Safety and efficacy of ultevursen for the treatment of *USH2A*-associated retinitis pigmentosa

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Introduction

- Biallelic pathogenic variants in the *USH2A* gene encoding usherin are the most common cause of autosomal-recessive retinitis pigmentosa (RP) and Usher syndrome type 2[1]
- No approved treatments are currently available
- Ultevursen (QR-421a), an investigational antisense oligonucleotide, modulates skipping of *USH2A* pre-mRNA to restore functional protein synthesis of usherin, aiming to stop or reverse visual function decline in RP[2]
- *In vitro* and *in vivo* studies demonstrate that ultevursen-induced exon skipping results in restoration of usherin protein expression and functional electroretinogram responses[3]
- Below, we present the safety and efficacy of ultevursen in participants with *USH2A*-associated RP, and compare baseline structure–function correlation data from the STELLAR and RUSH2A studies

RUSH2A: An ongoing, multicenter, international, prospective, natural history study run by the Foundation Fighting Blindness Clinical Consortium

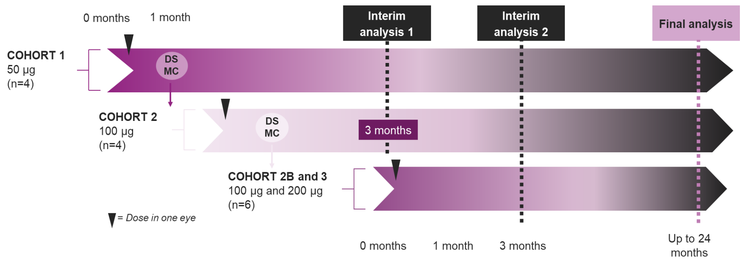
- RUSH2A is an ongoing, long-term, natural history study of 137 participants with *USH2A,* ~40% of whom have exon 13 mutations, with longitudinal data available for 103 participants
- The study is using a range of structural and functional measures to characterize the natural history of retinal degeneration in this population[4]

Methods

- STELLAR (NCT03780257) was a first-in-human, randomized, dose-escalation, sham-controlled, Phase 1b/2 study (**Figure 1**)
  - Participants received a single intravitreal ultevursen injection at a dose level of 50, 100, or 200 µg (n=14), or sham injection (n=6), administered unilaterally
  - The primary endpoint was frequency and severity of adverse events (AEs), and secondary endpoints were change in functional and structural outcome measures and serum pharmacokinetics
- Additionally, an aggregate safety analysis of participants treated with ultevursen in STELLAR and subsequent clinical studies was performed (**Figure 2**)
  - Participants who received ultevursen were followed for 72 to 1288 days
- Baseline structure–function data from STELLAR were compared with data from the RUSH2A natural history study
  - Pearson correlations are used to describe the structure–function relationships. In STELLAR, measurements in treatment and contralateral eyes are used; in RUSH2A, measurements from the study eye are used

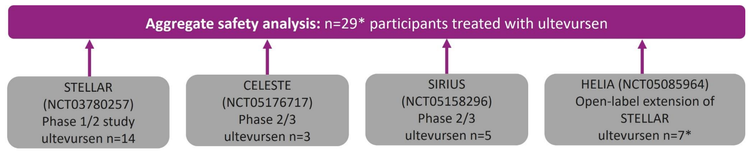
Methods (continued)

Figure 1. STELLAR and HELIA study designs



DSMC, Data Safety and Monitoring Committee.

Figure 2. Aggregate safety analysis, patient disposition



*Patients are included in the 'n' value for the study in which they were first treated with ultevursen. For certain individuals, follow-up data are captured in more than one study as patients rolled from STELLAR into HELIA.

Results

Aggregate safety analysis

- A total of 29 participants received ≥1 injection of ultevursen in ≥1 eye, with 20 participants treated bilaterally (mean age [range]: 45 [13–68] years)
- Systemic exposure to ultevursen was below the limit of quantification
- The most commonly reported AEs following treatment with ultevursen are presented in **Table 1**
- No serious ocular AEs, and no ocular AEs leading to discontinuation, were observed following ultevursen (**Table 1**). An AE of special interest (AESI), namely worsening of cystoid macular edema, was reported in one participant; no AESIs of cataract worsening or formation occurred

Table 1. Ocular adverse events occurring in ≥10% of participants treated with ultevursen (N=29)

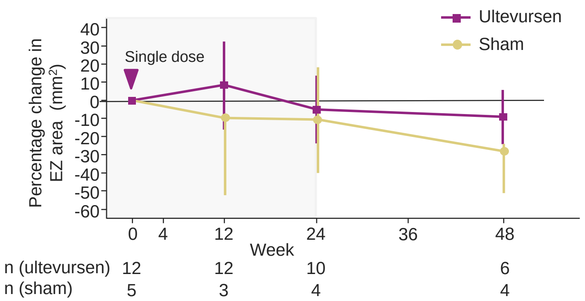
Adverse event	n (%)
Conjunctival hemorrhage	12 (41.4)
Eye pain	11 (37.9)
Lacrimation increased	5 (17.2)
Vision blurred	4 (13.8)
Conjunctival hyperemia	3 (10.3)
Eye irritation	3 (10.3)

STELLAR efficacy outcomes

- Change from baseline to Week 48 for ultevursen vs sham in the ellipsoid zone (EZ) area and microperimetry mean sensitivity (MPMS) data are shown in **Figures 3 and 4**
- Mean±SD change from baseline to Week 48 for ultevursen vs sham:
  - Best-corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study [ETDRS] letters): 2.2±4.2 vs –0.8±4.1, respectively (**Figure 5**)
  - Low luminance deficit (ETDRS letters): 0.4±3.3 vs –2.4±3.3, respectively

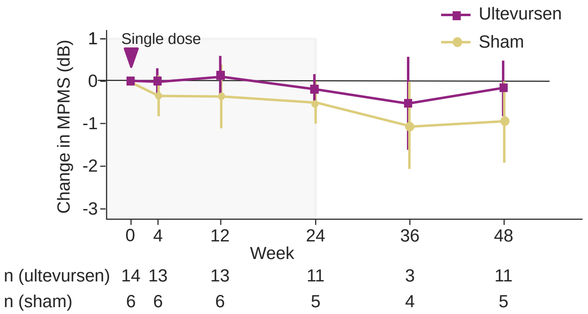
Results (continued)

Figure 3. Ellipsoid zone area: Estimated means (95% CI)



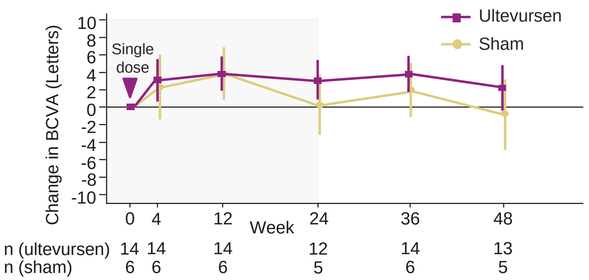
Only eyes with EZ area ≥0 are included in this analysis.
CI, confidence interval; EZ, ellipsoid zone; n, number.

Figure 4. Microperimetry mean sensitivity: Estimated means (95% CI)



CI, confidence interval; MPMS, microperimetry mean sensitivity; n, number.

Figure 5. BCVA: Estimated means (95% CI)



BCVA, best-corrected visual acuity; CI, confidence interval; n, number.

Comparison of STELLAR and RUSH2A

- Baseline characteristics from STELLAR are presented in **Table 2**, alongside corresponding data from RUSH2A[5]

Results (continued)

Table 2. Baseline characteristics from the STELLAR and RUSH2A studies

	STELLAR		RUSH2A (primary cohort)[5*]
	Ultevursen	Sham	
n	14	6	103
Mean age (years)	48	43	37
Female sex (n)	10	2	58
Disease type (%)			
nsRP/Auto Dom RP	50	67	38
Usher syndrome Type 2	50	33	62
Best-corrected visual acuity (ETDRS letters)			
Mean (SD)	64.8 (16.8)	67.0 (17.0)	80.8 (6.9)
Ellipsoid zone area (mm²)			
Mean (SD)	0.80 (0.92)	1.84 (3.44)	3.94 (5.32)
Median (min, max)	0.48 (0.0, 2.9)	0.54 (0.0, 8.9)	1.90 (0.0, 28.3)
Microperimetry mean sensitivity (dB)			
Mean (SD)	3.42 (1.77)	4.93 (5.28)	5.98 (4.99)
Median (min, max)	3.30 (0.3, 6.9)	3.15 (1.2, 15.4)	4.07 (0.3, 22.8)
Static perimetry mean sensitivity (dB)			
Mean (SD)	5.45 (4.13)	5.80 (2.72)	11.84 (5.74)
Median (min, max)	4.50 (0.8, 13.8)	4.70 (3.3, 10.3)	11.46 (2.5, 24.5)

*In the RUSH2A cohort, 'n' numbers vary in each analysis: BCVA n=104, EZ area n=102, MSMP n=89, MPSP n=99. Age, gender and disease type have been published previously[6]

Baseline Structure-Function correlation

- Although the Stellar population was somewhat more advanced that the RUSH2A population, baseline **correlations** between BCVA, EZ area, MPMS and static perimetry mean sensitivity (SPMS) were similar between the STELLAR and RUSH2A studies

Conclusions

- In 29 individuals with *USH2A*-associated RP, ultevursen had a favorable safety and tolerability profile to date
- A single injection of ultevursen in STELLAR showed trends toward stabilization of retinal structure and function compared to sham, with EZ emerging as a potential early structural biomarker for progression of *USH2A*-associated RP
- Baseline correlations between BCVA, EZ, MP and SP were similar in the STELLAR and RUSH2A study populations, suggesting that data from the RUSH2A study may be suitable as a natural history comparator arm for ultevursen data
- The safety and efficacy of ultevursen are being further evaluated in LUNA (NCT06627179), an ongoing Phase 2b study

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Disclosures for first author

Paul Yang has commercial relationships with 4D Molecular Therapeutics, AAVantarde Bio, Adverum, Astellas, Beacon Therapeutics, BlueRock Therapeutics, Eluminex Biosciences, Foundation Fighting Blindness, Janssen, MieraGTx, Nanoscope Therapeutics, Saliogen, and TeamedOn.

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