DIABETIC RETINOPATHY: UNDERSTANDING BARRIERS AND BUILDING EQUITY

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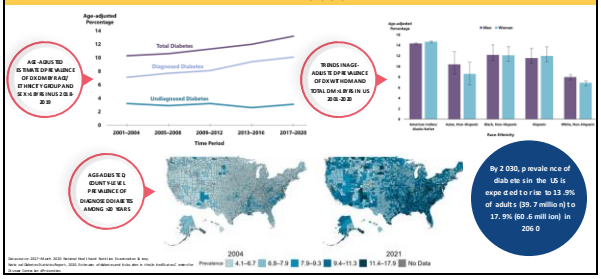
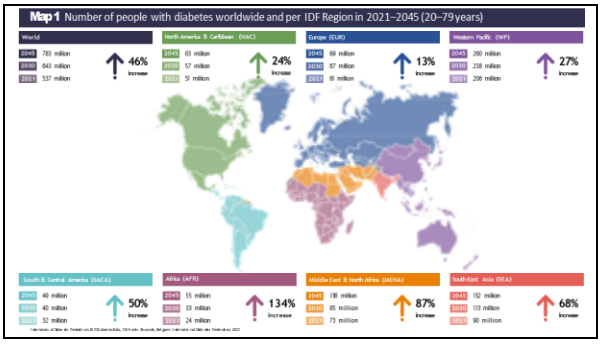
February 2025

Financial Disclosure

- Consultant: Alimera, Allergen, Alcon, Genentech, Ocuphire Pharm, Ocular Therapeutics, ANI Pharmaceuticals
- Investigator: Alimera, Genentech, Inc., Jaeb Center for Health Research, Regeneron, Novartis, Ocuphire Pharm, Parexel, Ocular Therapeutics
- Speaker: Genentech, Inc., Apellis, Astellas, Regeneron

DIABETES IS INCREASING IN PREVALENCE IN THE U.S.



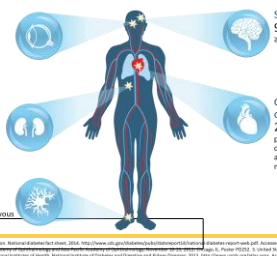


DIABETIC RETINOPATHY–RACIAL AND ETHNIC DISPARITIES

- Among those with diabetes, the prevalence of diabetic retinopathy was **33.4% in Hispanics** and **26.5% in Blacks** compared to **18.2% in Whites**[1]
- **Blacks** also had an **increased risk of developing moderate/severe retinopathy** compared to Caucasians[2]
- **Native Americans** have one of the highest prevalence rates of diabetic retinopathy, with a rate of **45.3%** compared with non-Native American populations[1]
- Compared to Caucasians, **Blacks and Hispanics have increased insulin resistance** and augmented insulin secretion/hyperinsulinemia independent of adiposity[3]

DIABETES-ASSOCIATED CO-MORBIDITIES

Primary providers of diabetes care coordinate with multiple specialties



Diabetic retinopathy[1]
28.5% of diabetes patients ≥40 years old have DR

≈13.6% have diabetic macular edema (DME)[2]

Diabetic nephropathy[3]
29.9% of patients with diabetes

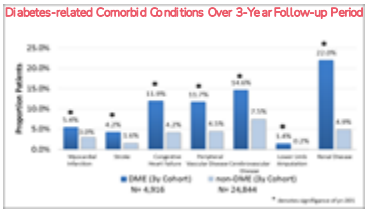
Diabetic neuropathy[1]
60%-70% of people with diabetes have some form of nervous system damage

Stroke[4]
9.1% of diabetes patients ≥35 years old

Coronary heard disease[4]
21.9% of diabetes patients ≥35 years old have coronary heart disease or angina or have had a myocardial infarction

Healthcare Utilization Among Diabetic Patients With & Without DME: Comorbid Conditions

The DME population exhibited more comorbid conditions at baseline compared with the non-DME diabetic cohort, and the disparity widened after 3 years of follow-up.



Wolfe C et al. Presented at the Association for Research in Vision and Ophthalmology 2024 Annual Meeting; May 4–8, 2024; Orlando, FL, USA

Demographic, Non-demographic & Social Factors in Health Disparity

"A health disparity is a particular type of health difference that is closely linked with social or economic disadvantage." —US government

Demographic
- Sex or gender
- Race or ethnicity
- Age
- Geography (rural vs urban)
- Genetics

Non-Demographic
- Comorbidities
- Disability
- Environmental factors
- Adherence
- Can be *historically, socially, and culturally determined*

Social
- Socioeconomic status/income
- Education/literacy
- Immigrant status
- Religion
- Food insecurity
- Includes those within SDOH

US = United States; SDOH = social determinants of health.

The Domains of SDOH

- Minority ethnicity, lower educational attainment, lower income, and lack of insurance are all associated with greater visual impairment in the United States
- Addressing SDOH will promote attainment of full potential for health and well-being for all

CDC. Social determinants of health. (https://health.gov/healthypeople/objectives-and-data/social-determinants-health). Accessed 5/2022. 2. American Academy of Ophthalmology (AAO). Basic and clinical science course (BSCC) 2022-2023. Section 1, Chapter 17. Social determinants of health

Comparative Study > Ophthalmic Epidemiol. 2020 Apr;27(2):93-97.
doi: 10.1080/09286586.2019.1680703. Epub 2019 Oct 28.

Associations of Social Determinants of Health and Self-Reported Visual Difficulty: Analysis of the 2016 National Health Interview Survey

Nancy H Su [1], Nathaniel R Moxon [1], Andrew Wang [2], Dustin D French [1 2 3]

- **Non-White race, lower educational attainment, lower income,** and **being uninsured** were associated with **higher rates of visual impairment**
- **Male gender** were associated with **decreased risk of visual impairment**

Gender				
Male	0.91	0.88	0.94	<0.001
Female	—	—	—	Reference
Race*				
Black	1.32	1.25	1.39	<0.001
Hispanic	1.61	1.53	1.70	<0.001
Other	1.36	1.27	1.45	<0.001
Multiracial	1.47	1.34	1.62	<0.001
White	—	—	—	Reference
Education				
Did not graduate high school	1.68	1.59	1.78	<0.001
Graduated high school	1.26	1.20	1.32	<0.001
Attended college or technical school	1.20	1.14	1.25	<0.001
Graduated college or technical school	—	—	—	Reference
Annual household income ($)				
< 25 000	4.56	4.31	4.83	<0.001
25 000–50 000	2.40	2.27	2.54	<0.001
50 000–75 000	1.48	1.38	1.59	<0.001
75 000+	—	—	—	Reference
Health insurance coverage				
No	1.07	1.01	1.13	0.023
Yes	—	—	—	Reference

> Ophthalmology. 2022 Apr;129(4):456-458. doi: 10.1016/j.ophtha.2021.10.012. Epub 2021 Oct 19.

Disparities in Self-Reported Difficulty Seeing in the United States

Sara Al Hussein Al Awamlh [1], Sean Berkowitz [1], Mark P Breazzano [2], Avni P Finn [1], Shriji Patel [3]

Table 1. Self-Reported Difficulty Seeing Based on Socioeconomic Demographics

Characteristic	Percentage	95% CI
Employment Status		
Employed	12.7	(12.2–13.3)
Not employed	22.9	(21.9–23.9)
Full-time	12.3	(11.7–13.0)
Part-time	14.5	(13.0–16.1)
Not employed but has worked previously	23.4	(22.4–24.4)
Not employed but has never worked	17.1	(13.5–21.1)
Education		
Less than high school diploma	25.8	(23.7–28.1)
High school diploma or GED	18.1	(17.1–19.2)
Some college	16.8	(15.8–17.8)
College degree or higher	12.2	(11.5–12.9)
Poverty Status		
Poor	24.8	(22.9–26.8)
Near poor	20.1	(18.8–21.5)
Not poor	14.0	(13.4–14.6)
Health Insurance Coverage: Adults Aged 18–64 Yrs		
Private	12.3	(11.7–12.9)
Medicaid or other public	22.9	(21.0–25.0)
Other coverage	21.6	(18.6–24.9)
Uninsured	16.5	(14.8–18.4)
Health Insurance Coverage: ≥ 65 Yrs		
Private	19.3	(17.9–20.7)
Medicare and Medicaid	35.2	(30.2–40.5)
Medicare Advantage	21.6	(19.8–23.5)
Medicare only (no Advantage)	21.5	(18.8–24.5)
Other coverage	24.0	(20.5–27.9)
Uninsured	Estimate does not meet National Center for Health Statistics standards of reliability	Estimate does not meet National Center for Health Statistics standards of reliability

CI = confidence interval; GED = General Educational Diploma.

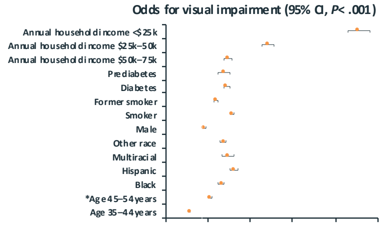
Difficulty seeing was reported at higher rates in *unemployed, lower educated, poor income, and lower tiered insurance*

Significant Visual Disparities Exist Across Race, Income & Comorbidities

Data from 2018 Behavioral Risk Factor Surveillance System (N = 426,302)

- Minority race and lower income are also associated with higher rates of visual impairment
- Causes of disparity are complex and ***likely influenced by*** **patient-, provider-, and healthcare systems-level factors**

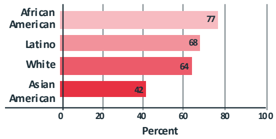
Odds for visual impairment (95% CI, *P* < .001)



Multivariate logistic regression; *P=.011; all other P-values <.001.
Uhr JH, et al. *Ophthalmology*. 2021;128:1102-1104.

Disproportionate Burden of Chronic Illness for Racial & Ethnic Minorities

Proportion of adults aged ≥50 years with chronic conditions,* by race/ethnicity



- Older African Americans and Latinos are more likely to have ≥1 of costliest chronic conditions*
- Higher morbidity and mortality
- Consequences can range from greater financial burden to higher activity limitations
  - African Americans and American Indians/Alaska Natives are more likely to be limited in activity
- **Poorly controlled and long-standing diabetes, obesity, and hypertension** are known risk factors for DR, AMD, and/or RVO

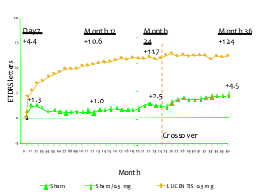
*Diagnosed with 1 of 7 chronic conditions (asthma, cancer, heart disease, diabetes, obesity, hypertension, or anxiety/depression).

AMD = age-related macular degeneration; RVO = retinal vein occlusion.

Georgetown University Health Policy Institute (HPI). Cultural competence in health care: is it important for people with chronic conditions? Accessed 5/3/2022 (https://hpi.georgetown.edu/cultural/) Flaxel CJ et al. *Ophthalmology.* 2020;127:P66-P145. Seddon JM et al. *Arch Ophthalmol.* 2003;121:785-792. Flaxel CJ et al. *Ophthalmology.* 2020;127:P288-P320.

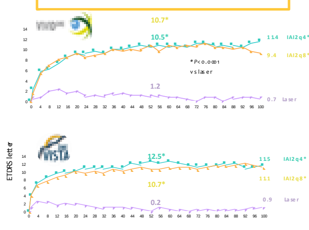
Delaying treatment with LUCENTIS resulted in worse VA gains after 12 months compared to prompt treatment

RISE and RIDE



Sham subjects who crossed over to LUCENTIS 0.5 mg at or after month 25: n=190

Mean Change in BCVA Through Week 100

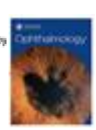


Compared with baseline; last observation carried forward.
VISTA: FAS Laser: n=154; IAI 2q4: n=154; IAI2q8 n=151 VIVID FAS Laser: n=132; IAI 2q4: n=136; IAI2q8 n=135.

Real World Data Study (2021)

Racial, Ethnic, and Insurance-Based Disparities Upon Initiation of Anti-VEGF Therapy for Diabetic Macular Edema in the United States

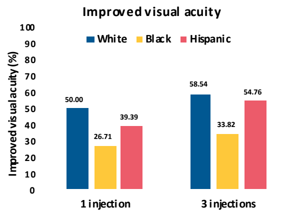
Nisha A. Malhotra, MPH, Tyler E. Greenlee, DO, Amogh I. Iyer, BS, Thais F. Conti, MD, Andrew X. Chen, BSE, Rishi P. Singh, MD



- Using IRIS registry data from 2012-2020
- n= 203,707 patients
- Black and Hispanics present with worse Baseline DR Severity

Race & Ethnicity Have Impact on Treatment Efficacy: Retrospective Cohort Study of Bevacizumab for DME

- Black patients had a ***significantly lower likelihood of visual acuity improvement*** following 3 injections of intravitreal bevacizumab (OR= 0.342)
- No difference on CMT reductions after 1 or 3 injections in any group
- If no improvement after first injection, likelihood of improving after 3 was low
- Race can potentially impact Tx response
- Further research is needed to understand the effect of race and ethnicity for optimal treatment of each individual patient



Osathanugrah P, et al. *Am J Ophthalmol*. 2021;222:310-317.

Disparities in Retinal Clinical Trials

Disparities in DME trials

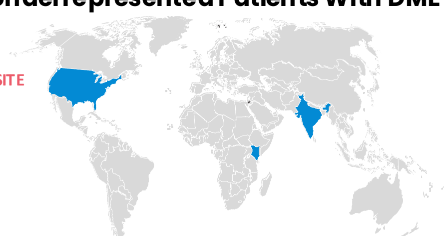
	Drug	% African American/ Black	% Latin American/ Hispanic	% White
Protocol T[1]	L/E/A	15.6	N/A	66.1
RIDE/RISE[2]	L	12.2	22.3*	79.4
BOULEVARD[3]	F/L	18.5	17.2*	76.9
YOSEMITE/RHINE[4]	F/E	6.5	16.6	78.5
VIVID/VISTA[5]	E	6.1	N/A	81.7

*Overlaps with White population. A=Avastin; E=Eylea; F=faricimab; L=LUCENTIS; N/A=not applicable.
1. Diabetic Retinopathy Clinical Research Network, et al. *N Engl J Med*. 2015;372(13):1193–1203. 2. Nguyen QD, et al. *Ophthalmology*. 2012;119(4):789–801. 3. Sahni J, et al. *Ophthalmology*. 2019;126(8):1155–1170.
4. Wyckoff CC, et al. Presented at: Angiogenesis, Exudation, and Degeneration 2021 – Virtual Edition; February 12–13, 2021. 5. Korobelnik JF, et al. *Ophthalmology*. 2014;121(11):2247–2254.

Minority populations have been **largely underrepresented in clinical trials** that led to FDA-approved ophthalmology therapies

Elevatum Study Design and Rationale: A Phase 4 Trial of Faricimab (VABYSMO) in Underrepresented Patients With DME

GLOBAL SITE MAP



Elevatum: Key Eligibility Criteria

Key General Inclusion Criteria

- ✓ **Patients ≥ 18 years** who self-identify as:
  - **Black/African American (~45%)**
  - **Hispanic/Latino American (~45%)**
  - **Native American/Alaska Native/Native Hawaiian** or other **Pacific Islander (~10%)**
- ✓ Patients with **type 1 or 2 diabetes mellitus** who are regularly using insulin, other injectable drugs, or oral anti-hyperglycemic agents
  - **HbA1c ≤ 10%** during screening (**up to 20%** of enrolled patients **may have HbA1c up to 12%**)

Key Ocular Inclusion Criteria for the Study Eye

- ✓ Patients* with **DME without prior** IVT **anti-VEGFs** or any IVT or periocular **corticosteroids**
- ✓ BCVA of **20–73** ETDRS **letters** (~20/40–20/400 Snellen) (both inclusive) at the initial testing distance of 4 meters at baseline (day 1)
- ✓ CST of **≥ 325 µm**†

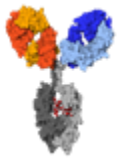
Key Ocular Exclusion Criteria for the Fellow Eye

Ongoing treatment with **brolucizumab** or **bevacizumab**

*Patients with HbA1c ≤10% during screening (up to 20% of patients enrolled may have HbA1c up to 12%). †CST measured from inner limiting membrane to Bruch's membrane.
BCVA, best-corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; HbA1c, hemoglobin A1c; IVT, intravitreal; VEGF, vascular endothelial growth factor.

ELEVATUM Preliminary Results (*presented at AAO 2024*)

- Of the 124 U.S. participants, 48% self-identified as Black and/or African American, and 45% self-identified as Hispanic and/or Latino
- Initial results showed clinically meaningful improvement in vision and reduction in retinal fluid
- Efficacy and safety results were consistent with data from the Faricimab-svoa Phase III DME studies.
- After one year of treatment with , Faricimab-svoa administered every eight weeks, participants could read an additional 12.3 letters on average
  - Hispanic and Latino participants started the study with the most severe disease and had an average vision gain of 14.1 letters at one year
  - African American and Black participants gained 11.3 letters at one year
- Faricimab-svoa was well tolerated, with no new safety events identified



Key Takeaways

- Diabetes is "a pandemic of unprecedented magnitude" now affecting one in 10 adults worldwide
- Disparities in diabetes are associated with age, race, ethnicity, socioeconomic status and access to healthcare.
- Racial and ethnic minorities with more SDOH have higher rates of morbidity and mortality
- Understand the differential responses to treatment
- Minority populations have been largely underrepresented in clinical trials that led to FDA-approved ophthalmology therapies
- Continue to develop safe, efficacious medications with better durability to decrease treatment burden

THANK YOU

Improving Outcomes in Patients With RVO: Tailoring Treatment

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

RVO: The Second Most Prevalent Retinal Vascular Disease

- RVO is estimated to affect **28 million** adults worldwide
- RVO is the **second most common** cause of **vision loss** due to retinal vascular disease (after diabetic retinopathy)
- The **most common reason** for **vision loss** in RVO is **macular edema**
- **BRVO** is **3 to 10 times more common than CRVO**

Prevalence increases with age
>1 million people >55 yr of age are currently affected by RVO in Europe (0.7% prevalence)

Affects men and women equally

Prevalence may be higher in Asian and Hispanic populations

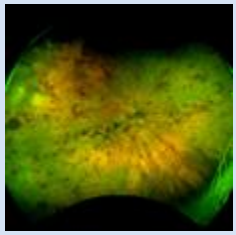
anglo.org/downloads/Informational_Guide-Science_of_CRVO.pdf .euretina.org. Lacout. Eye (Lond) . 2011;25:981. Mitry. Cochrane Database Syst Rev 2013;1:CD009510. Rogers S,et al. Ophthalmology. 2010;117:313. Song. J Glob Health.2019;9:010427.

Epidemiology

- Retinal vein occlusions (RVOs) are a leading cause of retinal vascular disease and include:
  - Central RVO (CRVO)
  - Hemi RVO (HRVO)
  - Branch RVO (BRVO)
- BRVOs account for nearly 80% of RVOs
- Average age: 65 yr
- VA and age are predictors of outcomes
- RVO risk factors include hypertension, diabetes mellitus, atherosclerosis, and open-angle glaucoma

Evaluation and Treatment RVO

- Systemic risk factors
- Treatment goals:
  - Address macular edema
  - Unable to resolve ischemia … ischemia may progress independent of treatment



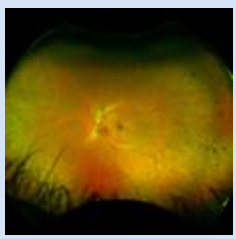
Systemic Evaluation

- No definitive guidelines
- Patients aged >50 yr with risk factors:
  - Refer back to primary care provider
  - Optimize blood pressure, lipids, and blood glucose
- Patients aged <50 yr without risk factors
  - Consider evaluation for inborn or acquired causes of hypercoagulability

Yau. Internal Med J. 2008;38:904.

Diagnosis of RVO

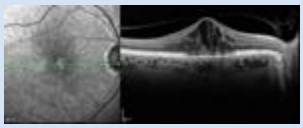
- Clinical diagnosis
  - Typically, dilation + tortuosity retinal veins AND retinal hemorrhages
  - Usually sufficient for diagnosis of acute cases
- Utility of multimodal imaging
  - Atypical/equivocal features/young patients
  - Chronic
  - Confirm diagnosis/presence of CME
  - Evaluate for coexisting features: PAMM, DRIL, outer retinal disruption, FAZ integrity
  - OCT biomarkers for prognosis
  - Quantify ischemia: peripheral or FAZ
  - Evaluate response to therapy and need for further therapy, direct treat-and-extend
  - Better understand pathogenesis



Talcott K. Review of Ophthalmology. https://www.reviewofophthalmology.com/article/rvo-diagnosis-and-management. Image courtesy of: Avni Finn MD, MBA

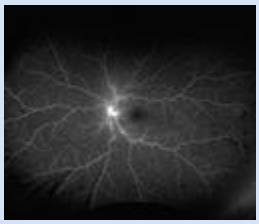
Options for Multimodal Imaging in RVO

- Clinical examination → treat
- OCT →
  - Confirm CME, tailoring treatment regimen
  - Rule out/in other pathology
  - Explain visual field deficits
  - Evaluate new therapies
  - OCT biomarkers: prognostic features, AI
- OCT angiography
  - Exploration of pathogenesis, reduce need for fluorescein angiography (FA)



Reihan N. Retina Today. 2018. https://retinatoday.com/articles/2018-apr/imagig-options-in-retinal-veh-occlusion. Image courtesy of: Avni Finn MD, MBA

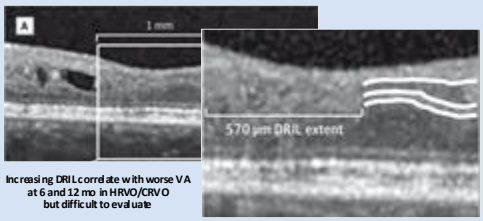
Options for Multimodal Imaging in RVO



- Fluorescein angiography
  - Confirm diagnosis especially atypical RVO, young patients
  - Ischemic index, predict neovascular response
  - Identify retinal artery occlusion (RAO), other vascular disease
- Widefield and multimodal imaging: individualized, machine learning, entire picture

Reihan N. Retina Today. 2018 Image courtesy

OCT Biomarkers – Disorganization of the Retinal Inner Layers



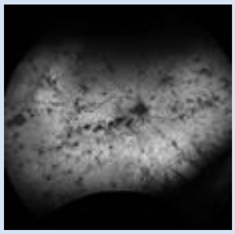
Increasing DRIL correlate with worse VA at 6 and 12 mo in HRVO/CRVO but difficult to evaluate

Sun K.JA MA Ophthalmol.2014;132:1329.

Factors That Affect Visual Prognosis

Baseline BCVA

- While poorer baseline VA ~ greater VA gains (likely ceiling effect), overall VA outcomes ~ initial VA
- BRVO natural history
  - Of eyes with initial VA ≥20/60, >75% maintained or improved vision
  - Of eyes with initial VA <20/60, over half had improved vision
- CRVO natural history
  - Of eyes with initial VA ≥20/40, 65% maintained vision in that range
  - Of eyes with initial VA <20/200, 80% stayed in that range



Hayreh SS, et al JAMA Ophthalmol 2014;132:13. The Central Vein Occlusion Study. Ophthalmology. 1995;102:1434. Image courtesy of: Avni Finn MD, MBA.

Factors That Affect Visual Prognosis

Age

- Older patients fare worse than younger patients, possibly related to the ability of photoreceptors to recover

Ischemic status

Type of RVO (CRVO versus BRVO)

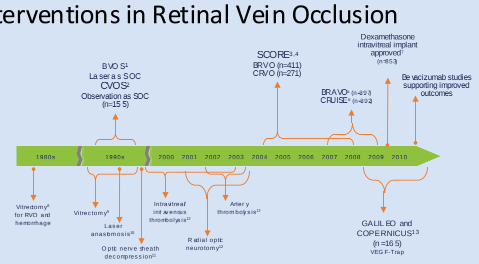
- BRVO has better prognosis than CRVO; over half of eyes will return to VA ≥20/40
- In nonischemic CRVO, approximately half return to baseline or near-baseline vision

Prompt treatment

- Shorter duration of CME is associated with better VA outcomes, especially in BRVO

The Central Vein Occlusion Study Group. Ophthalmology. 1995;102:1434 Scott IU. Ophthalmology. 2011;118:345. Ho AC. Retina Society 2010 Annual Meeting; September 23-26, 2010; San Francisco, CA. Hayreh SS. JAMA Ophthalmol. 2014;132:13. Blair K. StatPearls [Internet]. Updated December 26, 2022. Accessed September 5, 2023. https://www.ncbi.nlm.nih.gov/books/NBK551502/. Yeh WS. Ophthalmology. 2012;119:1190. Campochiaro PA. Ophthalmology. 2011;118:2041. Brown DM. Am J Ophthalmol. 2013;155:429..

Interventions in Retinal Vein Occlusion

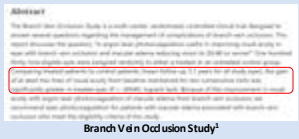


BVOS = Branch Vein Occlusion Study; CVOS = Central Vein Occlusion Study; SOC = standard of care; VEGF = vascular endothelial growth factor.

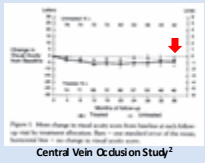
1. Branch Vein Occlusion Study Group. *Am J Ophthalmol.* 1984;98(3):271-282; 2. Central Vein Occlusion Study Group. *Ophthalmology.* 1995;102(10):1425-1433; 3. Ip MS, et al *Arch Ophthalmol.* 2009;127(9):1101-1114; 4. Scott IU, et al *Arch Ophthalmol.* 2009;127(9):1115-1128; 5. Campochiaro PA, et al *Ophthalmology.* 2010;117(6):1102-1112; 6. Brown DM, et al *Ophthalmology.* 2010;117(6):1124-1133; 7. Haller JA, et al. *Ophthalmology.* 2010;117(6):1134-1146; 8. Yeshaya A, et al. *Ann Ophthalmol.* 1983;15(7):615-617; 9. Amirikia A, et al. *Ophthalmology.* 2001;108(2):372-376; 10. McAllister IL, et al. *Arch Ophthalmol.* 1995;113(4):456-462; 11. Dev S, et al. *Ophthalmic Surg Lasers.* 1999;30(3):181-184; 12. Shahid H, et al. *Br J Ophthalmol.* 2006;90(5):627-639; 13. Pielen A, et al. *Clin Ophthalmol.* 2017;11:1533-1540.

Laser Treatment for Macular Edema (ME) following RVO

- Macular laser photocoagulation became standard of care for treatment of ME following RVO in BRVO due to findings in the Branch Vein Occlusion Study
- Laser was not beneficial for ME following RVO in the Central Vein Occlusion Study



Branch Vein Occlusion Study[1]

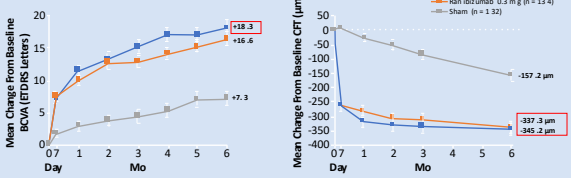


Central Vein Occlusion Study[2]

1. The Branch Vein Occlusion Study Group. Am J Ophthalmol. 1984;15; 98:271.
2. The Central Vein Occlusion Study Group. Ophthalmology. 1995;102:1425.

Phase III BRAVO: Results

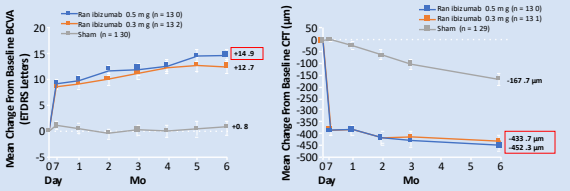
- The phase III BRAVO study established the efficacy of ranibizumab for treatment of ME from BRVO



Campochiaro. Ophthalmology. 2010;117:1102.

Phase III CRUISE: Results

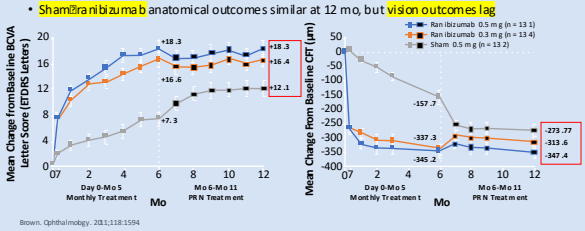
- Phase III CRUISE study established efficacy of ranibizubmab for treatment of ME from CRVO



Brown. Ophthalmology. 2010;117:1124

Phase III BRAVO: 12-Mo Results

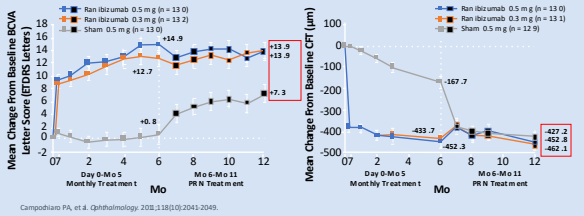
- Monthly ranibizumab PRN ranibizumab shows sustained effects
- Sham ranibizumab anatomical outcomes similar at 12 mo, but vision outcomes lag



Brown. Ophthalmology. 2011;118:1594

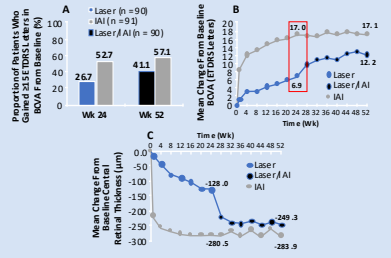
Phase III CRUISE: 12-Mo Results

- Monthly ranibizumab PRN ranibizumab shows sustained effects
- Sham ranibizumab anatomical outcomes similar at 12 mo, but vision outcomes lag



Campochiaro PA, et al. Ophthalmology. 2015;118(10):2041-2049.

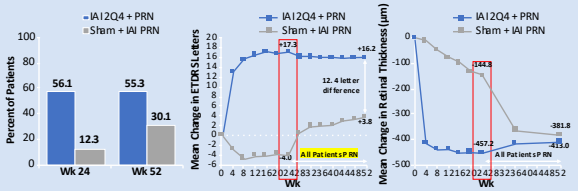
Phase III VIBRANT: Aflibercept for ME from BRVO: 6- and 12-Mo Results



- Monthly aflibercept q8 aflibercept shows sustained effects
- Laser aflibercept anatomical outcomes similar at 12 mo, but vision outcomes lag

Clark. Ophthalmology. 2016;123:330-336.

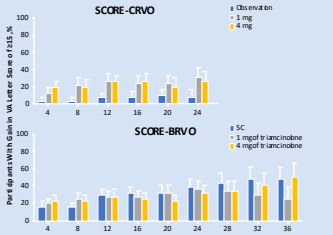
Phase III COPERNICUS: Aflibercept for ME from CRVO: 12-Mo Results



- Monthly aflibercept/PRN aflibercept shows sustained effects at Wk 52, although there was attrition of gains by Wk 102
- Sham/PRN aflibercept anatomical outcomes similar at 12 mo, but vision outcomes lag

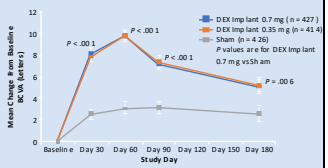
SCORE: Evaluated Triamcinolone for ME Following RVO

- The SCORE studies were 2 phase III trials comparing triamcinolone (1 or 4 mg) vs standard of care for BRVO and CRVO-associated CME
- For CRVO, triamcinolone was superior to observation
- For BRVO, triamcinolone did not show a difference in primary endpoint over laser photocoagulation



GENEVA: Evaluation of Dexamethasone for ME Following RVO

- The GENEVA studies were two 6-mo, randomized controlled trials including 1267 patients with BRVO and CRVO
- Patients were randomly assigned to dexamethasone (DEX) 0.7 or 0.35 mg vs sham
- Primary outcome was time to achieve a 15-letter BCVA improvement
  - Time was significantly less in both DEX groups vs sham



Mean Change in Central Retinal Thickness

	DEX Implant 0.7 mg (n = 427)	DEX Implant 0.35 mg (n = 414)	Sham (n = 426)	P Value vs Sham 0.35 mg/0.7 mg
Day 90 Adjusted (µm ± SD)	-208 ± 201	-177 ± 197	-85 ± 173	<0.001/<0.001
Day 180 Adjusted (µm ± SD)	-119 ± 203	-123 ± 212	-119 ± 188	NS/NS

GENEVA and SCORE: Cataract and IOP Events

- In GENEVA, there was no significant difference in cataract rate between groups over 180 days
  - In MEAD, cataract rate was about 65% over 3 yr for patients treated with DEX
- At day 60 in GENEVA, <16% of eyes had IOP ≥25 mm Hg; increases were typically transient, with no difference between groups by Day 180
  - Nearly all cases of elevated IOP were managed with observation or topical medications
- In SCORE studies, the rates of elevated IOP and cataract were similar for the observation and 1-mg groups, but higher in the 4-mg group

Burden of RVO

Regular appointments

- 53% of working patients take ≥1 day off work per appointment
- 71% of patients require caregiver assistance for appointments

Healthcare resource utilisation (HCRU) and increased costs

Patients with RVO:

- Have higher 1-yr HCRU than patients with hypertension or glaucoma
- Incur greater healthcare expenditures over the course of 1 and 3 yr compared with patients with hypertension or glaucoma

This increase is primarily driven by use of imaging services and treatments.*

Frequent injections

- Patients with RVO undergo intensive treatment regimens that require frequent long-term injections
- ~75% of patients reported experiencing injection anxiety; 54% reported anxiety for at least 2 days before the injection†

Patients primarily desire **fewer injections** and **fewer appointments** in their treatment regimen for the **same visual results**

*Except OCT. †This study included more patients with DME (n = 86) than patients with RVO (n = 45), and patients with DME reported being more uptight (62% vs 50%), having disease with greater effects on sleep (30% vs 18%), and having a greater reduction in concentration (17% vs 4%) when compared with patients with RVO.

Real-world Outcomes for Patients With RVO

Frequent injections

- In the real world, patients with RVO continue to require frequent anti-VEGF injections, which impose significant burden on patients
- A personalized treatment approach may help reduce the frequency of anti-VEGF injections and reduce patient burden

Worse vision gains and maintenance of visual gains

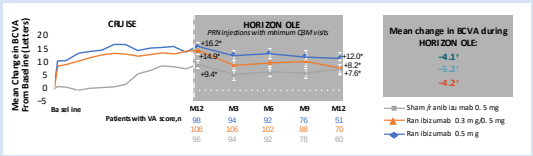
Observational studies have found worse vision gains and maintenance of visual gains with anti-VEGF therapies in the real world compared with clinical trials, in which there are high rates of treatment adherence

- Frequent office visits associated with anti-VEGF therapy are often not feasible in the real world
- Patients receive fewer injections than are needed in the real world, which results in worse vision gains and maintenance of visual gains

Developing RVO therapies that **improve visual outcomes** and **require less-frequent intravitreal injections** are needed to **reduce the burden of RVO** and may **improve compliance** in the **real world**

Vision Gains in RVO Clinical Trials Often Unsustained Over Longer Term

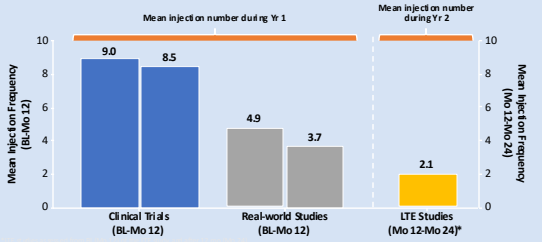
- Patients with CRVO experienced significant vision loss in the HORIZON OLE study
- **Patients with CRVO** who **completed** the **CRUISE** trial (12-mo phase III trial to assess the efficacy and safety of **ranibizumab** injections) were **enrolled in** the **HORIZON OLE** study
  - In HORIZON, the long-term safety and efficacy of **ranibizumab** were assessed for an **additional 12 mo**



*Values relative to CRUISE baseline. †Values relative to HORIZON baseline.
Vertical bars are ±1 SE of the mean.

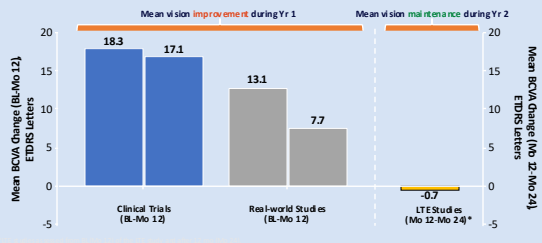
Adapted from Heier. Ophthalmology. 2012;119:802 with permission from Elsevier

Patients With BRVO in LTE and Real-world Studies Received Fewer Mean Injections Over 12 Mo Than Those in Clinical Trials



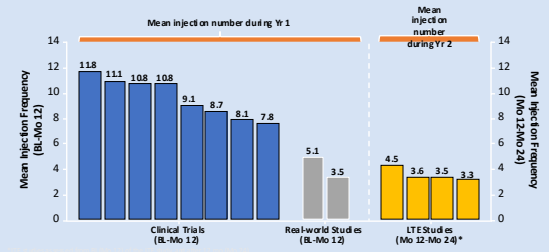
Bhistkul. Invest. Ophthalmol. Vis Sci. 2020;611304.

Patients With BRVO in Real-world Studies Achieved Smaller Gains Than in Clinical Trials, While Patients Maintained the Initial Vision Gains Achieved in Clinical Trials During LTE Studies



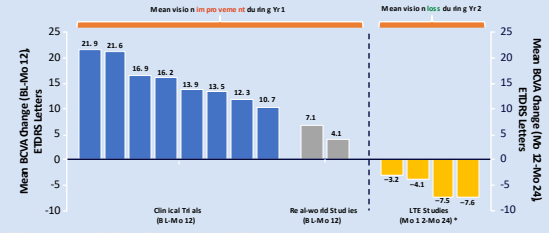
Bhistkul. Invest. Ophthalmol. Vis Sci. 2020;611304.

Patients With CRVO in LTE and Real-world Studies Received Fewer Mean Injections Over 12 Mo Than Those in Clinical Trials



Bhistikul. Invest Ophthalmol. Vis Sci. 2020;611304.

Patients With CRVO in Real-world Studies Achieved Smaller Gains Than in Clinical Trials, While Patients Did Not Maintain the Initial Vision Gains Achieved in Clinical Trials During LTE Studies



Bhistikul. Invest Ophthalmol. Vis Sci. 2020;611304.

CRVO Case Study

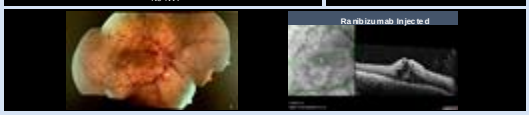
29 May 2012

59-yr-old woman

- Decreased vision for 1 wk in right eye, 20/400
- Left eye, 20/25
- No PMHx
- No APD
- IOP 14
- No NVI
- 1+ NS OU
- Otherwise, normal slit-lamp examination

Laboratory workup

- Elevated homocysteine and ATIII
- Patient referred to cardiology
- ASA 81 mg daily started

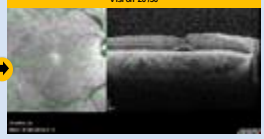


CRVO Case Study

16 November 2012
Patient switched to aflibercept

Status after ranibizumab × 5:
Vision 20/200

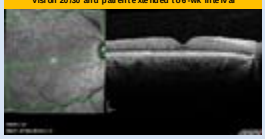
Status after aflibercept × 1:
Vision 20/50



CRVO Case Study

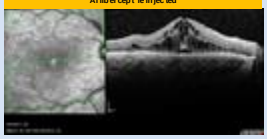
8 February 2013
Aflibercept (4th injection)

Status after aflibercept × 3:
Vision 20/30 and patient extended to 6-wk interval



22 March 2013

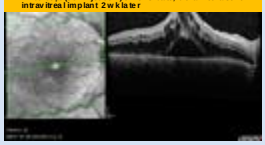
Vision decreased to 20/60 and recurrent edema
Aflibercept reinjected



CRVO Case Study

26 July 2013

- Patient unable to extend past 5 wk (had been coming monthly since May 2012)
- Vision dropped from 20/40 the previous mo to 20/80
- Aflibercept (8th injection) on this date; dexamethasone intravitreal implant 2 wk later



25 October 2013

- The patient still had edema but was tired of continuous injections and refused treatment on this occasion

8 November 2013

- After dexamethasone intravitreal implant, edema improved, but new nerve swelling with increased vascular tortuosity and more dot haemorrhages
- Now with presumed ischemic CRVO
- Aflibercept x 9 injected
- Patient returned 22 Nov 2013 for repeat FA followed by PRP

Ongoing treatment

- Multiple dexamethasone intravitreal implant injections
- More aflibercept injections
- PRP
- Cataract surgery

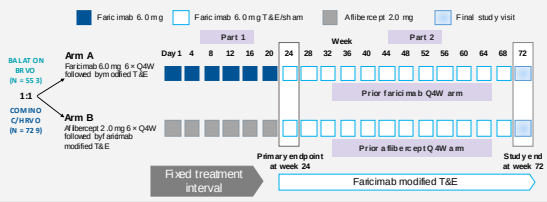
- Patient could no longer keep up with appointments
- Patient burnout after approximately every 4-6 wk for 3 yr
- Vision now at CF with or without edema

Recent/Ongoing Clinical Trials in RVO

- KSI-301 (tarcocimab tedromer)
  - BEACON phase III trial in BRVO/CRVO
    - Study met the primary endpoint, but tarcocimab development discontinued
- Faricimab
  - COMINO phase III trial in HRVO/CRVO
  - BALATON phase III trial in BRVO
    - approved for use in RVO
- Aflibercept 8 mg (vs Aflibercept 2 mg) for CRVO/BRVO
  - QUASAR study
  - Finished enrolling and recently met primary endpoint

Phase 3 Study Design (BALATON, N = 553; COMINO, N = 729)

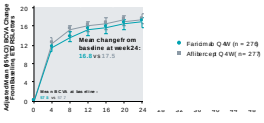
Population: Age ≥ 18 years; treatment-naive macular edema due to RVO; BCVA 73 to 19 letters (20/40 to 20/400)
Primary endpoint: Change from baseline in BCVA at week 24



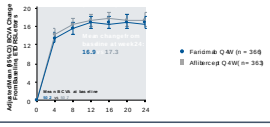
Change in BCVA Over Time: Robust BCVA Gains at Week 24, Comparable Between Treatment Arms

ITT Population

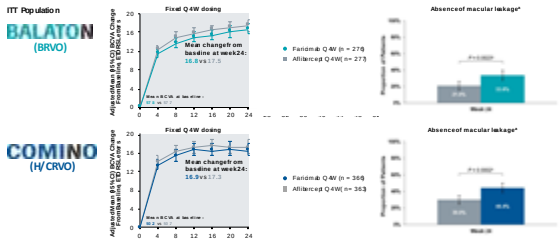
BALATON (BRVO)



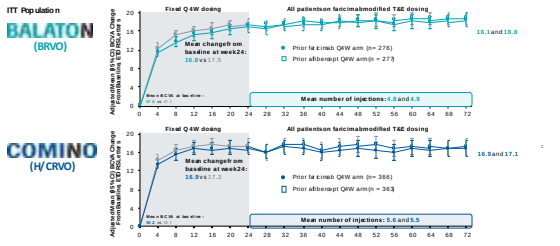
COMINO (H/CRVO)



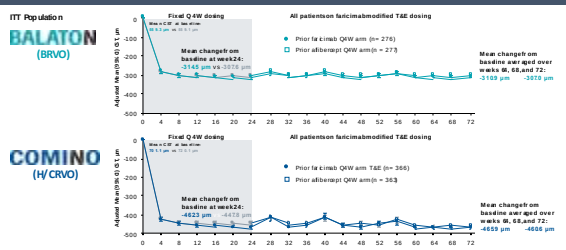
More Patients Achieved Absence of Macular Leakage[a] With Faricimab vs Aflibercept at Week 24



Change in BCVA Over Time: Robust BCVA Gains at Week 24 Maintained Through Week 72 for Both Arms



Change in CST Over Time: CST Reductions Maintained From Week 24 Through Week 72 for Both Arms

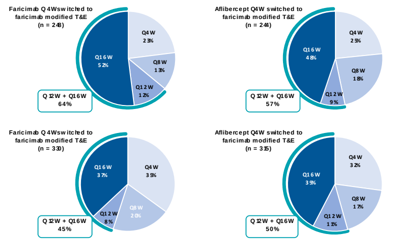


Proportion of Patients on Modified T&E Intervals at Week 68: More Than 57% of Patients in BALATON and More Than 45% in COMINO Achieved ≥ Q12W Dosing

ITT Population

BALATON (BRVO)

COMINO (H/CRVO)



Once reduced, the treatment interval could no longer be extended, except for patients who were on longer intervals and were directly reduced to Q4W (eg, Q16W → Q4W; such patients could be extended to Q12W, but not to Q16W). Treatment interval at a given visit was defined as the treatment interval decision made at that visit. Percentages are based on n: the number of randomized patients who had not discontinued the study at week 68. Descriptive summary is presented. BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; HRVO, hemiretinal vein occlusion; ITT, intent to treat; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

Faricimab Was Well Tolerated From Week 24 to 72, With no Change in Safety Profile

AEs From Week 24–72, Patients With ≥ 1 AE, n (%)	BALATON (BRVO) Aflibercept Q4W to Faricimab Modified T&E n = 267	BALATON (BRVO) Faricimab Q4W to Faricimab Modified T&E n = 270	COMINO (H/CRVO) Aflibercept Q4W to Faricimab Modified T&E n = 342	COMINO (H/CRVO) Faricimab Q4W to Faricimab Modified T&E n = 359
Ocular AEs	81 (30.3%)	76 (28.1%)	118 (34.5%)	130 (36.2%)
Serious ocular AEs	3 (11%)	4 (15%)	12 (35%)	26 (7.2%)
Ocular AEs of special interest	1 (04%)	1 (04%)	9 (26%)	21 (58%)
Intraocular inflammation events	3 (1.1%)	2 (0.7%)	5 (1.5%)	10 (28%)
Iridocyclitis	1 (04%)	1 (04%)	4 (12%)	3 (08%)
Iritis	2 (07%)	0	1 (03%)	3 (08%)
Vitritis	0	1 (04%)	0	4 (11%)
Uveitis	0	0	0	1 (03%)
Noninfectious endophthalmitis	0	0	0	1 (03%)
Keratic precipitates	0	0	0	1 (03%)
Endophthalmitis events	0	0	1 (0.3%)	0
Retinal vasculitis events	0	0	0	0
Retinal artery occlusion/embolism	0	1 (0.4)	2 (0.6%)	2 (0.6%)
Serious nonocular AEs	23 (86%)	25 (93%)	41 (12.0%)	30 (84%)
APTC events	8 (30%)	2 (07%)	6 (18%)	8 (22%)
AEs leading to treatment discontinuation from week 24–72	4 (1.5%)	0	6 (18%)	8 (2.2%)

Percentages are based on the n in the column headings. For prior faricimab, includes AEs with onset on or after the week 24 treatment or dose hold or if none on set on or after day 168 through week 72. For prior aflibercept, includes AEs with an onset on or after the date of the first faricimab dose through week 72. Multiple occurrences of the same AE in 1 individual are counted only once.
AE, adverse event; APTC, Antiplatelet Trialists' Collaboration; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; HRVO, hemiretinal vein occlusion; Q4W, every 4 weeks; T&E, treat-and-extend.

Dual Ang-2/VEGF-A Inhibition With Faricimab Offers Disease Control in Patients With RVO

- **BCVA gains** at week 24 **maintained** through week 72
- **CST reduction** at week 24 **maintained** through week 72

- More than **45% of patients on ≥ Q12W faricimab dosing** at week 68

- **Faricimab** was **well tolerated** with no change in safety profile

Faricimab approved in the **United States** for the treatment of **RVO**

Ang-2, angiopoietin-2; BCVA, best-corrected visual acuity; CST, central subfield thickness; Q12W, every 12 weeks; RVO, retinal vein occlusion; VEGF-A, vascular endothelial growth factor-A.

BRVO Switch Case

Carl J. Danzig, M.D.
Director of Retina Clinical Research
Rand Eye Institute
Deerfield Beach, FL

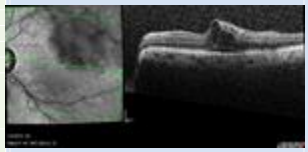
BRVO Initial presentation

Age	68
Gender	male
Race	Afro-Caribbean
Date of diagnosis	1/4/2019
BCVA	OD: HM OS: 20/60
IOP	13 OU
Previous Ocular History	1) Adv. Glaucoma OD> OS s/p SLT OU 2) Cataract ou
Meds	Latanoprost, Timolol

Left eye

Diagnosed with RVO: **4 Jan 2019**

Baseline BCVA: **20/60**



RVO in left eye

Baseline
4 Jan 2019

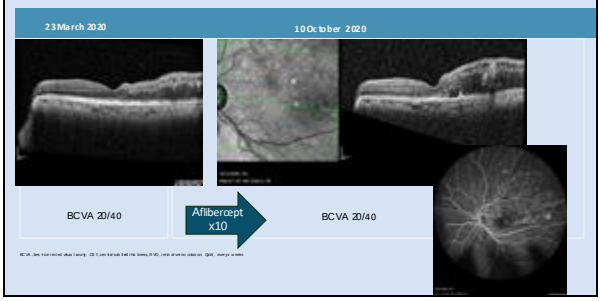
BCVA 20/60
CST 547 µm
Treatment Naïve
Treated with Bevacizumab #1

Bevacizumab x10

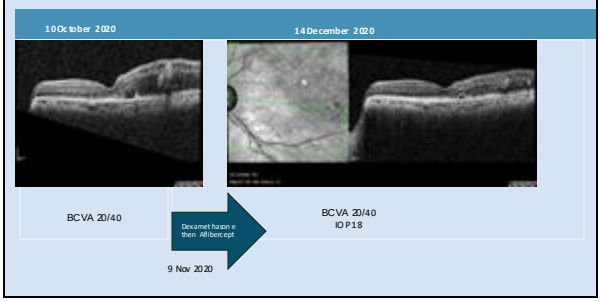
23 March 2020

BCVA 20/40

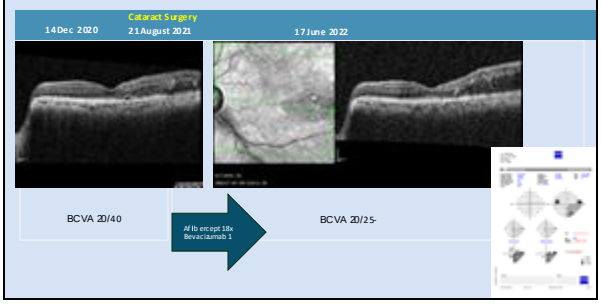
RVO in left eye



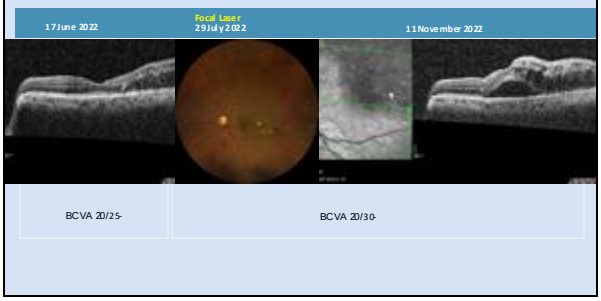
RVO in left **eye**



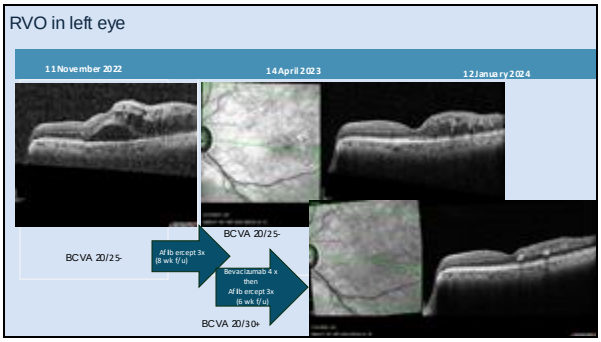
RVO in left eye



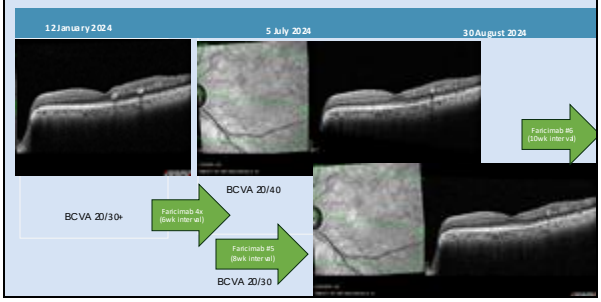
RVO in left eye



RVO in left eye

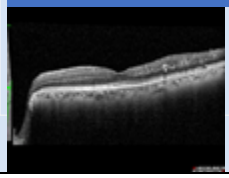


RVO in left eye switched to faricimab



Case Summary: RVO in left eye treated with faricimab

- Patient with BRVO OS diagnosed Jan 2019, with hx POAG OD> OS
- Bevacizumab #11, Aflibercept #31, , Dexamethasone #1 (no IOP spike, thankfully), focal laser
- Vabsymo x 6
  - Extended out to 10 weeks
  - Big improvement in volume of exudates
  - Vision 20/30



Summary

- Anti-VEGF agents have become first-line therapy for ME following RVO
  - Delays in treatment initiation may negatively impact vision prognosis
  - Personalize care to individual patient response to treatment
- Monthly dosing of anti-VEGF has been the most extensively studied regimen; however, data suggest that individualized treatment regimens may lead to comparable outcomes
- Steroids are effective for ME following RVO, but adverse effects of cataract and IOP elevation must be considered
- Peripheral laser photocoagulation does not improve vision outcomes or decrease anti-VEGF burden in ME following RVO

Thank you!

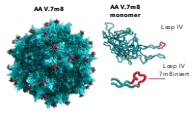
Ixoberogene Soroparvovec (Ixo-vec) Intravitreal Gene Therapy For Neovascular AMD: 52-Week Primary Efficacy and Safety Results From The Phase 2 LUNA Study

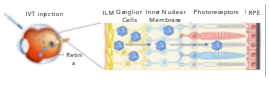
Michael Singer, M.D., PhD

On behalf of the LUNA Investigators and Study Team

New Orleans Ophthalmology Society• Sunday, February 23, 2025

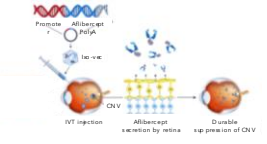
- This presentation discussed IRB/IEC approved research of an investigational medicine
- Studies funded by Adverum
- Michael Singer has the following financial interests or relationships to disclose:
  - sajajs
  - C=Consultant|R=Research Support| O=Stock Options





AAV.7m8: Created by Directed Evolution

- Engineered for IVT administration; peptide loop enables 7m8 to cross the inner limiting membrane (ILM)
- AAV.7m8 delivers aflibercept to the retina

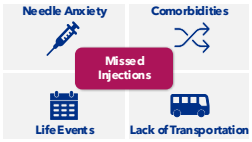


AAV.7m8 for IVT Gene Therapy

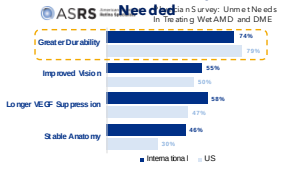
- Validated in 3 clinical programs
- Published in peer reviewed journals

3

Barriers to Treatment

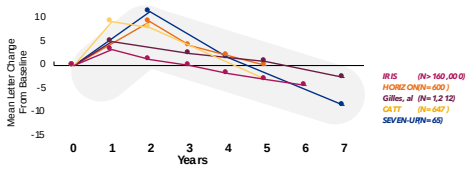


More Durable Treatment Options Are Needed



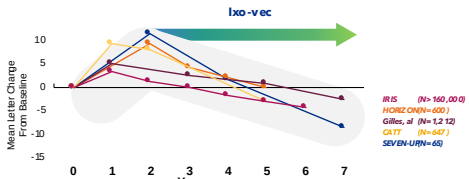
Ixo-vec: designed to address unmet need in wet AMD by delivering stable aflibercept

4



Up to ~**40% STOP anti-VEGF over 2 years** and up to **57% stop over 5 years**

5



Up to ~**40% STOP anti-VEGF over 2 years** and up to **57% stop over 5 years**

6

Primary Objective

Long-term safety and efficacy of Ixo-vec IVT in treatment experienced patients

Secondary Objectives

- Vision maintenance (BCVA)
- Anatomy (SD-OCT)
- Need for supplemental therapy

	Ixo-vec Dose	Corticosteroid Prophylaxis	Extension Scheduled Visits	Supplemental Aflibercept (2 mg IVT) Criteria:
Cohort 1 (n=6)	6E11	Oral, 13d	Quarterly assessments following completion of 2-year OPTIC parent study	• ≥10 letters BCVA (ETDRS) loss from baseline **OR**, • CST >75 µm increase from baseline **OR**, • New Vision-threatening hemorrhage due to AMD • After initial supplemental injection subsequent injections administered at investigator discretion
Cohort 2 (n=6)	2E11	Oral, 13d		
Cohort 3 (n=9)	2E11	Eye Drops, 6 wks		
Cohort 4 (n=9)	6E11	Eye Drops, 6 wks		

7

Baseline Characteristics	Cohort 1 6E11	Cohort 2 2E11	Cohort 3 2E11	Cohort 4 6E11	Total
Mean (range) Age, Years	79.0 (62–88)	79.8 (74–90)	77.4 (65–90)	79.9 (68–88)	79.0 (62–90)
Mean (range) Years Since nAMD Diagnosis	4.5 (0.9–10.6)	4.1 (0.5–6.8)	3.3 (0.7–8.0)	3.3 (0.2–8.0)	3.7 (0.2–10.6)
Mean (range) Number anti-VEGF Injections Since Initial Diagnosis*	38.2 (7–109)	34.0 (4–69)	24.8 (9–70)	25.7 (2–58)	29.6 (2–109)
Mean (range) Annualized anti-VEGF Injections Prior to Ixo-vec	9.7 (8.4–11.2)	10.4 (8.5–11.7)	9.6 (7.9–12.8)	9.9 (6.3–13)	9.9 (6.3 – 13.3)
Mean (range) BCVA, ETDRS Letters Approximate Snellen Equivalent	65.8 (57–77) 20/50	64.7 (53–72) 20/50	65.9 (53–75) 20/50	65.0 (54–77) 20/50	65.4 (53 – 77)
Mean (range) CST, µm	369.2 (293–561)	307.7 (235–339)	473.4 (301–857)	398.6 (255–538)	397.0 (235 – 857)
Participant Status					
Follow-up (Years)	4-5 (median 4.8)	4-5 (median 4.7)	4-5 (median 4.7)	3-4 (median 4.0)	3-5 (median 4.5)

Dramatic Treatment Burden Reduction

Nearly half of patients are injection free through 4 years

Durable Therapeutic Levels Demonstrated After One Injectio

Sustained aqueous aflibercept levels through 4 years

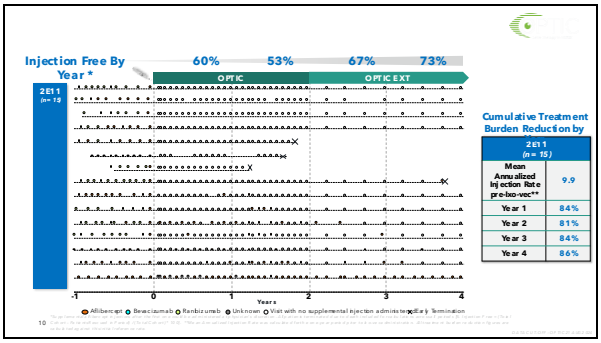
BCVA & CST Maintained Through 4 Years

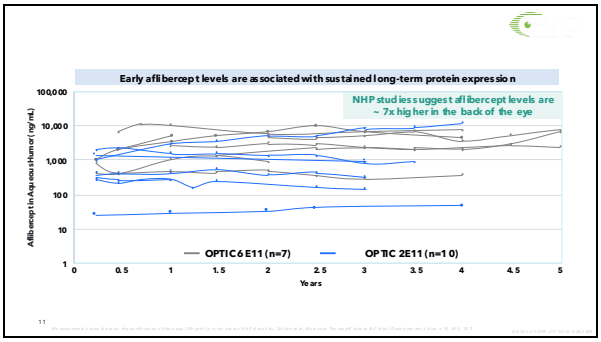
Demonstrated robust and durable activity

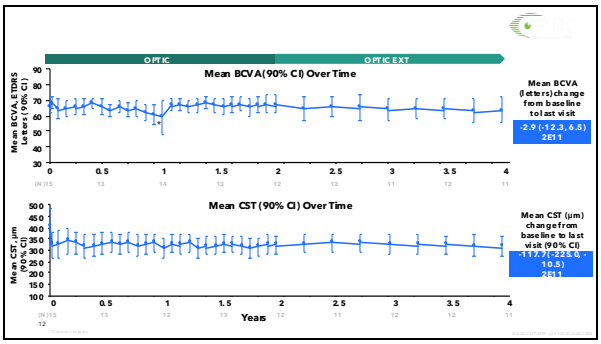
Low Dose Well Tolerated through 4 Years

100% of patients who had inflammation resolved by year 1

9

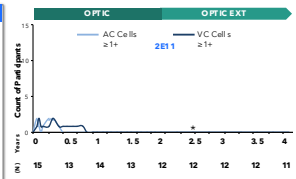

Injection Free By Year *
60%
53%
67%
73%
OPTIC
OPTIC EXT
2E11 (n= 15)
Years
Aflibercept
Bevacizumab
Ranibizumab
Unknown
Visit with no supplemental injection administered
Early Termination
Cumulative Treatment Burden Reduction by
2E11 (n= 15)
Mean Annualized Injection Rate pre-bxo-vec**
9.9
Year 1
84%
Year 2
81%
Year 3
84%
Year 4
86%


Early aflibercept levels are associated with sustained long-term protein expression
NHP studies suggest aflibercept levels are ~ 7x higher in the back of the eye
Aflibercept in Aqueous Humor (ng/mL)
OPTIC 6E11 (n=7)
OPTIC 2E11 (n=10)
Years


OPTIC
OPTIC EXT
Mean BCVA (90% CI) Over Time
Mean BCVA ETDRS Letters (90% CI)
Mean BCVA (letters) change from baseline to last visit
-2.9 (-12.3, 6.5)
2E11
Mean CST (90% CI) Over Time
Mean CST, µm (90% CI)
Mean CST (µm) change from baseline to last visit (90% CI)
-117.7 (-225.0, -10.5)
2E11
Years

OPTIC 2E11

- 2E11 was generally well tolerated through 4 years of follow up
  - No new ocular SAEs observed – including vasculitis, retinitis, choroiditis, vascular occlusions or hypotony
- Inflammation was dose dependent, did not impact vision and, when present, was responsive to local corticosteroids
- 100% inflammation resolved by year 1
  - No recurrence of inflammation after year 1



Short prophylactic regimen was 13 days oral prednisone or 6 weeks of topical drops

13

Objective I

Determine the Optimal Dose for Phase 3

Objective II

Optimize Phase 3 Prophylaxis

14

Multicenter, double-masked, randomized, parallel-group Phase 2 study

Key inclusion criteria: demonstrated response to anti-VEGF therapy and under active treatment for CNV secondary to nAMD (received a minimum of 2 injections within 4 months of entry), study eye BCVA in the range of 25 - 83 ETDRS letters

Corticosteroid Prophylaxis Regimen	Supplemental Injection Criteria
• Difluprednate 22 wks ± prednisone oral 10 wks • Ozurdex IVT + difluprednate after week 4 ± prednisone oral 10 wks* • Randomized 2:1 bilateral versus local + oral	• Increase in CST > 75 µm from BL confirmed by the CRC **OR** • Loss of ≥ 10 letters in BCVA from BL due to new/worsening IRF or SRF **OR** • New vision-threatening hemorrhage due to nAMD

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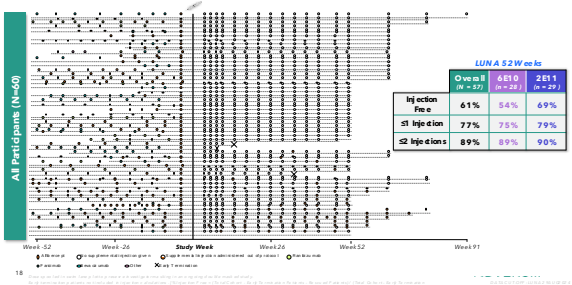
Demographics and Baseline Characteristics	LUNA 6E10 N = 30	LUNA 2E11 N = 30	LUNA Total N = 60
Mean age, years (SD)	75.4 (8.2)	77.7 (7.4)	76.6 (7.8)
Female, n (%)	16 (53%)	18 (60%)	34 (57%)
Race, n (%) White Asian	 27 (90%) 2 (7%)	 28 (93%) 2 (7%)	 55 (92%) 4 (7%)
Mean years since nAMD diagnosis in the study eye (SD)	3.0 (2.9)	3.0 (3.1)	3.0 (2.9)
Mean annualized anti-VEGF injections in year prior to Day 1 (SD)	10.2 (1.7)	10.0 (3.3)	10.1 (2.6)
Mean BCVA, ETDRS letters (SD)	72.9 (8.8)	71.8 (6.4)	72.3 (7.7)
Mean CST, µm (SD)	360.6 (112.0)	340.5 (119.3)	350.6 (115.2)
Phakic lens status, n (%)	11 (37%)	11 (37%)	22 (37%)

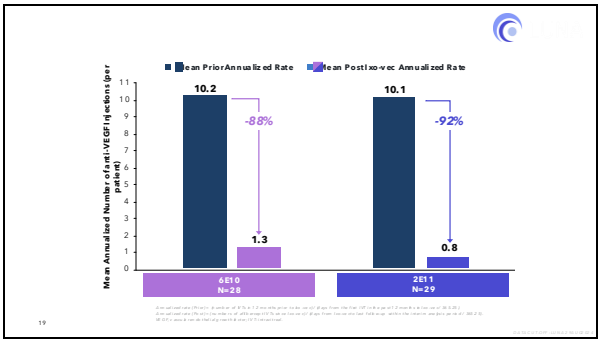
16

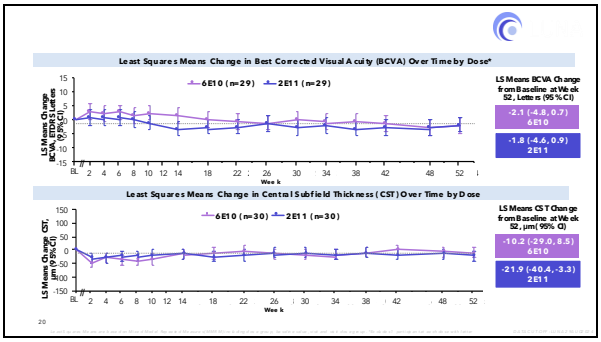
Participant Disposition (Through 52 Weeks)	
Number of participants randomized and dosed with Ixo-vec	60
Number of participants who completed Week 52	57
Number of participants who discontinued after Ixo-vec dosing	3
Reason for discontinuation (not related to Ixo-vec) • Death (1Abdominal mesenteric mass, multiple organ failure, and septic shock and 2Hypercapnic Respiratory Failure and Pleural Effusion – not related to study drug) • Adverse event (Dementia – not related to study drug)	 2 1
Mean Weeks of Follow-Up	59 (13.8)

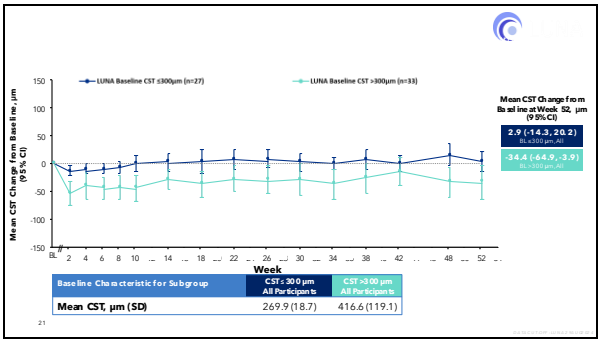
17

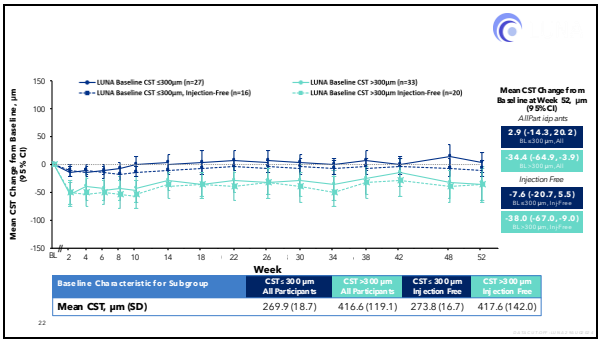


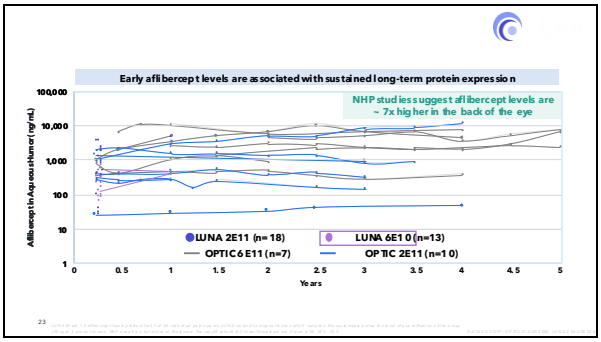
18

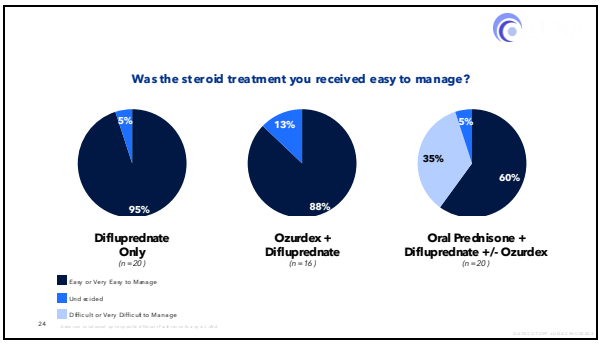

Mean Prior Annualized Rate
Mean Post Ixo-vec Annualized Rate
Mean Annualized Number of anti-VEGF Injections (per patient)
10.2
-88%
1.3
10.1
-92%
0.8
6E10
N=28
2E11
N=29
19

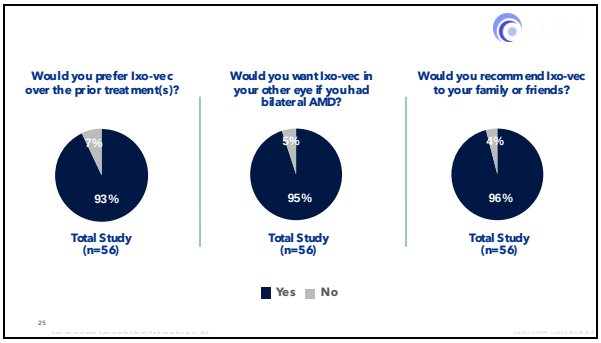

Least Squares Means Change in Best Corrected Visual Acuity (BCVA) Over Time by Dose*
6E10 (n=29)
2E11 (n=29)
LS Means Change from Baseline at Week 52, Letters (95% CI)
-2.1 (-4.8, 0.7)
6E10
-1.8 (-4.6, 0.9)
2E11
Least Squares Means Change in Central Subfield Thickness (CST) Over Time by Dose
6E10 (n=30)
2E11 (n=30)
LS Means CST Change from Baseline at Week 52, µm (95% CI)
-10.2 (-29.0, 8.5)
6E10
-21.9 (-40.4, -3.3)
2E11
20

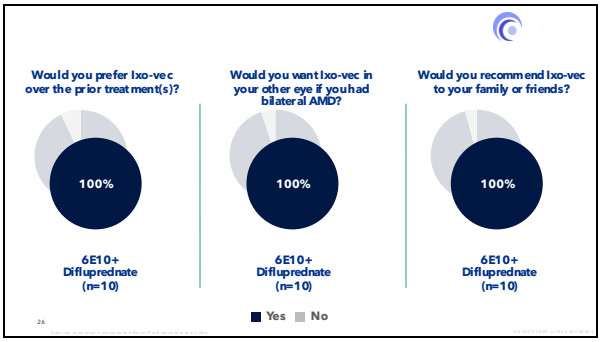

LUNA Baseline CST ≤300µm (n=27)
LUNA Baseline CST >300µm (n=33)
Mean CST Change from Baseline, µm (95% CI)
Week
Mean CST Change from Baseline at Week 52, µm (95% CI)
2.9 (-14.3, 20.2)
BL ≤300 µm, All
-34.4 (-64.9, -3.9)
BL >300 µm, All
Baseline Characteristic for Subgroup
CST ≤ 300 µm All Participants
CST >300 µm All Participants
Mean CST, µm (SD)
269.9 (18.7)
416.6 (119.1)
21

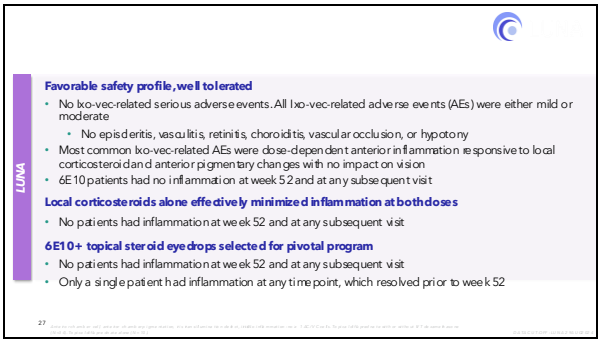

LUNA Baseline CST ≤300µm (n=27)
LUNA Baseline CST ≤300µm, Injection-Free (n=16)
LUNA Baseline CST >300µm (n=33)
LUNA Baseline CST >300µm Injection-Free (n=20)
Mean CST Change from Baseline, µm
Mean CST Change from Baseline at Week 52, µm (95% CI)
All Participants
2.9 (-14.3, 20.2)
BL ≤300 µm, All
-34.4 (-64.9, -3.9)
BL >300 µm, All
Injection Free
-7.6 (-20.7, 5.5)
BL ≤300 µm, Inj Free
-38.0 (-67.0, -9.0)
BL >300 µm, Inj Free
Week
Baseline Characteristic for Subgroup
CST ≤ 300 µm All Participants
CST >300 µm All Participants
CST ≤ 300 µm Injection Free
CST >300 µm Injection Free
Mean CST, µm (SD)
269.9 (18.7)
416.6 (119.1)
273.8 (16.7)
417.6 (142.0)

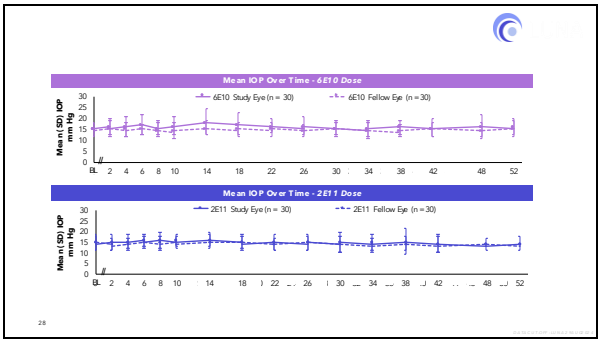

Early aflibercept levels are associated with sustained long-term protein expression
NHP studies suggest aflibercept levels are ~ 7x higher in the back of the eye
Aflibercept in Aqueous Humor (ng/mL)
LUNA 2E11 (n= 18)
LUNA 6E10 (n=13)
OPTIC 6E11 (n=7)
OPTIC 2E11 (n=10)
Years

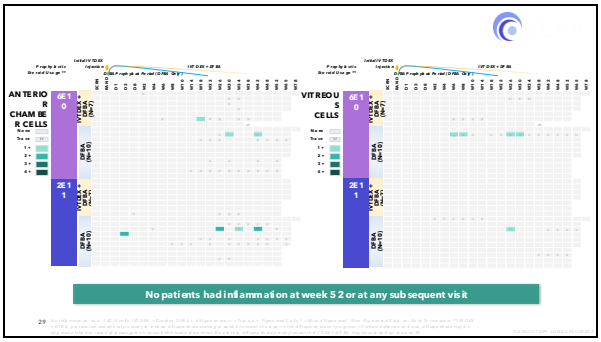

Was the steroid treatment you received easy to manage?
5%
95%
Difluprednate Only
(n =20)
13%
88%
Ozurdex + Difluprednate
(n =16)
5%
35%
60%
Oral Prednisone + Difluprednate +/- Ozurdex
(n =20)
Easy or Very Easy to Manage
Undecided
Difficult or Very Difficult to Manage

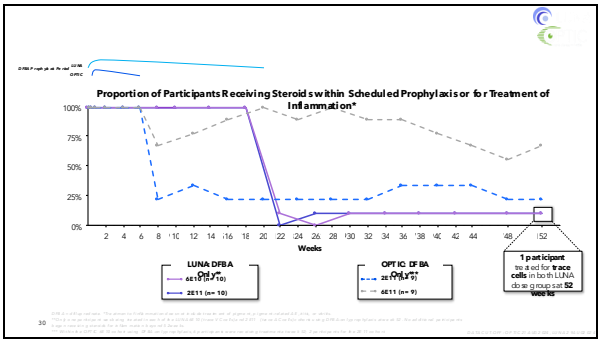

Would you prefer Ixo-vec over the prior treatment(s)?
7%
93%
Total Study (n=56)
Would you want Ixo-vec in your other eye if you had bilateral AMD?
5%
95%
Total Study (n=56)
Would you recommend Ixo-vec to your family or friends?
4%
96%
Total Study (n=56)
Yes
No
25


Would you prefer Ixo-vec over the prior treatment(s)?
100%
6E10+ Difluprednate (n=10)
Would you want Ixo-vec in your other eye if you had bilateral AMD?
100%
6E10+ Difluprednate (n=10)
Would you recommend Ixo-vec to your family or friends?
100%
6E10+ Difluprednate (n=10)
Yes
No
26


LUNA
Favorable safety profile, well tolerated
• No Ixo-vec-related serious adverse events. All Ixo-vec-related adverse events (AEs) were either mild or moderate
• No episcleritis, vasculitis, retinitis, choroiditis, vascular occlusion, or hypotony
• Most common Ixo-vec-related AEs were dose-dependent anterior inflammation responsive to local corticosteroid and anterior pigmentary changes with no impact on vision
• 6E10 patients had no inflammation at week 52 and at any subsequent visit
Local corticosteroids alone effectively minimized inflammation at both doses
• No patients had inflammation at week 52 and at any subsequent visit
6E10+ topical steroid eyedrops selected for pivotal program
• No patients had inflammation at week 52 and at any subsequent visit
• Only a single patient had inflammation at any time point, which resolved prior to week 52
27


Mean IOP Over Time - 6E10 Dose
6E10 Study Eye (n = 30)
6E10 Fellow Eye (n = 30)
Mean (SD) IOP mm Hg
Mean IOP Over Time - 2E11 Dose
2E11 Study Eye (n = 30)
2E11 Fellow Eye (n = 30)
Mean (SD) IOP mm Hg


ANTERIOR CHAMBER CELLS
VITREOUS CELLS
6E10
2E11
No patients had inflammation at week 52 or at any subsequent visit


Proportion of Participants Receiving Steroids within Scheduled Prophylaxis or for Treatment of Inflammation*
Weeks
LUNA DFBA
6E10 (n = 10)
2E11 (n = 10)
OPTIC DFBA
2E10 (n = 9)
6E11 (n = 9)
1 participant treated for trace cells in both LUNA dose groups at 52 weeks

	Efficacy	Safety
OPTIC	**Durable clinical benefit through 4 years** • >50% injection free & >80% treatment burden reduction • BCVA & CST levels maintained • Sustained aqueous aflibercept levels	**2E11 was generally well tolerated through 4 years of follow up** • Inflammation was dose dependent, did not impact vision and, when present, was responsive to local corticosteroids • 100% inflammation resolved by year 1
LUNA	**>50% injection free & >80% treatment burden reduction in hard-to-treat patients** **Consistent visual and anatomic benefit through 52 weeks** • BVCA maintenance through 52 weeks • Fluid reduction in patients with baseline CST >300 µm; maintenance in ≤300 µm **Consistent aflibercept expression levels, similar to OPTIC** **LUNA patient survey demonstrates strong patient preference for Ixo-vec** • ≥93% prefer Ixo-vec over prior anti-VEGFs, would recommend it to family and friends	**Favorable safety profile, well tolerated** • No Ixo-vec-related serious adverse events. Most common Ixo-vec-related AEs were dose-dependent anterior inflammation responsive to local corticosteroid and anterior pigmentary changes with no impact on vision **Local corticosteroids alone effectively minimized inflammation at both doses** • No patients had inflammation at week 52 and at any subsequent visit

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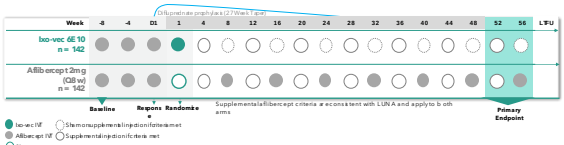
ARTEMIS Phase 3 Trial | **6E10** With steroid eyedrop prophylaxis | **US Study** Incorporates FDA EOP2 feedback | **Broad** Patient population | **284** Patients

Key Inclusion Criteria

Treatment-naïve and previously treated wet AMD

BCVA: 35 – 78 letters

Anti-VEGF responsive: After two aflibercept loading doses



Supplemental aflibercept criteria are consistent with LUNA and apply to both arms

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Early Onset Improvement of Best-Corrected Visual Acuity (BCVA) and Central Subfield Thickness (CST) with OCS-01 Eye Drops in Diabetic Macular Edema (DME): Results from a 12-week Phase 2/3 Study (Stage 1)

Carl J. Danzig, MD
Rand Eye Institute

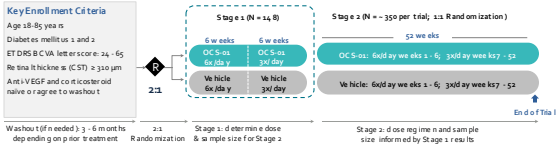
on behalf of the DIAMOND study group

Disclosures

1) Research Grant: Adverum, Alexion, Annexon, Aviceda, Bayer, Boehringer Ingelheim, Cognition, Curacle, Eyebio, Eyepoint, 4DMT, Genentech, Gyroscope, IvericBio/Astellas, Kodiak, Novartis, Ocular Therapeutix, Oculis, Regeneron, RegenxBio, Rezolute, Roche, Stealth, Unity
2) Consultant: Abbvie, Adverum, Alimera, Eyebio, 4DMT, Eyepoint, Galimedix, Genentech, IvericBio/Astellas, Kodiak, Novartis, Ocular Therapeutix, Oculis, Ocuphire, Opthea, Regeneron, Regenxbio, Roche, Samsung Bioepsis, Stealth, Unity
3) Speaker: Genentech, IvericBio/Astellas

OCS-01 | DIAMOND (DX-219) Evaluated OCS-01 in Patients With DME

Multicenter, randomized, double-masked, vehicle-controlled, two-stage phase 2/3 study of OCS-01 (OPTIREACH®-dexamethasone 15 mg/mL ophthalmic formulation)



Stage 1: Assess if loading dose optimizes efficacy

- **1° endpoint:** Mean change in BCVA ETDRS letters score from baseline at 6 weeks
- **2° endpoint:** Mean change in BCVA from baseline at 12 weeks
- **2° endpoint:** Percentage of patients with a ≥3-line gain in BCVA at 6 and 12 weeks
- **2° endpoint:** Mean change in CST[1] from baseline at 6 and 12 weeks

Stage 2: Two Phase 3's to support NDA filing for DME

- **1° endpoint:** Mean change in BCVA ETDRS letters score from baseline at 52 weeks
- **2° endpoint:** Percentage of patients with a ≥3-line gain in BCVA at 52 weeks
- **2° endpoint:** Mean change in CST[1] from baseline at 52weeks

[1] Ultrawide-field optical coherence tomography (UWF-OCT)

Baseline Demographics Were Well-Balanced Between the 2 Arms

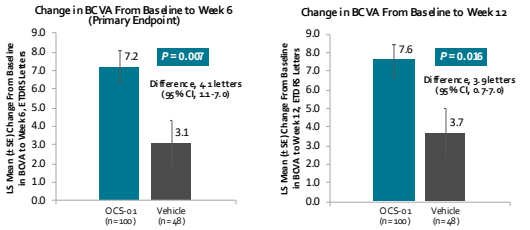
Study DX 219 (Stage 1) ITT Population

Parameter	OCS-01 (n =100)	Vehicle (n=48)
Age, mean (SD), years	61.9 (9.0)	63.9 (7.3)
Male, n (%)	53 (53.0)	26 (54.2)
Duration of DME, mean (SD), years	2.0 (2.6)	1.9 (2.7)
BCVA, mean (SD), ETDRS letter score	57.5 (9.3)	58.3 (7.5)
CST, mean (SD), µm	453.0 (131.8)	445.3 (112.5)
IOP, mean (SD), mm Hg	15.3 (3.0)	14.7 (3.0)

BCVA, best corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; Hg, mercury; IOP, intraocular pressure; SD, standard deviation.

Patients on OCS-01 Had a Significant Improvement in Mean BCVA from Baseline at Weeks 6 and 12 vs Vehicle

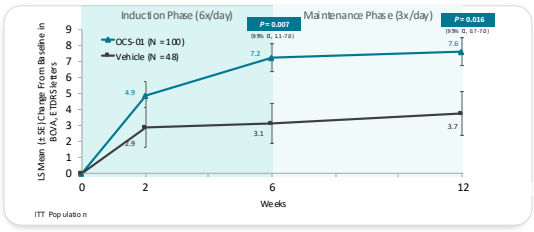
ITT population



Imputations rules are applied based on a pattern-mixture model approach.
BCVA, best corrected visual acuity; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intention-to-treat; LS, least square; SE, standard error.

Improvement in Vision with OCS-01 Sustained to Week 12

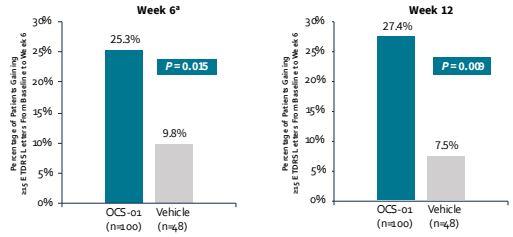
Rapid improvement in BCVA with induction and sustained with maintenance regimen



BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intention-to-treat; SD, standard deviation; SE, standard error.
Multiple imputations for missing data. Imputation rules are applied based on a pattern-mixed model approach.
Data, analysis and conclusions are preliminary, and subject to change as full analysis is ongoing.

Significantly More Patients on OCS-01 Had a ≥15 ETDRS Letter Improvement vs Vehicle

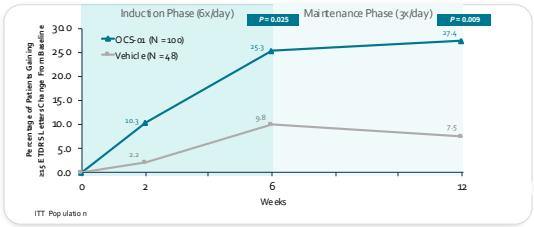
ITT population



[a]The mean odds of ≥3 lines (≥15 ETDRS letters) from baseline to Week 6 in either treatment group. P-values based on difference in marginal effects.
Imputation rules are applied based on a pattern-mixture model approach.
ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intention-to-treat.

Proportion of Patients with ≥15 ETDRS Letter Improvement with OCS-01 Sustained to Week 12

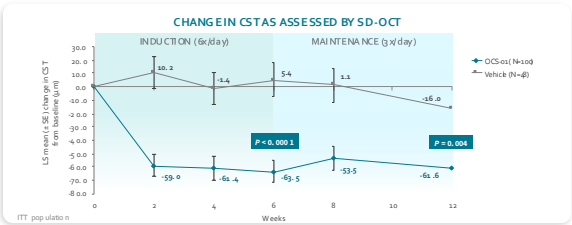
Rapid improvement in BCVA with induction and sustained with maintenance regimen



BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intention-to-treat
Multiple imputations for missing data. Imputation rules are applied based on a pattern-mixed model approach.
Data, analysis and conclusions are preliminary, and subject to change as full analysis is ongoing.

Effects of OCS-01 on Retinal Thickness (CST) Were Observed Early by Week 2 and Maintained Throughout the Study

Significant reductions in CST measured at weeks 6 and 12 for OCS-01 vs vehicle in the ITT population



Mean (±SD) baseline CST: OCS-01, 459.0 (±132.8) µm; vehicle, 445.3 (±132.4) µm. Imputation rules are applied based on a pattern-mixture model approach. Data, analysis, and conclusions are preliminary, and subject to change as full analysis is ongoing. CST (Central subfield thickness); ITT (Intention-to-treat); SD-OCT (Spectral domain optical coherence tomography).

OCS-01 Was Well-tolerated With No Unexpected AEs

Safety population

Treatment Emergent Adverse Events

>2.0% in the OCS-01 Arm or >4.0% in the Vehicle Arm	OCS-01 (n=100) n (%)	Vehicle (n=48) n (%)
Any TEAE	70(70.0)	30(62.5)
Diabetic retinal edema	10(10.0)	9 (18.8)
Intraocular pressure increased	14(14.0)	1(2.1)
Hypertension	10(10.0)	1(2.1)
Ocular hypertension	8 (8.0)	0 (0.0)
Macular edema	2 (2.0)	4 (8.3)
COVID-19	2 (2.0)	2 (4.2)
Dry eye	3(3.0)	1(2.1)
Diabetes mellitus	3(3.0)	0 (0.0)
Dizziness	3(3.0)	0 (0.0)
Dysgeusia	3(3.0)	0 (0.0)
Nasopharyngitis	2 (2.0)	1(2.1)
Type 2 diabetes	2 (2.0)	1(2.1)
Vitreous hemorrhage	2 (2.0)	1(2.1)
Arthralgia	2 (2.0)	0 (0.0)
Blood glucose increased	2 (2.0)	0 (0.0)
Visual acuity reduced	1(1.0)	2 (4.2)

Treatment Emergent Serious Adverse Events

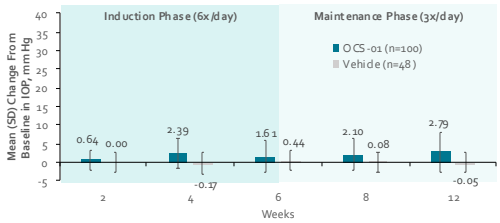
	OCS-01 (n=100) n (%)	Vehicle (n=48) n (%)
Any ocular SAE	1(1.0)	0 (0.0)
Vitreous hemorrhage	1(1.0)	0 (0.0)
Any non-ocular SAE	4 (4.0)	3(6.3)
Death	1(1.0)	0 (0.0)

- None of the SAEs reported were deemed related to study drug
- No evidence of cataract formation up to 12 weeks
- IOP increase consistent with literature
- Minimal mean IOP increase was similar across loading and maintenance phases

AE, adverse event; COVID-19, coronavirus disease 2019; IOP, intraocular pressure; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Mean Change in IOP Over Time

Safety population



Mean (SD) baseline IOP: OCS-01, 15.3 (3.2) mm Hg; vehicle, 14.7 (3.0) mm Hg.
IOP, intraocular pressure; SD, standard deviation.

OCS-01 Holds the Potential to Address the Current Unmet Need by Providing a Versatile Efficacious, Safe and Non-invasive Therapeutic Approach for DME

Rapid and sustained improvement with OCS-01 Eye Drops observed by week 2 through week 12

OCS-01 met **all Functional, Clinical and pharmacodynamic endpoints** in a robust, statistically superior manner

- **Functional Endpoint:** Improvement of visual acuity
- **Clinical Endpoint:** Increase in proportion of patients with a 3-line or greater gain
- **Pharmacodynamic Endpoint:** Reduction in macular edema as measured by OCT

No unexpected safety findings were observed

Based on the results of Stage 1 of (Study DX-219; DIAMOND 1), Stage 2 in currently ongoing

BCVA, best corrected visual acuity; DME, diabetic macular edema.