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Preliminary Safety and Efficacy Results from a Pilot Gene Therapy Study of FT-002 in Subjects with RPGR Gene Mutation associated X-linked Retinitis Pigmentosa (XLRP)

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Introduction and Objective

Disease Background: X-linked Retinitis Pigmentosa (XLRP) is a severe form of RP, characterized by night blindness, decreased visual acuity, progressive deterioration of the peripheral visual field and eventually becoming legal blind after 40s. Variants in the retinitis pigmentosa GTPase regulator (RPGR) gene account for more than 70% cases of XLRP and around 15% cases of all RPs. Mutation of *RPGR^{ORF15}* can lead to truncation of RPGR^{ORF15} protein and damage or loss of its function, resulting in mislocalization of opsin to the photoreceptor inner segment or endoplasmic reticulum, which in turn causes failure of photoreceptor cells to perform physiological functions. Prevalence of RPGR-XLRP patients is estimated to be 3.4-4.4/100,000 in males, with an estimate of 20,000 patients in the US and Europe, and 50,000 patients in China.

FT-002 is a recombinant adeno-associated virus type 5 vector codon optimized *hRPGR^{ORF15}* protein coding gene (rAAV5-*hRPGR^{ORF15}*), potentially to restore function of the *RPGR^{ORF15}* protein after transfection. FT-002 is produced by Baculovirus Expression Vector System.

Objective: To investigate safety, tolerability and preliminary efficacy of FT-002 in subjects with RPGR gene mutation associated XLRP.

Methods

Study Design:

- It's an open label, dose escalation study with FT-002 dose levels of 5×10^{10} vg/eye, 10×10^{10} vg/eye and 20×10^{10} vg/eye evaluated.
- 18 subjects were enrolled in this pilot study (6 in each dose cohort) and received a single dose of FT-002 via subretinal injection for the study eye.

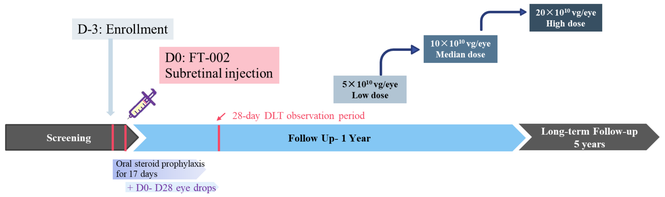

Figure 1 Overall Study Design

All participants will be followed up for 5 years with safety and efficacy evaluated. Efficacy was mainly assessed by improvement of retinal sensitivity, visual acuity and visual functional, measured by Microperimetry, Best-Corrected Visual Acuity (BCVA, ETDRS chart) and Mobility Test (ORA-VNC^{TM}), respectively.

Results

Baseline characteristics and follow-ups:

All enrolled 18 subjects were males diagnosed of RPGR gene mutation associated XLRP, with mean age 30 years old. Till March 31, 2024, in the low dose cohort, 4 subjects completed D364 visit, 1 subject completed D168 and 1 subject withdrew after D84 due to personal reason; all subjects completed D168 in the medium dose cohort; all subjects completed D84 in the high dose cohort. Baseline characteristics of subjects in each cohort were summarized in **Table 1**.

Table 1 Baseline characteristics of enrolled subjects

Parameters Mean (SD)	Low dose (n=6) (5×10^{10} vg/eye)	Medium dose (n=6) (10×10^{10} vg/eye)	High dose (n=6) (20×10^{10} vg/eye)	Total (n=18)
Mean Age (years)	34.8 (5.9)	27.8 (5.3)	27.3 (7.2)	30 (7.1)
BCVA (ETDRS letters)	50.8 (11.8)	64.2 (7.0)	56.7 (5.5)	58.3 (6.0)
Microperimetry-68 sites (dB)	4.3 (4.7)	5.4 (2.7)	3.9 (2.0)	4.5 (3.4)
Ora-VNC Mobility Test Score	ND	4.0 (1.2)*	3.2 (1.7)*	3.5 (1.6)

*4 subjects in medium dose and 6 subjects in high dose conducted the Ora-VNC Mobility test. Subject 016 in the high dose cohort failed LCVNC and was tested under HCVNC model, not included in the analysis.

Safety:

FT-002 was safe and well tolerated in all 18 subjects, with no DLT/SUSAR/Death/Ocular SAE observed. Nine TEAEs in 6 subjects were considered possibly related to FT-002, seven of those are signs of ocular inflammation but controllable via topical use of steroid. No dose-dependent manner was observed as per AE frequency (**Figure 2**).

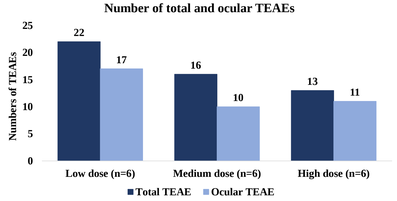

Figure 2 Number of Total and Ocular TEAEs in Each Dose Cohort

Efficacy:

Subjects in medium and high dose cohorts showed significant improvement in retinal sensitivity in the treated eye, measured by microperimetry. In the 68 Loci grid, a mean improvement of 2.02 dB on D84 and 2.48 dB on D168 was observed in the medium dose cohort, and a mean improvement of 1.42 dB on D84 was observed in the high dose cohort (**Figure 3A**). In medium dose, 2/6 (33.3%) and 3/6 (50%) subjects achieved ≥5 loci with ≥7 dB pointwise improvement in microperimetry on D84 and D168 respectively, and 3/6 (50%) subjects achieved ≥5 loci with ≥7 dB improvement in the high dose cohort on D84 (**Figure 3B**).

Trend of improvement in visual function in the treated eye was observed. In medium dose cohort, 2/4 (50%) had one light level improvement on D84 by Mobility Test, and 3/4 (75%) had one light level improvement on D168. In high dose cohort, 3/6 (50%) had one light level improvement on D84. (**Figure 3C and 3D**)

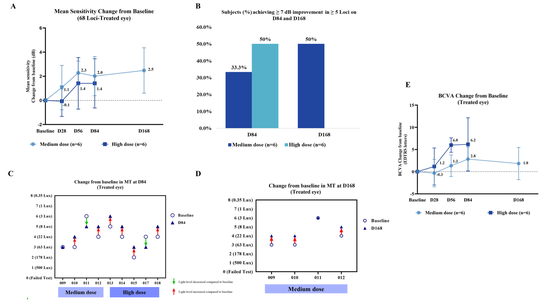

Figure 3 Efficacy Evaluation in Microperimetry, Mobility Test and BCVA

Trend of improvement in visual acuity has also been observed. In high dose cohort, a mean improvement of 6 EDTRS letters in BCVA in the treated eye was observed on D56 and maintained till most recent visit, D84. (**Figure 3E**).

Conclusion

FT-002 is safe and well tolerated in subjects with RPGR gene mutation associated XLRP. After one time's subretinal administration, significant improvement in retinal sensitivity was seen in the medium and high dose cohort, evaluated by microperimetry; a trend of improvement was seen in visual acuity and visual function, quantified by BCVA and Mobility Test score improvement.

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