Efficacy and Safety of a Novel RPGR^{ORF15} Gene Therapy (FT-002) for the Treatment of RPGR-Associated XLRP

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Introduction

X-linked retinitis pigmentosa (XLRP) is a rare inherited retinal disease manifesting as impaired night vision and peripheral vision loss that progresses to legal blindness. One of the most common causes of XLRP is pathogenic variants in the retinitis pigmentosa guanosine triphosphatase regulator (*RPGR*) gene. Unfortunately, treatments for *RPGR*-XLRP are currently not available.

Frontera developed FT-002, a AAV2/5 based vector, carrying a codon-optimized hRPGR^{ORF15} gene under the control of a GRK1 promoter to rescue the functional and structural loss of the photoreceptor cells and improve visual function via subretinal administration. Vector design is shown in Figure 1.

Here, we evaluated the *in vitro* transduction efficiency of FT-002 and polyglutamylated hRPGR-ORF15 protein in CHO-K1 cells, the efficacy and biodistribution of subretinal delivered FT-002 at 5.80×10^7, 1.83×10^8 and 5.80×10^8 vg/eye in *Rpgr*-deficient mice, and the safety of FT-002 in a GLP compliant 13-week study in cynomolgus monkeys. The preclinical results demonstrate that FT-002 is a promising AAV gene therapy to treat RPGR-associated XLRP patients and is currently advancing into Ph I/II clinical study in China.

Figure 1. Structure of FT-002 Vector Genome. FT-002 consists of the human retinitis pigmentosa GTPase regulator ORF5 isoform (hRPGRORF15) expression cassette flanked by two ITRs. The hRPGRORF15 expression cassette starts with the GRK1 promoter and SV40 intron, followed by a codon optimized hRPGRORF15 coding DNA, and ends with the SV40 poly(A) signal.

Result

In vitro, FT-002 efficiently expresses polyglutamylated hRPGR-ORF15 protein in the CHO-K1 cells in a dose-dependent manner

FT-002 efficiently expressed a dose-dependent hRPGR-ORF15 protein at day 3 after transduction in CHO-K1 cells using western blot, which can be polyglutamylated to functional form.

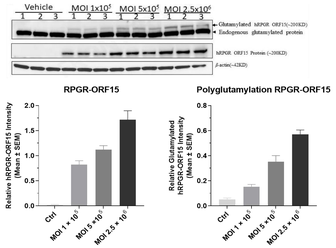

Figure 2. Expression of functional hRPGR-ORF15 after transducing CHO-K1 cells with FT-002 at different MOIs

FT-002 significantly preserved retinal structure and rescued the function of photoreceptor cells of *Rpgr*-deficient mice in a dose dependent manner

In *Rpgr*-deficient mice, FT-002 significant rescued ONL thickness (Figure 3), and increased ERG amplitudes at both scotopic and photopic waves which resulted in the improvement of retinal function (Figure 4).

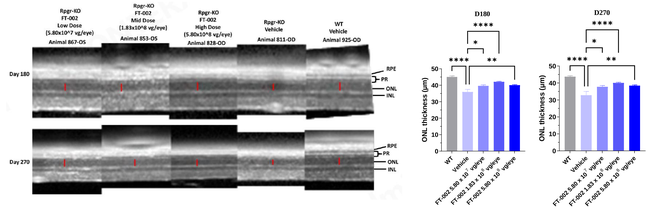

Figure 3. Measurement of ONL thickness and representative OCT Images on D180 and D270 post-dose

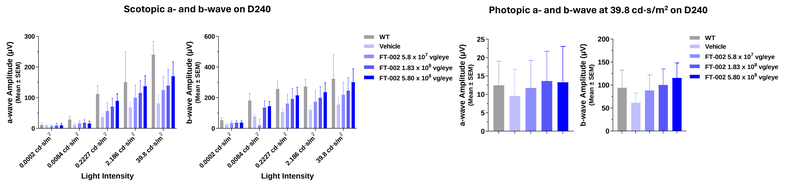

Figure 4. Scotopic and Photopic a- and b-wave ERG amplitudes on D240 post-dose

Biodistribution of FT-002 in *Rpgr*-deficient mice and NHPs

In *Rpgr*-deficient mice, FT-002 efficiently transduced the ONL of the retina, resulting in a persistent expression of hRPGR-ORF15 protein (up to Day 270 post injection), and a time-dependent progressive rescue of rhodopsin mis-localization in the inner segment (IS) of the photoreceptor layer.

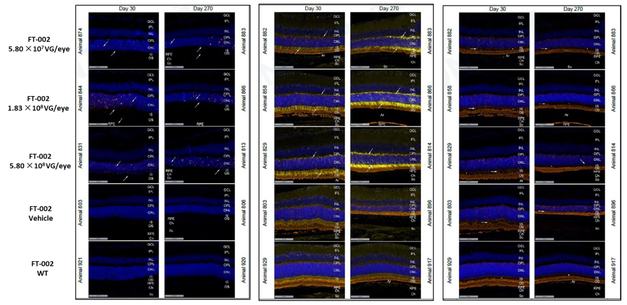

Figure 5. Representative images of FT-002 VG DNA by FISH staining, hRPGR-ORF15 protein detection (yellow, indicated by arrows) and correction of rhodopsin mis-localization (arrows) by IF in mice

In NHPs, copies of RPGR gene were primarily distributed in ocular tissues including sclera, retina, and choroid in a dose dependent manners, and persisted to D92

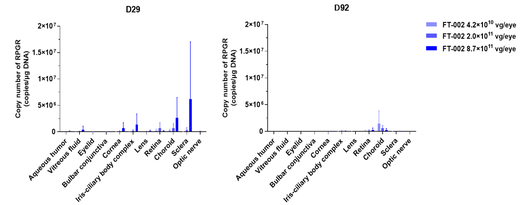

Figure 6. Copy number of RPGR gene detected in ocular tissues of NHPs on D29 and D92

GLP-compliant NHP tox study established well-tolerated doses of FT-002

A single dose toxicity of FT-002 at 4.2×10^{10}, 2.0×10^{11} and 8.7×10^{11} vg/eye were assessed by subretinal injection to cynomolgus monkeys with a 4 & 13-week recovery period.

- All animals were well tolerated, and no adverse systemic clinical signs were observed.
- Ophthalmic abnormalities including intraocular inflammation, structural changes in the covered area of fundus liquid and his-pathological changes of local retina were noted at 4W post-dose, and recovered or showed a recovery trend at 13W post-dose, which were considered to be not toxicological significant because of the lack of obvious effect in retinal function (ERG amplitude).
- NOAEL was determined at 2.0×10^{11}vg/eye.

Conclusion

- Subretinal administration of FT-002 led to a preservation of retinal function and structure in *Rpgr*-deficient mice.
- Subretinal administration of FT-002 was well tolerated by NHP subjects.
- The comprehensive preclinical assessment demonstrated that subretinal delivery of FT-002 allowed for the hRPGR-ORF15 expression in retina that provided therapeutic benefit for the treatment of RPGR-associated XLRP patients, supporting the initiation of Ph I/II clinical study.

Acknowledgement

We thank Qilin Gu, Jessica Nguy, and Jiayue Zhang for their contributions in the early stage of development. We thank Pengcheng Zhou for his contribution in the preclinical studies. Pharmaron conducted the efficacy study in Rpgr-deficient mice. JOINN (Suzhou) ran the GLP-compliance NHP study.