Poster #A0075

Interim Results from the PRISM Randomized Phase 2 Dose Expansion Trial Evaluating 4D-150 in High Anti-VEGF Need Individuals with Neovascular (Wet) Age-Related Macular Degeneration

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Background and Rationale

- Neovascular (wet) age-related macular degeneration (nAMD) is a degenerative retinal disease and a leading cause of irreversible visual impairment in adults >50 years of age
- Repeated injections of anti-vascular endothelial growth factor (VEGF) agents slow vision loss in the majority of treatment-compliant patients; however, many patients fail to maintain initial therapeutic benefits owing to noncompliance with the burdensome treatment regimen
- 4D-150 is an intravitreal (IVT) genetic medicine comprising the retinotropic AAV vector R100 and a dual-transgene cassette containing a codon-optimized sequence encoding aflibercept and an miRNA sequence targeting VEGF-C (figure 1)

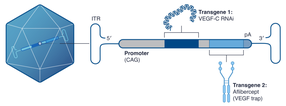


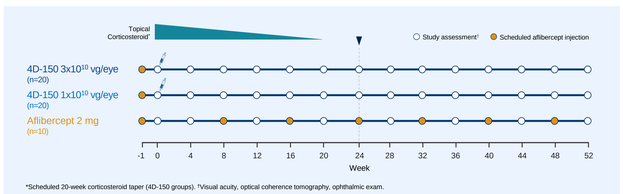
Figure 1. 4D-150 gene therapy product design.

- In a Phase 1 dose exploration study, IVT administration of 4D-150 ($6x10^9$–$3x10^{10}$ vg/eye) to adults with nAMD and a need for frequent anti-VEGF injections was well tolerated and resulted in durable clinical activity
- Here we report initial results from the PRISM randomized phase 2 dose expansion study

Methods

Study Design

- PRISM is a multicenter, Phase 1/2 open-label dose exploration and randomized dose expansion study evaluating 4D-150 (NCT05197270)
- In the PRISM Phase 2 dose expansion stage, eligible participants were randomly assigned (2:2:1) to receive a single IVT injection of 4D-150 ($3×10^{10}$ or $1×10^{10}$ vg/eye) or IVT aflibercept 2 mg administered every 8 weeks (figure 2)



*Scheduled 20-week corticosteroid taper (4D-150 groups). †Visual acuity, optical coherence tomography, ophthalmic exam.

Figure 2. PRISM Phase 2 dose expansion study diagram.

Key Eligibility Criteria

- Study eye macular neovascularization secondary to AMD
- Best corrected visual acuity (BCVA) of 34–83 letters (Snellen 20/200–20/25)
- Central subfield thickness (CST) ≥325 μm ***and*** presence of intraretinal/subretinal fluid
- ≥6 anti-VEGF injections during the prior 12 months

Study Outcomes

- Primary: Incidence and severity of adverse events
- Secondary: Annualized number of supplemental anti-VEGF injections, change from baseline in BCVA, and change from baseline in CST

Criteria for Supplemental Anti-VEGF injection

- BCVA: Loss of ≥10 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters from the average of the Day –7 and Day –1 values attributable to intra- or subretinal fluid, ***or***
- CST: ≥75 μm increase from the average of the Day –7 and Day –1 values, ***or***
- New vision-threatening hemorrhage due to nAMD

Results

Baseline Characteristics

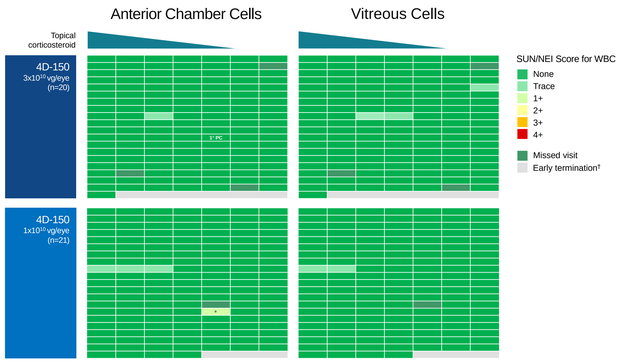
	4D-150 $3x10^{10}$ vg/eye (N=20)	4D-150 $1x10^{10}$ vg/eye (N=21)	Aflibercept 2 mg q8w (N=10)	Total (N=51)
Mean ±SD age, years	77 ±8.0	77 ±8.6	80 ±4.1	77 ±7.7
Female, n (%)	8 (40)	11 (52)	5 (50)	24 (47)
Race, n (%) White Asian	 18 (90) 2 (10)	 21 (100) 0	 9 (90) 1 (10)	 48 (94) 3 (6)
Mean ±SD time since diagnosis, years	4.0 ±3.0	2.9 ±2.2	1.9 ±1.5	3.1 ±2.5
Mean ±SD BCVA, ETDRS letters	68 ±11.3	71 ±12.4	71 ±13.2	70 ±11.9
Mean ±SD central subfield thickness, μm	429 ±89.3	465 ±114.1	419 ±64.3	442 ±96.9
Mean prior annualized injection rate*	10.0	9.9	9.0	9.8
Mean ±SD actual injections in prior 12 m*	9.9 ±2.4	9.4 ±2.1	9.3 ±0.9	9.6 ±2.0

*Includes Day -7 aflibercept injection. BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor.

- Baseline characteristics consistent with severe disease activity (mean CST, 442 μm) and high treatment burden (mean actual injections in prior 12 months, 9.6)

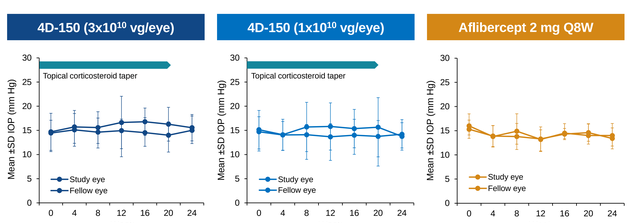
Clinical Safety

Ophthalmic Examination



*Mixed white blood cells and pigmented cells; managed with a temporary increase in topical corticosteroid dose (taper completed by Week 26). †Unrelated to study treatment.
NEI, National Eye Institute; PC, pigmented cells; SUN, Standardization of Uveitis Nomenclature.

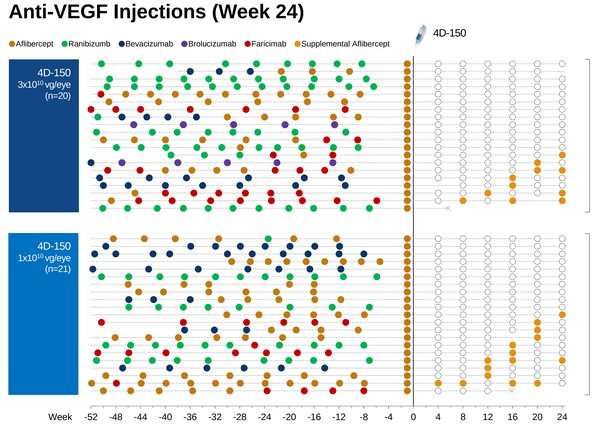
Intraocular Pressure (IOP)



- 4D-150 was safe and generally well tolerated during the initial 24 weeks of follow up
  - No 4D-150–related serious adverse events
  - No clinically significant or recurrent intraocular inflammation
  - No hypotony, endophthalmitis, choroidal effusions, or retinal vasculitis/occlusions
- 97% (38 of 39) completed the 20-week topical corticosteroid taper on schedule; no participant restarted steroids during up to 48 weeks of follow up

Clinical Activity

Anti-VEGF Injections (Week 24)

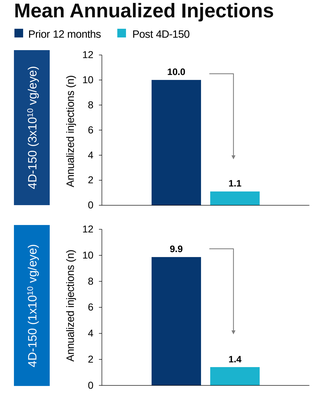


89% Reduction in annualized anti-VEGF injection rate
84% ≤1 injection
63% Injection-free

85% Reduction in annualized anti-VEGF injection rate
90% ≤1 injection
50% Injection-free

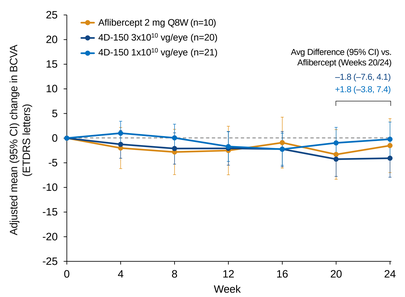
X denotes early termination (unrelated to study treatment).

Mean Annualized Injections



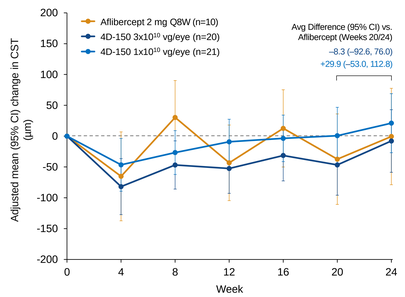
Visual and Anatomic Outcomes

Best Corrected Visual Acuity



Difference (95% CI) vs. Aflibercept	Week 20	Week 24
4D-150 ($3x10^{10}$ vg/eye):	–1.0 (–7.2, 5.3)	–2.6 (–9.3, 4.2)
4D-150 ($1x10^{10}$ vg/eye):	2.3 (–3.6, 8.3)	1.3 (–5.2, 7.8)

Central Subfield Thickness



Difference (95% CI) vs. Aflibercept	Week 20	Week 24
4D-150 ($3x10^{10}$ vg/eye):	–9.3 (–97.9, 79.3)	–7.3 (–101, 86.2)
4D-150 ($1x10^{10}$ vg/eye):	38.1 (–48.9, 125.2)	21.7 (–70.4, 113.8)

- Stable visual acuity through Week 24 in both 4D-150 dose groups
- Strong anatomic control following administration of 4D-150 $3x10^{10}$ vg/eye
  - Sustained reduction in CST through Week 24
  - Stabilization of fluctuations in central retinal thickness compared to bimonthly aflibercept injections

Baseline=Day -7. Adjusted mean, difference in adjusted mean, and 95% CI estimated from a mixed–effect model (MMRM) for repeated measures including observed data (weeks 4–24) without imputation of missing values.
CI, confidence interval; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study.

Conclusions

- 4D-150 was safe and well tolerated through Week 24 in adults with wet AMD with severe disease activity and a high anti-VEGF treatment burden
  - No 4D-150–related serious adverse events and no clinically significant or recurrent intraocular inflammation
- Stable visual acuity was observed in both 4D-150 dose groups
- 4D-150 $3x10^{10}$ vg/eye resulted in an 89% reduction in mean annualized anti-VEGF injection rate, sustained reduction in CST, and stabilization of CST fluctuations
- Initiation of Phase 3 clinical trial anticipated in Q1 2025

Disclosures (AMK): Consultant: 4DMT, AbbVie, Adverum, Alcon, Amgen, Annexin, Annexon, Apellis, Aviceda Therapeutics, Beacon Therapeutics Clearside Biomedical, Complement Therapeutics, Exegenesis, EyePoint, Fronterra Therapeutics, Genentech, Gyroscope Therapeutics, i-Lumen Scientific, Iveric Bio, Janssen, Kodiak Sciences, Kriya Therapeutics, Nanoscope, Novartis, Ocular Therapeutix, Oculis, Ocuphire, OcuTerra, Olive BioPharma, Opthea, Oxular, Oxurion, Perfuse, Ray Therapeutics, Recens Medical, Regeneron, Regenxbio, Revive, RevOpsis, Roche, Sanofi, Stealth BioTherapeutics, Thea Pharma, Unity Biotechnology, Vanotech, and Vial; Research support: 4DMT, Aviceda, Adverum, Alexion, Annexon, Apellis, Aviceda Therapeutics, Eyepoint, Exegenesis, Genentech, Gyroscope Therapeutics, Iveric Bio, Janssen, Kodiak, Neurotech, Ocular Therapeutix, Oculis, OcuTerra, Opthea, Oxular, Oxurion, Regenxbio, Roche, Vanotech, and Unity Biotechnology; Stock options: Aviceda Therapeutics, Oculis, Opthea, PolyPhotonix, Recens Medical, Perfuse, RevOpsis, and Vial; Speaker: Iveric Bio.