B0245

Safety and Efficacy of a Novel Gene Therapy Drug (FT-001) for the Treatment of RPE65 Biallelic Variation-associated Retinal Degeneration

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Introduction and Objective

Inherited Retinal Dystrophy (IRD) is a group of genetical retinal disorders that can cause progressive vision loss due to the degeneration in photoreceptors or retinal pigment epithelium (RPE) cells. IRD due to RPE65 mutations includes a group of serious and sight-threatening genetic retinal diseases, where Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP) are the most common clinical diagnosis characterized by night blindness, progressive deterioration of the peripheral visual field and visual acuity reduction. FT-001, developed by Frontera Therapeutics (Shanghai) Co., Ltd., is recombinant adeno-associated virus type 2 vector containing codon-optimized hRPE65 protein coding gene (rAAV2-hRPE65) produced Baculovirus Expression Vector System. Objective of this phase I/II study (NCT05858983) was to investigate safety, tolerability and efficacy of FT-001 in subjects with RPE65 biallelic variation-associated retinal degeneration.

Methods

Phase I Study:

- Dose escalation study with dose levels 1.5E10 vg/eye, 7.5E10 vg/eye and 15E10 vg/eye evaluated.
- 9 subjects were enrolled in Phase I (3 in each dose group) and received a single dose of FT-001 via subretinal injection for the first eye.

Phase II Study:

- Contralateral eye injection of subjects who participated in Phase I.
- 5 subjects met eligibility criteria and received contralateral eye administration of FT-001 15E10 vg/eye.

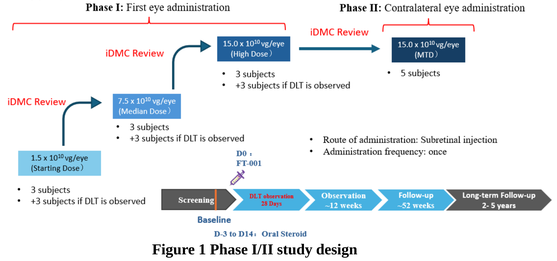

Figure 1 Phase I/II study design

All participants will be followed up for 5 years with safety and efficacy evaluated. Efficacy was mainly assessed by improvement of visual function and retinal sensitivity, measured by Mobility Test (ORA-VNC^{TM}) and Full-field Stimulus Test (FST), respectively.

Results

Baseline Characteristics and Follow Ups: Among the 9 enrolled subjects, 6 of them were diagnosed of LCA2 while 3 were diagnosed of RP, and 6 of them were males while 3 were females with mean age 26.2 years old (ranging from 10 to 43). All 9 subjects completed the phase I study with the longest follow ups over 1 year and 5 subjects of them who entered phase II have all completed D56 with the longest follow-up up to D84.

Safety Profile: FT-001 demonstrated a good safety and tolerability profile in all dose cohorts, with no DLT observed. In phase I, 7 TEAEs in 4 subjects were considered possibly related to IP: cataract reported in 2 subjects, ocular inflammation reported in 2 subjects (controllable with topic use of steroid) and 1 retinal detachment. Majority (83.3%) of IP-related AEs were ≤ grade 2. In phase II, no SAE or IP-related TEAE was observed so far.

Phase I Efficacy: Mobility Test (MT) score in the study eye improved significantly since D28 after receiving FT-001, and the effect continued until the most recent visit, with the longest follow-up to D255 (MT was performed in all 6 subjects in medium and high dose cohorts). On D84, the mean score of the study eye in the medium and high dose cohorts increased by 3.3 and 3 light levels compared to baseline (**Table 1**), and the number of subjects with ≥2 levels' improvement from baseline was 100% (Figure 2A). Up to their longest follow ups, a mean improvement of 3 light levels was observed among all 6 subjects, and the number of subjects with ≥2 levels' improvement from baseline was 83.3% (**Figure 2B**). For biliteral eye performance, a mean score increased by 2.3 light levels was observed on D84 (**Figure 3C**), and 2.1 light levels up to the longest follow ups (**Figure 3D**).

Table 1: Phase I Mobility Test Score Improvement from Baseline (Study Eye)

	D28	D56	D84*
Medium Dose（n=3）	2.0±1.00	3.0±1.73	3.3±2.31
High Dose（n=3）	2.3±1.15	2.7±2.08	3.0±1.73
Total (n=6)	2.2±0.98	2.8±1.72	3.2±1.83

*Means on days after D84 were not reported as 5 subjects entered phase II and no longer followed the visit schedule for phase I.

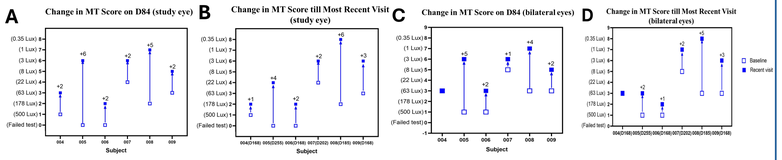

Figure 2 Mobility Test Score (Study Eye & Bilateral Eyes) in Phase I Study

Retinal sensitivity measured by FST performance showed an improvement in all dose cohorts in the study eye since D28, with a mean improvement of 1.36 log units, 1.74 log units and 2.01 log units in low, medium and high dose cohort, respectively on D84 (**Table 2**). Seven subjects were observed FST improvement under white light condition since D28 and maintained till their latest visit (**Figure 3**). Similar effects were observed under blue light condition.

Table 2: Phase I FST Improvement from Baseline under White Light [-Log10(cd.s/m2)] (Study Eye)

	D28	D56	D84*
Low Dose (n=3)	1.537±1.037	0.880±1.098	1.357±1.433
Medium Dose（n=3）	1.224±1.565	2.063±2.997	1.737±1.514
High Dose（n=3）	1.627±1.130	2.363±1.025	2.006±2.154
Total (n=6)	1.463±1.111	1.769±1.809	1.700±1.525

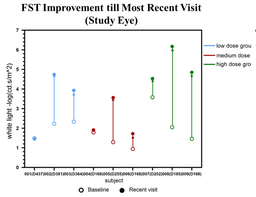

Figure 3 Individual FST Improvement in Phase I

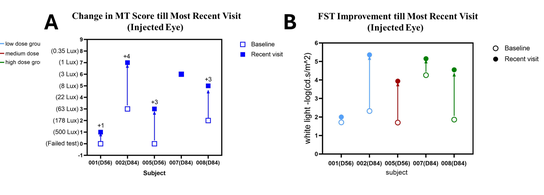

Figure 4 MT score and FST Improvement in Phase II

Phase II Efficacy: Up to the latest visit, 4 out of 5 subjects had an improvement in MT score, in which 3 subjects had a ≥3 light levels' improvement from baseline in the injected eye (**Figure 4A**); FST showed a similar improvement trend with 3 subjects showing > 2 log units' improvement under white light condition (**Figure 4B**). Longer follow up data will be further collected from the phase II study.

Conclusion

FT-001 was safe and well tolerated in subjects with RPE65 biallelic variation-associated retinal degeneration. After one time's subretinal administration of FT-001, subjects' functional vision and retinal sensitivity were greatly improved since week 4 and remained effective till the latest visit up to one year. FT-001 holds great promise to be an effective treatment for patients with RPE65 associated retinal degeneration.

Acknowledgement

The authors would like to thank all participants, families, clinicians, collaborators, trial managers, coordinators and technicians!