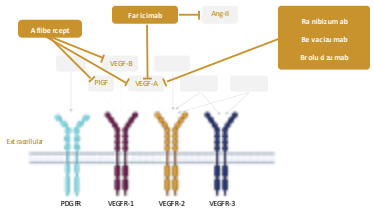
Intravitreal Axitinib Implant (OTX-TKI) for the Treatment of Retinal Vascular Diseases:

Phase 1 Data from nAMD and NPDR Trials

The following presentation discusses an investigational drug, OTX-TKI (also referred to as AXPAXLI®), in development. OTX-TKI's efficacy and safety profiles have not been established, and it has not been approved for marketing by the U.S. Food and Drug Administration (FDA) or any other health agency.

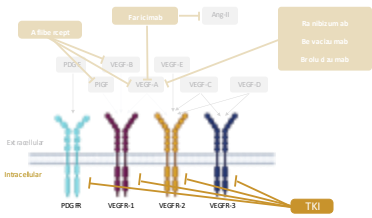
Current Anti-VEGF Therapies Selectively Target Only Extracellular VEGF ligands

Anti-VEGFs act on the extracellular side by binding selective ligands, like VEGF-A, to prevent receptor binding and pro-angiogenic activity



Axitinib Acts Intracellularly to Inhibit VEGF Receptors

TKIs bind the intracellular tyrosine kinase domains of VEGF receptors, inhibiting ATP binding and preventing activation of pro-angiogenic signaling



Axitinib: Highly Selective, Potent Pan-VEGFR Inhibitor

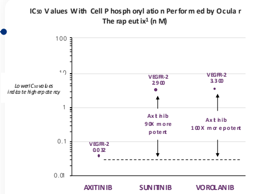
Axitinib in OTX-TKI

~100X more potent for VEGFR-2 compared with sunitinib and vorolanib[1]
- High potency allows for incorporation of smaller drug quantities into a single implant

Highly selective for all VEGF receptors
- Potentially maximizes efficacy and minimizes off-target effects
- No TIE2 inhibition at physiological tissue concentrations* via the gold standard cell phosphorylation assay performed in intact, living cells

Small molecule
- Less prone to drug-related immunogenicity

Low water solubility
- Enables optimal control of extended drug release



IC50 values for axitinib and sunitinib are **consistent with literature**[2,3]

*Following extensive protein and melanin binding in ocular tissues.
TIE2 (Tyrosine kinase with immunoglobulin-like and epidermal growth factor-like domains-2); VEGFR (Vascular endothelial growth factor receptor).
1. Unpublished data; Data on File. In vitro cell-based assays used to characterize IC50 values of axitinib for receptors VEGFR (using HUVECs), PDGFR-Beta (immune fibroblast cells) and a non-target receptor TIE2 (utilizing CHO cells). 2. Hu-Lowe DD, et al. Clin Cancer Res. 2008;14(22):7272-7283. 3. McTigue M, et al. Proc Natl Acad Sci USA. 2012;109(45):18281-18289.

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Hydrogel-Based Drug Delivery of Axitinib

KEY CHARACTERISTICS

NETWORK:	• Polymer customized to the dose and solubility of axitinib
FORMATION AND STRUCTURE:	• Multi-arm polymers cross-link to form a continuous hydrogel matrix that entraps micronized axitinib throughout
RELEASE MECHANISM:	• Drug must dissolve in water to elute from the gel, known as "diffusion controlled" drug release
BIODEGRADATION:	• Bioresorbs completely into inert polymer chains

HYDROGELS USED IN OVER 5 MILLION PATIENTS ACROSS MULTIPLE SPECIALTIES[1]

Ocular applications of hydrogel include **contact lenses, artificial tears, corneal wound repair, and sealants**[2-4]

Nearly **500,000 eyes** treated to date with Dexamethasone[5]

1. Stuart M. Instylla: An easy, predictable, and simpler way to embolize tumors. Med Tech Strategist 2021. 2. Mulgrave CSA, Fang F. Materials (Basel). 2019;12(2):261. 3. Foulks GN. Drugs Today (Barc). 2007;43(12):887-896. 4. Fernandes-Cunha GM, et al. Sci Rep. 2020;10(1):16671. 5. Ocular Therapeutix Data on File.

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OTX-TKI: Sustained-release Axitinib in Hydrogel

Drug	Inhibitory Concentrations for VEGFR2/KDR (Kinase Domain Receptor) in nM (lower Inhibitory Concentration-50 values indicate higher affinity)
Axitinib[5]	0.2
Sunitinib[6]	40
Vorolanib[6]	64

ELUTYX TECHNOLOGY
Bioresorbable, Targeted, Sustained Drug Delivery
- Proprietary bioresorbable polymer matrix is a hydrogel-based, versatile, biocompatible platform for localized sustained drug delivery

AXITINIB
Multi-target Tyrosine Kinase Inhibitor
- ~100X more potent for VEGFR-2 compared to sunitinib and vorolanib[1-3]
- Highly selective for all VEGF receptors[4-6] with no TIE2 inhibition at physiologic tissue concentrations[1]

OTX-TKI
Single Intravitreal Bioresorbable Implant
- Sustained axitinib release allowing a redosing interval for 6-12 months
- Administered by a 25G needle
- Patent coverage through 2044[7]

Abbreviations: IC (inhibitory concentration); KDR (kinase domain receptor); TIE2 (Tyrosine kinase with immunoglobulin-like and EGF-like domains-2); TKI (Tyrosine kinase inhibitor); VEGF (Vascular endothelial growth factor [receptor]).
References: 1. Unpublished data; Data on File. 2. Hu-Lowe DD, et al. Clin Cancer Res. 2008;14(22):7272-7283. 3. McTigue M, et al. Proc Natl Acad Sci USA. 2012;109(45):18281-18289. 4. Zhao Y, et al. Oncologist. 2015;20(6):660-673. 5. Gross-Goupil M, et al. Clin Med Insights Oncol. 2013;7:269-277. 6. Liang C, et al. Mol Ther Oncolytics. 2022;24:577-584. 7. Blizzard CD, et al. US Patent: Ocular implant containing a tyrosine kinase inhibitor. Published online September 13, 2022. Accessed September 26, 2022.

OTX-TKI in Neovascular Age-Related Macular Degeneration

Results from the Phase 1 Australia Dose-escalation and Phase 1 US Randomized Trials

Our Phase 1 Trials Established Proof of Biological Activity for OTX-TKI in Two Patient Populations

Australia
Phase 1 Trial

PROOF OF CONCEPT: Does OTX-TKI have biological activity?

Open-label, Dose Escalation Trial[1]

- 29 patients dosed with OTX-TKI
- To evaluate the safety and biological activity of OTX-TKI in **treatment naive or previously treated active** wet AMD patients
- Study initiated in **2019**
- Interim results demonstrated potential as a durable **sustained-release product demonstrating biological activity in subjects with pre-existing fluid**

U.S.
Phase 1 Trial

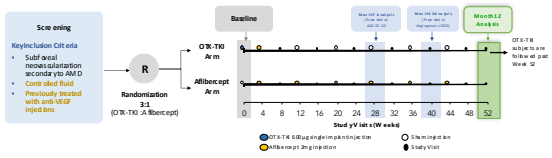
DURABILITY: How long does the biological activity of OTX-TKI last?

Randomized, Masked, Controlled Trial[2]

- 16 patients dosed with OTX-TKI
- To evaluate the safety and biological activity of OTX-TKI in **previously treated controlled** wet AMD patients compared to aflibercept Q8W
- Study initiated **2021**
- 12-month results showed potential as a durable **sustained-release maintenance therapy for 6-12 months in subjects with controlled retinal fluid**

OTX-TKI U.S.-based Wet AMD Clinical Trial Design

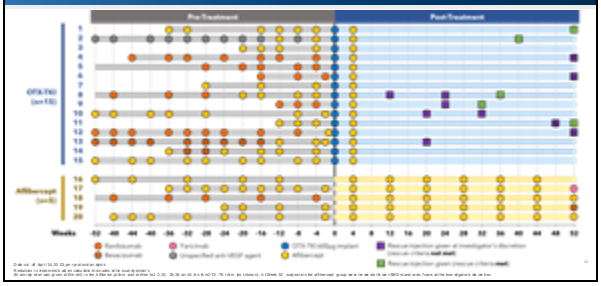
Multicenter, Randomized, Double-masked Trial



Rescue Anti-VEGF Injection Criteria:

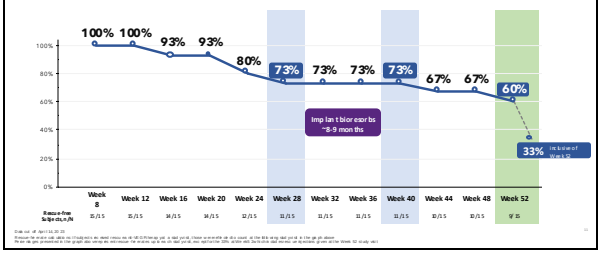
- Loss of ≥10 letters from best previous BCVA with current BCVA worse than baseline, or
- Evidence of ≥75µm CST increase from previous best value and ≥5 letter loss from best previous BCVA, or
- New macular hemorrhage

Reduction in Anti-VEGF Injections Following OTX-TKI at 12 Months
89% reduction in treatment burden with OTX-TKI at 12 months

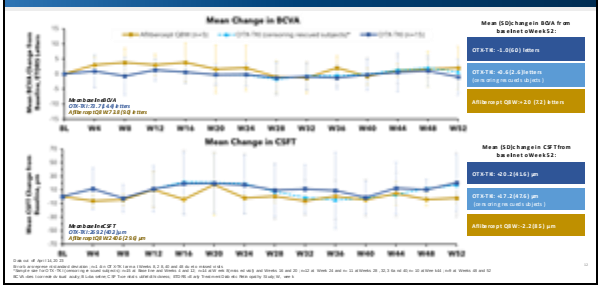


OTX-TKI Demonstrated Extended Duration of Action
60% were rescue-free up to 12 months with 4 additional subjects rescued at 12 months

Percentage of OTX-TKI Subjects Rescue-Free Up to Each Visit (n=15)

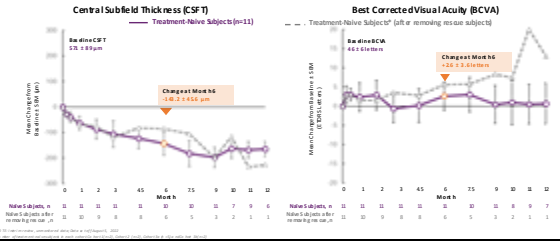


Vision and CSFT with OTX-TKI were Comparable to Aflibercept Q8W



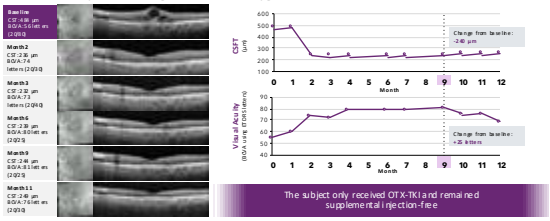
Post-Hoc Analysis of Australia Phase 1 Trial: Treatment Naïve Subjects

Evidence of biological activity observed after single treatment with OTX-TKI



OTX-TKI Case Study: Sustained Response Observed in Treatment-naïve Subject

CSFT and Vision Improved Following Treatment with 600 µg OTX-TKI



The subject only received OTX-TKI and remained supplemental injection-free

Safety Data Showed OTX-TKI was Generally Well Tolerated in the Phase 1 Program

IN THE AUS AND US PHASE 1 STUDIES[1,2]:

No drug-related ocular or systemic serious AEs were reported with OTX-TKI

No retinal detachment, retinal vasculitis, or implant migration into the anterior chamber AEs were reported in subjects who received OTX-TKI

AUS STUDY[1]

Ocular AEs in the Study Eye Reported by Severity	Cohort1 200µg n=6	Cohort2 400µg n=7	Cohort3a 600µg n=6	Cohort3b 400µg + anti-VEGF n=4	Total N=23
Ocular AEs	4	7	6	3	20
Mild	4	7	6	3	20
Moderate	0	3	3	1	7
Severe	0	0	1*	0	1*
Serious AEs	0	0	0	0	0

US STUDY[2]

Ocular AEs in the Study Eye Reported by Severity	OTX-TKI 600µg n=16	Aflibercept n=6
Ocular AEs	16	3
Mild	14	2
Moderate	2*	1*
Severe	0	0
Serious AEs	1**	0

SOL Program

SOL

SOL-1

Designed to show superior durability

SOL-R

Designed to compare OTX-TKI to standard of care

Both SOL-1 and SOL-R are acceptable as registrational trials

SOL-1: OTX-TKI Pivotal Clinical Trial in Treatment-Naïve Wet AMD

SOL

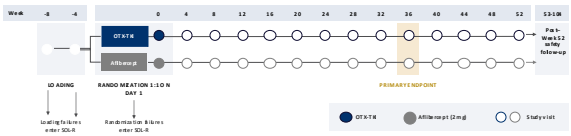
MULTICENTER, DOUBLE-MASKED, RANDOMIZED, PARALLEL-GROUP TRIAL

DESIGN

Two-arm trial with ~150 subjects per group

PRIMARY ENDPOINT (36 WEEKS)

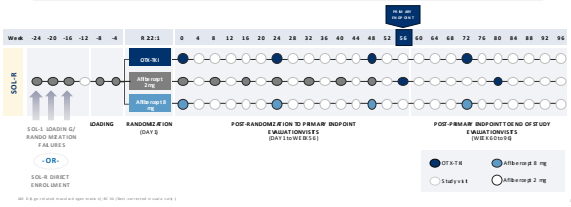
Proportion of subjects who maintained visual acuity, defined as <15 ETDRS letters of BCVA loss at Week 36



SOL-R Phase 3 Wet AMD Study Design

THE PRIMARY OBJECTIVE

Demonstrate that OTX-TKI is non-inferior to fixed-dose aflibercept 2 mg with respect to mean change in BCVA at Week 48 from baseline in nAMD patients

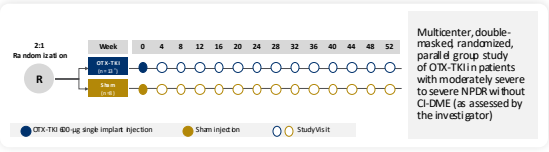


OTX-TKI in Moderately Severe to Severe Non-Proliferative Diabetic Retinopathy

Results from the HELIOS Phase 1 Trial

HELIOS Phase 1 Study of OTX-TKI in NPDR

HELIOS



Multicenter, double-masked, randomized, parallel group study of OTX-TKI in patients with moderately severe to severe NPDR without CI-DME (as assessed by the investigator)

STUDY OUTCOMES

PRIMARY: Safety and tolerability of OTX-TKI

SECONDARY: DRSS changes, rescue therapy, BCVA, and CSFT changes

Baseline Characteristics

Characteristic	OTX-TKI (N=14)	Sham (N=8)
Age, mean, years	53.7 (14.7)	64.0 (7.1)
Sex, n (%) Female Male	 5 (35.7) 9 (64.3)	 5 (62.5) 3 (37.5)
DRSS, n (%) Level 47 (Moderately severe NPDR) Level 53 (Severe NPDR)	 0 14 (100)	 2 (25.0) 6 (75.0)
BCVA, mean (SD), ETDRS letters Approximate Snellen equivalent	 82.9 (5.2) 20/25	 84.5 (5.2) 20/20
CSFT, mean (SD), µm	268.7 (21.5)	283.0 (32.1)

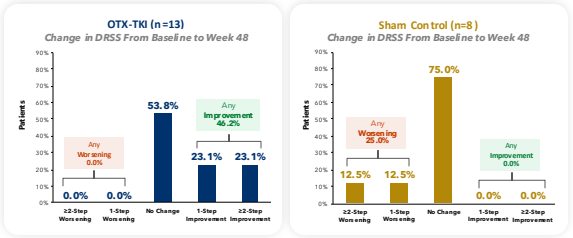
HELIOS Safety Overview at Week 48

OTX-TKI was generally well tolerated, with no ocular SAEs reported

- OTX-TKI was generally well tolerated
- All AEs were mild and balanced across the two arms, with no moderate or severe AEs reported in either arm
- No ocular SAEs reported in either arm
- No treatment- or injection procedure-related intraocular inflammation, iritis, vitritis, or vasculitis
- No subjects in either arm received rescue medication

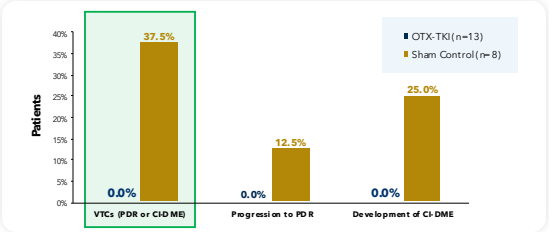
DRSS Changes at Week 48:

23.1% in OTX-TKI arm had a ≥2-step DRSS improvement vs 0% in sham



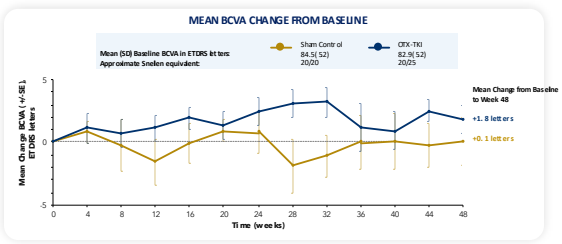
Vision-Threatening Complications (VTCs) at Week 48:

0% in OTX-TKI arm developed PDR or CI-DME vs 37.5% in sham



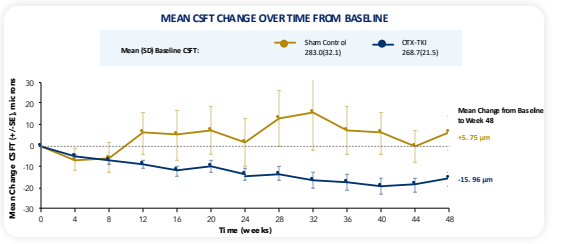
Mean BCVA Change from Baseline Over Time:

OTX-TKI-treated patients demonstrated stable vision through 48 weeks

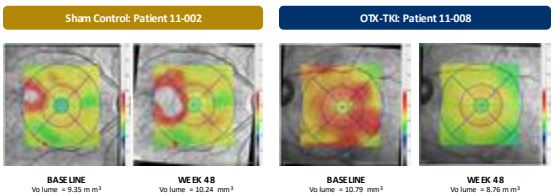


Mean CSFT Change from Baseline Over Time:

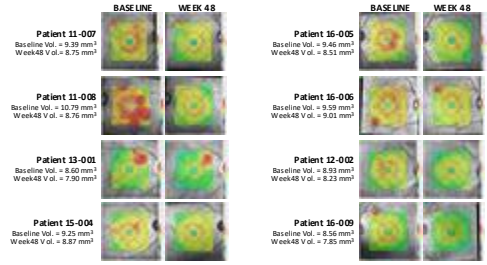
Strong trend towards consistent CSFT reduction observed with OTX-TKI



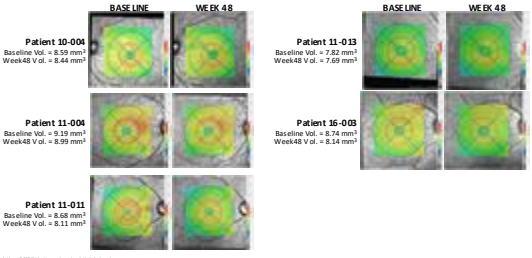
DME Changes from Baseline to Week 48: Sham vs OTX-TKI



Improvement in DME in Patients Receiving OTX-TKI



OTX-TKI-treated Patients without Initial DME Remained DME-Free Through Week 48



Thank you!!

Interim Results from the PRISM Phase 1/2 Clinical Trial Evaluating Intravitreal 4D-150 in Adults with Neovascular Age-related Macular Degeneration

Carl J. Danzig, M.D.
Rand Eye Institute, Deerfield Beach, FL

Disclosures*

Investigator: 4DMT, Adverum, Alexion, Annexion, Astellas/IvericBio, Aviceda, Bayer, Curacle, EyeBio, EyePoint, Genentech, Gyroscope, Kodiak, Ocular Therapeutix, Regeneron, Regenxbio, Rezolute, Roche, Stealth, Unity

Consultant: 4DMT, Adverum, Alimera, Astellas, Eyebio, EyePoint, Galimedix, Genentech, Kodiak, Ocular Therapeutix, Oculis, Ocuphire, Opthea, Regeneron, Regenxbio, Roche, Samsung Bioepsis, Stealth

Speaker: Astellas, Genentech

*Disclosures are disqualified roles during the last calendar year.

Key Takeaways

PRISM Phase 2 Clinical Trial Interim Results

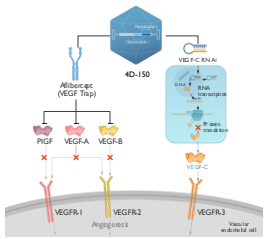
- 4D-150: dual-transgene intravitreal gene therapy
  - Evolved retinotropic AAV vector, dual-transgene payload (aflibercept, VEGF-C RNAi)
- PRISM Phase 1/2 clinical trial: Evaluation of 4D-150 in a broad wet AMD population
- PRISM Phase 2 interim results (Week 24)—3×10^{10} vg/eye:
  - 4D-150 was safe and well tolerated
    - No 4D-150-related serious adverse events and no clinically significant inflammation
    - 100% (49/49) of participants completed prophylactic corticosteroid regimen on schedule
  - Durable clinical activity observed in both Phase 2 cohorts
    - 89% reduction in annualized anti-VEGF injections
    - Stable visual acuity
    - Sustained reduction in CST, stabilization of CST fluctuations

AAV, adeno-associated virus; VEGF, vascular endothelial growth factor.

4D-150

Dual-Transgene Intravitreal Gene Therapy

- Primate-evolved intravitreal R100 capsid carrying a dual-transgene payload
  - Aflibercept and VEGF-C RNAi
- Single-dose intravitreal administration
- Widespread delivery to all major regions and layers of the macula
- Robust pan-retinal transgene expression
- Inhibition of 4 distinct VEGF family members: VEGF-A, -B, -C, and PIGF



PlGF: placental growth factor; VEGF: vascular endothelial growth factor.

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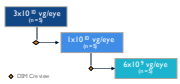
PRISM Phase 1/2 Clinical Trial

Evaluation of 4D-150 in a Broad Range of Wet AMD Populations

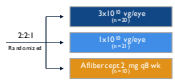
PRISM

Phase 1 Dose Exploration



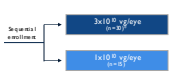
Key Inclusion Criteria
- Anti-VEGF injections in the prior 12 months: ≥6
- CST: ≥300 µm **or** presence of subretinal or intraretinal fluid
- BCVA: 25–78 ETDRS letters

Phase 2a Dose Expansion



Key Inclusion Criteria
- Anti-VEGF injections in the prior 12 months: ≥6
- CST: ≥325 µm **and** presence of subretinal or intraretinal fluid
- BCVA: 34–83 ETDRS letters

Phase 2b Population Extension



Key Inclusion Criteria
- Anti-VEGF injections in the prior 12 months: 1–6 (≥1 in last 12 wks)
- CST: No minimum
- BCVA: 34–83 ETDRS letters

[a]Includes participants in the alternate exercise cohort who enrolled under the Population Extension eligibility criteria (n=13).

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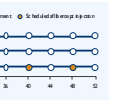
Study Design

Phase 2 Dose Expansion and Population Extension Cohorts

PRISM

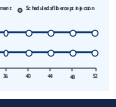
Phase 2a Dose Expansion

Key Eligibility Criteria
- ≥6 anti-VEGF injections during prior 12 months
- CST: ≥325 µm **and** presence of subretinal or intraretinal fluid
- BCVA: 34–83 ETDRS letters



Phase 2b Population Extension

Key Eligibility Criteria
- 1–6 anti-VEGF injections during prior 12 months (≥1 injection in the last 12 weeks)
- CST: No minimum
- BCVA: 34–83 ETDRS letters



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Baseline Characteristics (Phase 2)
Broad Range of Disease Activity and Anti-VEGF Injection Burden

	Dose Expansion			Population Extension	
	4D-150 3×10^10 vg/eye (N=20)	4D-150 1×10^10 vg/eye (N=21)	Aflibercept 2 mg Q8W (N=10)	4D-150 3×10^10 vg/eye (N=30)	4D-150 1×10^10 vg/eye (N=15)
Mean ±SD age, years	77 ±8.0	77 ±8.6	80 ±4.1	77 ±7.7	78 ±8.6
Female, n (%)	8 (40)	11 (52)	5 (50)	20 (67)	6 (40)
Race, n (%) White	18 (90)	21 (100)	9 (90)	30 (100)	14 (93)
Asian	2 (10)	0	1 (10)	0	1 (7)
Mean ±SD time since diagnosis, years	4.0 ±3.0	2.9 ±2.2	1.9 ±1.5	1.8 ±3.5	0.7 ±0.9
Mean ±SD BCVA, ETDRS letters	68 ±11.3	71 ±12.4	71 ±13.2	71 ±9.9	73 ±8.8
Mean ±SD central subfield thickness, µm	429 ±89.3	465 ±114.1	419 ±64.3	336 ±135.0	314 ±70.8
Mean prior *annualized* injection rate*	10.0	9.9	9.0	8.3	10.7
Mean ±SD *actual* injections, prior 12 mo*	9.9 ±2.4	9.4 ±2.1	9.3 ±0.9	4.4 ±2.0	4.3 ±2.1

*Includes Day -7 AFLB injection. BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation.

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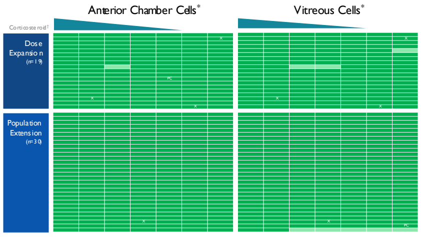
PRISM Phase 2 Interim Results
4D-150 3×10^10 vg/eye (Phase 3 Dose)

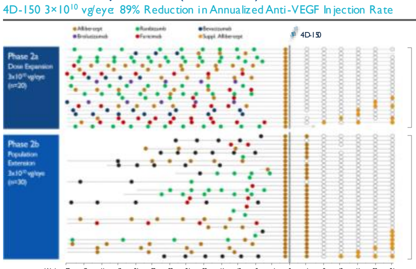


- No clinically significant inflammation
- 100% (49/49) completed prophylactic steroid regimen on schedule
- No participant restarted steroids during follow up through 24 weeks

*SUN and NEI Scores for white blood cells. †Either difluprednate ophthalmic emulsion, triamcinolone acetonide with prednisolone taper, or dexamethasone. NEI, National Eye Institute; PC, pigmented cells; SUN, Standardization of Uveitis Nomenclature; X=missed visit.

8

Anti-VEGF Injections (Week 24)
4D-150 3×10^10 vg/eye: 89% Reduction in Annualized Anti-VEGF Injection Rate



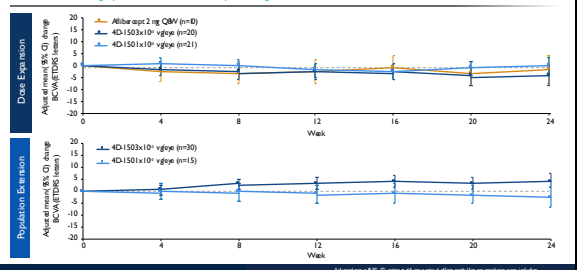
Phase 2a Dose Expansion 3x10^10 vg/eye (n=20):
- 89% reduction in annualized anti-VEGF injection rate
- 84% ≤1 injection
- 63% injection free

Phase 2b Population Extension 3x10^10 vg/eye (n=30):
- 89% reduction in annualized anti-VEGF injection rate
- 93% ≤1 injection
- 77% injection free

9

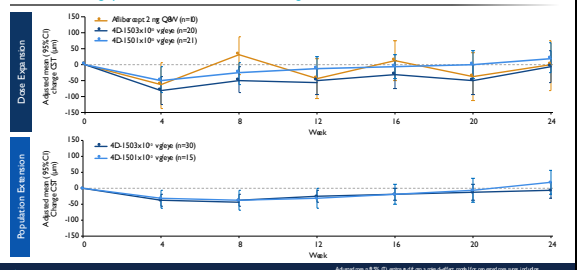
Best Corrected Visual Acuity (BCVA)

4D-150 3×10^{10} vg/eye: Stable Visual Acuity Through Week 24



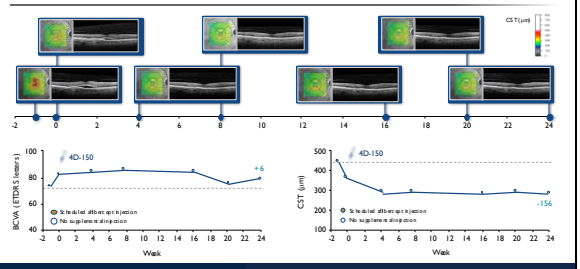
Central Subfield Thickness (CST)

4D-150 3×10^{10} vg/eye: Stable Anatomic Control Through Week 24



Case Study

Population Extension (4D-150 3×10^{10} vg/eye): 4 Anti-VEGF Injections in Prior 6 Months



Summary and Conclusions

- PRISM Phase 1/2 clinical trial
  - Broad wet AMD population with a wide range of disease activity and anti-VEGF treatment burden
- Phase 2 interim results (Week 24)—3×10^{10} vg/eye:
  - 4D-150 was safe and well tolerated
    - No 4D-150-related serious adverse events and no clinically significant inflammation
    - No hypotony, endophthalmitis, retinal vasculitis, choroidal effusions, or retinal artery occlusions
    - 100% (49/49) of participants completed prophylactic corticosteroid regimen on schedule
  - Durable clinical activity observed in both Phase 2 cohorts
    - 89% reduction in annualized anti-VEGF injections
    - Stable visual acuity
    - Sustained reduction in CST, stabilization of CST fluctuations
- Initiation of Phase 3 clinical trial anticipated in early 2025

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Retina Consultants Medical Group Sacramento, CA

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California Retina Consultants Oxnard, CA

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University Retina and Macula Associates Oak Forest, IL

John Wells
Palmetto Retina Center West Columbia, SC

Carol Chung
4D Molecular Therapeutics, Inc Emeryville, CA

Somayeh Honarmand
4D Molecular Therapeutics, Inc Emeryville, CA

Robert Kim
4D Molecular Therapeutics, Inc Emeryville, CA

David Kim
4D Molecular Therapeutics, Inc Emeryville, CA

Combination Therapy: Anti-VEGF and Steroid

Michael Singer, M.D.
Preston O'Brien, M.S.
Clinical Professor of Ophthalmology
UT Health San Antonio
Director of Clinical Research
Medical Center Ophthalmology, San Antonio Texas

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  Service d'Ophtalmologie
- Hôpital de la Croix-Rousse CHU de LYON,

Combination Therapy: Studies you may know
Anti-VEGF and then steroid implant

- History first studied in 2005 in relation to retinal vein occlusion
- DRCR Protocol U 2017 (Dexamethasone implant)
- Reinforce 2018 (Dexamethasone implant)

True or False:
All DME patients are VEGF responsive

False: Approximately 1/3 of DME patients are functional non-responders to anti-VEGF[1,2,3]

Clinical trial	Functional non-responders at Year 1 (%)
Protocol I	28%[3]
Restore	35%[2]
Boreal-DME	40%[3]

DRCR.net definitions
Functional non-responders VA gain < 5 letters[3,4]
Anatomical non-responders OCT thickness reduction < 20%[4]

DME, diabetic macular edema; VEGF, vascular endothelial growth factor
1. DRC Ret, Elman MJ, et al. Ophthalmology 2010;117:1064–1077.e35. 2. Mitchell P, et al. Ophthalmology 2011;118:615–625.
3. Clinical Gaucher C, et al. ARVO 2017, abstr. 1958/B619.

True or False: There are more non responders to steroids than to anti-VEGF in DME

False: The percentage of functional and anatomical non-responders in DME is higher with anti-VEGF than with steroids

	ANTI-VEGF	STEROIDS (DEX-implant)
% FUNCTIONAL non-responders	25% to 40% (≈ 1/3)[1-3]	≈ 16% (≈ 1/6)[5]
% ANATOMICAL non-responders	25% to 35% (≈ 1/3)[3-4]	≈ 14% (≈ 1/6)[5]

Definitions
Functional non-responders   VA gain < 5 letters[1-2]
Anatomical non-responders   OCT thickness reduction < 20%[3]

DEX-I, dexamethasone implant

1. DRCRnet Elman et al Ophthalmology 2010 Jan;117(6):1064-1077.e35
2. RESTORE 1 years. Mitchell et al Ophthalmology 2011;118:615–625
3. Gonzalez et al AJO 2016;172:72-79
4. Bressler SB, et al. Arch Ophthalmol 2012;130(9):1153-1161
5. Bellocq et al Pediamex Ophthalmol Retina 2017

True or false: If you give enough anti-VEGF shots everyone will respond

False: The rate of non-responders to anti-VEGF does not really vary over time, meaning that they may not be dependent on the number of injections!

Clinical trial	Functional non-responders at Year 1 (%)	Functional non-responders at Year 2 (%)	Functional non-responders at Year 3 (%)
Protocol I [1-3]	28%[1]	31%[2]	33%[3]
Restore [4-6]	35%[4]	34%[5]	34%[6]
Clinical trial	Functional non-responder at Month 3 (%)	Functional non-responder at Month 6 (%)	Functional non-responder at Year 1 (%)
Boreal-DME [7]	43%	39%	40%

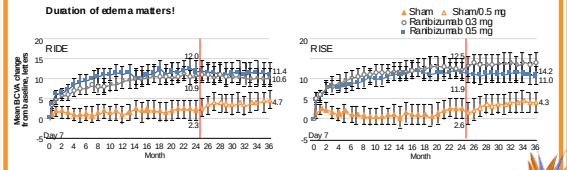
Obstinacy does not guarantee success

VEGF, vascular endothelial growth factor; DME, diabetic macular edema; VA, visual acuity; IVI, intravenous injections.
1. DRCRnet. Elman et al. Ophthalmology. 2010 Jun;117(6):1064-1077.e35. 2. DRCRnet. Elman et al. Ophthalmology. 2012;119(9):1-6. 3. DRCRnet. Elman et al. Ophthalmology. 2012 November;119(11):2312-2318. 4. RESTORE. Lyons. Mitchell et al. Ophthalmology. 2011;118(4):615-25. 5. RISE/RIDE. 2 years. Lang et al. Ophthalmology. Ophthalmology. 2013;120(8):1658-65. 6. RESTORE. Lyons. Schmidt-Erfurth et al. Ophthalmology. 2016 May;123(5):1013-8. 7. P. Massin et al. Communication SFO 2017. 8. Comert Gunther et al., abstr. 1745. ARVO 2017

True or false: Time is not a factor in visual improvement in anti-VEGF treatment (Waiting is OK)

False: Delayed treatment is a loss of opportunity

Duration of edema matters!



If we treat effectively but too late, visual recovery will be lower

Brown et al, Ophthalmology 2013; 120:2013-22.

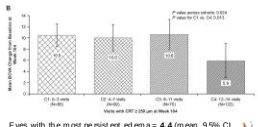
True or false: The amount of edema has no effect on visual recovery

False: Persistance of macular edema is a negative prognostic factor for long-term visual acuity improvement in DME

Relationship between duration and extent of oedema and visual acuity outcome with ranibizumab in diabetic macular oedema: A post hoc analysis of Protocol I data

The longer the duration of DME, the more the VA decreases

Edema duration = number of study visits with CRT ≥ 250 µm during the first year of treatment by ranibizumab (Protocol I)

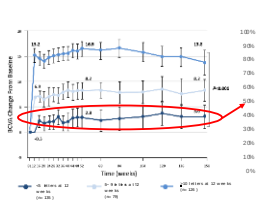


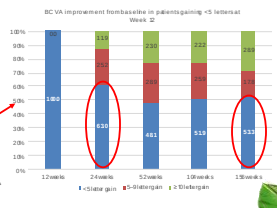
Eyes with the most persistent edema = **4.4** (mean, 95% CI 0.1–8.7) **fewer ETDRS letters gain at week 156** than eyes with the least persistent edema *(p=0.044)*

Lyon 1 Sadda et al Eye 2019online

When can we predict functional response to anti-VEGF therapy?

The EARLY Study



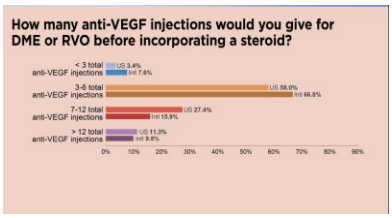


Functional predictability with anti-VEGF seems to exist after the first three to six injections
Therefore, we have to wait 5 to 6 months after treatment initiation before switching… [1]

1. Gonzalez VH, et al. Am J Ophthalmol. 2016;172:72-79.

True or False: As a result of the Early study most US retina specialists give how many injections

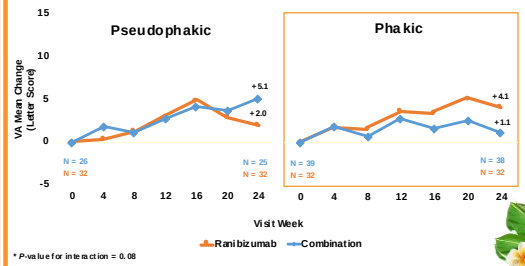
PAT Survey 2023



Protocol U by DRCR showed that thee was not a difference is vision between patients who had combination therapy with dex implant and ranibizumab vs monthly ranibizumab.

True or False: In Protocol U, there was no difference in visual acutiy between patients treated who were phakic vs pseudophakic

False: VA Mean Change: Baseline Lens Status



True or False: In terms of Protocol U, there was no difference in the percent of patients who were 2-line and 3-line gainers

False: Binary VA Outcomes

	Combination Group (N = 63)	Ranibizumab Group (N = 64)	*P*-value
VA at 24 Weeks			
20/20 or better	6%	5%	0.70
20/40 or better	51%	52%	0.80
20/200 or worse	6%	5%	0.70
Changes at 24 Weeks			
≥15 letters improvement	11%	2%	0.03
≥10 letters improvement	22%	14%	0.34
≥15 letters worsening	6%	5%	0.62
≥10 letters worsening	13%	6%	0.09

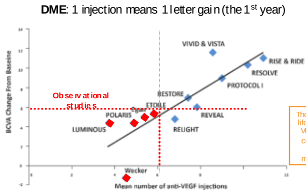
* Pre-planned secondary outcomes

True or False: Both anti-VEGF and steroid underperform in real-life studies

False: Interventional vs observational (Real-life) studies of DME with anti-VEGF to date- Observational studies underperform

DME: 1 injection means 1 letter gain (the 1st year)

In real life, mean number of anti-VEGF injections and letter gain are below six
→ Persistence of DME



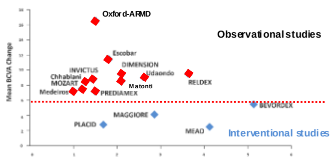
Interventional studies

The disconnect between RCTs and real-life outcomes is a major issue with anti-VEGF treatments, mainly due to non-compliance with the tight schedule of monitoring and injections that is mandatory to achieve best outcomes

Adapted from Kiss S, et al. Clinical Ophthalmology 2014;8:1611–1621; Brown DM, et al. Ophthalmology 2013;120:2013–2022; Pearce I, Ophthalmology 2015;122(9):1811–1819; Mitchell P, et al. Ophthalmology 2011;118:615–625; DRCR.net. Ophthalmology 2010;117:1064–1067; Massin P, et al. Diabetes Care 2010;33:2399–2405; Korobelnik J-F, et al. Ophthalmology 2014;121:2247–2254;37:21193–1203; Ohji M, et al. Abstract 4664, presented at ARVO, Fort Lauderdale, Florida, USA; 2012; Bandello C, et al. Abstract presented at 16th EURETINA Congress, 8-11 September 2016, Bella Center Copenhagen; Bayer Healthcare. Clinical synopsis POLARIS study. Available at https://clinicaltrials.bayer.com/study/1324 Accessed March 2019; Fourmaux E, et al. Poster B0498 presented at ARVO 2017 Annual Meeting, 7–11 May 2017, Baltimore, USA; Egan C, et al. Br J Ophthalmol 2017;101:75–80; Wecker T, et al. Br J Ophthalmol 2017;101:353–359.

False: Interventional vs observational (Real life) studies of DME with dexamethasone implant to date: Real life overperforms

The real-life outcomes are comparable if not superior to those of clinical trials



In real life, gain with dexamethasone is **greater than six** letters

DME, diabetic macular edema; BCVA, best corrected visual acuity.
Udaondo P, et al. Poster PO213 [slide presentation] presented at AAO, New Orleans, USA;2013; Medeiros MD et al. Ophthalmologica 2014;231:141–146; Escobar-Barranco JJ, et al. Ophthalmologica 2015;233(3–4):176–85; Guigou S, et al. J Fr Ophtalmol 2014;37:480–485; Akinin I, et al. Ophthalmologica 2016;235(4):187–188; Chhablani J, et al. Eye (Lond). 2016 Mar;30(3):426–430; Matonti F, et al. Eur J Ophthalmol. 2016 Aug 4;26(5):454–459; INVICTUS, Comet A, et al. Acta Ophthalmologica February 2019, 10.1111/aos.14057; PREDIAMEX Bellocq D, et al Ophthalmol Retina 2018;(6):567–573; DIMENSION, Akesbi J, et al. Slides presentation SFO, France; 2017; Maldès A, et al. Retina. 2017 Apr;37(4):753–760; Callanan DG, et al Ophthalmology. 2013 Sep;120(9):1843–1851; Callanan DG, et al Graefes Arch Clin Exp Ophthalmol. 2017 Mar;255(3):463–473; Boyer DS, et al. Ophthalmology. 2014 Oct;121(10):1904–1914; Fraser-Bell S, et al. Ophthalmology. 2016 Jun;123(6):1399–1401

True or False: Similar to anti-VEGF, early treatment with steroids is associated with better vision sooner

- TRUE

True or False: Treating eyes with better vision is associated with better final vision

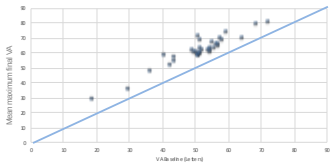
True: What may favor good functional results?

To treat early!

The better the baseline VA, the better the final VA[1]


Review Article

Pharmacological Management of Diabetic Macular Edema in Real-Life Observational Studies



n=1703 eyes
Adapted from Kodjikian et al, 2018.

VA, visual acuity
Kodjikian L, et al. Biomed Res Int. 2018 Aug 28;2018:8289253

Lyon 1

Hospices de Lyon

Combination therapy: A subset of the Reinforce dataset

Real life study USA: REINFORCE: A Prospective Multicenter Study of Dexamethasone Intravitreal Implant (DEX) in Diabetic Macular Edema (DME)

Michael A. Singer, MD1; Pravin U. Dugel, MD2; Howard F. Fine, MD3; Antonio Capone, Jr., MD4; John Maltman, PhD5

Introduction

- Dexamethasone intravitreal implant (DEX) has shown efficacy in patients with diabetic macular edema (DME) in controlled trials
- Data on real-world outcomes in DME patients receiving DEX as monotherapy or adjunctive therapy are limited

Study Objective

- To assess the effectiveness, safety, and real-world use of DEX in clinical practice in patients with DME

Study Design / Methods

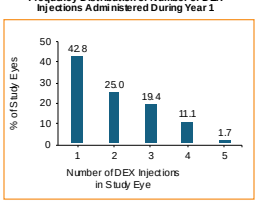
- Prospective, multicenter, observational registry study
- Study did not provide, nor require by protocol, any treatment beyond the initial DEX treatment required for registry inclusion
- Ocular history, treatment, and outcomes data were collected at the patient's first DEX injection and each subsequent visit up to 1 year
- Assessments and schedule of follow-up visits at the discretion of the physician
- Amount of data collected depended upon the number of follow-up visits
- Snellen visual acuity was converted to approximate ETDRS letters for analysis using the method of Gregori et al

Primary Endpoints

- Mean maximum BCVA change (best improvement) from baseline following each DEX injection
- Percentage of patients with ≥ 15-letter improvement in BCVA
- Average improvement in BCVA (area-under-the-curve [AUC] approach)

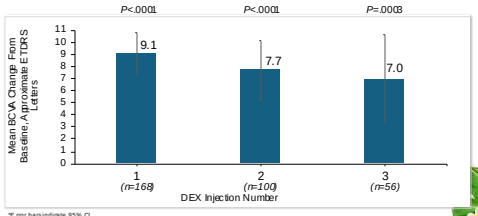
DEX Usage

Frequency Distribution of Number of DEX Injections Administered During Year 1



- Mean DEX injection frequency was 2.0 (± 1.1, SD) injections in Year 1
- Mean time between DEX injections was 152.7 (± 64.5, SD) days
- DEX was used as monotherapy in 99 (55.0%) study eyes
- 81 study eyes (45%) received 1 or more other intravitreal injections during the study
- Most common: aflibercept, ranibizumab, or bevacizumab

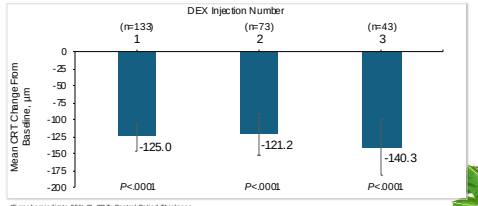
Mean Peak Improvement in BCVA From Baseline After Each DEX Injection



*Error bars indicate 95% CI

2017 RetinaWorld Congress, Singer et al

Mean Change in CRT From Baseline After Each DEX Injection



*Error bars indicate 95% CI, CRT: Central Retinal Thickness

2017 RetinaWorld Congress, Singer et al

Other Key Efficacy Endpoints

Outcome Measure	Result	P Value
Percentage of study eyes with ≥15-letter improvement in BCVA from baseline during the study	36.0% (62/172)	
Mean average improvement in BCVA from baseline during the study using the AUC approach (95% CI)	3.6 letters (2.3, 5.0)	
Mean maximum change in BCVA from baseline during the study (95% CI)	11.7 letters (10.0, 13.5)	<.0001
Mean maximum change in CRT from baseline during the study (95% CI)	−137.7 µm (−158.2, −117.3)	<.0001
Percentage of study eyes achieving BCVA of 20/40 or better and CRT ≤300 µm at the same visit[a]	19.4% (19/98)	

[a] Percentage calculated among study eyes that had baseline BCVA worse than 20/40 and baseline CRT >300 µm.
AUC = area-under-the-curve; BCVA = best-corrected visual acuity; CI = confidence interval; CRT = central retinal thickness.

2017 Retina World Congress, Singer et al

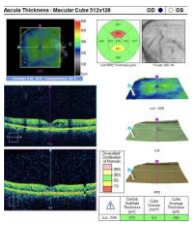
Combination Therapy: Similar results in terms of vision and slightly better drying

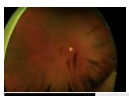
TABLE 3
Subgroup Analysis of Key Efficacy Parameters

Subgroup	Mean ± SD Maximum Improvement in BCVA After Each Injection, Letters: Injection 1	Injection 2	Injection 3	Mean ± SD Maximum Improvement in CRT Across All Months, µm
Baseline Lens Status				
Phakic	8.6 ± 11.5 (n = 52)	8.5 ± 14.8 (n = 29)	5.2 ± 17.8 (n = 13)	−120.8 ± 113.5 (n = 42)
Pseudophakic	9.4 ± 11.6 (n = 100)	7.4 ± 11.1 (n = 60)	7.6 ± 12.4 (n = 37)	−142.4 ± 123.9 (n = 85)
Duration of DME				
<1 year	9.7 ± 8.9 (n = 62)	7.8 ± 11.0 (n = 36)	0.5 ± 9.2 (n = 15)	−145.0 ± 121.4 (n = 48)
1–2 years	8.9 ± 12.5 (n = 36)	10.1 ± 10.5 (n = 19)	9.4 ± 10.8 (n = 14)	−118.7 ± 110.0 (n = 31)
>2 years	8.6 ± 12.3 (n = 70)	6.5 ± 13.9 (n = 45)	9.3 ± 15.6 (n = 27)	−142.1 (124.1) (n = 55)
Prior Laser Treatment for DME				
Yes	10.1 ± 13.6 (n = 56)	10.3 ± 13.0 (n = 34)	10.7 ± 14.7 (n = 21)	−134.9 ± 115.6 (n = 35)
No	8.5 ± 9.7 (n = 112)	6.3 ± 11.7 (n = 66)	4.8 ± 12.3 (n = 35)	−138.7 ± 121.5 (n = 99)
Intravitreal Treatment During the Study				
DEX only	9.4 ± 11.7 (n = 92)	7.3 ± 12.7 (n = 51)	7.9 ± 14.0 (n = 31)	−134.7 ± 122.8 (n = 74)
DEX and other treatment	8.6 ± 10.5 (n = 76)	8.0 ± 12.0 (n = 49)	5.9 ± 12.8 (n = 25)	−141.5 ± 116.4 (n = 60)
History of Vitrectomy				
Yes	12.5 ± 13.3 (n = 48)	12.6 ± 13.7 (n = 27)	13.1 ± 14.7 (n = 11)	−159.0 ± 132.5 (n = 37)
No	7.7 ± (9.9) (n = 120)	5.8 ± 11.3 (n = 73)	5.5 ± 12.8 (n = 45)	−129.6 ± 113.9 (n = 97)

SD = standard deviation; BCVA = best-corrected visual acuity; CRT = central retinal thickness; DME = diabetic macular edema; DEX = dexamethasone intravitreal implant

Case 2





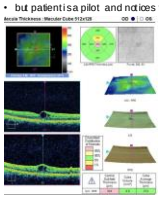
Age	48 commercial pilot
Gender	Male
Race	White
Diagnosis	Vitheme mild DME OD
BCVA	20/50-2
Previous Ocular History	phakic

All case images are courtesy of Dr. Singe r unlesso therwise noted. BCVA = best-corrected visual acuity; DME = diabetic macular edema; ILM = inner limiting membra ne; NPDR = non proliferative diab etic r etino pathy; RPE = r etinal pigme nt epithelium.

Patient received 3 bevacizumab injections to clear vitreous hemorrhage

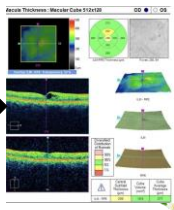
Last bevacizmab 1 month ago ago

- BCVA 20/40 → 20/30
- CST 324 to 298
- but patient is a pilot and notices the distortion



Faricimab x1

1 mo later; (1 month s/p, faricimab)

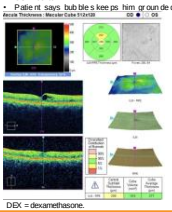


CST = central subfield thickness; mo = months; s/p = status post.

Faricimab/DEX Implant Within 1 Month

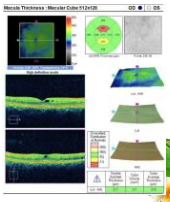
1 month s/p, faricimab x3

- BCVA 20/40+1 → 20/30
- CST 298 to 271
- Patient says bubbles keeps him grounded



Faricimab x1; 2 wk

2 weeks after Faricimab #2

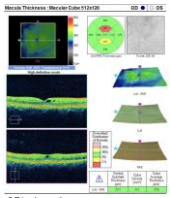


DEX = dexamethasone.

Faricimab/DEX Implant Within 1 Month

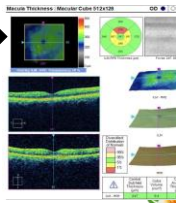
1 month s/p, faricimab x2

- BCVA 20/30 → 20/20
- CST 271 to 247



Dex implant

2month after DEX implant

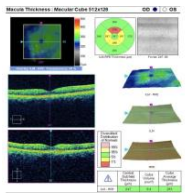


DEX = dexamethasone.

Faricimab/DEX Implant

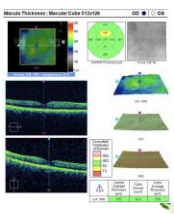
2 mo later; s/p faricimab/DEX combo

- BCVA 20/20
- CST 247-275



observe

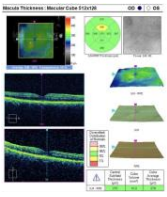
4 mo s/p faricimab/DEX combo



Faricimab/DEX Implant

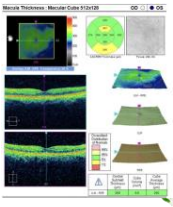
4 month; s/p faricimab/DEX combo

- BCVA 20/20
- CST 275-269



observe

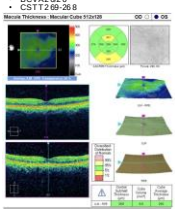
6 mo s/p faricimab/DEX combo



Faricimab/DEX Implant

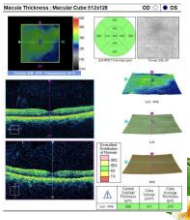
6 month; s/p faricimab/DEX combo

- BCVA 20/20
- CST 269-268



observe

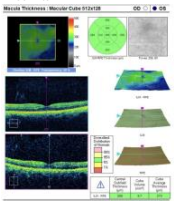
8 mo s/p faricimab/DEX combo



Faricimab/DEX Implant

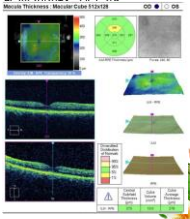
8 month; s/p faricimab/DEX combo

- BCVA 20/20+3
- OCT 268



observe

11 mo s/p faricimab/DEX combo



Conclusion: Dexamethasone intravit

Label in first and second line

EFFICACY

- Interventional studies: not inferiority to anti-VEGF in RCTs[1-3]
- Observational (real-life) studies: good outcomes, good observational results vs anti-VEGF[4]
- Ozurdex is effective and has rapid onset of action[5]
- Duration of efficacy up to 6 months[5]

SAFETY (Generally predictable, transient and manageable side effects)

- Hypertension: rarer in DME, topical treatment alone sufficient in 97%, detected after the 1st or 2nd injection (80% of the hypertonic cases)[6,7]
- Cataract: Ozurdex permits a good control of DME during surgery (no worsening of the DME after the surgery & no delay in visual recovery)[8-10]

LESS BURDEN

- Less intravitreal injections, therefore less visits, than anti-VEGF[11-14]
- Better observance?[15]

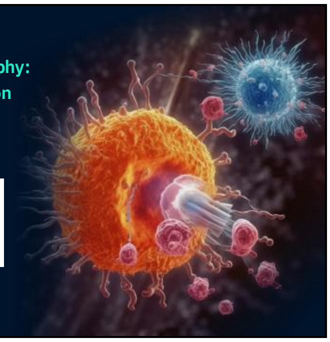
FAVORABLE COST/EFFECTIVENESS RATIO FOR THE SOCIETY AND THE PAYORS[16-18]

VEGF, vascular endothelial growth factor

1. Callanan DS, et al Graefes Arch Clin Exp Ophthalmol 2017 255(3):463-73; 2. Gillies MC, et al Ophthalmology 2014 121(12):2473-81; 3 Fraser-Bell S, et al. Ophthalmology 2014 121(12):2473-81. 4. Kodjikian L, et al Biomed Res Int. 2018 Aug 28;2018:8289253. 5. Pacella, et al Ophthalmol Eye Dis. 2016; 8:1 1-16. 6. Rezkallah A, et al. J Glaucoma 2019 28(1):e5-e9. 7. Rezkallah A, et al. Safodex2 Retina. 2020. 8. Panozzo et al. Eur J Ophthalmol. 2017 27(4):433-437. 9. Calvo et al. Retina. 2018; 38(3):490-496. 10. Furino et al. J Ophthalmol. 2017 2017:4896036. 11. Callanan DS, et al Graefes Arch Clin Exp Ophthalmol 2017 255(3):463-73; 12. Gillies MC, et al Ophthalmology 2014 121(12):2473-81; 13. Fraser-Bell S, et al. Ophthalmology 2014; 121(12):2473-81; 14. Kodjikian L, et al Biomed Res Int. 2018 Aug 28 2018:8289253 15. Based on authors our opinion. 16. Lozano López V, et al Arch Soc Esp Oftalmol. 2015 Jan 90(1):14-21 17. Cavusoglu Sezen S, et al Value Health. 2015 Nov; 18(7):A4 221 8. Squires H, et al Br J Ophthalmol. 2019 Feb 11

AVD-104 for Geographic Atrophy: Glyco-immunologic Modulation of Macrophage Activity

SIGLEC



Complement Inhibition Is Efficacious, but AEs May Suggest Another Approach Is Needed[1-4]

DERBY, OAKS, and GATHER

Trial Drug	↓ in GA vs sham (%)[a]	Rate of CNV Conversion
Pegcetacoplan EOM (24-month data)	16%-18%[b]	7%
Pegcetacoplan EM (24-month data)	19%-22%[b]	12%
Avacincaptad pegol 2 mg EOM (24-month data)	19%	4%
Avacincaptad pegol 2 mg EM (24-month data)	14%	7%
Avacincaptad pegol 4 mg EM (18-month data)	30%	16%

Reported AEs

- Increased CNV conversion
- Inflammation
- Ischemic optic neuropathy
- Occlusive vasculitis*

*Post-marketing AE with pegcetacoplan in the US (ASRS listserv, July 15, 2023)

Reduction of complement overactivation shows efficacy but may increase treatment-associated side effects

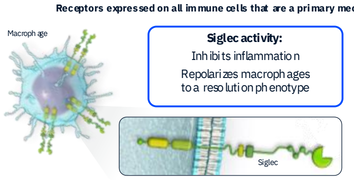
1. Patel SS, et al. *Eye (Lond)*. 2023;10.1038/s41433-023-02497-w. 2. Langer HF, et al. *Blood*. 2010;116(22):4395-4403.
3. Apellis Pharmaceuticals Inc., 2022. Available at: https://investors.apellis.com/news-releases/news-release-details/apellis-announces-24-month-results-showing-increased-effects
4. Khanani A. Oral presentation at: American Academy of Ophthalmology (AAO) Annual meeting; November 2023.

[a]Reduction in GA lesion growth rate. [b]DERBY and OAKS results.
AE (Adverse event), CNV (Choroidal neovascularization), EM (Every month), EOM (Every other month), GA (Geographic atrophy)

Siglec Receptors on Macrophages Control Polarization[1-4]

SIGLECS = Sialic acid–binding immunoglobulin-like lectins

Receptors expressed on all immune cells that are a primary mechanism of immune resolution



Siglec activity:
Inhibits inflammation
Repolarizes macrophages to a resolution phenotype

Siglecs bind sialic acids presented on other cells to identify them

Siglecs have inhibitory signaling pathways (ITIM) similar to PD-1 receptors on T-cells, which are targeted by oncology immune checkpoint inhibitors (ICI)

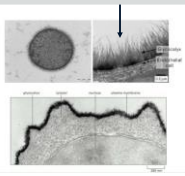
1. Crocker PR. *Nat Rev Immunol*. 2007 Apr;7(4):255-66. 2. Pillai S. *Annu Rev Immunol*. 2012;30:357-392. 3. Gray MA, et al. *Nat Chem Biol*. 2020;16(12):1376-1384.
4. Macauley MS. *Nat Rev Immunol*. 2014;14(10):653-666.

ITIM (Immunoreceptor tyrosine-based inhibitory motif)

Siglecs Recognize Sialic Acids on Other Cells

"Self" or "non-self" patterns modulate macrophage activity

Sialic acids (moieties of glycan sugars) are on all vertebrate cell surfaces as **immune markers**



Sialic acid patterns are like cell barcodes

Macrophage **Siglecs** bind **sialic acids** on other cells to recognize them as either **"self" or "non-self"**

"Self"	"Non-self"
Healthy and native body cells	Diseased, damaged, and foreign cells
Immune system OFF	Immune system ON

Macauley MS. Nat Rev Immunol 2014;14(10):653-66.

4

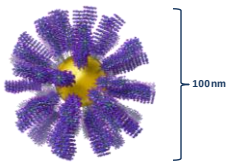
HALOS™-Generated Lead: AVD-104, a Polysialic Acid-Coated Nanoparticle that Inhibits Siglecs on Macrophages and Binds CFH

Ligands

- Nanoparticle coated with high-affinity polysialic acid ligands
- Tunable multivalent selectivity for desired Siglecs

Core & Linkers

- Biodegradable PLGA co-polymer core creates surface attachment and enhances durability and is established in IVT injection application[1]
- PEG polymer enables high density and proper orientation of ligands
- Amide, azide and other conjugation linkages

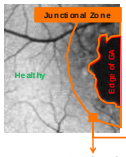


Molecular weight ~20 kDa

1 Clarix Pradegimab. AbVie 2022

Confidential | 13

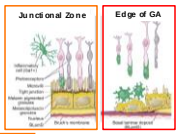
Addressing Disease Progression in the Junctional Zone is Critical for an Effective, Disease Modifying Treatment for GA



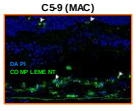
In the GA junctional zone, not all photoreceptors/RPE cells are dead – some may be dying, stunned, etc.

Rescuing the cells that are not yet dead may enable functional and structural stabilization or improvement

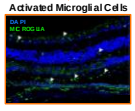
GA junctional zone is measured by hyper autofluorescence



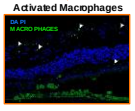
C5-9 (MAC)



Activated Microglial Cells



Activated Macrophages



Bonilha, V., Bell, B., Hu, J. et al. Geographic Atrophy. Retina Cell Biology (2021)

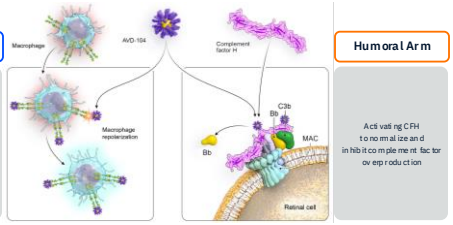
Confidential | 11

AVD-104 Employs a Dual MOA to Treat GA

Modulating cellular and humoral parts of the immune response

Cellular Arm

Inhibiting overactive macrophages and repolarizing to the resolution phenotype



Humoral Arm

Activating CFH to normalize and inhibit complement factor overproduction

CFH (Complement factor H, GA(Geographic atrophy), MAC(Membrane attack complex), MOA(Mechanism of action))

7

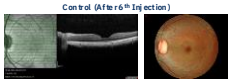
No Safety Signals Seen in Ongoing 9-Month Repeat-Dose IND Toxicology Study

No structural abnormalities or functional changes

AVD-104 (GLP) IVT injections in non-human primates (9-month study)

Treatment	Dosing	Clinical Dosing
Low dose (monthly)	0.5 mg/eye	1 mg/eye
Mid dose (EOM)	1 mg/eye	2 mg/eye
High dose (EOM)	1.5 mg/eye	3 mg/eye

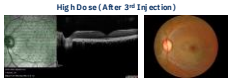
Control (After 6th Injection)



Low Dose (After 6th Injection)

Mid Dose (After 3rd Injection)

High Dose (After 3rd Injection)



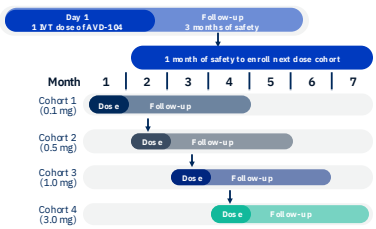
Unpublished Avecia data submitted for peer review publication.

EOM(Every other month), GLP(Good Laboratory Practice), IVT(Intravitreal)

8

SIGLEC Phase 2a US Clinical Trial for GA Secondary to AMD*

Trial Design: First-in-Human, Single-Dose Safety



Multicenter (6 US sites), open-label, single-dose study, 30 patients

Primary Endpoints

Safety and tolerability (ocular and systemic), dose-limiting toxicity

Secondary Endpoints

Efficacy (changes in BCVA and GA by FAF), biomarkers

Inclusion Criteria

- Center-involving GA secondary to dry AMD
- BCVA 20/80-20/800
- Lesion size must be larger than 1.25 mm²

*NCT05899061.

AMD (Age-related macular degeneration), BCVA (Best-corrected visual acuity), FAF (Fundus autofluorescence), GA(Geographic atrophy), IVT (Intravitreal)

9

SIGLEC Phase 2a US Clinical Trial for GA

Part I Demographics & Baseline Data

	Cohort 1 (0.1mg) (N=3)	Cohort 2 (0.5mg) (N=9)	Cohort 3 (1.0mg) (N=9)	Cohort 4 (3.0mg) (N=9)	Total (N=30)
Study Eyes:					
Females n (%)	1 (33.3%)	8 (88.9%)	6 (66.7%)	4 (44.4%)	19 (63.3 %)
Males n (%)	2 (66.7%)	1 (11.1%)	3 (33.3%)	5 (55.6%)	11 (36.7%)
Age (Years) (Mean)	74.0	82.7	81.9	81.0	81.1
BCVA(Mean)	33.7	39.1	37.1	37.3	37.4
GADDAF Area in mm² (Mean)	37.7	13.0	15.5	13.5	16.4
GAPeri-lesional Area in mm² (Mean)	0.59	0.64	0.40	0.28	0.46
Patients w/ Multifocal GALesions n (%)	3 (100%)	5 (55.6%)	5 (55.6%)	6 (66.7%)	19 (63. 3%)
Fellow Eyes – All Patients Had Bilateral GA:					
BCVA(Mean)	59.3	44.7	66.1	52.3	54.9
GADDAF Area in mm² (Mean)	28.1	16.3	10.8	10.8	14.3
GAPeri-lesional Area in mm² (Mean)	0.36	0.17	0.16	0.11	0.17

Source: Unpublished Aviana data
Note: All patients enrolled had advanced GA in both eyes

SIGLEC Phase 2a US Clinical Trial for GA

Part I Demographics & Baseline Data

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GAPeri-lesional Area in mm² (Mean)	0.36	0.17	0.16	0.11	0.17

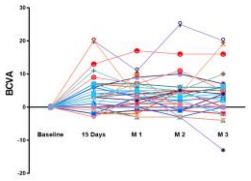
Source: Unpublished Aviana data
Note: All patients enrolled had advanced GA in both eyes

SIGLEC Phase 2a US Clinical Trial for GA

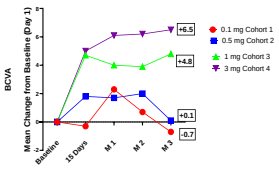
Efficacy Data: BCVA (1 of 2)

Majority of Patients Showed Positive Visual Gain with Single Injection; Greater Benefit in Cohorts 3 & 4

Change in Baseline BCVA (All Patients)



Change in Baseline BCVA (All Patients)



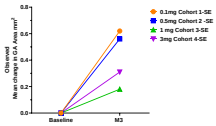
Source: Unpublished Aviana data
Note: Single patient in Cohort 2 had a 13 letter loss at the M3 visit. Loss of vision was not deemed drug related and was lost to subsequent visits

SIGLEC Phase 2a US Clinical Trial for GA

Efficacy GA: GA Lesion Growth Analysis (DDAF)

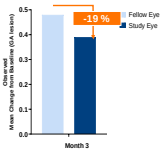
AVD-104 Showed Substantial Slowing of GA Lesion Growth at 3 Months after Single Injection

Mean Change from Baseline (All Cohorts) DDAF (Area, mm2)

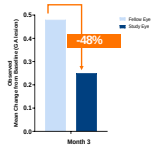


Difference in Percent Change from Baseline (Study vs Fellow Eyes) DDAF (Area, mm2)

All Cohorts



Cohorts 3 & 4



*Source: Unpublished Area data.

SIGLEC Phase 2b US Clinical Trial for GA

Trial Design: Efficacy and Safety Endpoints (Potentially Pivotal)

	0-12 months	12-24 months
AVD-104 (1.0 mg)	Monthly	Monthly
AVD-104 (2.0 mg)	Q2M	Q2M
Active comparator (Avacincaptad pegol)	Monthly	Monthly

6-month evaluation of efficacy and safety

Pre-Phase 3 FDA report to include 12-month efficacy, safety, and tolerability data

Multicenter, double masked, randomized, active comparator, ~300 patients, 45 US sites

Primary Endpoints

Rate of change from baseline in area of GA (by FAF) at month 12 (slope efficacy), evaluation of adverse events

Key Secondary Endpoints

Change from baseline in BCVA (by ETDRS) at month 12; prevention of BCVA loss from baseline (maintained vision < 15-letter loss; ≥ 15-letter loss); loss of retinal pigment epithelium or ellipsoid zone as measured by SD-OCT at month 12

Inclusion/Exclusion Criteria

Fellow eye may be treated for GA; no history of CNV in study eye; lesion > 2.5 and < 17.5 mm²; BCVA 20/320 or better

Note: EOM = Every other month; ETDRS = Early Treatment of Diabetic Retinopathy Study; SD-OCT = Spectral domain optical coherence tomography.

AVD-104: A New-Wave Dual-MOA Treatment for GA

Repolarizing macrophages and inhibiting complement overactivation to target pathobiology in GA

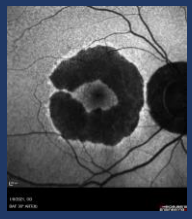
- **AVD-104 (a sialic acid–coated nanoparticle) repolarizes overactivated macrophages and inhibits overamplified complement system**
- **SIGLEC phase 2a US clinical trial is completed with Phase 2 enrollment complete**
- **No AVD-104 drug-related SAEs (ocular or systemic) have been reported**
- **In Phase 2a there is evidence of a beneficial effect of AVD-104 on GA progression and BCVA**

GA: The basics of diagnosis and treatment in the real world

- Carl J. Danzig, MD
- Rand Eye Institute
  - Deerfield Beach, FL

A special thank you for providing formatted slides and images for this presentation

- Alexion
- Allegro
- Alzheon
- Annexon
- Apellis
- Aviceda
- Cognition
- Galimedix
- Genentech
- Gyroscope (Novartis)
- Heidelbeg
- Ionis
- IveticBio
- Janssen
- Stealth Therapeutics



Topics for today

- Introduction
  - Demographics and Natural course of disease
  - Coding
  - Imaging
- Early and mid-phase trials
- Phase III
- Safety
- Real-world cases and decisions

Age-Related Macular Degeneration (AMD)

- One of the most common causes of severe, irreversible vision loss
- Worldwide prevalence: 196 million in 2020 projected to be 288 million in 2040[1]
- Approximately 11 million people in US have AMD

[1] American Academy of Ophthalmology Preferred Practice Patterns 2019

GA and neovascular AMD (nAMD)

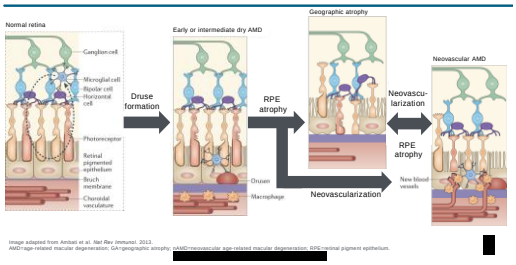


Image adapted from Ambati et al. *Nat Rev Immunol*. 2013.
AMD=age-related macular degeneration; GA=geographic atrophy; nAMD=neovascular age-related macular degeneration; RPE=retinal pigment epithelium.

Stages of Dry AMD

- Early
- Intermediate
- Advanced
  - Extrafoveal
  - Subfoveal

Early and Intermediate AMD

- Early (H35.3111, H35.3121, H35.3122)
  - characterized by a combination of multiple small drusen, few intermediate drusen (63–124 µm in diameter)
- Intermediate (H35.3112, H35.3122, H35.3132)
  - extensive medium drusen (63–124 µm in diameter) or one or more large drusen (≥125 µm in diameter) with any pigmentary abnormalities

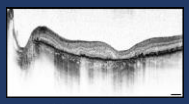
[1]American Academy of Ophthalmology Preferred Practice Patterns 2019

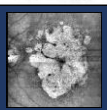
Advanced AMD

- Extrafoveal (H35.3113, H35.3123, H35.3133)
  - Patients usually have good central vision in absence of other pathology
  - May have difficulty with near-vision activities
- Fovea-involving (H35.3114, H35.3124, H35.3134)
  - Central vision is often moderately or severely impaired
  - approximately 10% of all AMD-related visual loss of 20/200 or worse

[1]American Academy of Ophthalmology Preferred Practice Patterns 2019

- When secondary to age-related macular degeneration (AMD), GA is defined by the presence of sharply demarcated atrophic lesions of the outer retina
- Lesions result from the loss of photoreceptors, retinal pigment epithelium (RPE), and underlying choriocapillaris
- These anomalies lead to irreversible vision loss





Rademaker M, et al. Ophthalmology 2008;115:1049-50

GA is an advanced form of age-related macular degeneration

Images from: https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/AMD.htm; https://imagebank.asrs.org/file/6296/age-related-macular-degeneration-geographic-atrophy

Early non-neovascular AMD
combination of multiple small drusen, few intermediate drusen (63-124 µm), or mild RPE atrophy

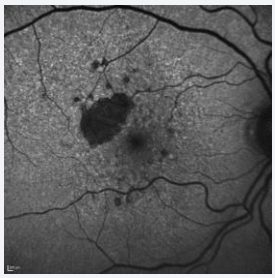
Intermediate AMD
large drusen (>125 µm), presenting as sharply defined, usually round or oval areas of atrophy in the RPE

Advanced AMD
may present as neovascular disease or geographic atrophy (GA). GA is characterized by large, confluent regions of atrophied RPE

AMD=age-related macular degeneration; RPE=retinal pigment epithelium
Ambati J, et al. *Nat Rev Immunol*. 2013;13:438-51. Images from: https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/AMD.htm https://imagebank.asrs.org/file/6296/age-related-macular-degeneration-geographic-atrophy

GA progression is relentless

Courtesy Frank Hdz., MD

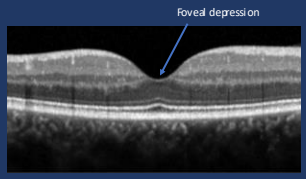


How to Follow Patients with GA

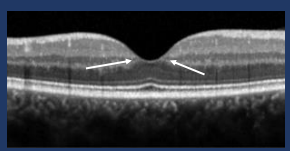
- OCT, OCT, OCT
- Fundus Autofluorescence Photos
  - Can use Blue Peak Autofluorescence (but not for clinical trials)
- Fundus Color Photos

Normal Anatomy

How do I identify the Foveal Center?

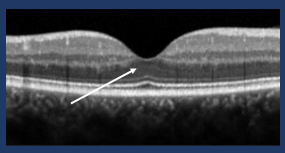


How do I identify the Foveal Center?



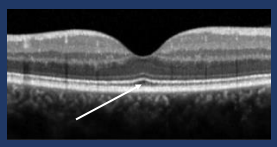
Ganglion cell complex tapers to a point on either side of foveal center

How do I identify the Foveal Center?



Triangular outer nuclear complex (triangle with base down)

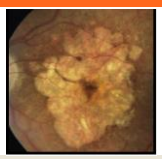
How do I identify the Foveal Center?



Elongated photoreceptor outer segments "bumping up" ellipsoid zone and external limiting membrane

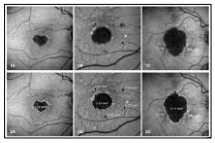
Imaging studies identify the clinical features of GA

A. Fundus photograph of geographic atrophy



Adapted from reference 1

B. Detection and quantification of atrophy on FAF

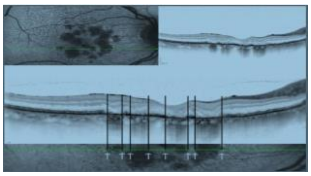


Adapted from reference 2

ETDRS=Early Treatment Diabetic Retinopathy Study; FAF=fundus autofluorescence; GA=geographic atrophy.
1. Fleckenstein M, et al. Ophthalmology 2018;125:369-390.
2. Davis RP, et al. Invest Ophthalmol Vis Sci. 2013;54:4549-59.

Degeneration of RPE and photoreceptor cell death are key features of GA

Severely decreased FAF over areas of atrophy is spatially confined to **a loss of photoreceptors on the SD-OCT**



Adapted from Holz FG, et al. 2014.

GA=geographic atrophy; RPE=retinal pigment epithelium; FAF=fundus autofluorescence.
Holz FG, et al. Ophthalmology. 2014;121:1079-91.

2018 CAM classification system of GA is based on OCT findings

CAM criteria for diagnosing cRORA

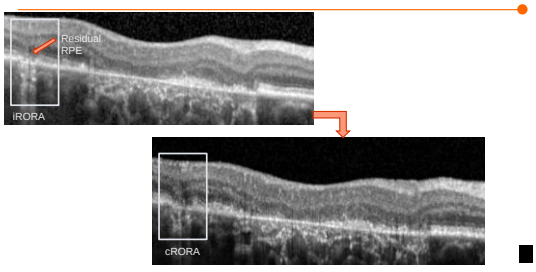
1. Region of hypertransmission ≥250 µm in diameter
2. RPE zone of attenuation/disruption ≥250 µm in diameter
3. Evidence of overlying photoreceptor degeneration
4. Absence of scrolled RPE or other signs of an RPE tear

CAM Consensus Classification of Atrophy in AMD

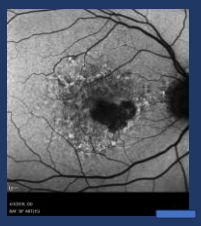
Term	Abbreviation
Complete RPE and outer retinal atrophy	cRORA
Incomplete RPE and outer retinal atrophy	iRORA
Complete outer retinal atrophy	cORA
Incomplete outer retinal atrophy	iORA

CAM terms may be used to describe atrophy in the presence or absence of CNV

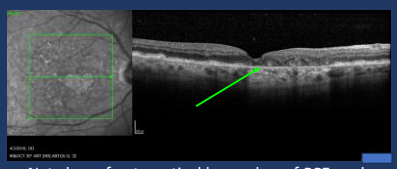
AMD=age-related macular degeneration; CAM=Classification of Atrophy Meetings; CNV=choroidal neovascularization; GA=geographic atrophy; OCT = optical coherence tomography; RPE=retinal pigment epithelium.
Sadda SR, et al. Ophthalmology. 2018;125:537-48.



Non Foveal Centered GA?

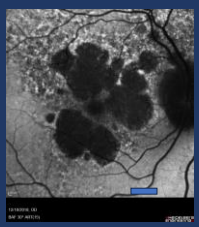


Use OCT!

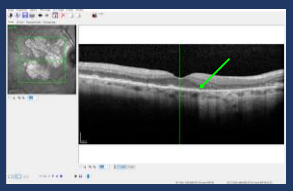


Note loss of outer retinal layers, loss of RPE, and choroidal hypertransmission to right of green arrow

Non Central GA?

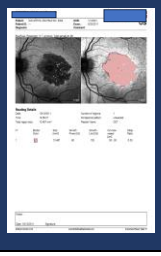


Use OCT!



Here the region of outer retinal loss, RPE loss, and hyper-transmission (green arrow) is clearly away from foveal center (vertical green line)

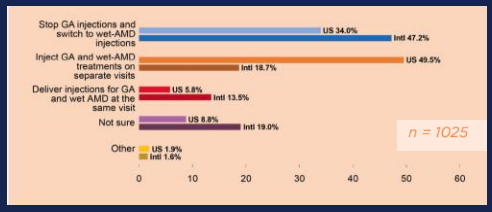
Determining Lesion Size: Region Finder



Cavitations: Not CNV

Note irregular shaped hyporeflective spaces corresponding to degenerative cavitations (tip of arrow)

How Do You Manage an Eye That Develops Wet AMD During Ongoing GA Treatment?



SYFOVRE (pegcetocoplan) and IZERVAY (avacincaptad pegol)

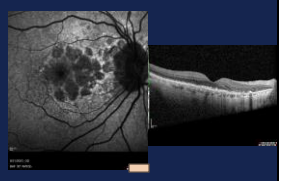
Real-world clinical challenges

- GA lesion(s) characteristics and treatment risk:benefit
  - Safety concerns…IOI/CNVM
- Bilateral GA
  - Treat better eye or worse eye first?
  - Same day bilateral treatment?
- GA and concomitant wet AMD eye treated with anti-VEGF
  - Should we treat these patients?
  - When to treat for GA and when to treat for wet AMD? Same day? Alternate?
- Patients with history of vitrectomy
- Patients with significant glaucoma or history of glaucoma surgery
- Patients with concurrent port delivery system

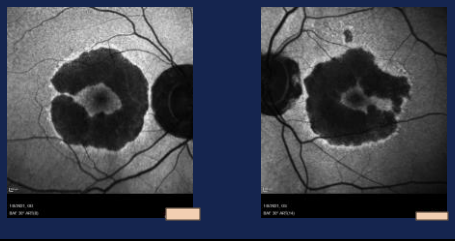
73 y.o female….monocular

- BCVA 20/30 OD, CF OS
- Hx untreated CNVM OS w/ disciform scar

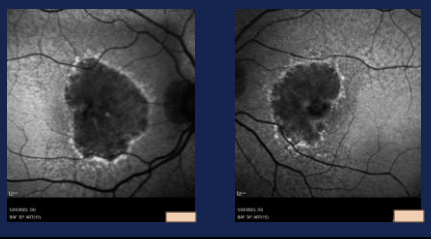
October 2022 → August 2023



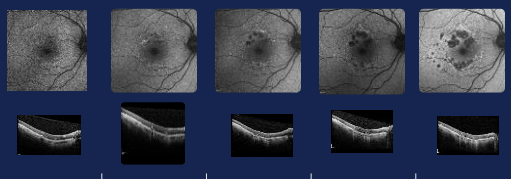
87 y.o. female....20/40 ou...GA is growing OU



87 y.o. female 20/400 od, 20/200 os complaining of worsening vision, and depressed



78 y.o retired male; hx wet AMD OS



	Baseline	7 months	1 year 8 months	2 years 3 months	3 years 4 months
Lesion area	0. 15 mm²	0. 27 mm²	0. 34 mm²	1. 49 mm²	5. 09 mm²
Distance to fovea center	1001 µm	935 µm	859 µm	571 µm	503 µm
BCVA	20/30	20/30 *	20/40 -1	20/40 -1	20/40 -1