1) safety of SR injection of 1×10$^{10}$ GC/eye RGX-381 in NHPs; (2) correlation of the NHP data with data from human CLN2-derived ROs; and (3) allometric scaling of dose volume based on eye size to translate from cynomolgus monkeys to children.
- A first-in-human, open-label, single ascending dose study of SR RGX-381 for the treatment of ocular manifestations of CLN2 disease will commence to evaluate safety and tolerability.

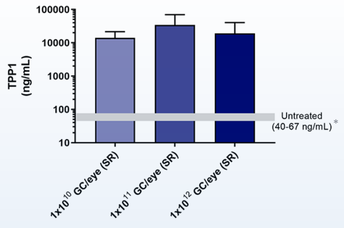
## References

1. Schulz et al, 2018
2. Clinical Review Report-Brineura, 2019
3. Kim et al. WORLD 2023 presentation
4. Kim et al. WORLD 2023 poster
5. Buss et al. WORLD 2021 poster
6. Chan et al. WORLD 2023 poster

## Preclinical Studies: NHP

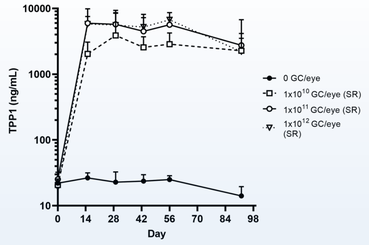
In healthy cynomolgus monkeys, a single SR dose of RGX-381 led to elevated and sustained TPP1 concentrations over 3 months in aqueous and vitreous humor at multiples over wild-type, showing no observed adverse effects at 1x10$^{10}$ GC/eye.[5]

**Increased TPP1 concentration in the vitreous humor of NHPs 92 days following RGX-381 delivery**

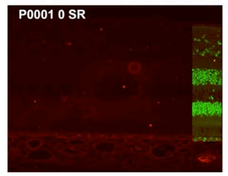



*Values from healthy NHP vitreous samples in assay qualification report

**Increased TPP1 concentration in the aqueous humor of NHPs 92 days following RGX-381 delivery**

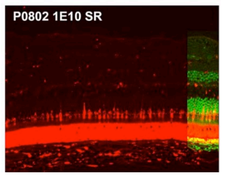



Immunostaining, optimized and counterstained with TrueBlack® to abolish background histofluorescence, demonstrated greater human TPP1 protein presence in widespread areas of the retina treated with RGX-381 compared with vehicle-treated animals.[5]



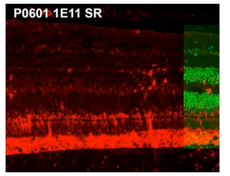

**Vehicle**

Minimal TPP1 immunoreactivity across the retina



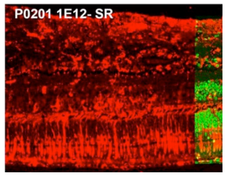

**1×10$^{10}$ GC/eye**

Intense TPP1 immunoreactivity in the retinal pigment epithelium (RPE), a proportion of the PR outer segments and only occasional labeling of horizontal or amacrine cells




**1×10$^{11}$ GC/eye**

More evident TPP1 immuno-reactivity in the RPE, PR outer segments, and occasional horizontal or amacrine cells

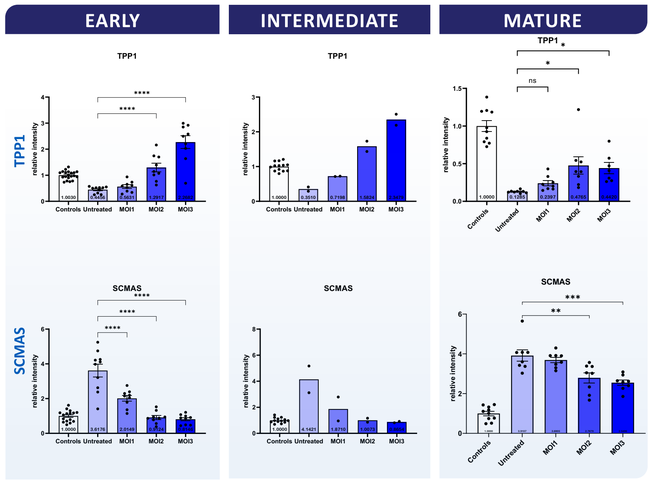



**1×10$^{12}$ GC/eye**

Intense TPP1 immunoreactivity across the entire depth of the retina

## Preclinical Studies: In Vitro CLN2 Retinal Model

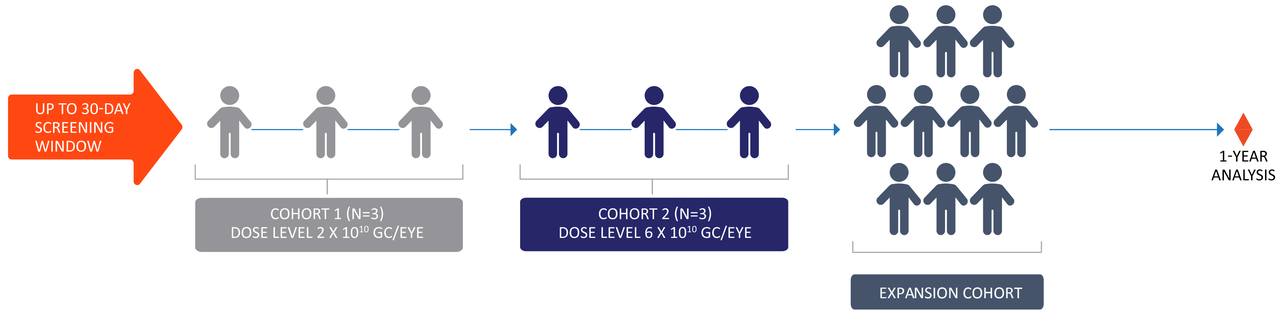

In human CLN2-derived ROs and RoC, RGX-381 restored TPP1 expression and prevented or reduced accumulation of lysosomal storage material in a dose-dependent manner.[3,4]
RO results are shown below.




* p < 0.1, ** p < 0.01, *** p < 0.001, **** p < 0.0001
SCMAS: subunit C of mitochondrial adenosine triphosphate synthase, a storage material that accumulates in CLN2 disease
TPP1: tripeptidyl peptidase 1, the deficient enzyme in CLN2 disease

## RGX-381-1102 First-in-Human Clinical Trial Design

**Open-label, single ascending dose**




### TRIAL DESIGN

- 2 dose cohorts of 3 patients each, with staggered enrollment for safety evaluations, followed by an expansion cohort
- Fellow eye control
- SR administration
- Duration: 1 year

### KEY INCLUSION CRITERIA

- Biallelic CLN2 mutations with decreased leukocyte TPP1 activity
- Age ≥12 months and ≤144 months
- Currently receiving ICV cerliponase alfa
- Meets retinal thickness and visual acuity criteria

### KEY ENDPOINTS

- Primary: Safety
- Secondary: Change in photoreceptor parameters measured on optical coherence tomography (OCT), TPP1 expression measured in aqueous humor, vector shedding
- Exploratory: Change in visual function and functional vision measures, immunogenicity