Redefining the Management of Neovascular AMD

February 27, 2026

49th Annual Macula Society Meeting | Coronado, CA

OCULAR THERAPEUTIX

Retina experience redefined™

Forward-Looking Statements and Disclaimers

Any statements in this presentation about future expectations, plans, and prospects for the Company, including statements regarding the development and regulatory status of the Company's or its competitors' product candidates, including statements regarding the SOL-1 Phase 3 superiority trial being conducted under a Special Protocol Assessment (SPA) agreement with the U.S. FDA and aligned with FDA draft guidance for neovascular AMD drug development; the timing, design, enrollment, randomization, conduct and retention of subjects in the Company's clinical trials, including the Company's SOL-1 trial and its SOL-R Phase 3 non-inferiority trial of OTX-TKI for the treatment of wet age-related macular degeneration (wet AMD), also known as neovascular age-related macular degeneration (nAMD); statements regarding the potential utility or adoption of OTX-TKI or its competitors, if approved; statements regarding the Company's intention to submit a new drug application for OTX-TKI, based on data from the Company's SOL-1 trial in wet AMD, subject to planned formal discussions with the FDA; if approved, of any of the Company's product candidates; and other statements containing the words "anticipate", "become", "believe", "estimate", "expect", "intend", "designed", "goal", "may", "might", "plan", "position", "predict", "project", "target", "potential", "will", "would", "could", "should", "continue", and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors. Such forward-looking statements involve substantial risks and uncertainties that could cause the Company's development programs, future results, performance, or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, the design, timing, conduct and outcomes of ongoing and planned clinical trials, including the SOL-R trial and the second year of the SOL-1 trial; the risk that the FDA will not agree with the Company's interpretation of the written agreements under the Special Protocol Assessments for OTX-TKI, including for the SOL-1 trial; uncertainty as to whether the FDA will accept a new drug application for OTX-TKI on the basis of a single pivotal clinical trial, namely SOL-1; uncertainty as to the minimum clinical data required to demonstrate the safety of a proposed product candidate such as OTX-TKI, even if the FDA recognizes that only one pivotal clinical trial may be required to demonstrate efficacy; the risk that even though the FDA has agreed with the overall design of the SOL-1 trial, the FDA may not find that the data generated by the trial and submitted by the Company are sufficient to demonstrate the safety and efficacy of OTX-TKI to the degree necessary to support marketing approval for wet AMD; uncertainty as to whether the Company will be able to timely satisfy the FDA's other requirements for regulatory approval of OTX-TKI, including the FDA's Chemistry, Manufacturing and Control's requirements, even if the Company can satisfy the FDA's clinical requirements to demonstrate safety and efficacy; uncertainty as to what restrictions, if any, may be imposed on the label for OTX-TKI, if approved, pending the receipt of additional clinical data or otherwise; the risk that the FDA might not agree to the Company's design, protocol, and statistical analysis plan of the SOL-R trial; the risk that the Company and the FDA may not agree on the registrational pathway for any of its product candidates, including OTX-TKI; uncertainty as to whether the data from earlier clinical trials will be predictive of the data of later clinical trials, particularly later clinical trials that have a different design or utilize a different formulation than the earlier trials; uncertainty as to whether preliminary or interim data from a clinical trial will be predictive of final data from such trial; uncertainties regarding the potential commercial advantages and/or position of the Company's product candidates; availability of data from clinical trials and expectations for regulatory submissions and approvals; the Company's scientific approach and general development progress; uncertainties inherent in estimating the Company's cash runway, future expenses and other financial results, including its ability to fund future operations, including clinical trials; and other factors discussed in the "Risk Factors" section contained in the Company's quarterly and annual reports on file with the Securities and Exchange Commission. In addition, the forward-looking statements included in this presentation represent the Company's views as of the date of this presentation. The Company anticipates that subsequent events and developments may cause the Company's views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so, whether as a result of new information, future events or otherwise, except as required by law. These forward-looking statements should not be relied upon as representing the Company's views as of any date subsequent to the date of this presentation.

This presentation discusses investigational product candidates in development. Their efficacy and safety profiles have not been established, and they have not been approved for marketing by the FDA or any other regulatory agency.

OCULAR THERAPEUTIX Retina experience redefined™

Faculty

Mark R. Barakat, MD

Founder and Director of Clinical Research, Retina Macula Institute of Arizona, Scottsdale, AZ

Dilsher S. Dhoot, MD

Vitreoretinal Specialist, California Retina Consultants, Santa Barbara, CA

Jeffrey S. Heier, MD

Chief Scientific Officer, Ocular Therapeutix, Inc.

Peter K. Kaiser, MD

Chief Development Officer, Ocular Therapeutix, Inc.

Arshad M. Khanani, MD

Managing Partner, Director of Clinical Research, Director of Fellowship, Sierra Eye Associates, Reno, NV

Patricio G. Schlottmann, MD

Director of Research, Charles Ophthalmic Center, Buenos Aires, Argentina

Adnan Tufail, MBBS, MD

Consultant Ophthalmic Surgeon, Moorsfield Eye Hospital, London, UK

OCULAR THERAPEUTIX Retina experience redefined™

Disclosures

Mark R. Barakat

- **Consultant:** AbbVie Inc, Adverum, Alcon, Alkeus, Annexon Biosciences, Apellis, Astellas, Bausch and Lomb, Beacon, Biocryst, Boehringer Ingelheim, Celltrion, Cencora, Clearside, Eyepoint Pharma, Genentech, Glaukos, Harrow, Janssen, Kodiak Sciences, Ocular Therapeutix, Oculis, Opthea, Outlook Therapeutics, Palatin Technologies, Regeneron, RegenxBio, RevOpsis Therapeutics, Roche, Sanofi, Stealth Biotherapeutics, Surrozen
- **Research Support:** 4DMT, Adverum, Annexon Biosciences, Astellas, Beacon, Boehringer Ingelheim, Clearside, Eyebio, Eyepoint Pharma, Genentech, Glaukos, Kanghong/Vanotech, Kodiak Sciences, Ocular Therapeutix, Oculis, Opthea, Perfuse, Perceive Bio, Regeneron, RegenxBio, Sanofi, Stealth Biotherapeutics
- **Speaker:** Alcon, ANI Pharmaceuticals, Apellis, Astellas, Genentech, Regeneron,
- **Stock/Stock Options:** NeuBase, Oxurion, RevOpsisTherapeutics

---

Dilsher S. Dhoot

- **Consultant**: Alcon Pharmaceuticals; Alimera Sciences, Inc.; Allergan; Annexon; Apellis Pharmaceuticals, Inc.; Bayer Healthcare Pharmaceuticals, Inc.; Biocryst; Coherus; EyePoint Pharmaceuticals; Genentech; IvericBio; Novartis; Ocular Therapeutix; Optos, Inc.; Outlook Therapeutics; Oxular; Regeneron; REGENXBIO; Roche; Santen, Inc.
- **Research Support**: Ocular Therapeutix, Inc.

Jeffrey S. Heier

- **Chief Scientific Officer for Ocular Therapeutix**
- **Consultant:** 4DMT, Aavantgarde, Abbvie/Regenxbio, Annexon, Aviceda, Bayer, Beacon, Boehringer Ingleheim, Breye Therapeutics, Caeregen, Cogent, Cognition, Complement Therapeutics, Endogena, Focus Biosciences, Frontera, Galimedix, Genentech/Roche, Inflammx, Kaigene, Kanghong, Lilly, Manistee, Nanoscope, Notal Vision, Novartis, Ocugen, Ocuphire, Ora, Inc., Osanni Bio, Perceive Biotherapeutics, Ray Therapeutics, Samsung Bioepis, Sanofi, Stealth Biotherapeutics, Laboratoires Thea, Vanotech, Visgenx
- **Research support:** 4DMT, Abbvie/Regenxbio, Annexon, Apellis, Astellas, Bayer, Beacon, Boehringer Ingleheim, Cognition Therapeutics, Curacle, Genentech/Roche, Janssen R&D, Kodiak, Notal Vision, Novartis, Oculis, Perceive Bio, Regeneron, Sanofi, Skyline, Stealth Biotherapeutics, Vanotech
- **Stock/Stock options:** Adverum, Aldeyra, Alzheon, Aviceda, Caeregen, Inflammx, jCyte, Ocular Therapeutix, Osanni Bio, Ray Therapeutics, RevOpsis, Vinci, Visgenx, Vitranu

Disclosures

Peter K. Kaiser	• **Chief Development Officer for Ocular Therapeutix** • **Consultant:** Abbvie, Alexion, Alkeus, Allgenesis, Alzheon, Amaros, Annexon Biosciences, Astellas, Augen Therapeutics, Aviceda, Bayer, Biogen Idec, Carl Zeiss Meditec, Celltrion Healthcare Co., Cognition Therapeutics, Complement Therapeutics, Eli Lilly, Endogena Therapeutics, Eyestem, Frontera Therapeutics, Galimedix, Innovent, Invirsa, iRenix, Isarna, Janssen, jCyte, Kanaph Therapeutics, Kanghong, Kera Therapeutics, Kriya Therapeutics, Movu/Santec, Nanoscope Therapeutics, Ocugenix, Oculis, Omeros, Ophthalmx, Osanni Bio, Panther Pharmaceuticals, Ray Therapeutics, RegenxBio, Resonance Medicine Inc., Restore Vision, Retinal Sciences, ReVana, RevOpsis, Roivant, Samsung Bioepis, Sandoz, SGN Nanopharma Inc., SmileBiotek Zhuhai Ltd, Stealth Biotherapeutics, Stuart, Sudo Biosciences, Sustained Nano Systems, Théa, Tilak, Vanotech, VisgenX • **Stock/Stock Options**: AAVAntgarde Bio, Alzheon, Aviceda, Inflammx, jCyte, Ocular Therapeutix, Osanni Bio, Ray Therapeutics, RevOpsis, Vitranu • **Board of Directors:** AAVAntgarde Bio
Arshad M. Khanani	• **Consultant:** Abbvie, ADARx Pharmaceuticals, Adverum, Alcon, Alkeus, Allgenesis, Amgen, Annexin, Annexon, Apellis Pharmaceuticals, Ashvattha, Therapeutics, Astellas, Aviceda Therapeutics, Beacon Therapeutics, Boehringer Ingelheim, Clearside Biomedical, Complement Therapeutics, 4DMT, Entarada, Exegenesis, EyePoint Pharmaceuticals, Fronterra Therapeutics, Genentech, Harrow, i-Lumen Scientific, InFocus, Iveric Bio, Janssen Pharmaceuticals, Kriya Therapeutics, Kyowa Kirin, Lexitas, Merit, Neurotech, Nanoscope, Novartis, Ocugen, Ocular Therapeutix, Oculis, Ollin, Opthea, Opus Genetics, Perfuse, Recens Medical, Regeneron Pharmaceuticals, Regenxbio, Revive, RevOpsis, Roche, Samsung, Sanofi, Stealth BioTherapeutics, Sun Pharma, Surrozen, Thea Pharma, Therini, Unity Biotechnology, Vanotech, Vial, ZipBio • **Research support:** Aviceda, Adverum, Alexion, Annexon, Astellas, Aviceda Therapeutics, Biojiva Complement Therapeutics, 4DMT, Eyepoint Pharmaceuticals, Exegenesis, Genentech, Gyroscope Therapeutics, Iveric Bio, Janssen, Kyowa Kirin, Ocular, Ollin, Therapeutix, Regenxbio, Roche, Sanofi, Vanotech • **Stock options:** Ashvattha, Aviceda Therapeutics, Oculis, Ollin, PolyPhotonix, Recens Medical, Perfuse, RevOpsis, Vial, ZipBio • **Board of Directors:** Oculis
Patricio G. Schlottmann	• **Consultant**: Ocular Therapeutix, Novartis, Roche/Genentech, Janssen, Ora, Nanoscope, EyeBio/Merck, 4DMT, Kodiak, Oculis, Abbvie, Horizon Surgical, Adverum, Revopsis, Merit, Amgen, Kodiak • **Research support:** Ocular Therapeutix, 4DMT, EyeBio/Merck, Roche/Genentech, Priovant, Kodiak
Adnan Tufail	• **Consultant**: 4DMT, Adverum, Annexon, Apellis, Aviceda, Boehringer Ingleheim, Eyebio, Iveric, Janssen, Kanghong, Nanoscope, Novartis, OcuTerra, Ocular Therapeutix, Regenxbio, Roche/Genentech • **Stockholder**: Oculogics, Cellio • **Research support**: Novartis, Bayer

OCULAR THERAPEUTIX Retina experience redefined™

Agenda

Background
Dilsher S. Dhoot, MD

OTX-TKI Overview
Peter K. Kaiser, MD

SOL-1 Phase 3 Trial

- **Trial Design**
  Jeffrey S. Heier, MD
- **Efficacy Results**
  Arshad M. Khanani, MD
- **Safety Results**
  Patricio G. Schlottmann, MD
- **Cases**
  Mark R. Barakat, MD

Key Insights
Adnan Tufail, MBBS, MD

Panel Discussion

OCULAR THERAPEUTIX Retina experience redefined

Background

Limitations of Current Standard of Care

Dilsher S. Dhoot, MD

OCULAR THERAPEUTIX Retina experience redefined

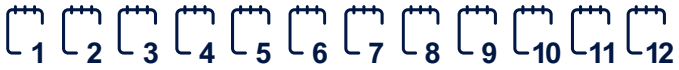
Treatment Burden Remains a Significant Unmet Need in nAMD

INJECTION BURDEN

up to
12 injections/yr for patients[1]

90% of patients require injection **every 1-3 months**[2]

up to
12 days off/yr for patients and caregivers



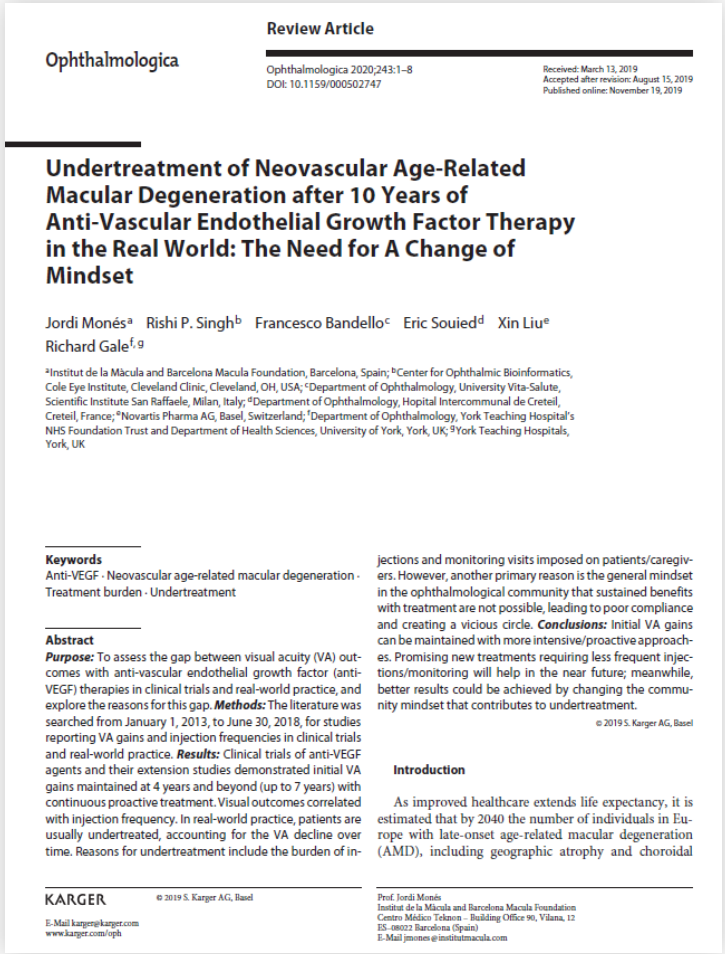
Frequent injections and visits **disrupt patients' daily routines** and activities[3]

40% discontinue treatment in the first year due to heavy treatment burden[4]

OCULAR THERAPEUTIX Retina experience redefined™

1. MacCumber MW, et al. *Can J Ophthalmol*. 2023;58(3):252-261. 2. Reitan G, et al. *Clin Ophthalmol*. 2023;17:1465-1474. 3. Higashide T, et al. Ophthalmic Res Educ. 2023;67(1):311-318. 4. Khanani AM, et al. *Ophthalmology Retina*. 2020;4(2):122-133.
nAMD, neovacular age-related macular degeneration

Suboptimal Frequency of Injections Contribute to Declining Real-World Outcomes



Ophthalmologica

Review Article

Ophthalmologica 2020;243:1–8
DOI: 10.1159/000502747

Received: March 13, 2019
Accepted after revision: August 15, 2019
Published online: November 19, 2019

Undertreatment of Neovascular Age-Related Macular Degeneration after 10 Years of Anti-Vascular Endothelial Growth Factor Therapy in the Real World: The Need for A Change of Mindset

Jordi Monés[a] Rishi P. Singh[b] Francesco Bandello[c] Eric Souied[d] Xin Liu[e] Richard Gale[f, g]

[a]Institut de la Màcula and Barcelona Macula Foundation, Barcelona, Spain; [b]Center for Ophthalmic Bioinformatics, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA; [c]Department of Ophthalmology, University Vita-Salute, Scientific Institute San Raffaele, Milan, Italy; [d]Department of Ophthalmology, Hopital Intercommunal de Creteil, Creteil, France; [e]Novartis Pharma AG, Basel, Switzerland; [f]Department of Ophthalmology, York Teaching Hospital's NHS Foundation Trust and Department of Health Sciences, University of York, York, UK; [g]York Teaching Hospitals, York, UK

Keywords
Anti-VEGF · Neovascular age-related macular degeneration · Treatment burden · Undertreatment

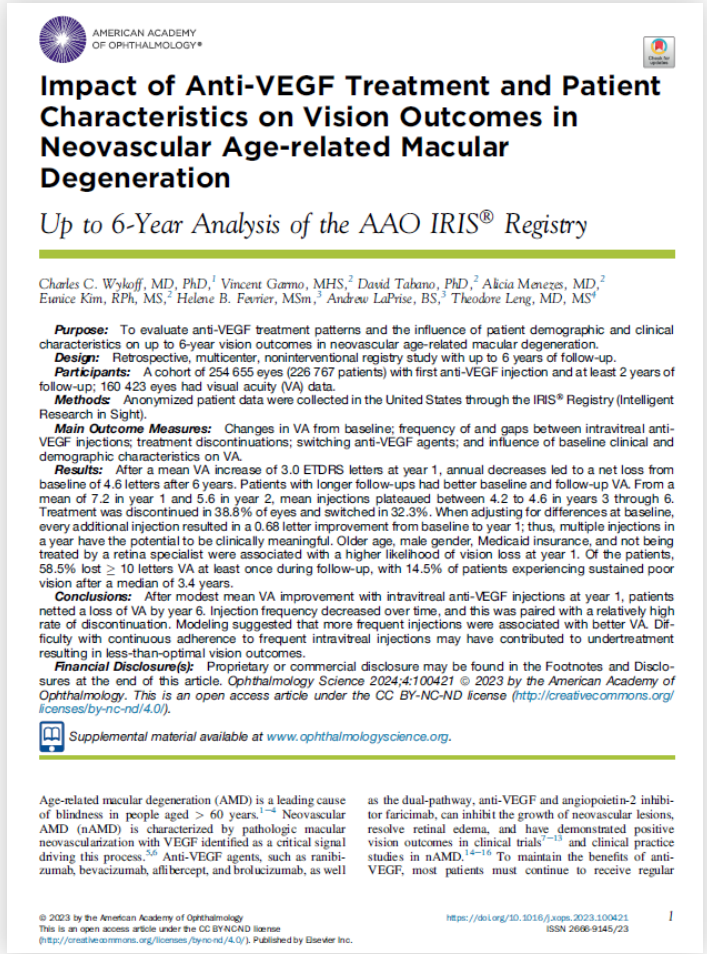
Abstract
Purpose: To assess the gap between visual acuity (VA) outcomes with anti-vascular endothelial growth factor (anti-VEGF) therapies in clinical trials and real-world practice, and explore the reasons for this gap. ***Methods:*** The literature was searched from January 1, 2013, to June 30, 2018, for studies reporting VA gains and injection frequencies in clinical trials and real-world practice. ***Results:*** Clinical trials of anti-VEGF agents and their extension studies demonstrated initial VA gains maintained at 4 years and beyond (up to 7 years) with continuous proactive treatment. Visual outcomes correlated with injection frequency. In real-world practice, patients are usually undertreated, accounting for the VA decline over time. Reasons for undertreatment include the burden of injections and monitoring visits imposed on patients/caregivers. However, another primary reason is the general mindset in the ophthalmological community that sustained benefits with treatment are not possible, leading to poor compliance and creating a vicious circle. ***Conclusions:*** Initial VA gains can be maintained with more intensive/proactive approaches. Promising new treatments requiring less frequent injections/monitoring will help in the near future; meanwhile, better results could be achieved by changing the community mindset that contributes to undertreatment.

Introduction

As improved healthcare extends life expectancy, it is estimated that by 2040 the number of individuals in Europe with late-onset age-related macular degeneration (AMD), including geographic atrophy and choroidal

KARGER
E-Mail karger@karger.com
www.karger.com/oph

Prof. Jordi Monés
Institut de la Màcula and Barcelona Macula Foundation
Centro Médico Teknon – Building Office 90, Vilana, 12
ES–08022 Barcelona (Spain)
E-Mail jmones@institutmacula.com



AMERICAN ACADEMY OF OPHTHALMOLOGY®

Impact of Anti-VEGF Treatment and Patient Characteristics on Vision Outcomes in Neovascular Age-related Macular Degeneration

Up to 6-Year Analysis of the AAO IRIS® Registry

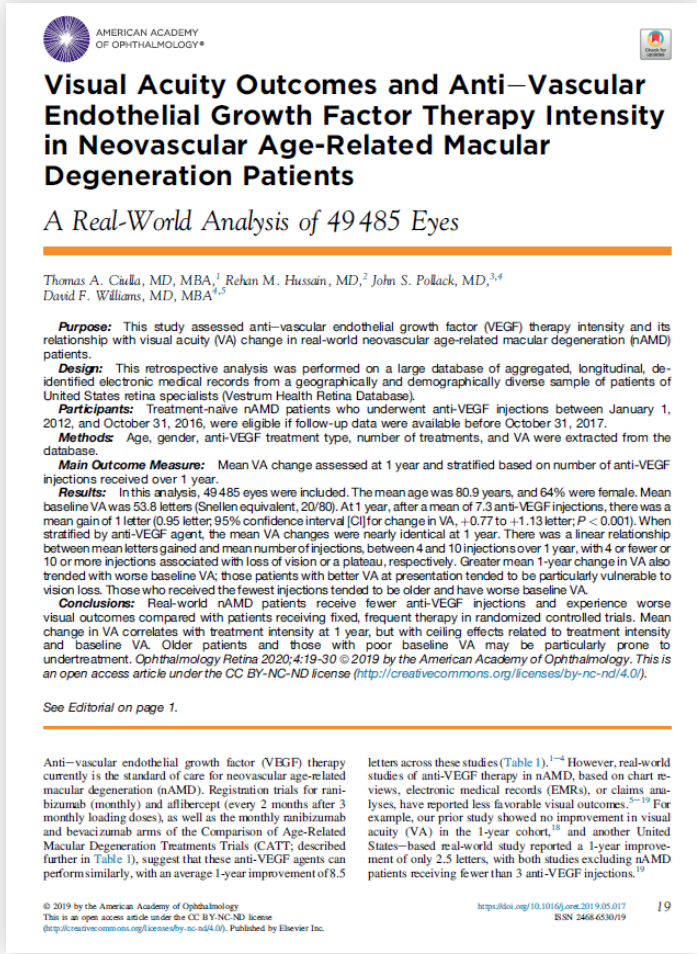
Charles C. Wykoff, MD, PhD,[1] Vincent Garmo, MHS,[2] David Tabano, PhD,[2] Alicia Menezes, MD,[2] Eunice Kim, RPh, MS,[2] Helene B. Fevrier, MSm,[3] Andrew LaPrise, BS,[3] Theodore Leng, MD, MS[4]

Purpose: To evaluate anti-VEGF treatment patterns and the influence of patient demographic and clinical characteristics on up to 6-year vision outcomes in neovascular age-related macular degeneration.
Design: Retrospective, multicenter, noninterventional registry study with up to 6 years of follow-up.
Participants: A cohort of 254 655 eyes (226 767 patients) with first anti-VEGF injection and at least 2 years of follow-up; 160 423 eyes had visual acuity (VA) data.
Methods: Anonymized patient data were collected in the United States through the IRIS® Registry (Intelligent Research in Sight).
Main Outcome Measures: Changes in VA from baseline; frequency of and gaps between intravitreal anti-VEGF injections; treatment discontinuations; switching anti-VEGF agents; and influence of baseline clinical and demographic characteristics on VA.
Results: After a mean VA increase of 3.0 ETDRS letters at year 1, annual decreases led to a net loss from baseline of 4.6 letters after 6 years. Patients with longer follow-ups had better baseline and follow-up VA. From a mean of 7.2 in year 1 and 5.6 in year 2, mean injections plateaued between 4.2 to 4.6 in years 3 through 6. Treatment was discontinued in 38.8% of eyes and switched in 32.3%. When adjusting for differences at baseline, every additional injection resulted in a 0.68 letter improvement from baseline to year 1; thus, multiple injections in a year have the potential to be clinically meaningful. Older age, male gender, Medicaid insurance, and not being treated by a retina specialist were associated with a higher likelihood of vision loss at year 1. Of the patients, 58.5% lost $\geq$ 10 letters VA at least once during follow-up, with 14.5% of patients experiencing sustained poor vision after a median of 3.4 years.
Conclusions: After modest mean VA improvement with intravitreal anti-VEGF injections at year 1, patients netted a loss of VA by year 6. Injection frequency decreased over time, and this was paired with a relatively high rate of discontinuation. Modeling suggested that more frequent injections were associated with better VA. Difficulty with continuous adherence to frequent intravitreal injections may have contributed to undertreatment resulting in less-than-optimal vision outcomes.
Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Science 2024;4:100421 © 2023 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.ophthalmologyscience.org.

Age-related macular degeneration (AMD) is a leading cause of blindness in people aged > 60 years.[1–4] Neovascular AMD (nAMD) is characterized by pathologic macular neovascularization with VEGF identified as a critical signal driving this process.[5,6] Anti-VEGF agents, such as ranibizumab, bevacizumab, aflibercept, and brolucizumab, as well as the dual-pathway, anti-VEGF and angiopoietin-2 inhibitor faricimab, can inhibit the growth of neovascular lesions, resolve retinal edema, and have demonstrated positive vision outcomes in clinical trials[7–13] and clinical practice studies in nAMD.[14–16] To maintain the benefits of anti-VEGF, most patients must continue to receive regular

https://doi.org/10.1016/j.xops.2023.100421
ISSN 2666-9145/23



AMERICAN ACADEMY OF OPHTHALMOLOGY®

Visual Acuity Outcomes and Anti–Vascular Endothelial Growth Factor Therapy Intensity in Neovascular Age-Related Macular Degeneration Patients

A Real-World Analysis of 49 485 Eyes

Thomas A. Ciulla, MD, MBA,[1] Rehan M. Hussain, MD,[2] John S. Pollack, MD,[3,4] David F. Williams, MD, MBA[4,5]

Purpose: This study assessed anti–vascular endothelial growth factor (VEGF) therapy intensity and its relationship with visual acuity (VA) change in real-world neovascular age-related macular degeneration (nAMD) patients.
Design: This retrospective analysis was performed on a large database of aggregated, longitudinal, de-identified electronic medical records from a geographically and demographically diverse sample of patients of United States retina specialists (Vestrum Health Retina Database).
Participants: Treatment-naive nAMD patients who underwent anti-VEGF injections between January 1, 2012, and October 31, 2016, were eligible if follow-up data were available before October 31, 2017.
Methods: Age, gender, anti-VEGF treatment type, number of treatments, and VA were extracted from the database.
Main Outcome Measure: Mean VA change assessed at 1 year and stratified based on number of anti-VEGF injections received over 1 year.
Results: In this analysis, 49 485 eyes were included. The mean age was 80.9 years, and 64% were female. Mean baseline VA was 53.8 letters (Snellen equivalent, 20/80). At 1 year, after a mean of 7.3 anti-VEGF injections, there was a mean gain of 1 letter (0.95 letter; 95% confidence interval [CI] for change in VA, +0.77 to +1.13 letter; $P < 0.001$). When stratified by anti-VEGF agent, the mean VA changes were nearly identical at 1 year. There was a linear relationship between mean letters gained and mean number of injections, between 4 and 10 injections over 1 year, with 4 or fewer or 10 or more injections associated with loss of vision or a plateau, respectively. Greater mean 1-year change in VA also trended with worse baseline VA; those patients with better VA at presentation tended to be particularly vulnerable to vision loss. Those who received the fewest injections tended to be older and have worse baseline VA.
Conclusions: Real-world nAMD patients receive fewer anti-VEGF injections and experience worse visual outcomes compared with patients receiving fixed, frequent therapy in randomized controlled trials. Mean change in VA correlates with treatment intensity at 1 year, but with ceiling effects related to treatment intensity and baseline VA. Older patients and those with poor baseline VA may be particularly prone to undertreatment. *Ophthalmology Retina 2020;4:19-30 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

See Editorial on page 1.

Anti–vascular endothelial growth factor (VEGF) therapy currently is the standard of care for neovascular age-related macular degeneration (nAMD). Registration trials for ranibizumab (monthly) and aflibercept (every 2 months after 3 monthly loading doses), as well as the monthly ranibizumab and bevacizumab arms of the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT; described further in Table 1), suggest that these anti-VEGF agents can perform similarly, with an average 1-year improvement of 8.5 letters across these studies (Table 1).[1–4] However, real-world studies of anti-VEGF therapy in nAMD, based on chart reviews, electronic medical records (EMRs), or claims analyses, have reported less favorable visual outcomes.[5–19] For example, our prior study showed no improvement in visual acuity (VA) in the 1-year cohort,[18] and another United States–based real-world study reported a 1-year improvement of only 2.5 letters, with both studies excluding nAMD patients receiving fewer than 3 anti-VEGF injections.[19]

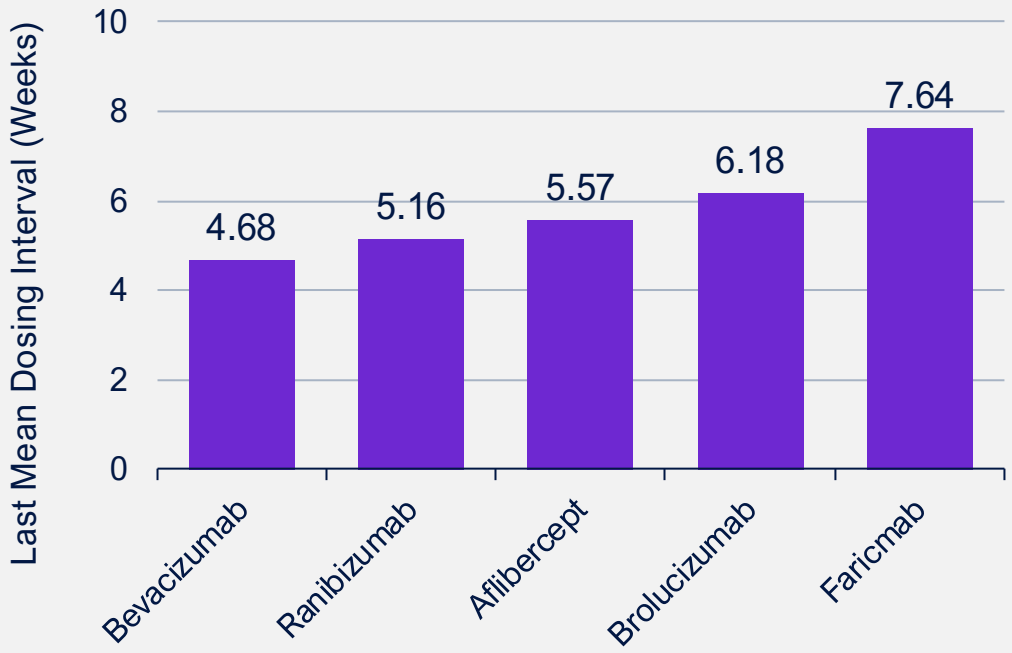
https://doi.org/10.1016/j.oret.2019.05.017
ISSN 2468-6530/19

OCULAR THERAPEUTIX Retina experience redefined™

1. Wykoff CC et al. Impact of anti-VEGF treatment outcomes using IRIS Registry (6-year analysis). *Ophthalmology Science*. 2024. 2. Monés J, et al. *Ophthalmol Ther*. 2023;12(2):589-602. 3. Ciulla TA, et al. *Ophthalmol Retina*. 2020;4(1):19–30.

Second Generation nAMD Agents Extend Injection Intervals Incrementally Over Previous Agents in the Real World

Comparison of Intravitreal Injection Intervals (n=190)[1]



Real World Use of Aflibercept 8 mg: IRIS Registry Data[2]

Group	Achieved Interval
Treatment-naïve (n=1361)	**~12 weeks**
Switchers (n=8311)	**~73% at <10 weeks** after switch from 2 mg to 8 mg

OCULAR THERAPEUTIX Retina experience redefined™

1. Leung EH, Oh DJ, Alderson SE, et al. Clin Ophthalmol. 2023;17:1287-1293. 2. Do DV, Moll K, Murdock D, et al. Real-world use of aflibercept 8 mg in nAMD or DME: IRIS® Registry analysis. Presented at: AAO Retina Subspecialty Day; Oct 17–18, 2025; Palo Alto, CA.
nAMD, neovascular age-related macular degeneration;

Existing Literature Underestimates True Attrition in nAMD

Themes in Attrition Literature

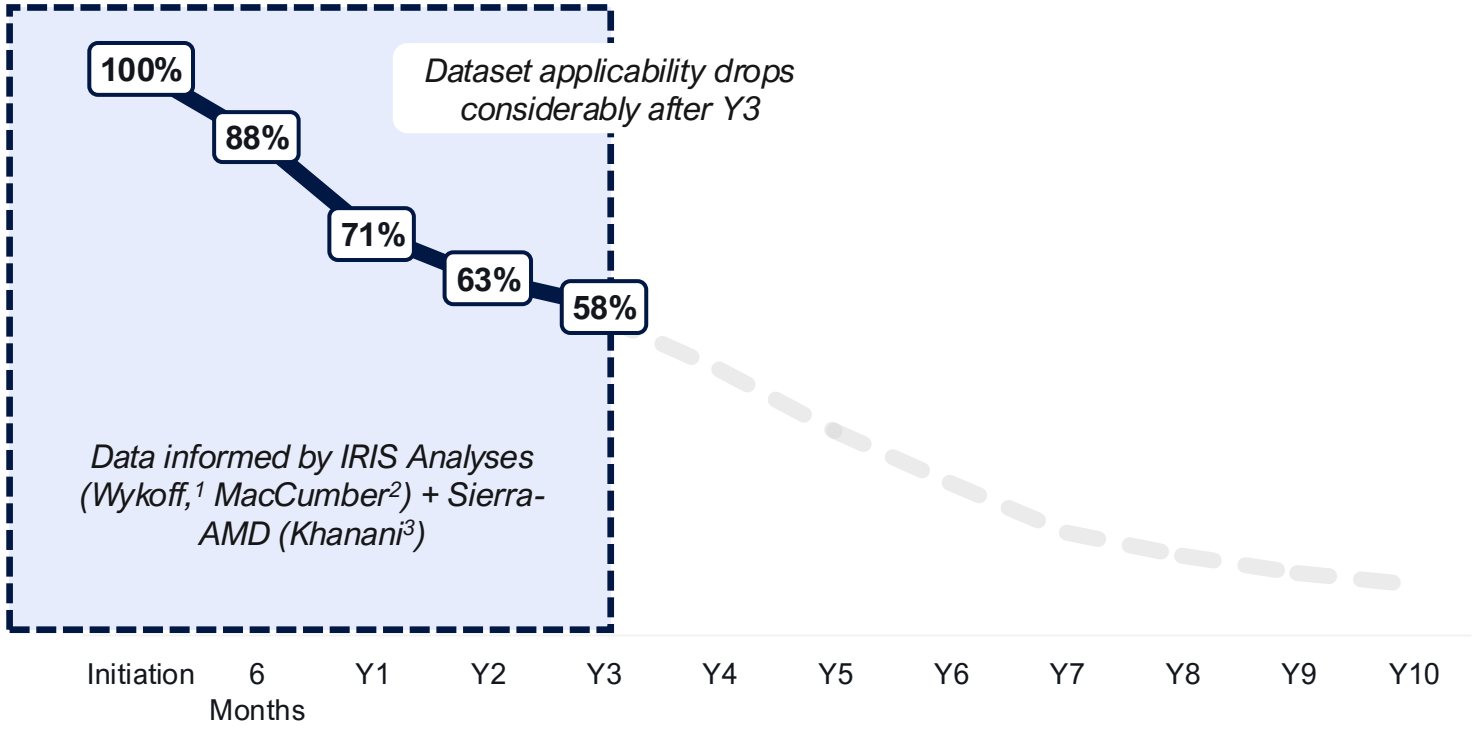
Varying Definitions of Discontinuation
Ranging from **6-12 Months**

Strict Inclusion Criteria Limit Relevance
Prior registry analyses required 1.5 & 2 years of **follow-up**

Limited Longer-Term Follow-Up
Large studies **rarely follow patients** beyond first **2-3 years**

Attrition appeared to be a secondary focus
in large registry analyses with anti-VEGFs in nAMD

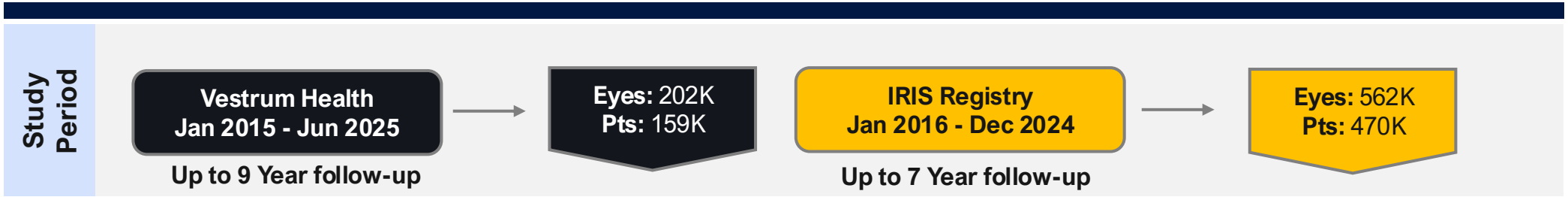
Literature-Based Attrition Curve*



OCULAR THERAPEUTIX Retina experience redefined™

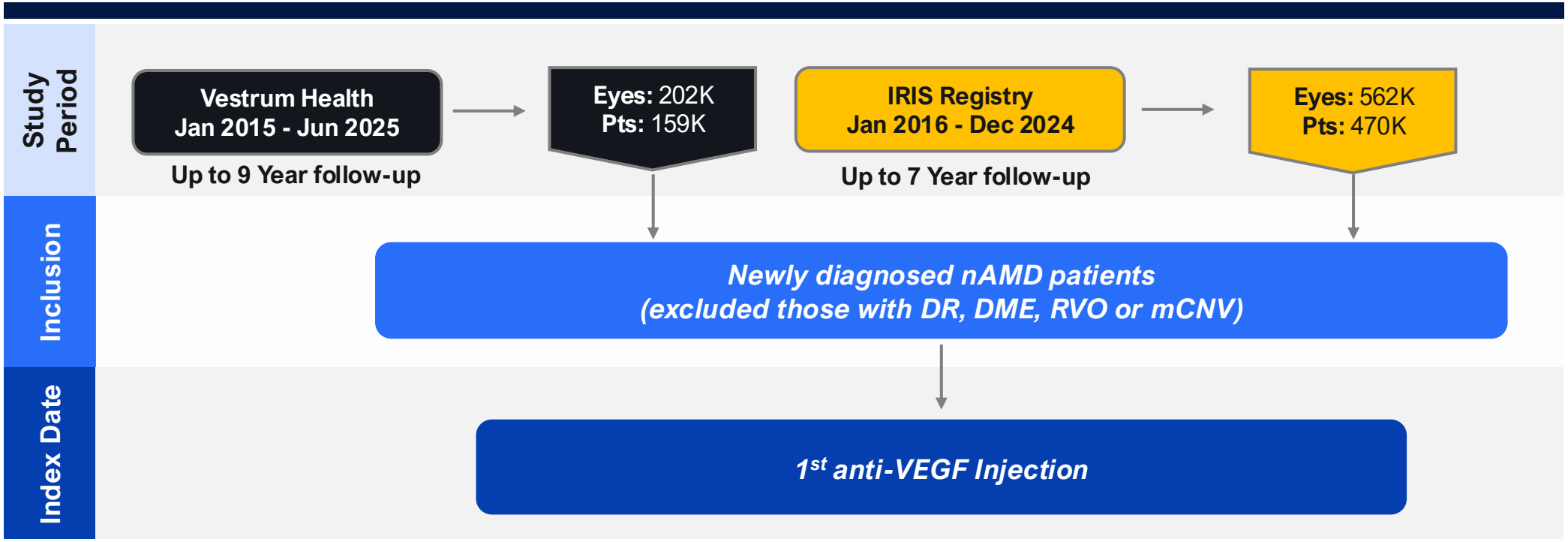
**Literature-Based Attrition Curve generated by Ocular Therapeutix by analysis of references 1-3.
1. Wykoff CC et al. Impact of anti-VEGF treatment outcomes using IRIS Registry (6-year analysis). Ophthalmology Science. 2024. 2. MacCumber MW et al. Anti-VEGF agents for wet AMD: IRIS Registry analysis. Can J Ophthalmol. 2023. 3. Khanani AM et al. SIERRA-AMD real-world anti-VEGF patterns. Ophthalmology Retina. 2020
nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

Curated Retrospective Attrition Analysis of Treatment-Naïve nAMD Eyes Across Two National Registries With Up to 7–9 Years of Follow-Up



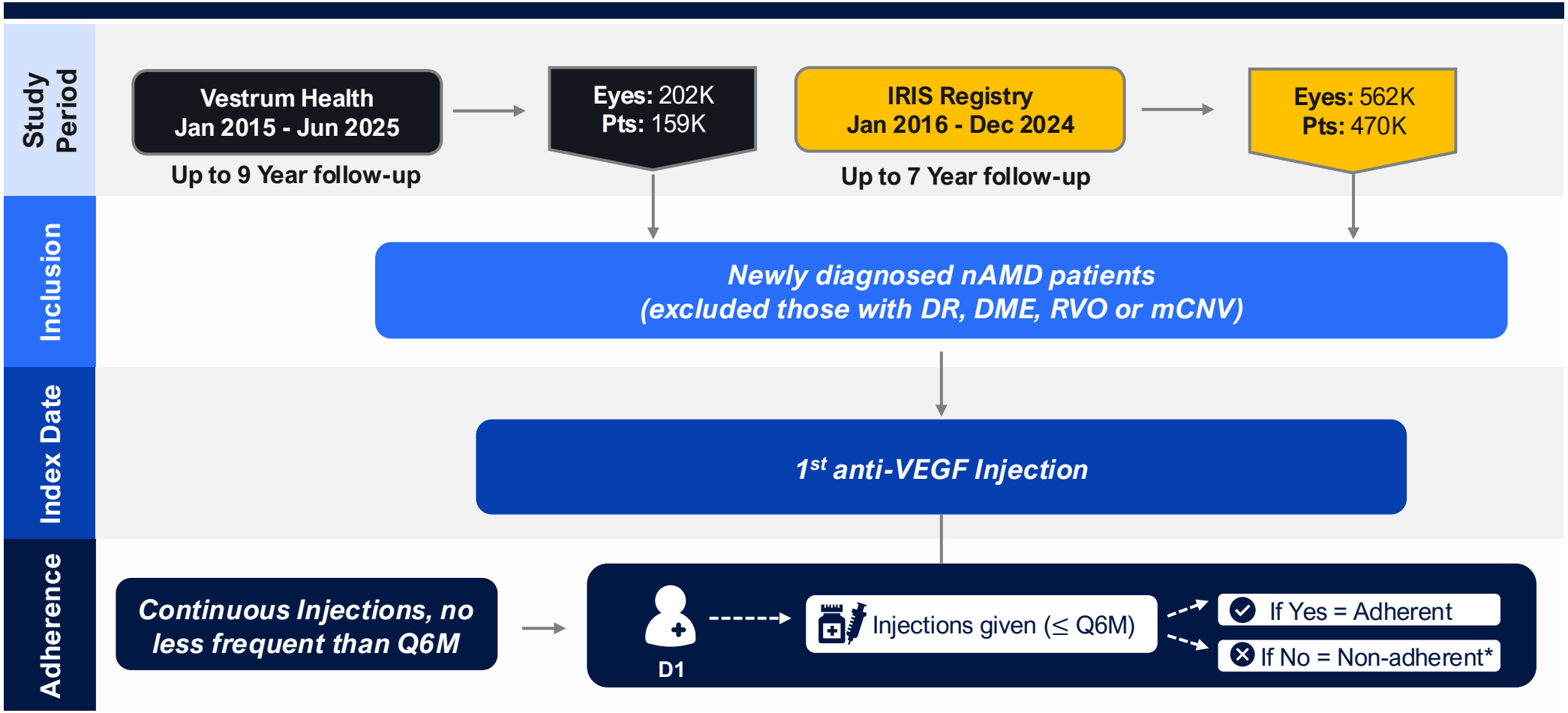
*Non-Adherence Captures: Discontinuation and Lost To Follow-Up
Data on File, Ocular Therapeutix
DR, diabetic retinopathy; DME, diabetic macular edema; RVO, retinal vein occlusion; mCNV, myopic choroidal neovascularization;' VEGF, vascular endothelial growth factor

Curated Retrospective Attrition Analysis of Treatment-Naïve nAMD Eyes Across Two National Registries With Up to 7–9 Years of Follow-Up



*Non-Adherence Captures: Discontinuation and Lost To Follow-Up
Data on File, Ocular Therapeutix
DR, diabetic retinopathy; DME, diabetic macular edema; RVO, retinal vein occlusion; mCNV, myopic choroidal neovascularization;' VEGF, vascular endothelial growth factor

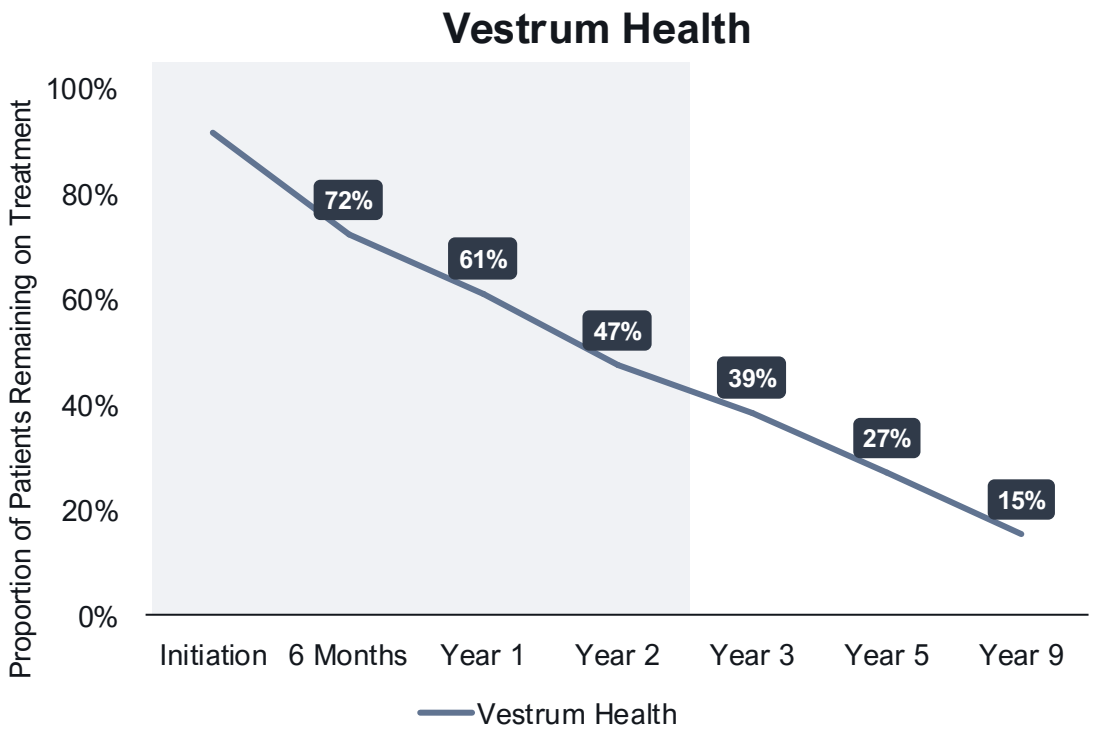
Curated Retrospective Attrition Analysis of Treatment-Naïve nAMD Eyes Across Two National Registries With Up to 7–9 Years of Follow-Up

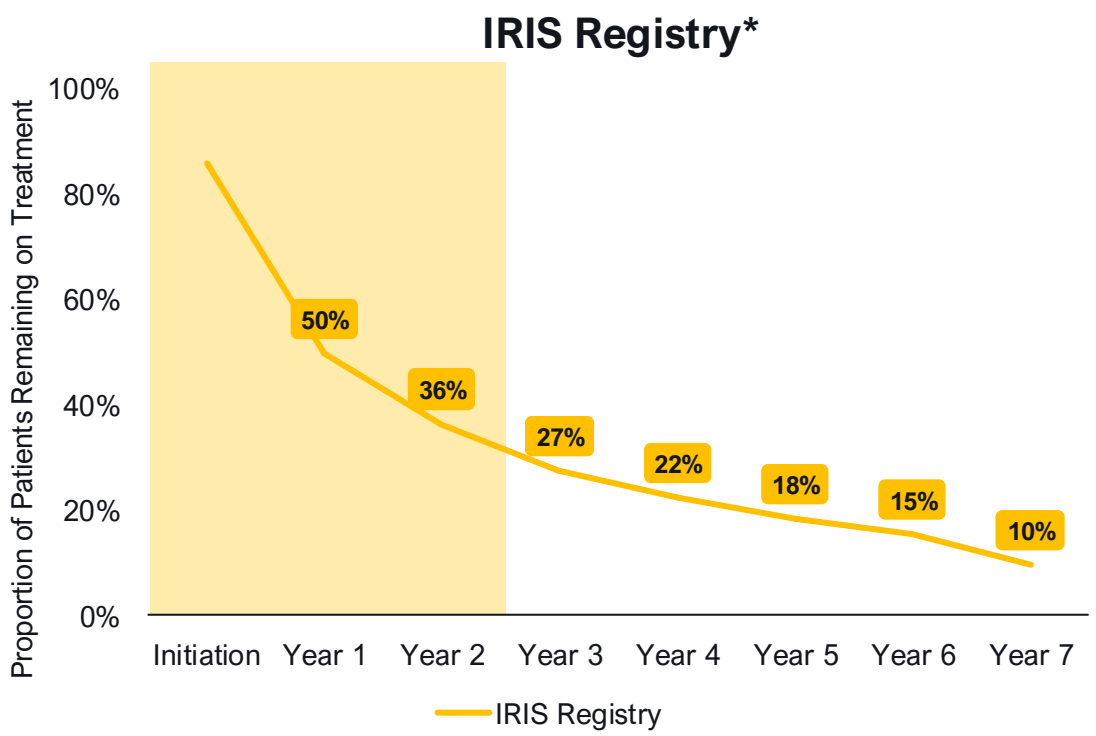


*Non-Adherence Captures: Discontinuation and Lost To Follow-Up
Data on File, Ocular Therapeutix
DR, diabetic retinopathy; DME, diabetic macular edema; RVO, retinal vein occlusion; mCNV, myopic choroidal neovascularization;' VEGF, vascular endothelial growth factor

High Real-World Discontinuation Highlights Unmet Need for Durable, Low-Burden nAMD Therapy

Steepest Drop-Off in Years 1–2; Continued Decline Through Years 3–7+



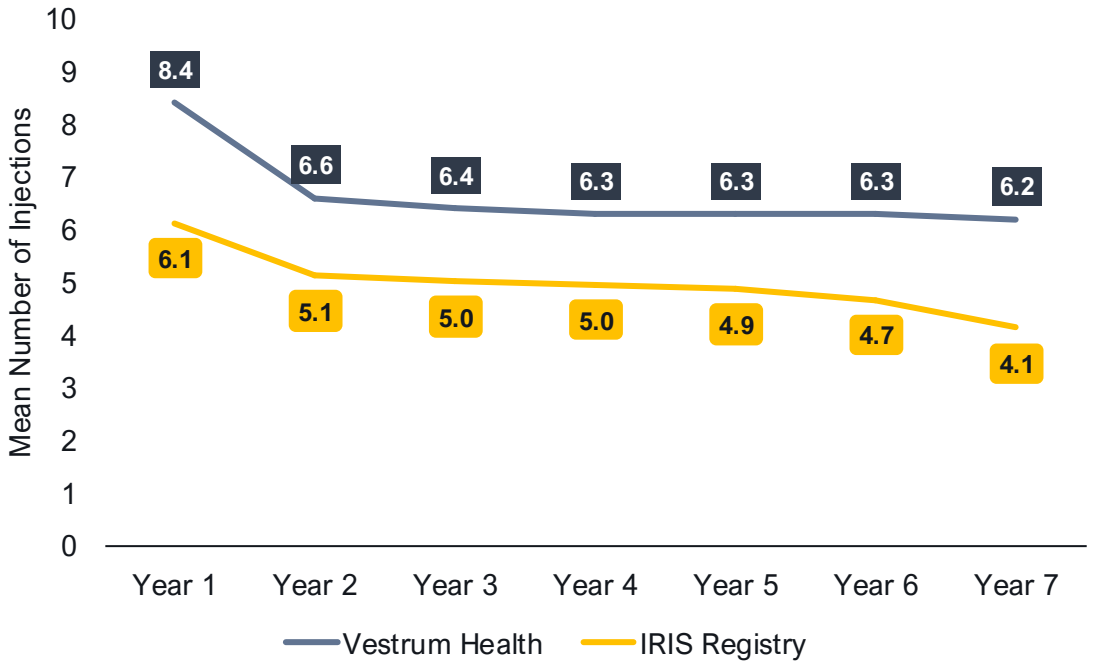


OCULAR THERAPEUTIX Retina experience redefined™

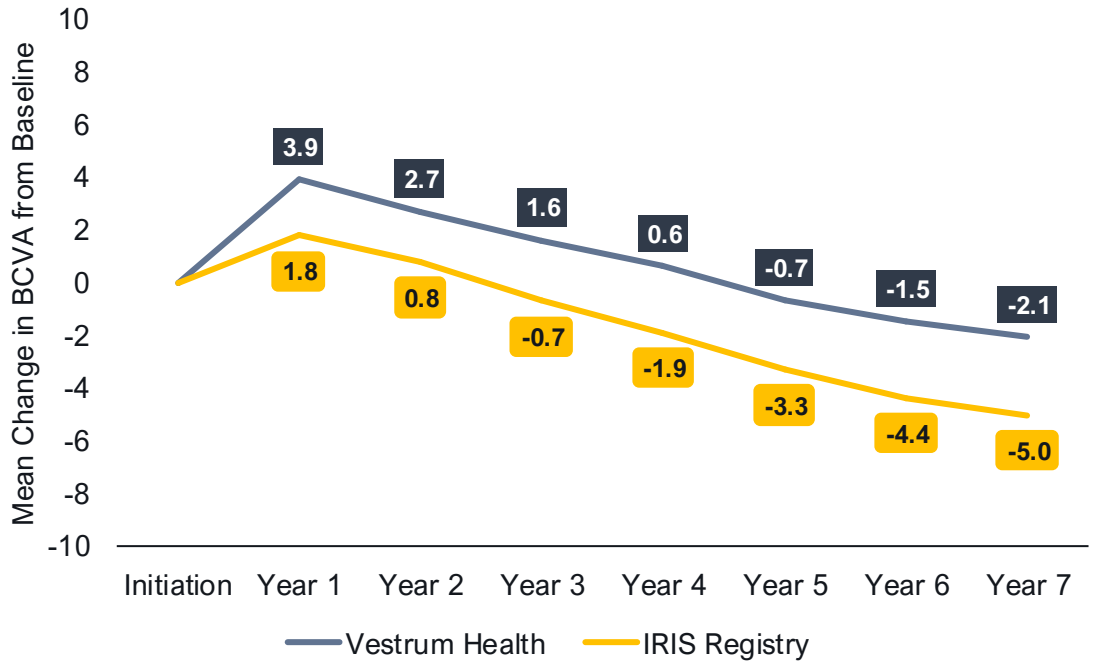
*Cohort with the longest observation period for IRIS Registry with 67,156 eyes
Data on File, Ocular Therapeutix

Real-World Anti-VEGF Use Shows Fewer Injections Over Time, Driving Initial Vision Gains Followed by Gradual Decline

Injection Frequency



Long-Term Visual Outcomes*



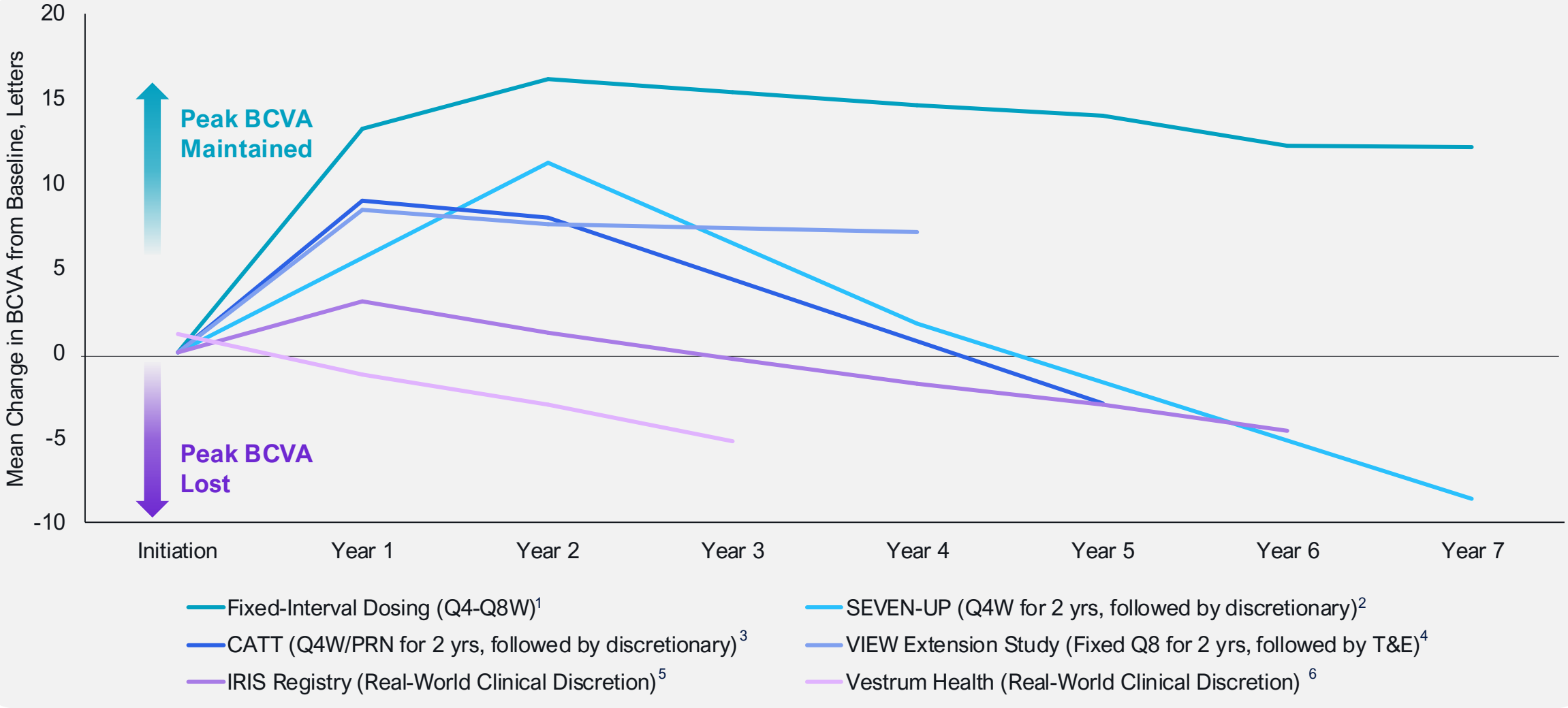
Injection Frequency Declines Over Time in Both Databases
Vestrum Health drops from 8.4 at Year 1 to 6.2 by Year 7
IRIS Registry drops from 6.1 at Year 1 to 4.1 by Year 7

Both Databases Show Early Gains Followed by Long-Term Decline
Vestrum Health: +3.9 letters at Year 1 to –2.1 by Year 7
IRIS Registry: +1.8 letters at Year 1 to –5.0 by Year 7

OCULAR THERAPEUTIX Retina experience redefined™

Data on File, Ocular Therapeutix
*Visual outcomes: mean change from baseline in ETDRS letters

Persistent Dosing Could Provide for Sustained Visual Outcomes, Emphasizing the Need for Therapies that Deliver Continuous, Consistent Treatment



OCULAR THERAPEUTIX Retina experience redefined™

1 Peden, M. C., et al (2015). Ophthalmology, 122(4), 803–808. 2. Rofagha S, Bhisitkul RB, Boyer DS, Sadda SR, Zhang K; SEVEN-UP Study Group. Ophthalmology. 2013;120(11):2292–2299. 3. Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Research Group, et al. Ophthalmology. 2016;123(8):1751–1761. 4. VIEW Extension Studies: Schmidt-Erfurth U, et al. Ophthalmology. 2014;121(1):193–201, Kaiser PK, et al. Ophthalmol Retina. 2017;1(4):304–313, 5. Wykoff, C. C., et al (2023). Ophthalmology science, 4(2), 100421. 6. Khanani, A. M., et al (2020). Ophthalmology. Retina, 4(2), 122–133.

Redefining nAMD Therapy: What can we do better?

Match treatment to real-world adherence	Lower treatment burden	Provide continuous VEGF suppression	Enable long-acting disease control
Therapies must work even when patients cannot maintain frequent injections	Fewer visits and injections may improve long-term persistence	Avoid the cycle of suppression and rebound	Sustained control without frequent dosing may better preserve vision over time

OCULAR THERAPEUTIX Retina experience redefined™

OTX-TKI

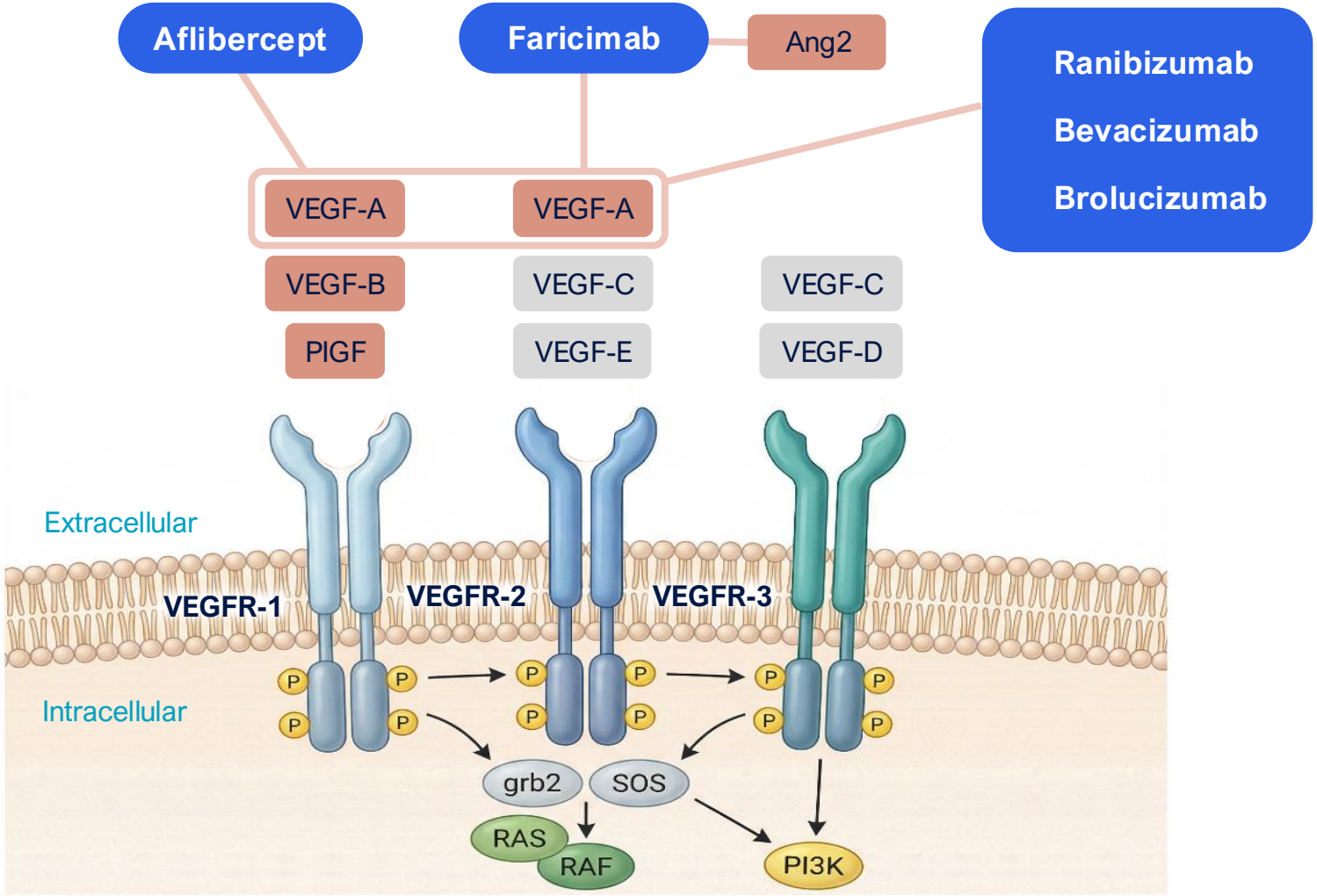
The Science Behind the Therapy

Peter K. Kaiser, MD

OCULAR THERAPEUTIX Retina experience redefined

Current Anti-VEGF Therapies Selectively Target Only Extracellular VEGF

Current **Anti-VEGF** agents act **extracellularly by binding selective ligands**, like VEGF-A, preventing receptor binding and activation[1,2]



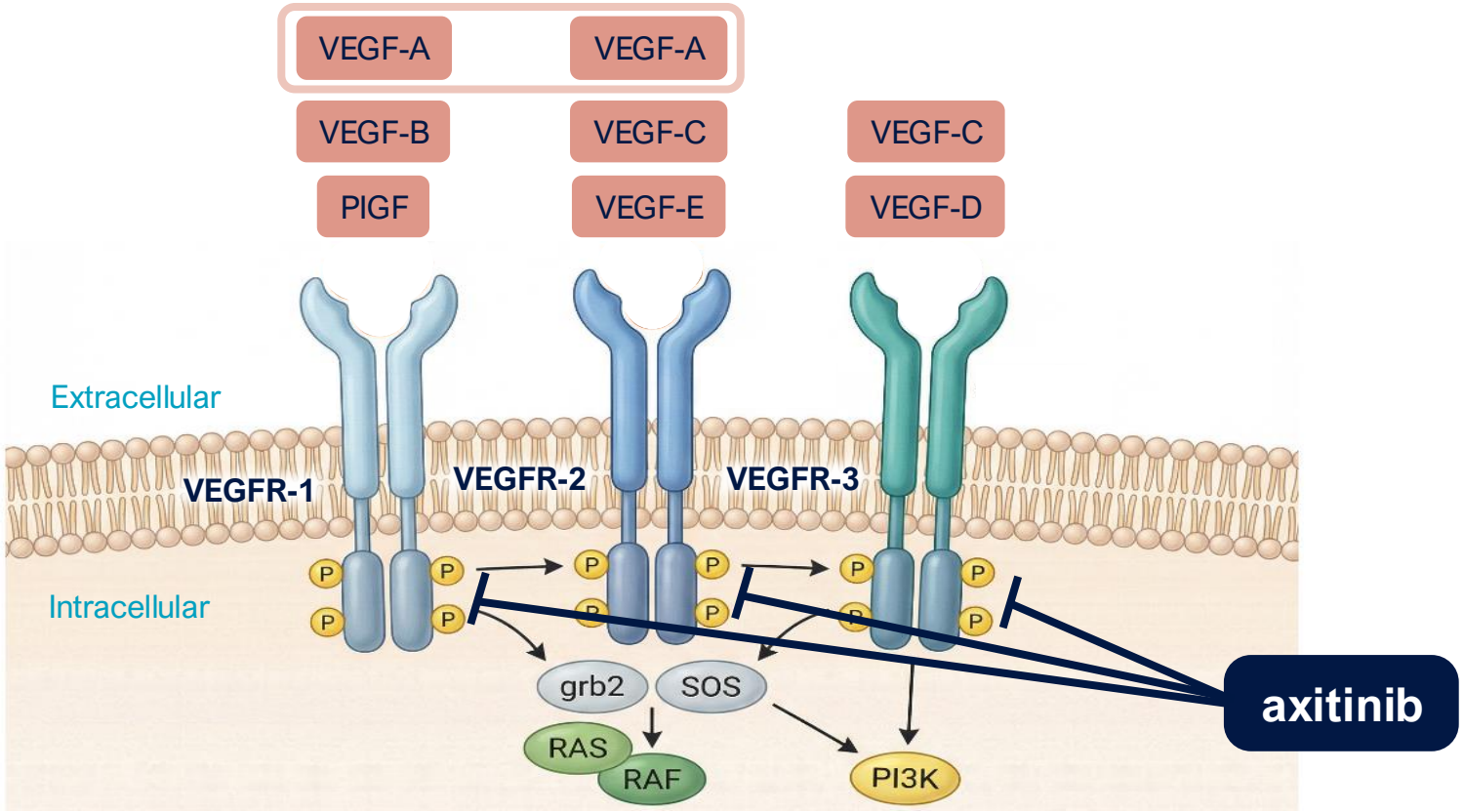
Select extracellular target binding of VEGF, PlGF and Ang-II to inhibit angiogenesis. Adapted from Zhao et al. 2015.[2-4]

OCULAR THERAPEUTIX Retina experience redefined™

1. Hu-Lowe DD, et al. *Clin Cancer Res*. 2008;14(22):7272-7283. 2. Zhao Y, et al. *Oncologist*. 2015;20(6):660-673. 3. Tan CS, et al. *Clin Ophthalmol*. 2022;16:917-933. 4. Khachigian LM, et al. *J Transl Med*. 2023;21(1):133.
PlGF, placenta growth factor; VEGF(R), vascular endothelial growth factor (receptor); P, phosphate; grb2, growth factor receptor-bound protein 2; SOS, son of sevenless; RAS, rat sarcoma viral oncogene homolog; RAF, rapidly accelerated fibrosarcoma; PI3K, phosphatidylinositol 3-kinase; TKI, tyrosine kinase inhibitor.

Tyrosine Kinase Inhibitors Act Intracellularly to Inhibit Receptor Signaling

Tyrosine Kinase Inhibitors (TKI) bind at the **intracellular tyrosine kinase domains** of VEGF receptors, inhibiting ATP binding and preventing activation of pro-angiogenic signaling[1,2]



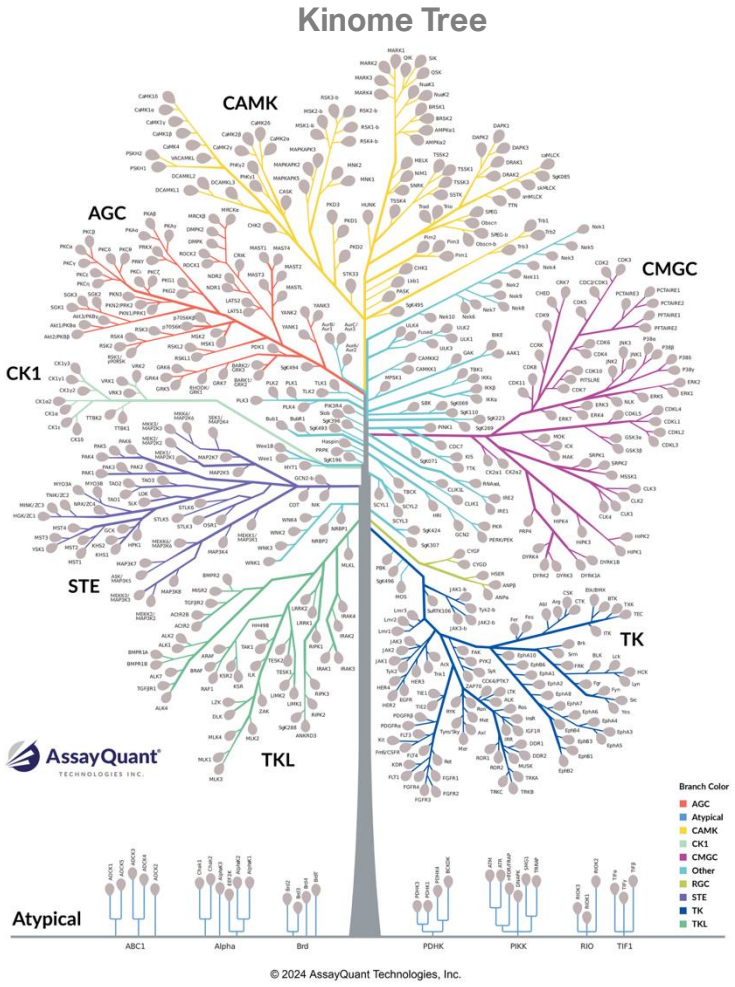
Select angiogenesis intracellular targets of inhibition for tyrosine kinase inhibitors. Adapted from Zhao et al. 2015.[2-4]

OCULAR THERAPEUTIX Retina experience redefined™

1. Hu-Lowe DD, et al. *Clin Cancer Res*. 2008;14(22):7272-7283. **2.** Zhao Y, et al. *Oncologist*. 2015;20(6):660-673. **3.** Tan CS, et al. *Clin Ophthalmol*. 2022;16:917-933. **4.** Khachigian LM, et al. *J Transl Med*. 2023;21(1):133.
PlGF, placenta growth factor; VEGF(R), vascular endothelial growth factor (receptor); P, phosphate; grb2, growth factor receptor-bound protein 2; SOS, son of sevenless; RAS, rat sarcoma viral oncogene homolog; RAF, rapidly accelerated fibrosarcoma; PI3K, phosphatidylinositol 3-kinase; TKI, tyrosine kinase inhibitor.

AssayQuant Kinome Tree

Independent, Quantifiable, Simultaneous Evaluation of Inhibition Activity of TKI drugs



Adapted from AssayQuant.[1]

AssayQuant Kinome tree is an independent, standardized visualization of kinase profiling data[1]

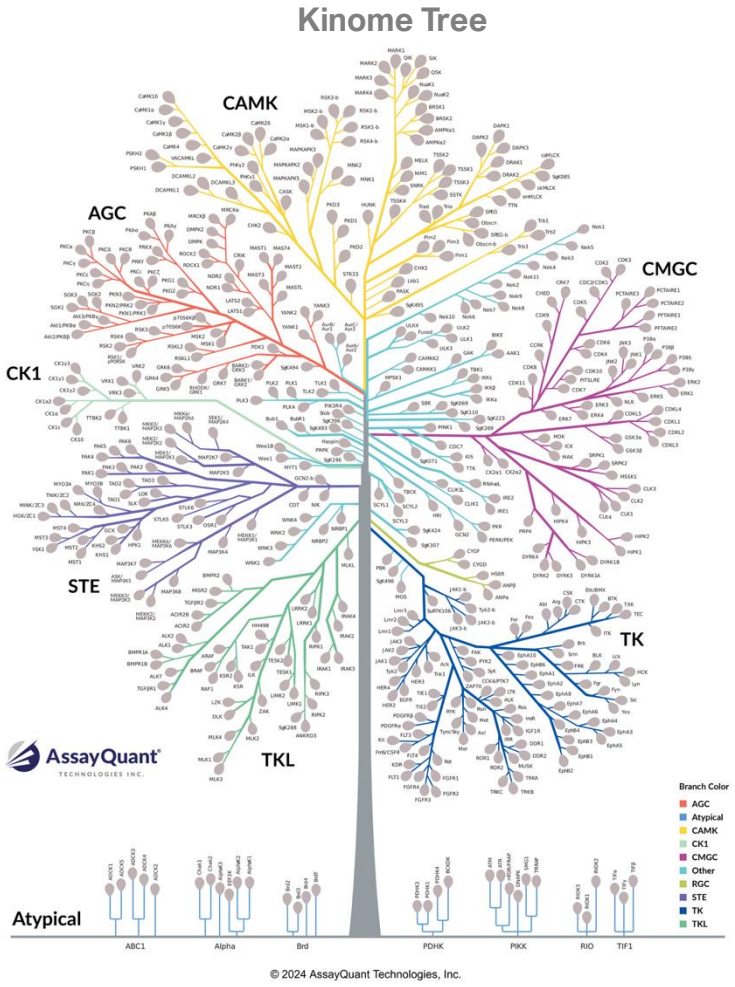
Each kinase receptor is a node with color intensity reflecting magnitude of inhibition[1,2]

OCULAR THERAPEUTIX Retina experience redefined™

AssayQuant is an independent, standardized visualization of kinase profiling data.
1. Activity-based Biochemical Kinase Panel Screening and Profiling Services. https://www.assayquant.com/kinsightservices/kinome-profiling/. Accessed February 23, 2026. 2. González-Vera JA, et al. *Proteomes*. 2015;3(4):369-410.

AssayQuant Kinome Tree

Critically important to understand testing conditions to interpret Kinome Tree Inhibition



Adapted from AssayQuant.[1]

ATP competes with TKI drugs for receptor binding

Apparent % inhibition depends on ATP + drug concentration

OCULAR THERAPEUTIX Retina experience redefined™

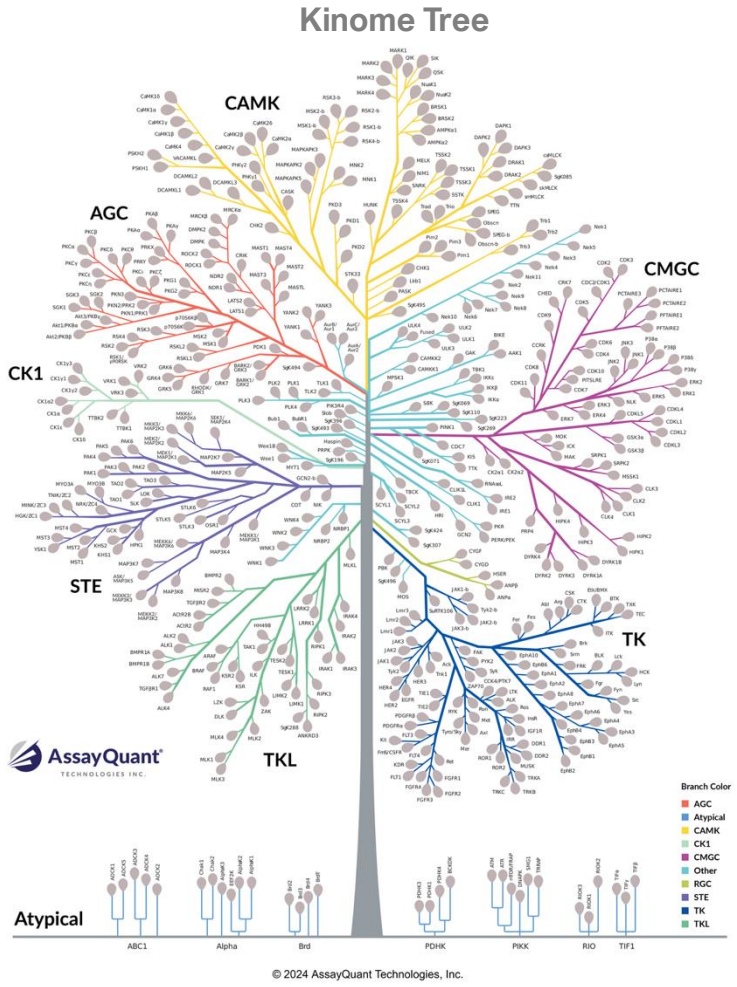
AssayQuant is an independent, standardized visualization of kinase profiling data.

1. Activity-based Biochemical Kinase Panel Screening and Profiling Services. https://www.assayquant.com/kinsight-services/kinome-profiling/. Accessed February 23, 2026. 2. Greiner JV, et al. Biology (Basel). 2021;10(11):1166. 3. Ye SS, et al. Front Pharmacol. 2021;12:654445. 4. Hulin A, et al. Clin J Am Soc Nephrol. 2024;19(7):927-938.

ATP, adenosine triphosphate; TKI, tyrosine kinase inhibitor.

AssayQuant Kinome Tree

Critically important to understand testing conditions to interpret Kinome Tree Inhibition



Adapted from AssayQuant.[1]

ATP competes with TKI drugs for receptor binding

Apparent % inhibition depends on ATP + drug concentration

ATP Testing Levels

Low ATP levels reduce competition and increase % apparent inhibition

Physiologic ATP levels (~**1-4 mM**)[2]

Local ATP elevated in retinal disease[3]

Drug Testing Levels

Supratherapeutic concentrations artificially increase % apparent inhibition

TKIs are highly protein bound (eg. albumin and melanin)[4]

Testing should reflect unbound drug levels in target tissue

OCULAR THERAPEUTIX Retina experience redefined™

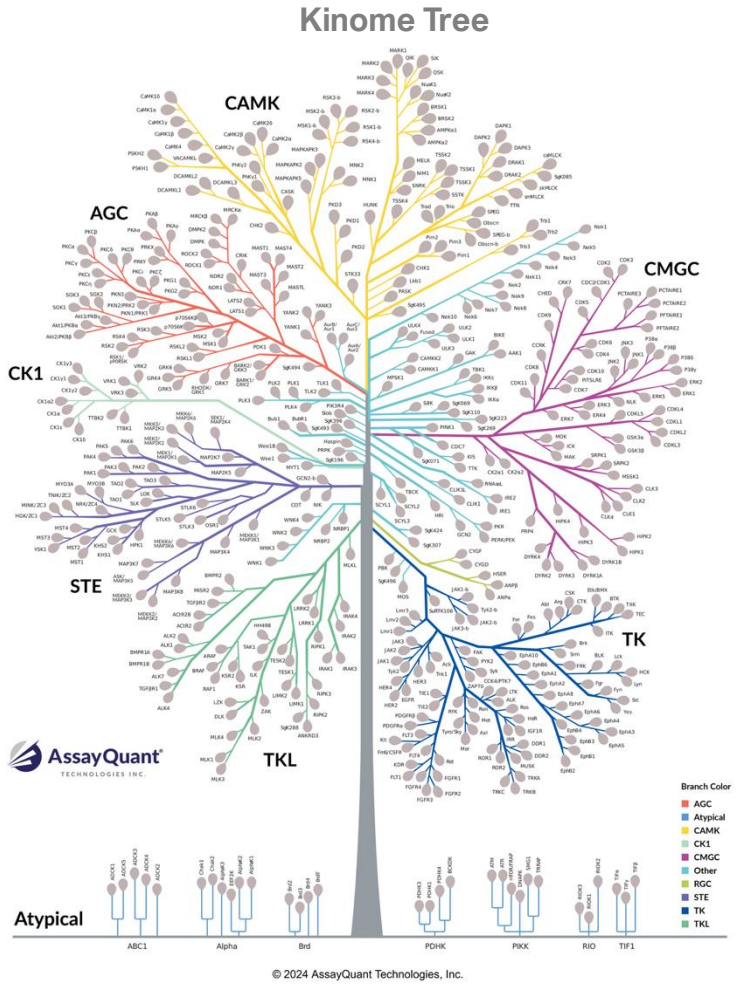
AssayQuant is an independent, standardized visualization of kinase profiling data.

1. Activity-based Biochemical Kinase Panel Screening and Profiling Services. https://www.assayquant.com/kinsight-services/kinome-profiling/. Accessed February 23, 2026. 2. Greiner JV, et al. Biology (Basel). 2021;10(11):1166. 3. Ye SS, et al. Front Pharmacol. 2021;12:654445. 4. Hulin A, et al. Clin J Am Soc Nephrol. 2024;19(7):927-938.

ATP, adenosine triphosphate; TKI, tyrosine kinase inhibitor.

AssayQuant Kinome Tree

Always look for testing conditions when evaluating claims about receptor inhibition



Adapted from AssayQuant.[1]

ATP competes with TKI drugs for receptor binding

Apparent % inhibition depends on ATP + drug concentration

ATP Testing Levels

Low ATP levels reduce competition and increase % apparent inhibition

Physiologic ATP levels (~**1-4 mM**)[2]

Local ATP elevated in retinal disease[3]

Drug Testing Levels

Supratherapeutic concentrations artificially increase % apparent inhibition

TKIs are highly protein bound (eg. albumin and melanin)[4]

Testing should reflect unbound drug levels in target tissue

Thus, there can be **different kinome trees** for the *same compound* depending on ATP and drug concentrations used in test

OCULAR THERAPEUTIX Retina experience redefined™

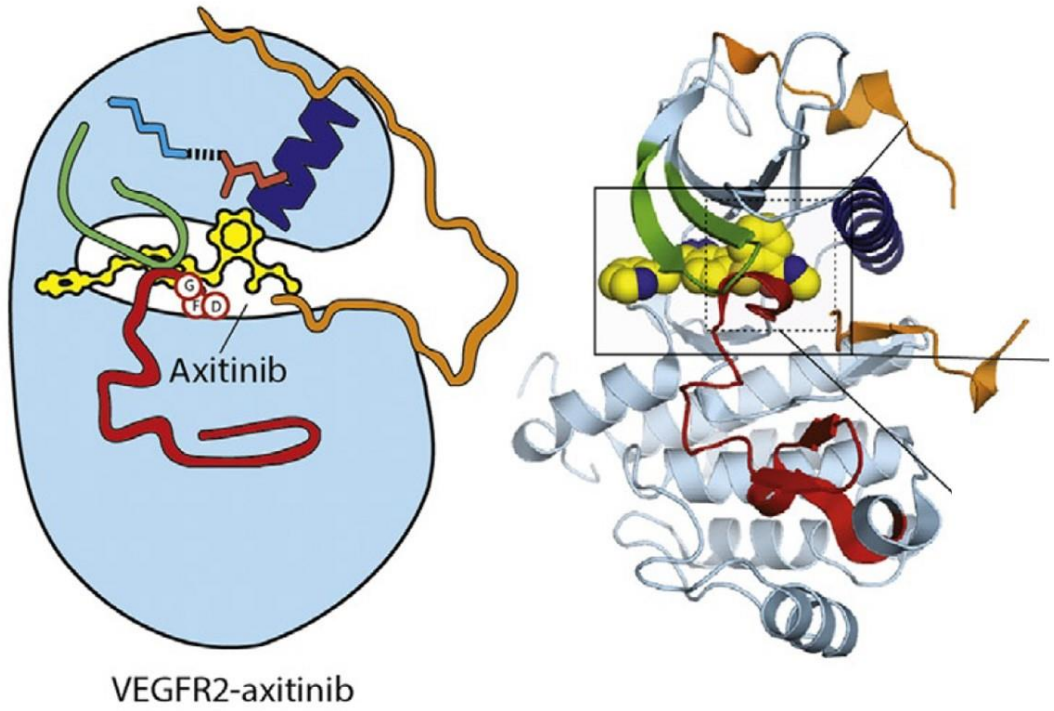
AssayQuant is an independent, standardized visualization of kinase profiling data.

1. Activity-based Biochemical Kinase Panel Screening and Profiling Services. https://www.assayquant.com/kinsight-services/kinome-profiling/. Accessed February 23, 2026. 2. Greiner JV, et al. Biology (Basel). 2021;10(11):1166. 3. Ye SS, et al. Front Pharmacol. 2021;12:654445. 4. Hulin A, et al. Clin J Am Soc Nephrol. 2024;19(7):927-938.

ATP, adenosine triphosphate; TKI, tyrosine kinase inhibitor.

Axitinib: Highly Selective, Potent Pan-VEGFR Inhibitor

- 2nd generation TKI, approved in 2012 (Inlyta, Pfizer) for treatment of advanced renal cell carcinoma
- Axitinib's high potency and selectivity relates to its interaction inside the pocket of the kinase receptor domain combined with its interaction with the juxtamembrane segment (this links the cell membrane to the kinase domain)[1]
- Potent inhibitor for VEGFR and PDGFR isoforms and has minimal inhibition against "off-target" protein kinases[2,3,4]

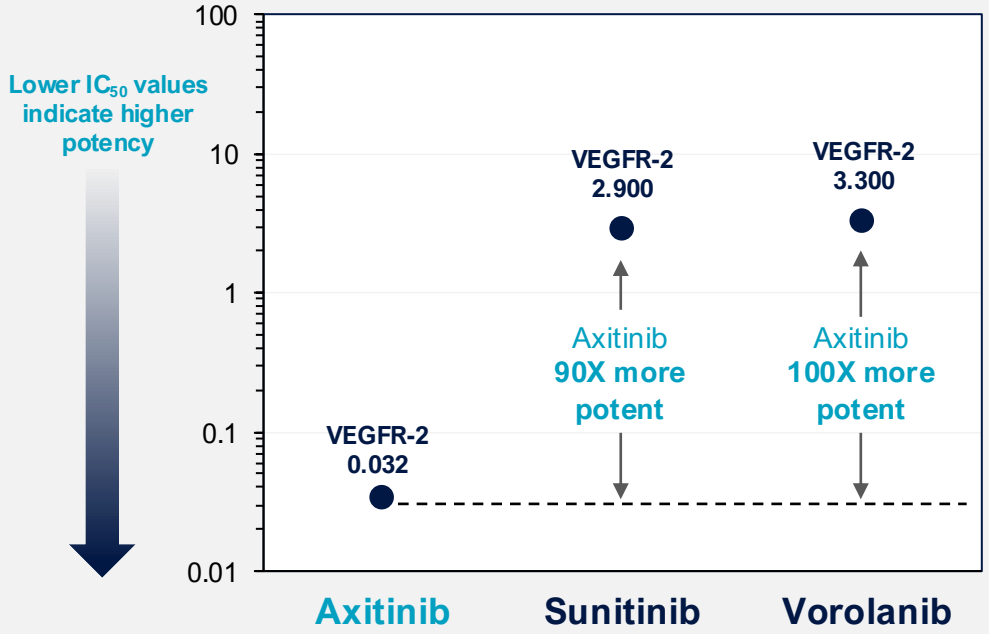


VEGF(R), vascular endothelial growth factor [receptor]; TKI, tyrosine kinase inhibitor; PlGF, placental growth factor; Ang, angiopoietin ATP, Adenosine triphosphate

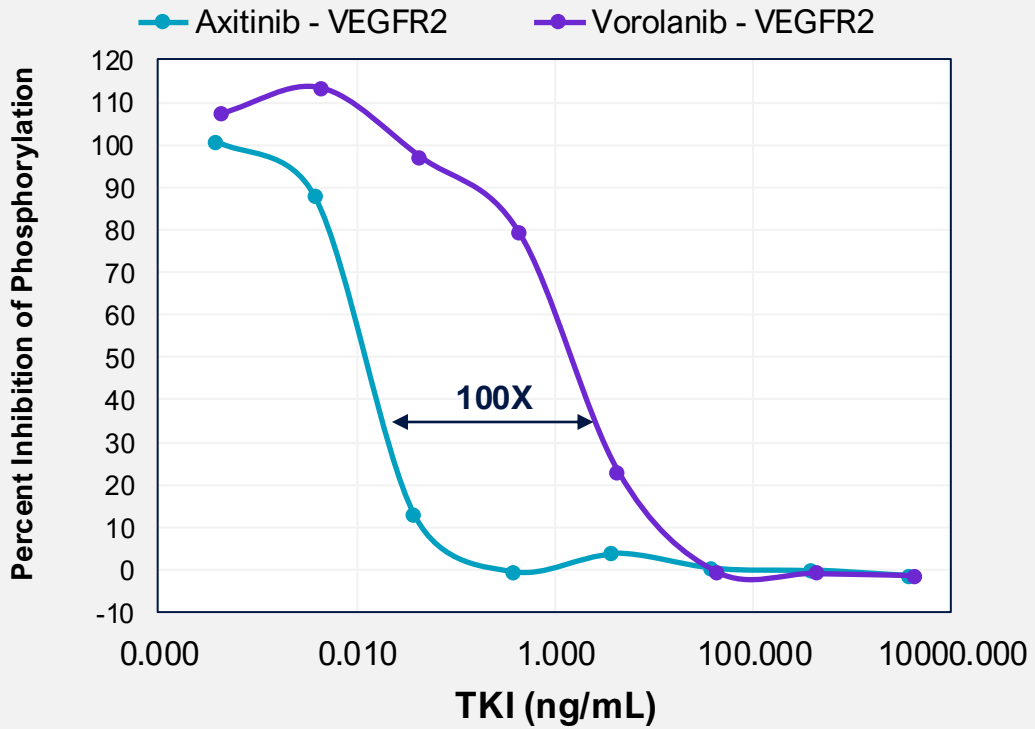
1. Wang et al., 2014; McTigue et al., 2012; Solowiej et al., 2009 2.Hu-Lowe DD, et al. Clin Cancer Res. 2008;14(22):7272-7283. 2. Zhao Y, et al. Oncologist. 2015;20(6):660-673. 3. Tan CS, et al. Clin Ophthalmol. 2022;16:917-933. 4. Adapted from: Wang, Q., Zorn, J.A. and Kuriyan, J., 2014. A structural atlas of kinases inhibited by clinically approved drugs. Methods in enzymology, 548, pp.23-67.

Axitinib: Highly Selective, Very Potent Pan-VEGFR Inhibitor

IC_{50} Values with Cell Phosphorylation (nM)[1]



Percent Inhibition of Phosphorylation[3]



Highly selective for all VEGF receptors[1]

~100X more potent for VEGFR2 compared to vorolanib[2]

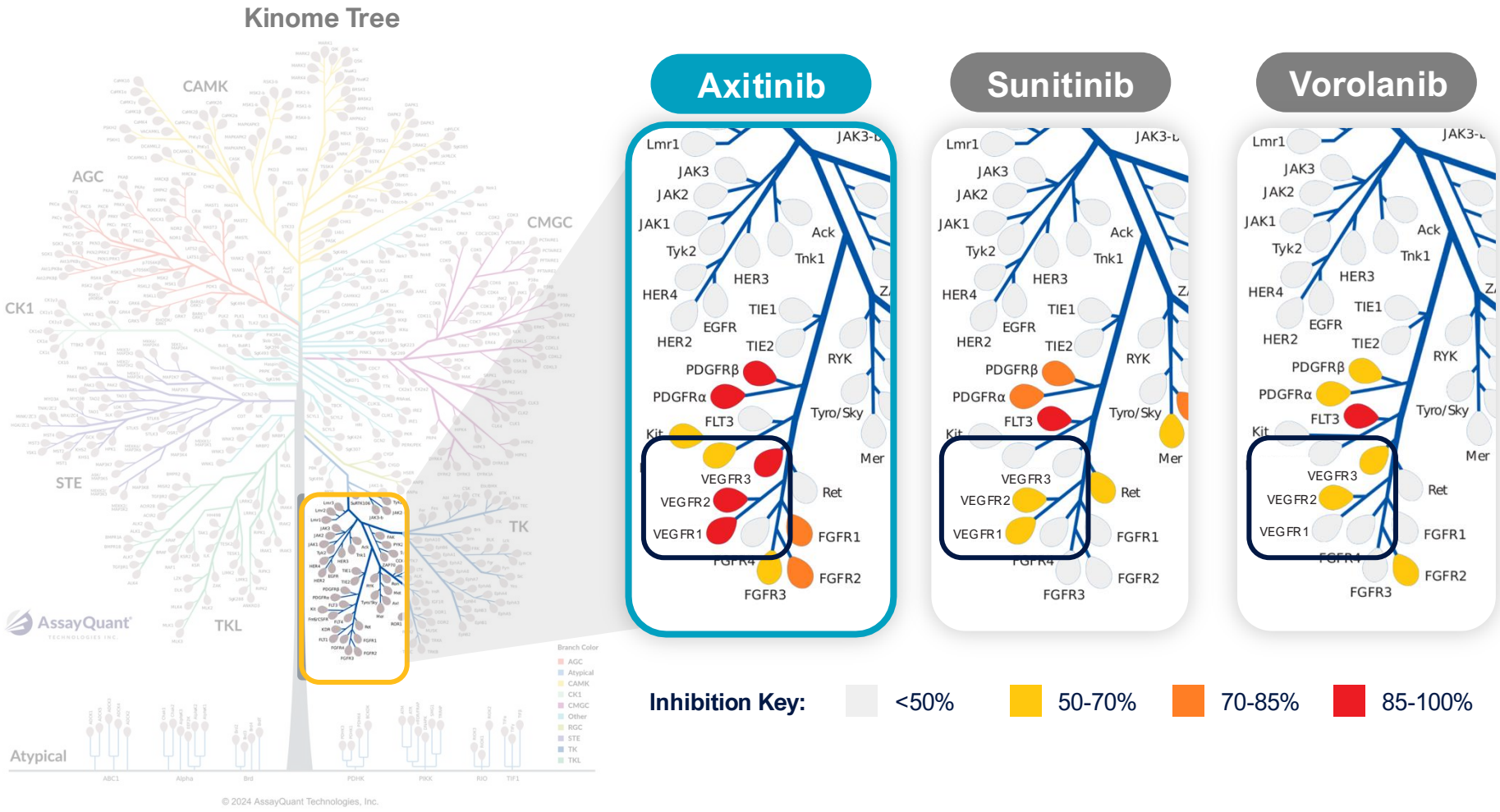
OCULAR THERAPEUTIX Retina experience redefined™

1. Patel C, et al. Target and Selectivity Profiling of Axitinib in Cell-Based and Biochemical Assays. Presented at Association in Vision and Ophthalmology. May 4, 2025. Salt Lake City, UT.**2.** Blizzard, C et al. Pharmacodynamic efficacy of optimized intravitreal axitinib implant (OTX-TKI) in a VEGF challenge rabbit model. Presented at the Association in Vision and Ophthalmology. May 9, 2024. Seattle, WA, US. **3.**VEGF-R2 Cellular Phosphorylation Assay Service. https://www.reactionbiology.com/datasheet/vegf-r2_cell_phospho_freiburg/. Accessed February 24, 2026.

VEGFR, vascular endothelial growth factor receptor; IC50, inhibitory concentration 50%; TKI, tyrosine kinase inhibitor.

Axitinib: Highly Selective, Potent Pan-VEGFR Inhibitor

Independent AssayQuant Kinome Tree Analysis



At physiologic ATP concentrations and therapeutic TKI concentrations, **axitinib***:

VEGFR 1/2/3:
>90% inhibition[1,2]

*Kinome Tree inhibition analysis conducted in collaboration with AssayQuant; Analysis conducted at 1mM ATP, 1µM drug concentration.
1. Data on file, Ocular Therapeutix. 2. Patel C, et al. Target and Selectivity Profiling of Axitinib in Cell-Based and Biochemical Assays. Presented at the Association for Research in Vision and Ophthalmology. May 8, 2025, Salt Lake City, UT.
TKI, tyrosine kinase inhibition; VEGFR, vascular endothelial growth factor receptor; ATP, adenosine triphosphate.

AssayQuant Independent Potency Comparison Among TKIs

Tyrosine Kinase Inhibitor Potency (% Inhibition)

*Evaluated at physiologic ATP levels (1mM) & Drug Concentrations (1μM)**

TK Receptors[1,2]	Axitinib *Most Potent VEGFR, PDGFR TKI*	Vorolanib *Derivative of Sunitinib*	Sunitinib *Development in retina terminated*
VEGF RECEPTORS			
FDA-APPROVED INDICATIONS	Renal cell carcinoma[3]	Not approved by FDA; X-82 approved in China in combination with everolimus for advanced renal cell carcinoma[4]	Renal cell carcinoma Gastrointestinal stromal tumors Pancreatic neuroendocrine tumors[5,6]

OCULAR THERAPEUTIX Retina experience redefined™

*Kinome Tree inhibition analysis conducted in collaboration with AssayQuant. Analysis conducted at 1mM ATP, 1μM drug concentration.

1. Data on file, Ocular Therapeutix. 2. Patel C, et al. Target and Selectivity Profiling of Axitinib in Cell-Based and Biochemical Assays. Presented at the Association for Research in Vision and Ophthalmology. May 8, 2025, Salt Lake City, UT. 3. INLYTA (axitinib) prescribing information. U.S. Food and Drug Administration; 2012. Accessed February 27, 2026. 4. Sheng X, et al. *EBioMedicine.* 2020;55:102755. 5. Blumenthal GM, et al. *Oncologist.* 2012;17(8):1108-1113. 6. SUTENT (sunitinib malate) prescribing information. U.S. Food and Drug Administration; 2006. Accessed February 27, 2026.

TKI, tyrosine kinase inhibitor; ATP, adenosine triphosphate; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; JAK, janus kinase.

AssayQuant Independent Potency Comparison Among TKIs

Tyrosine Kinase Inhibitor Potency (% Inhibition)

*Evaluated at physiologic ATP levels (1mM) & Drug Concentrations (1μM)**

TK Receptors[1,2]	Axitinib *Most Potent VEGFR, PDGFR TKI*	Vorolanib *Derivative of Sunitinib*	Sunitinib *Development in retina terminated*
VEGF RECEPTORS			
VEGFR1	100%	32%	59%
VEGFR2	**98%**	**53%**	**51%**
VEGFR3	92%	51%	41%
FDA-APPROVED INDICATIONS	Renal cell carcinoma[3]	Not approved by FDA; X-82 approved in China in combination with everolimus for advanced renal cell carcinoma[4]	Renal cell carcinoma Gastrointestinal stromal tumors Pancreatic neuroendocrine tumors[5,6]

OCULAR THERAPEUTIX Retina experience redefined™

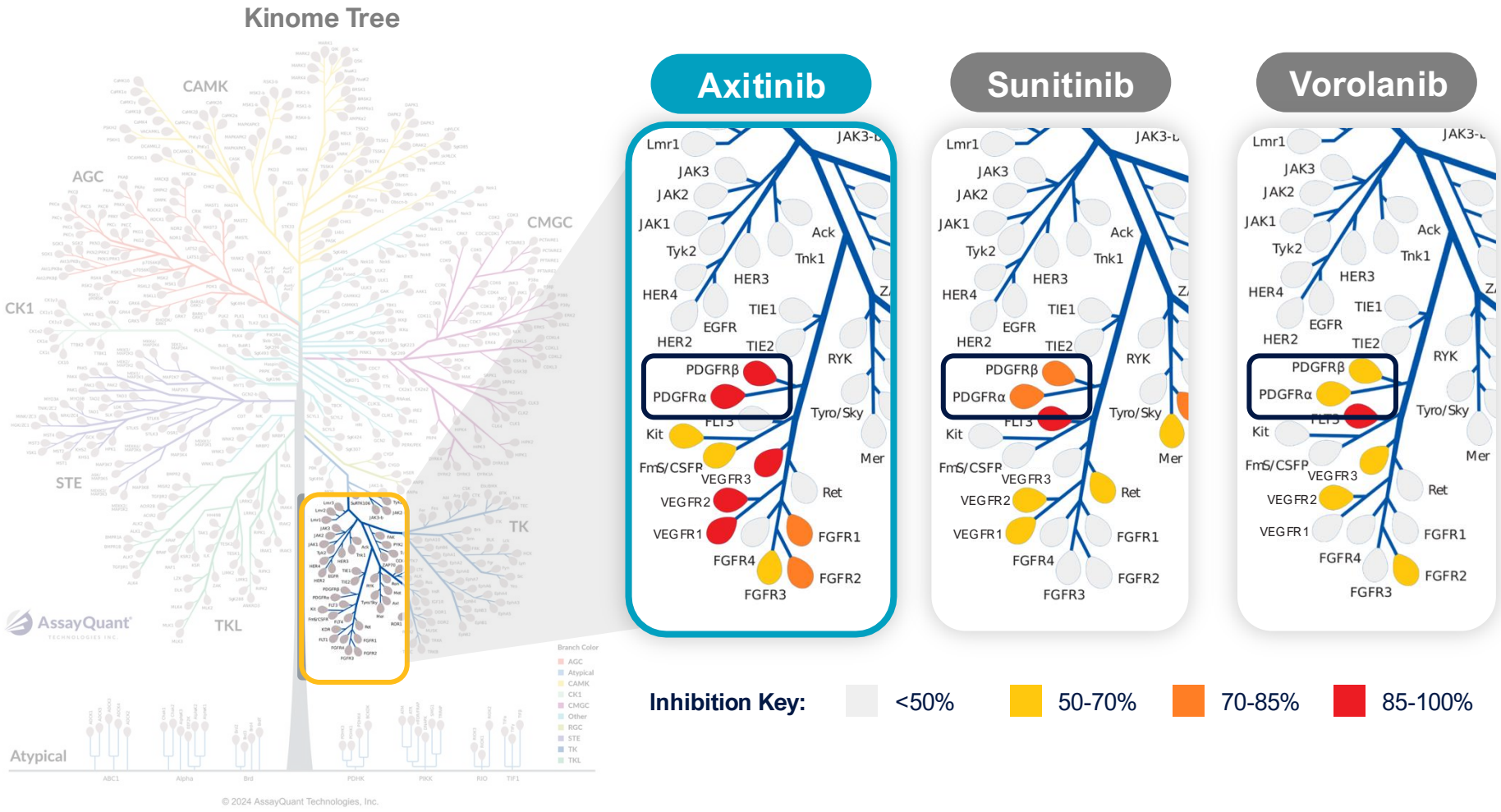
*Kinome Tree inhibition analysis conducted in collaboration with AssayQuant. Analysis conducted at 1mM ATP, 1μM drug concentration.

1. Data on file, Ocular Therapeutix. 2. Patel C, et al. Target and Selectivity Profiling of Axitinib in Cell-Based and Biochemical Assays. Presented at the Association for Research in Vision and Ophthalmology. May 8, 2025, Salt Lake City, UT. 3. INLYTA (axitinib) prescribing information. U.S. Food and Drug Administration; 2012. Accessed February 27, 2026. 4. Sheng X, et al. *EBioMedicine.* 2020;55:102755. 5. Blumenthal GM, et al. *Oncologist.* 2012;17(8):1108-1113. 6. SUTENT (sunitinib malate) prescribing information. U.S. Food and Drug Administration; 2006. Accessed February 27, 2026.

TKI, tyrosine kinase inhibitor; ATP, adenosine triphosphate; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; JAK, janus kinase.

Axitinib: Highly Selective, Potent Pan-VEGFR Inhibitor

Independent AssayQuant Kinome Tree Analysis



At physiologic ATP concentrations and therapeutic TKI concentrations, **axitinib***:

VEGFR 1/2/3:
>90% inhibition[1]

PDGFR α/β:
>85% inhibition[1]

*Kinome Tree inhibition analysis conducted in collaboration with AssayQuant; Analysis conducted at 1mM ATP, 1µM drug concentration.
1. Data on file, Ocular Therapeutix. 2. Patel C, et al. Target and Selectivity Profiling of Axitinib in Cell-Based and Biochemical Assays. Presented at the Association for Research in Vision and Ophthalmology. May 8, 2025, Salt Lake City, UT.
TKI, tyrosine kinase inhibition; VEGFR, vascular endothelial growth factor receptor; ATP, adenosine triphosphate; PDGFR, platelet-derived growth factor receptor.

AssayQuant Independent Potency Comparison Among TKIs

Tyrosine Kinase Inhibitor Potency (% Inhibition)

*Evaluated at physiologic ATP levels (1mM) & Drug Concentrations (1μM)**

TK Receptors[1,2]	Axitinib *Most Potent VEGFR, PDGFR TKI*	Vorolanib *Derivative of Sunitinib*	Sunitinib *Development in retina terminated*
VEGF RECEPTORS			
VEGFR1	100%	32%	59%
VEGFR2	**98%**	**53%**	**51%**
VEGFR3	92%	51%	41%
OTHER RECEPTORS			
PDGFRα	94%	65%	70%
PDGFRβ	88%	64%	78%
FDA-APPROVED INDICATIONS	Renal cell carcinoma[3]	Not approved by FDA; X-82 approved in China in combination with everolimus for advanced renal cell carcinoma[4]	Renal cell carcinoma Gastrointestinal stromal tumors Pancreatic neuroendocrine tumors[5,6]

OCULAR THERAPEUTIX Retina experience redefined™

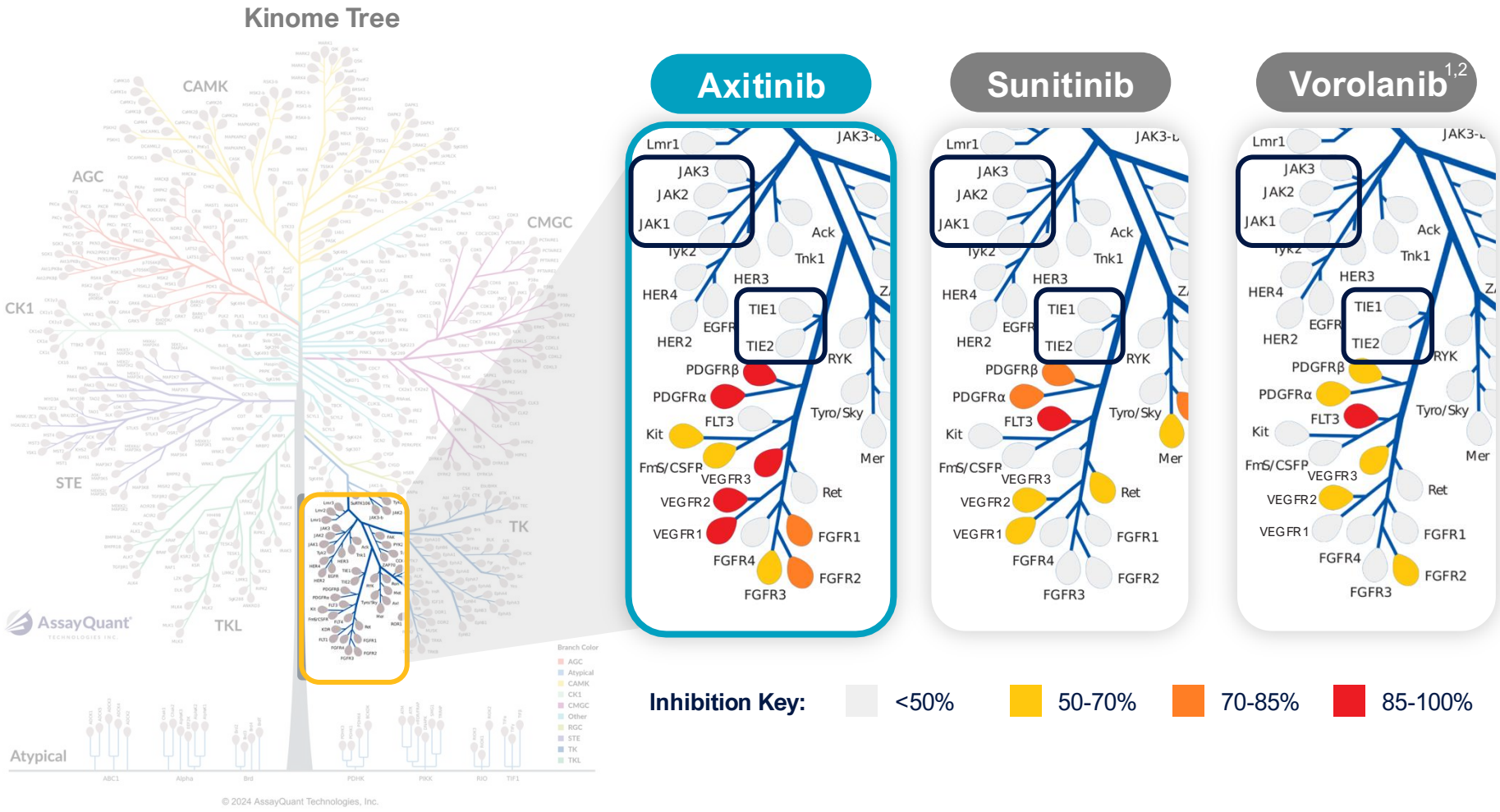
*Kinome Tree inhibition analysis conducted in collaboration with AssayQuant. Analysis conducted at 1mM ATP, 1μM drug concentration.

1. Data on file, Ocular Therapeutix. 2. Patel C, et al. Target and Selectivity Profiling of Axitinib in Cell-Based and Biochemical Assays. Presented at the Association for Research in Vision and Ophthalmology. May 8, 2025, Salt Lake City, UT. 3. INLYTA (axitinib) prescribing information. U.S. Food and Drug Administration; 2012. Accessed February 27, 2026. 4. Sheng X, et al. *EBioMedicine.* 2020;55:102755. 5. Blumenthal GM, et al. *Oncologist.* 2012;17(8):1108-1113. 6. SUTENT (sunitinib malate) prescribing information. U.S. Food and Drug Administration; 2006. Accessed February 27, 2026.

TKI, tyrosine kinase inhibitor; ATP, adenosine triphosphate; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; JAK, janus kinase.

Axitinib: Highly Selective, Potent Pan-VEGFR Inhibitor

Independent AssayQuant Kinome Tree Analysis



At physiologic ATP concentrations and therapeutic TKI concentrations*:

No meaningful JAK1 or TIE2 inhibition[1]

*Kinome Tree inhibition analysis conducted in collaboration with AssayQuant; Analysis conducted at 1mM ATP, 1μM drug concentration.

1. Data on file, Ocular Therapeutix. 2. Patel C, et al. Target and Selectivity Profiling of Axitinib in Cell-Based and Biochemical Assays. Presented at the Association for Research in Vision and Ophthalmology. May 8, 2025, Salt Lake City, UT.

TKI, tyrosine kinase inhibition; VEGFR, vascular endothelial growth factor receptor; ATP, adenosine triphosphate; JAK,janus kinase; TIE2, tyrosine kinase with immunoglobulin-like and epidermal growth factor–like domains-2.

OCULAR THERAPEUTIX Retina experience redefined™

AssayQuant Independent Potency Comparison Among TKIs

Tyrosine Kinase Inhibitor Potency (% Inhibition)

*Evaluated at physiologic ATP levels (1mM) & Drug Concentrations (1μM)**

TK Receptors[1,2]	Axitinib *Most Potent VEGFR, PDGFR TKI*	Vorolanib *Derivative of Sunitinib*	Sunitinib *Development in retina terminated*
VEGF RECEPTORS			
VEGFR1	100%	32%	59%
VEGFR2	**98%**	**53%**	**51%**
VEGFR3	92%	51%	41%
OTHER RECEPTORS			
PDGFRα	94%	65%	70%
PDGFRβ	88%	64%	78%
JAK1	9%	15%	16%
JAK2	9%	16%	17%
FDA-APPROVED INDICATIONS	Renal cell carcinoma[3]	Not approved by FDA; X-82 approved in China in combination with everolimus for advanced renal cell carcinoma[4]	Renal cell carcinoma Gastrointestinal stromal tumors Pancreatic neuroendocrine tumors[5,6]

OCULAR THERAPEUTIX Retina experience redefined™

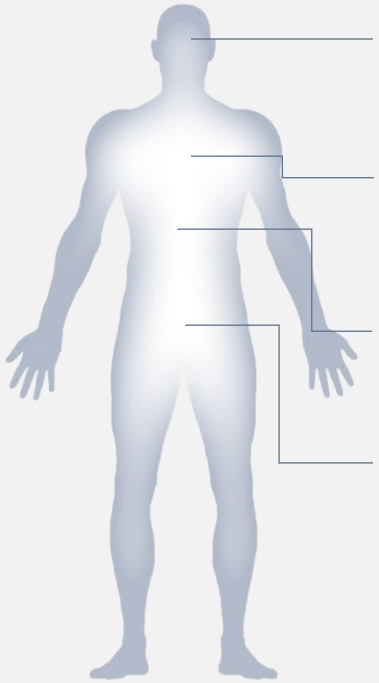
*Kinome Tree inhibition analysis conducted in collaboration with AssayQuant. Analysis conducted at 1mM ATP, 1μM drug concentration.

1. Data on file, Ocular Therapeutix. 2. Patel C, et al. Target and Selectivity Profiling of Axitinib in Cell-Based and Biochemical Assays. Presented at the Association for Research in Vision and Ophthalmology. May 8, 2025, Salt Lake City, UT. 3. INLYTA (axitinib) prescribing information. U.S. Food and Drug Administration; 2012. Accessed February 27, 2026. 4. Sheng X, et al. *EBioMedicine.* 2020;55:102755. 5. Blumenthal GM, et al. *Oncologist.* 2012;17(8):1108-1113. 6. SUTENT (sunitinib malate) prescribing information. U.S. Food and Drug Administration; 2006. Accessed February 27, 2026.

TKI, tyrosine kinase inhibitor; ATP, adenosine triphosphate; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; JAK, janus kinase.

Hydrogel-Based Platform Widely Utilized

Other Medical Specialties



Neurosurgery
DuraSeal® Dural Sealant System[1]

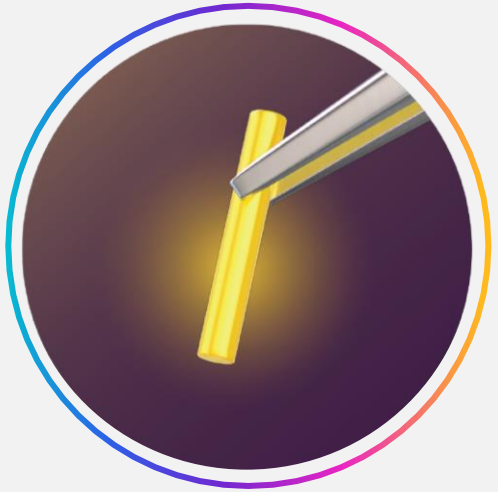
Vascular Surgery
MYNXGRIP® Vascular Closure Device[2]

Interventional Radiology
Nellix® Endovascular Aneurysm Sealing System[3]

Urology
SpaceOAR™[4]

Polyethylene Glycol Hydrogels Used in Over 5 Million Subjects Across Multiple Specialties[5]

Hydrogel in Ophthalmology



Ocular applications of polyethylene glycol hydrogel include **contact lenses, artificial tears, corneal wound repair,** and **sealants**[6-8]

More than **700,000 eyes** treated to date with DEXTENZA[9]

OCULAR THERAPEUTIX Retina experience redefined™

1. Weinstein JS, et al. *J Neurosurg*. 2010;112(2):428-433. 2. MynxGrip Vascular Closure Device [Instructions for Use]. Cardinal Health 3. Choo, et al. *Medical Devices*. 2019-12 65–79 4. Hamstra DA, et al. *Int J Radiat Oncol Biol Phys*. 2017;97(5):976-985. 5. Stuart M. *MedTech Strategist*. 2021. 6. Musgrave CSA, et al. *Materials (Basel)*. 2019;12(2):261. 7. Foulks GN. *Drugs Today (Barc)*. 2007;43(12):887-896. 8. Fernandes-Cunha GM, et al. *Sci Rep*. 2020;10(1):16671. 9. Data on File. Ocular Therapeutix

OTX-TKI: Axitinib via Hydrogel Allows for Tunable Sustained Release

AXITINIB

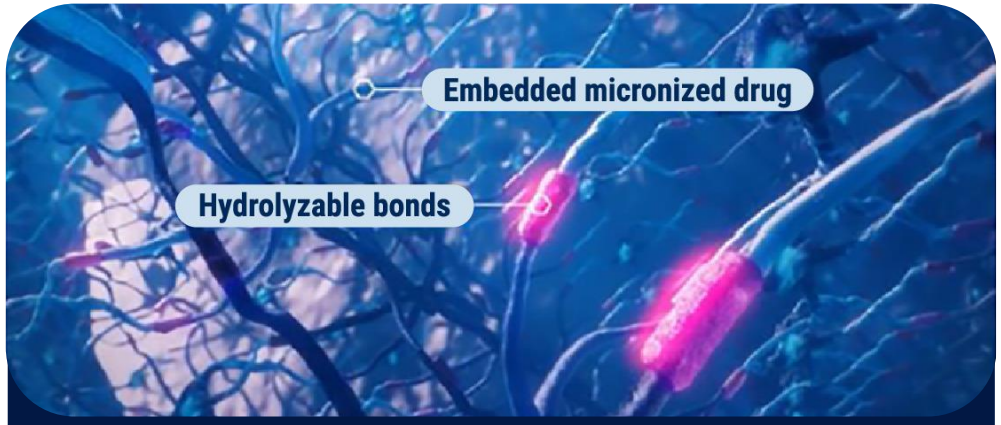
Multi-target Tyrosine Kinase Inhibitor (TKI)

Highly selective pan VEGF inhibitor[1]
Highly potent TKI[2]

+

ELUTYX™ TECHNOLOGY

Bioresorbable, Sustained Drug Delivery



Proprietary hydrogel
Versatile, biocompatible, tunable platform[3]

OTX-TKI

is being developed with the aim to provide:

A single injection, single hydrogel insert[3,4]

Continuous and consistent delivery up to 12 months[3,5]

Complete and predictable bioresorption[3,5]

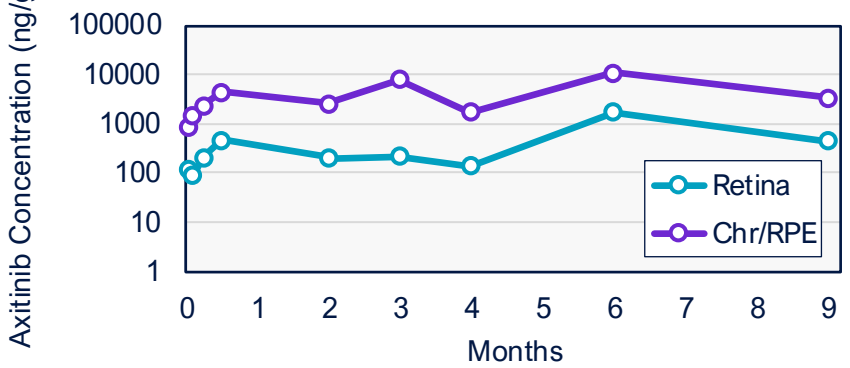
OCULAR THERAPEUTIX Retina experience redefined™

1. Zhao Y, et al. *Oncologist.* 2015;20(6):660-673. 2. Gross-Goupil M, et al. *Clin Med Insights Oncol*. 2013;7:269-277. 3. Blizzard CD, et al. Ocular Implant Containing a Tyrosine Kinase Inhibitor. US Patent 11,439,592 B2. September 13, 2022. 4. Tan CS, et al. *Clin Ophthalmol*. 2022;16:917-933. 5. Data on File 036. Ocular Therapeutix.
TKI, Tyrosine Kinase Inhibitor; VEGF, Vascular Endothelial Growth Factor

OTX-TKI is Designed to Release Axitinib and Maintain Intraocular Drug Levels Over Time with Complete Bioresorption

- Rapid, continuous and consistent axitinib delivery[1]
- Targeted drug delivery to retina and choroid[1]
- Complete, predictable, tunable bioresorption[1]

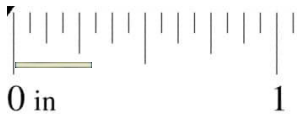
Axitinib concentrations in the retina and choroid/RPE following a single OTX-TKI over 9 months in NHPs[1]

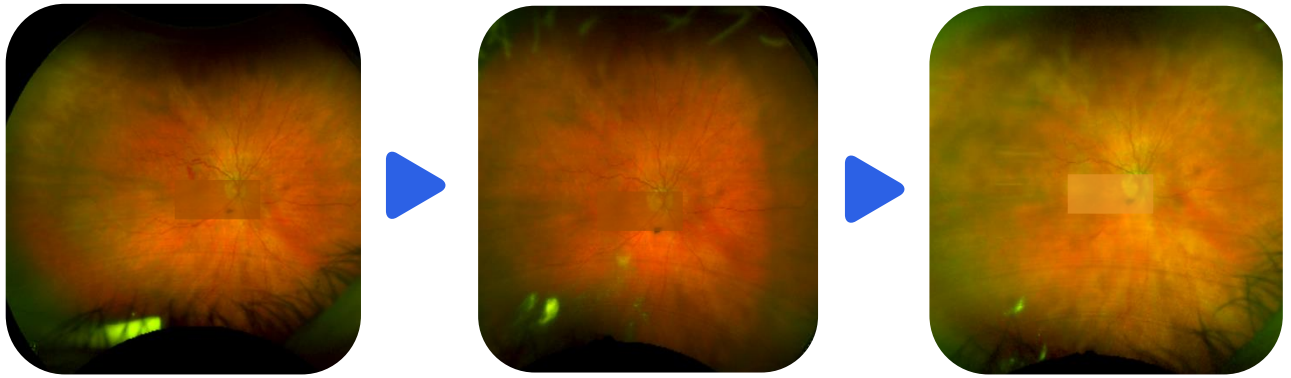


Timepoints for Day 1, 3, 7 and 14 shown

OTX-TKI hydrogel bioresorbs via hydrolysis for potential redosing.[2,3]

Dry OTX-TKI Dimensions
7mm length, 0.4mm diameter





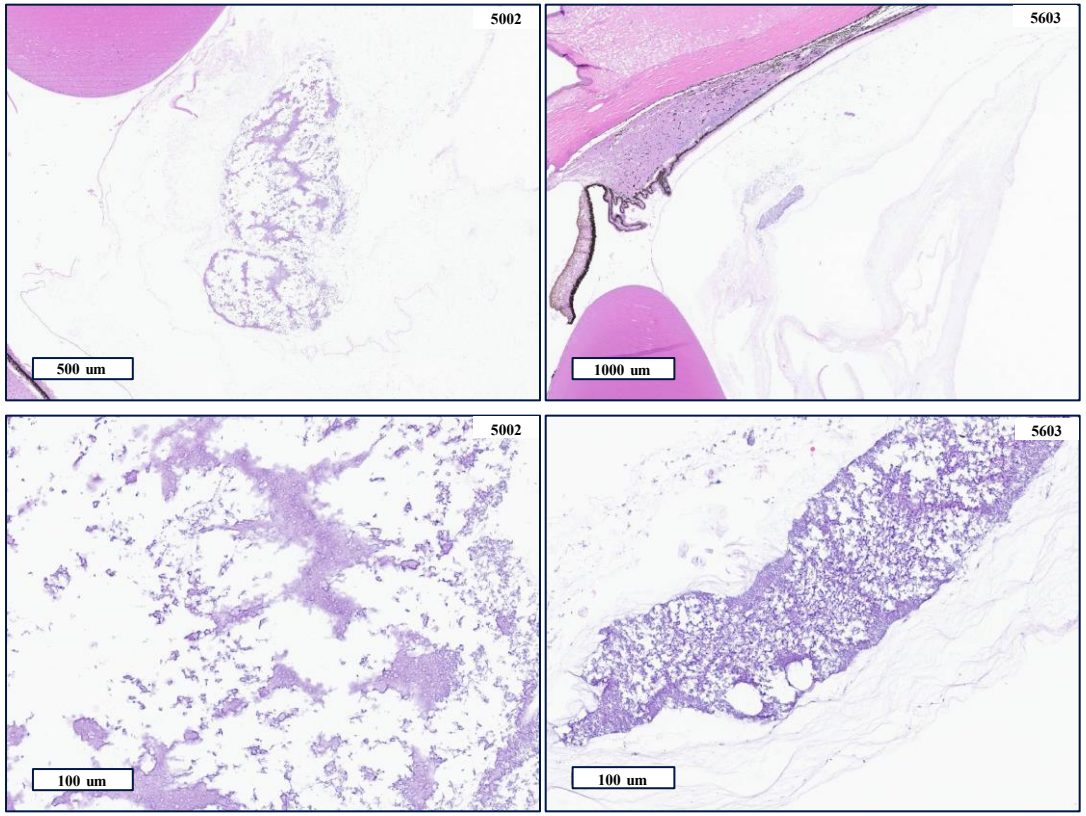
Day 1 | Week 36 | Week 52

OCULAR THERAPEUTIX Retina experience redefined™

1. Data on File. Ocular Therapeutix. 2. Li J, et al. *Nat Rev Mater.* 2016;1(12):16071. 3. Müller DA, et al. *J Orthop Surg Res*. 2016;11(1):111.
Chr, choroid; RPE, retinal pigment epithelium; NHP, non-human primate.

Histology of Ocular Tissues Demonstrates Axitinib Elution with No Inflammatory Cells

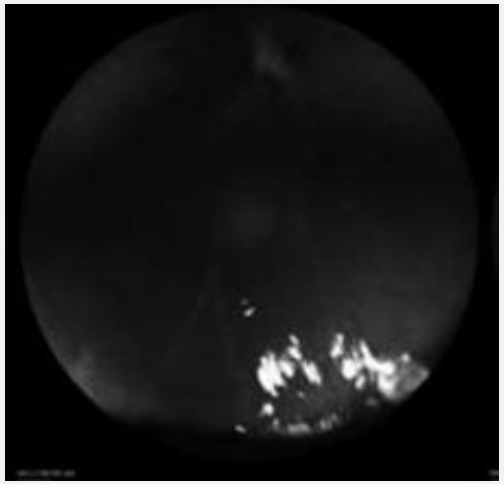
Histology of Ocular Tissues from 0.7 mg OTX-TKI



Microscopic Findings

White, refractile, basophilic, granular axitinib in the vitreous

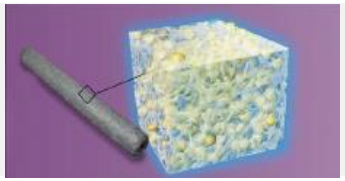
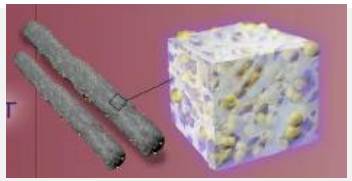
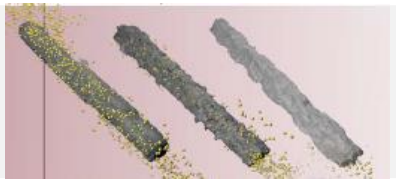
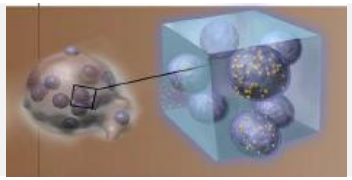
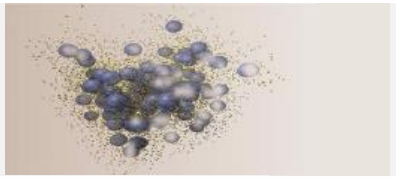
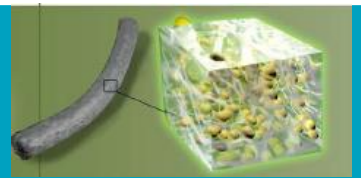
No inflammatory cells in vitreous, retina, or AC



OCULAR THERAPEUTIX Retina experience redefined™

Data on File, Ocular Therapeutix
AC, anterior chamber.

Comparison of Hydrogel vs Other Retinal Polymer Implants

	Implant (Full View)	Implant Dimensions (Length x Diameter)	Needle Size	Matrix Degradation & Release	Polymer Byproduct	Implant Remnants at 12 Months
OZURDEX abbvie		6mm x 0.46mm*	22-gauge*		Lactic acid and glycolic acid†	Lasts >12 months ‡
EYP-1901 EyePoint Pharmaceuticals		Two implants with length of 8mm¶	22-gauge#		>75KDa polyvinyl alcohol‖	Two remnants that last 18-24 mos**
GB-102 graybug		N/A	27-gauge††		Lactic acid and glycolic acid††	N/A
OTX-TKI OCULAR THERAPEUTIX		**7mm x 0.40mm^**	**25-gauge^**		**Inert hydrogel PEG chains^**	**No remnants^**

OCULAR THERAPEUTIX Retina experience redefined™

*. Li M, et al. *Heliyon.* 2022;8(12):e12219. †. Pellegrini GABP, et al. *Int J Retina Vitreous.* 2025;11(1):7. ‡. Kim JT, et al. *Retina*. 2020; 40(11):p 2226-2231. §. Schmit-Eilenberger VK. Clin *Ophthalmol.* 2015;9:801-811. ¶. Diameter of EYP-1901 unconfirmed; EyePoint Pharmaceuticals. Clinical Study Protocol. Protocol No. EYP-1901-201. Published January 25, 2024. ClinicalTrials.gov identifier: NCT05381948. 10. Ocular Therapeutix. Data on File. . #. EyePoint Pharmaceuticals DAVIO2 Topline Results Conference Call, December 4, 2023. ||. Wykoff CC, et al. *J Vitreoretin Dis*. 2024;8(5):577-586. **. EyePoint Pharmaceuticals. TD Cowen 44th Annual Health Care Conference. March 5, 2024. https://investors.eyepointpharma.com/events-and-presentations. ††. Graybug Vision Inc. Clinical Study Protocol. Protocol No. GBV-102-002. Published September 8, 2020. ClinicalTrials.gov identifier: NCT03953079. ^. Ocular Therapeutix. Data on File.

OTX-TKI is Designed for Seamless, Immediate Adoption

Ideal Target Product Profile

Pan-VEGF and PDGF
inhibitory activity[1]

Axitinib has Best-in-class (TKI) Potency[1]

Best-in-class durability
up to 12 months[2]

OCULAR THERAPEUTIX Retina experience redefined™

1. Gross-Goupil M, et al. *Clin Med Insights Oncol*. 2013;7:269-277. 2. Eichenbaum, DA, et al. American Academy of Ophthalmology Annual Meeting; October 18-21, 2024; Chicago, IL. 3. Blizzard C, et al. *Clin Ophthalmol.* 2021;15:2055-2061. 4. Ocular Therapeutix Data on File 039. 5. Almony A. *Am J Manag Care*. 2023;29(suppl 6):S81-S89 .
VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; IVT, intravitreal.

OTX-TKI is Designed for Seamless, Immediate Adoption

Ideal Target Product Profile

Pan-VEGF and PDGF inhibitory activity[1]

Axitinib has Best-in-class (TKI) Potency[1]

Best-in-class durability up to 12 months[2]

Single Bioresorbable Hydrogel

No remnants after drug depletion[3]

Tunable hydrogel used in DEXTENZA[3]

Excellent safety profile in over 700,000 DEXTENZA cases[4]

OCULAR THERAPEUTIX Retina experience redefined™

1. Gross-Goupil M, et al. *Clin Med Insights Oncol*. 2013;7:269-277. 2. Eichenbaum, DA, et al. American Academy of Ophthalmology Annual Meeting; October 18-21, 2024; Chicago, IL. 3. Blizzard C, et al. *Clin Ophthalmol.* 2021;15:2055-2061. 4. Ocular Therapeutix Data on File 039. 5. Almony A. *Am J Manag Care*. 2023;29(suppl 6):S81-S89 .
VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; IVT, intravitreal.

OTX-TKI is Designed for Seamless, Immediate Adoption

Ideal Target Product Profile

Pan-VEGF and PDGF inhibitory activity[1]

Axitinib has Best-in-class (TKI) Potency[1]

Best-in-class durability up to 12 months[2]

Single Bioresorbable Hydrogel

No remnants after drug depletion[3]

Tunable hydrogel used in DEXTENZA[3]

Excellent safety profile in over 700,000 DEXTENZA cases[4]

Optimizing Retina Practices

Familiar IVT injection with 25g needle[5]

Predictable schedule for patients[2]

Designed for **improved treatment adherence**[2]

OCULAR THERAPEUTIX Retina experience redefined™

1. Gross-Goupil M, et al. *Clin Med Insights Oncol*. 2013;7:269-277. 2. Eichenbaum, DA, et al. American Academy of Ophthalmology Annual Meeting; October 18-21, 2024; Chicago, IL. 3. Blizzard C, et al. *Clin Ophthalmol.* 2021;15:2055-2061. 4. Ocular Therapeutix Data on File 039. 5. Almony A. *Am J Manag Care*. 2023;29(suppl 6):S81-S89 .
VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; IVT, intravitreal.

Trial Design

Addressing Regulatory and Clinical Objectives

Jeffrey S. Heier, MD

SOL-1

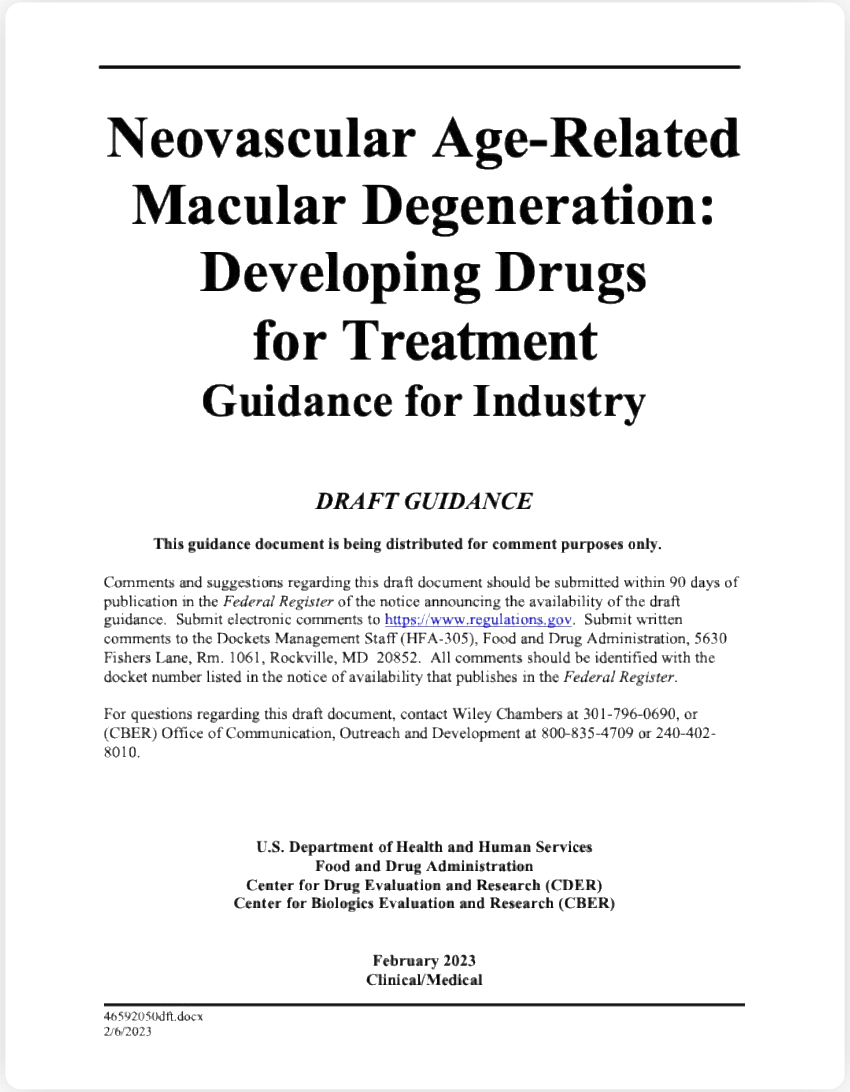
OCULAR THERAPEUTIX Retina experience redefined

FDA Draft Guidance for Industry

2023

Q1

New FDA Drug Development Guidance released



Neovascular Age-Related Macular Degeneration: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Wiley Chambers at 301-796-0690, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2023
Clinical/Medical

46592050dft.docx
2/6/2023

OCULAR THERAPEUTIX Retina experience redefined™

U.S. Food and Drug Administration. Neovascular AMD: Developing Drugs for Treatment Guidance for Industry. 2023 Q1, quarter 1

SOL-1 Trial is Designed to Align with FDA Guidance

FDA Guidance for Neovascular AMD Trials

One comparator arm should have the same dosing schedule as the investigational drug[1]

Sham injections are not recommended due to inadequate masking[2,3]

OCULAR THERAPEUTIX Retina experience redefined™

1. U.S. Food and Drug Administration. Neovascular AMD: Developing Drugs for Treatment Guidance for Industry. 2023.. **2.** Type C WRO [written response only] Aug 2024. **3.** Weiss J, Boyd B, Event: Q&A with FDA, at the American Academy of Ophthalmology Annual Meeting, October 20, 2024

AMD, age-related macular degeneration

SOL-1 Trial is Designed to Align with FDA Guidance

FDA Guidance for Neovascular AMD Trials	SOL-1 Trial Design
One comparator arm should have the same dosing schedule as the investigational drug[1]	**Both study arms have the same dosing schedule**
Sham injections are not recommended due to inadequate masking[2,3]	**No sham injections in either arm**

OCULAR THERAPEUTIX Retina experience redefined™

1. U.S. Food and Drug Administration. Neovascular AMD: Developing Drugs for Treatment Guidance for Industry. 2023.. **2.** Type C WRO [written response only] Aug 2024. **3.** Weiss J, Boyd B, Event: Q&A with FDA, at the American Academy of Ophthalmology Annual Meeting, October 20, 2024

AMD, age-related macular degeneration

SOL-1 Trial is Designed to Align with FDA Guidance

FDA Guidance for Neovascular AMD Trials	SOL-1 Trial Design
One comparator arm should have the same dosing schedule as the investigational drug[1]	**Both study arms have the same dosing schedule**
Sham injections are not recommended due to inadequate masking[2,3]	**No sham injections in either arm**

Given study adherence to the FDA Guidance,
SOL-1 is being conducted under a Special Protocol Assessment (SPA)

OCULAR THERAPEUTIX Retina experience redefined™

1. U.S. Food and Drug Administration. Neovascular AMD: Developing Drugs for Treatment Guidance for Industry. 2023.. **2.** Type C WRO [written response only] Aug 2024. **3.** Weiss J, Boyd B, Event: Q&A with FDA, at the American Academy of Ophthalmology Annual Meeting, October 20, 2024

AMD, age-related macular degeneration

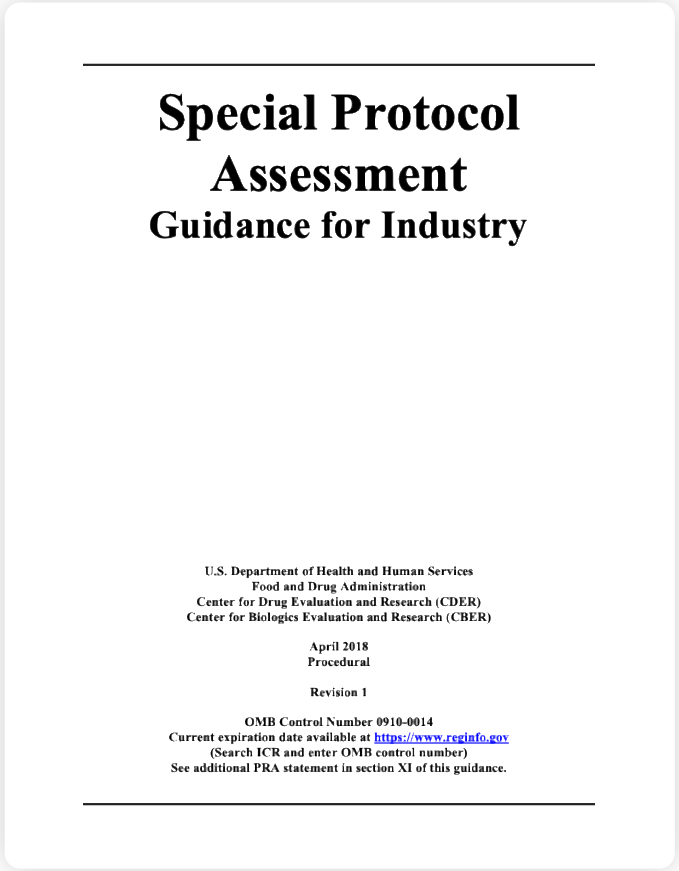
Special Protocol Assessment (SPA)

Agreement with FDA on critical design elements and statistical analysis plan (SAP) to support approval

With acceptance of SPA, study design, endpoints, and SAP cannot be changed

Adhering to protocol is critical to ensuring trial will be considered adequate and well-controlled

Conducting a trial under a SPA helps to derisk the regulatory process



Special Protocol Assessment

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2018
Procedural

Revision 1

OMB Control Number 0910-0014
Current expiration date available at https://www.reginfo.gov
(Search ICR and enter OMB control number)
See additional PRA statement in section XI of this guidance.

U.S. Food and Drug Administration. Special Protocol Assessment Guidance for Industry. 2018

FDA Recommendation for Endpoints to Demonstrate Superiority

≥15-Letter Decrease
Statistically significant **smaller** % of subjects with ≥15-letter decrease at 9 months or later

≥15-Letter Increase
Statistically significant **greater** % of subjects with ≥15-letter increase at 9 months or later

≥15-Letter Difference
Statistically significant **difference** between groups in mean BCVA of ≥15 letters at 9 months or later

SOL-1 Primary Endpoint: Proportion of subjects who maintained visual acuity, defined as <15 ETDRS letters of BCVA loss from baseline at Week 36

OCULAR THERAPEUTIX Retina experience redefined™

U.S. Food and Drug Administration. Neovascular AMD: Developing Drugs for Treatment Guidance for Industry. 2023
BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study

OTX-TKI Evaluated in a Superiority Trial for nAMD

SOL-1

Compares a **Single OTX-TKI (0.45 mg) Dose** to a **Single Aflibercept (2 mg) Dose**

Multicenter, Double-Masked, Randomized Parallel-Group Trial

Designed to Assess Safety and Efficacy, including Durability, of OTX-TKI

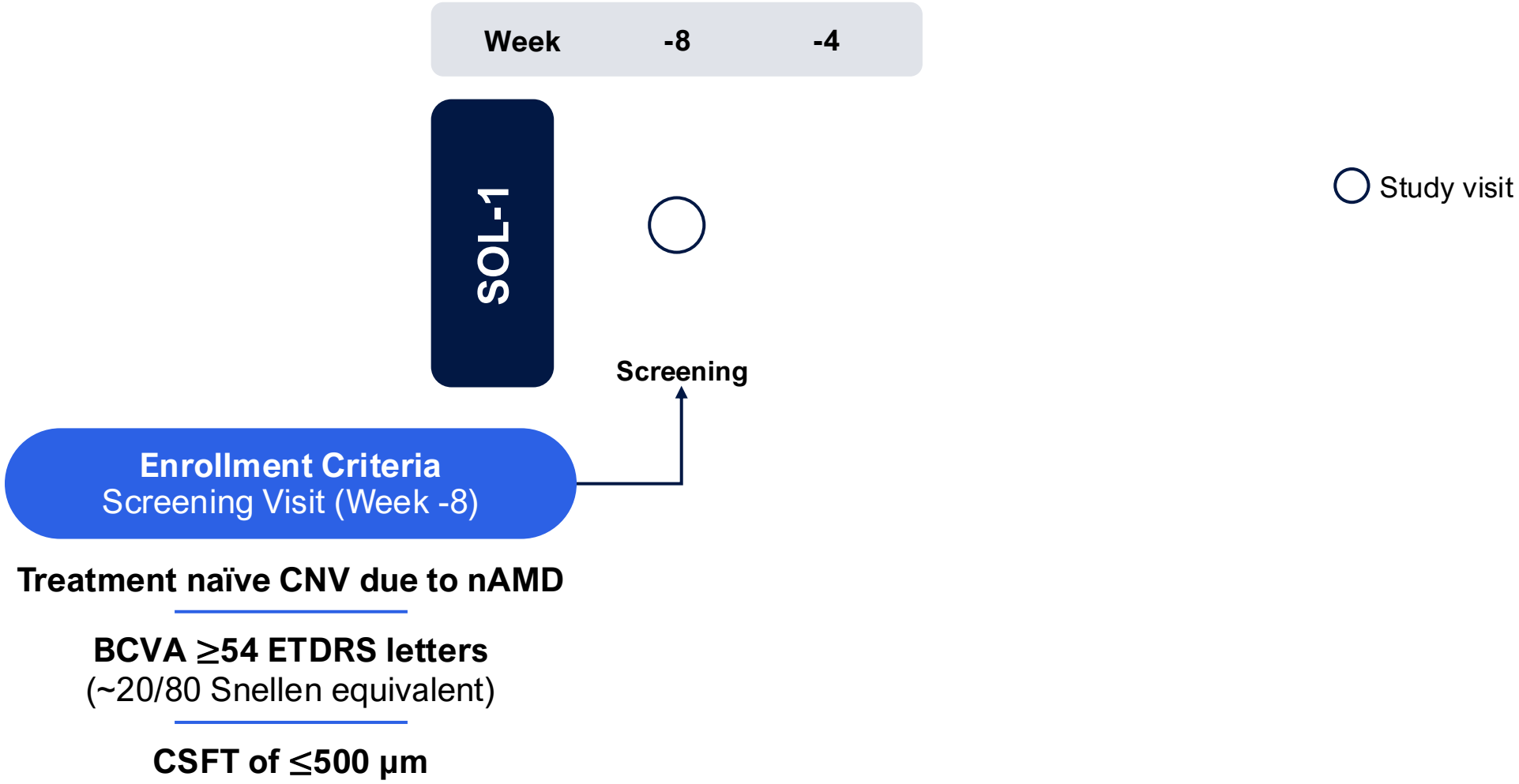
OCULAR THERAPEUTIX Retina experience redefined™

ClinicalTrials.gov. identifier: NCT06223958

nAMD, neovascular age-related macular degeneration

Eligibility and Enrollment Criteria

Key Inclusion Criteria

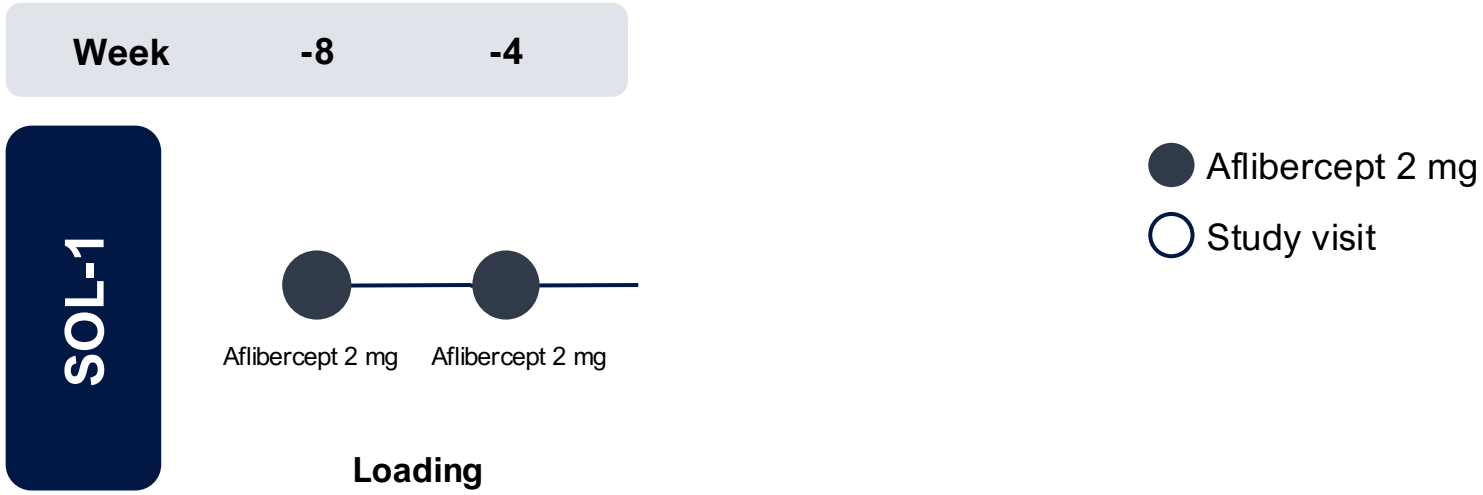


ClinicalTrials.gov. identifier: NCT06223958

CNV, choroidal neovascularization; nAMD, neovascular age-related macular degeneration; BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; CSFT; central subfield thickness, measured from the internal limiting membrane to the retinal pigment epithelium

Eligibility and Enrollment Criteria

Key Inclusion Criteria



Enrollment Criteria
Screening Visit (Week -8)

Treatment naïve CNV due to nAMD

BCVA ≥54 ETDRS letters
(~20/80 Snellen equivalent)

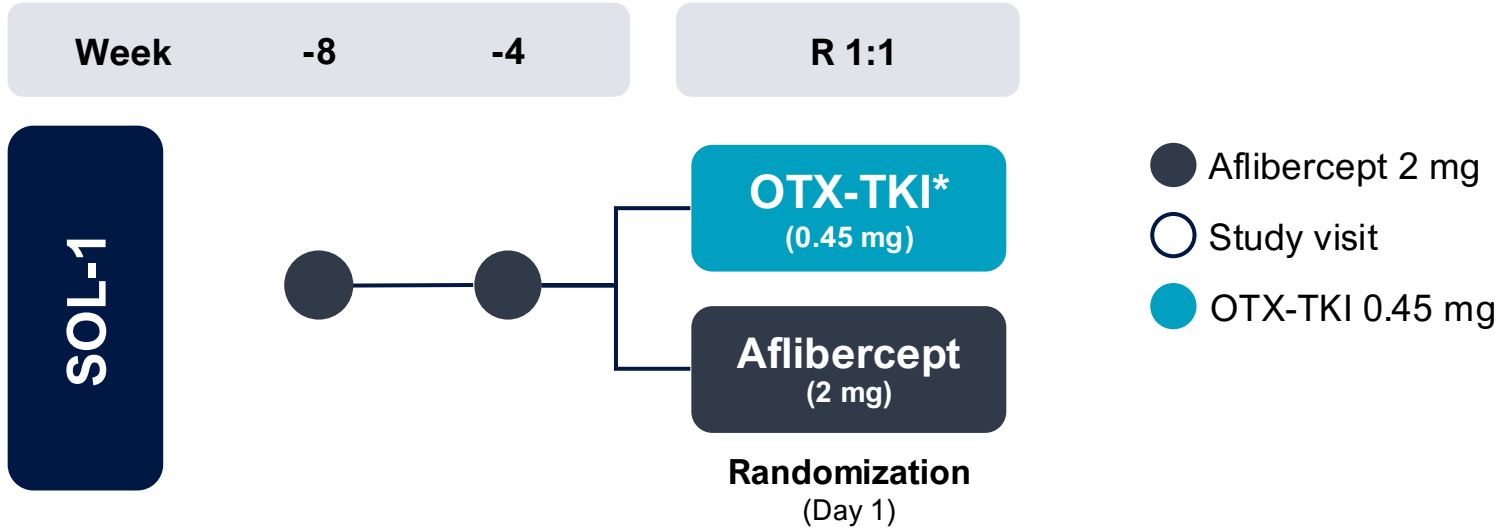
CSFT of ≤500 µm

ClinicalTrials.gov. identifier: NCT06223958

CNV, choroidal neovascularization; nAMD, neovascular age-related macular degeneration; BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; CSFT; central subfield thickness, measured from the internal limiting membrane to the retinal pigment epithelium

Eligibility and Enrollment Criteria

Key Inclusion Criteria



Enrollment Criteria
Screening Visit (Week -8)

Treatment naïve CNV due to nAMD

BCVA ≥54 ETDRS letters
(~20/80 Snellen equivalent)

CSFT of ≤500 µm

Randomization Criteria
Baseline Visit (Day 1)

BCVA gain ≥10 ETDRS letters

- OR -

BCVA ≥84 ETDRS letters
(~20/20 Snellen equivalent)

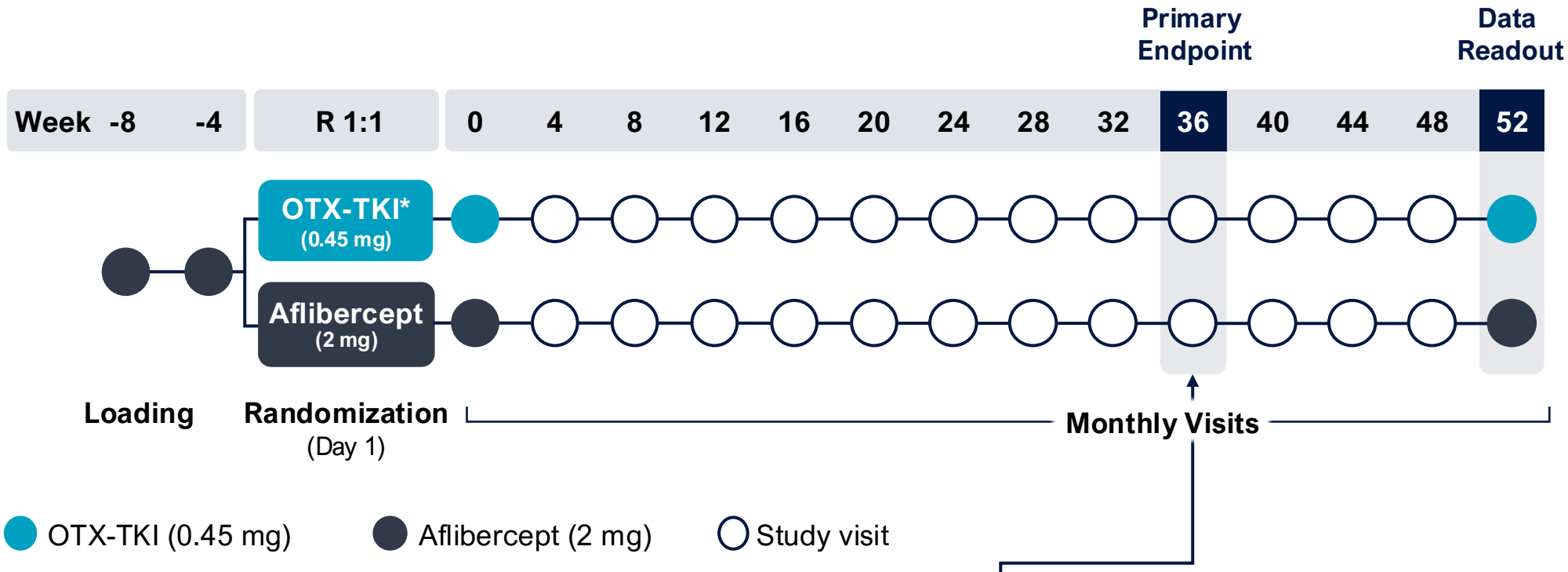
CSFT of ≤350 µm

*No aflibercept injection is given at baseline

ClinicalTrials.gov. identifier: NCT06223958

CNV, choroidal neovascularization; nAMD, neovascular age-related macular degeneration; BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; CSFT; central subfield thickness, measured from the internal limiting membrane to the retinal pigment epithelium

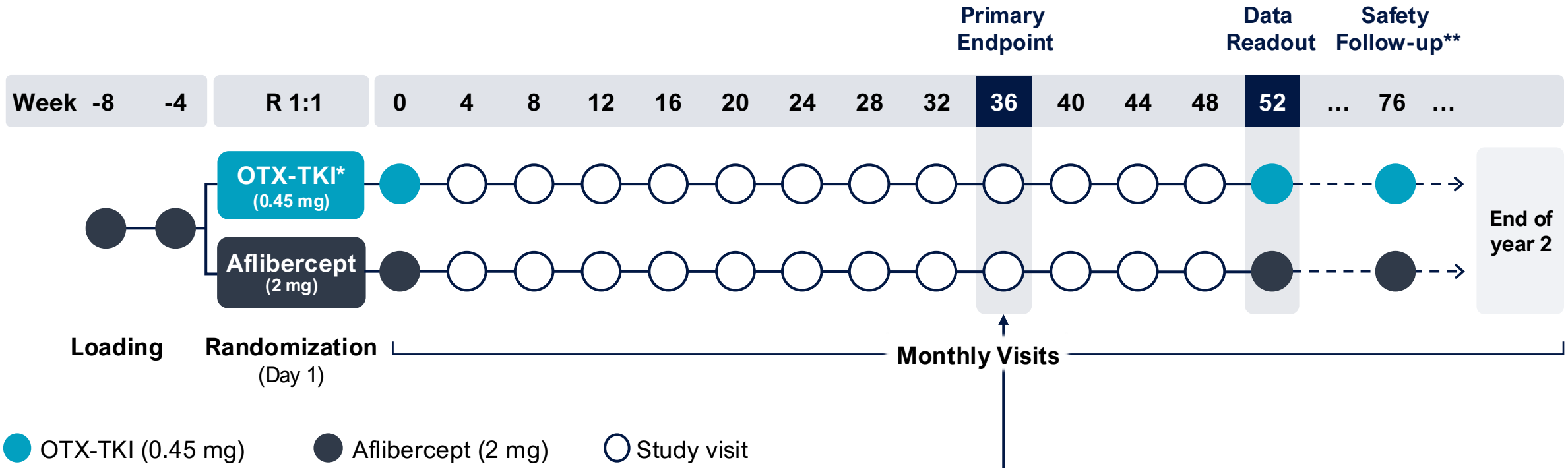
Direct Comparison: OTX-TKI and Aflibercept



Primary Endpoint (Week 36)
Proportion of subjects who maintained visual acuity, defined as <15 ETDRS letters of BCVA loss from baseline at Week 36

*No aflibercept injection is given at baseline; ClinicalTrials.gov identifier: NCT06223958
ETDRS, early treatment diabetic retinopathy study; BCVA, best-corrected visual acuity

Direct Comparison: OTX-TKI and Aflibercept



Primary Endpoint (Week 36)
Proportion of subjects who maintained visual acuity, defined as <15 ETDRS letters of BCVA loss from baseline at Week 36

*No aflibercept injection is given at baseline; **Trial subjects and designated personnel will remain masked through end of year 2
ClinicalTrials.gov identifier: NCT06223958
ETDRS, early treatment diabetic retinopathy study; BCVA, best-corrected visual acuity

Rescue Treatment Criteria and Execution

Rescue Treatment Criteria

BCVA loss ≥15 ETDRS letters from baseline due to nAMD

OR

New macular hemorrhage that would likely lead to irreversible vision loss if left untreated in the opinion of the investigator after discussion with Medical Monitor

ClinicalTrials.gov identifier: NCT06223958

BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; nAMD, neovascular age-related macular degeneration

Rescue Treatment Criteria and Execution

Rescue Treatment Criteria

BCVA loss ≥15 ETDRS letters from baseline due to nAMD

OR

New macular hemorrhage that would likely lead to irreversible vision loss if left untreated in the opinion of the investigator after discussion with Medical Monitor

Trial Conduct

After the first rescue injection, rescue therapy can be provided at investigator discretion per their clinical judgement with aflibercept 2mg

Independent rescue monitor team of retina specialists were designated to provide guidance

ClinicalTrials.gov identifier: NCT06223958

BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; nAMD, neovascular age-related macular degeneration

Disclaimer

The following presentations discuss OTX-TKI - an investigational product candidate that has not been approved by the FDA or any other regulatory body; safety and effectiveness have not been established

SOL-1

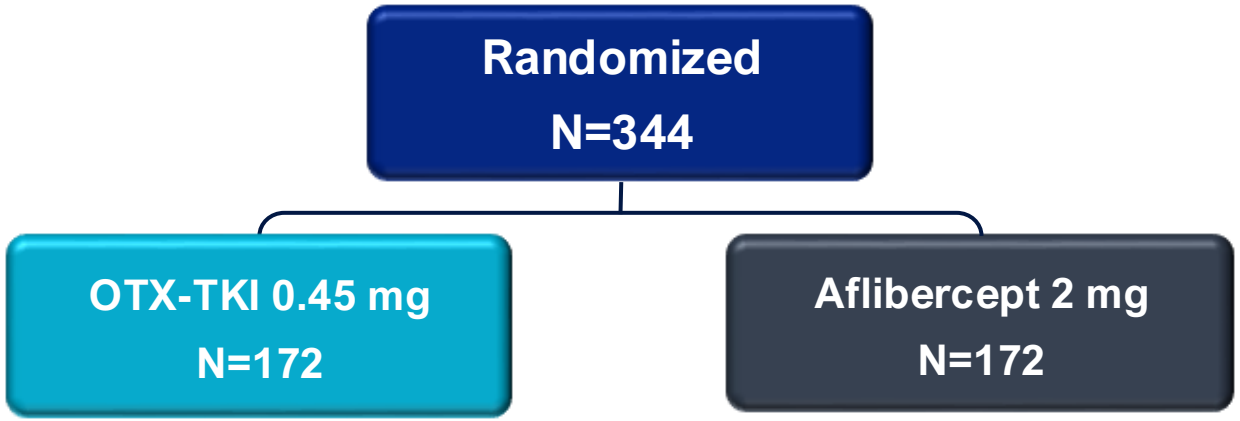
Efficacy Results

Key Outcomes through Week 52

Arshad M. Khanani, MD

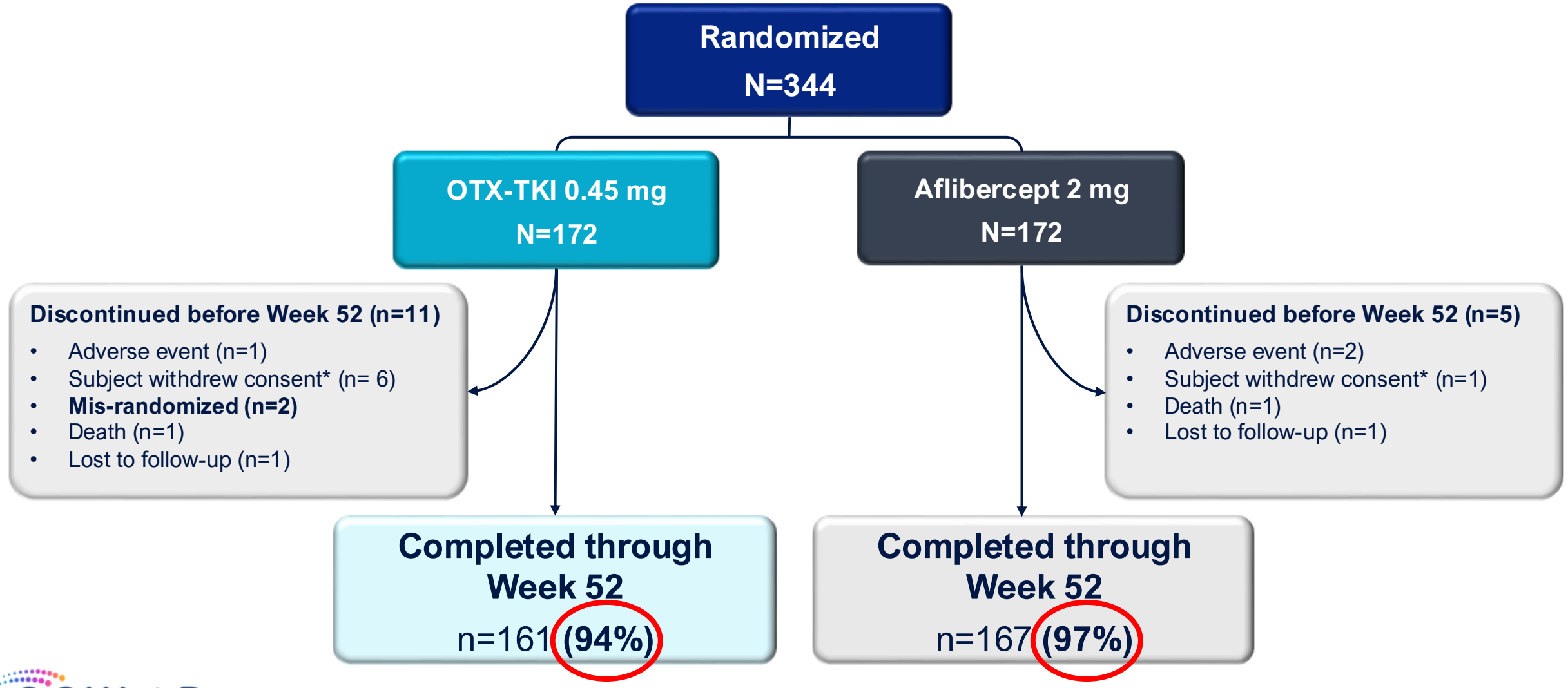
OCULAR THERAPEUTIX Retina experience redefined

Subject Disposition



Subject Disposition

Strong subject retention maintained through Week 52



* Reasons included: personal, reason, no reason, travel, offered another treatment at a different practice; only Day 1 completed, subject refused week 52 assessment

Baseline Demographics

Treatment groups were well matched at baseline

Demographics	OTX-TKI 0.45 mg N = 172	Aflibercept 2 mg N = 172
Age, years, mean (SD)	75.7 (8.3)	76.3 (7.4)
Sex, n (%)		
Female	103 (59.9)	108 (62.8)
Ethnicity, n (%)		
Hispanic or Latino	33 (19.2)	47 (27.3)
Not Hispanic or Latino	139 (80.8)	125 (72.7)
Race, n (%)		
White	168 (97.7)	170 (98.8)
Asian	3 (1.7)	0
Native Hawaiian or Other Pacific Islander	1 (0.6)	0
American Indian or Alaska Native	1 (0.6)	2 (1.2)
Black or African American	0	1 (0.6)

SD, standard deviation

Ocular Characteristics: Best-Corrected Visual Acuity

SOL-1

Majority of subjects demonstrated ≥10-letter gain prior to baseline and had excellent vision at study entry

Screening Visit *(Week -8)*

Study Eye Characteristics	OTX-TKI 0.45 mg N = 172	Aflibercept 2 mg N = 172
BCVA, ETDRS letter score, mean (SD) Snellen Equivalent	70.9 (11.3) ~20/40	69.5 (10.8) ~20/40

Baseline *(Randomization)*

Study Eye Characteristics	OTX-TKI 0.45 mg N = 172	Aflibercept 2 mg N = 172
BCVA, ETDRS letter score, mean (SD) Snellen Equivalent	80.8 (7.6) ~20/25	79.2 (7.9) ~20/25
Change from Screening to Baseline, n (%) ≥ 10 ETDRS letter gain ≥84 ETDRS letters (~20/20)	 107 (62.9) 63 (37.1)	 114 (67.1) 56 (32.9)

OCULAR THERAPEUTIX Retina experience redefined™

BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; SD, standard deviation.

Ocular Characteristics: Central Subfield Thickness

SOL-1

Baseline CSFT improved from screening after two aflibercept injections

Screening Visit *(Week -8)*

Study Eye Characteristics	OTX-TKI 0.45 mg N = 172	Aflibercept 2 mg N = 172
BCVA, ETDRS letter score, mean (SD) Snellen Equivalent	70.9 (11.3) ~20/40	69.5 (10.8) ~20/40
CSFT, µm, mean (SD)	303.6 (72.5)	302.7 (78.3)

Baseline *(Randomization)*

Study Eye Characteristics	OTX-TKI 0.45 mg N = 172	Aflibercept 2 mg N = 172
BCVA, ETDRS letter score, mean (SD) Snellen Equivalent	80.8 (7.6) ~20/25	79.2 (7.9) ~20/25
CSFT, µm, mean (SD)	219.3 (37.1)	226.8 (42.1)

OCULAR THERAPEUTIX Retina experience redefined™

BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; CSFT, central subfield thickness, measured from the internal limiting membrane to the retinal pigment epithelium; SD, standard deviation

Ocular Characteristics at Baseline

Well-balanced between treatment arms

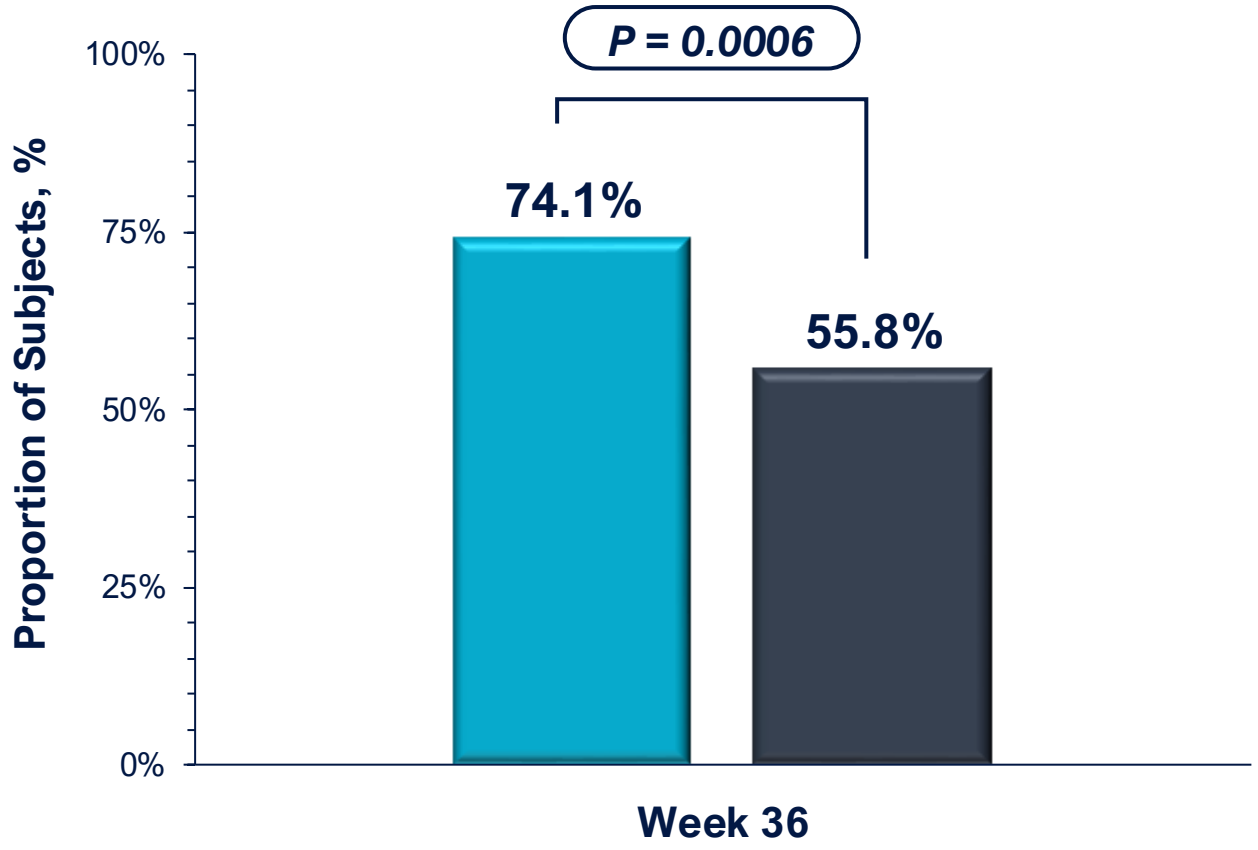
Study Eye Characteristics	OTX-TKI 0.45 mg N = 172	Aflibercept 2 mg N = 172
BCVA, ETDRS letter score >71 letters (~ 20/40)*, n (%)	145 (85.3)	136 (79.1)
Presence of Any Fluid (IRF and/or SRF), n (%) Presence of IRF, n (%) Presence of SRF, n (%)	63 (36.6) 34 (19.8) 33 (19.2)	72 (41.9) 36 (20.9) 48 (27.9)
Presence of Hemorrhage, n (%)	69 (40.6)	60 (34.9)
Phakic, n (%)	74 (43.5)	78 (45.3)

*Stratification category
BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; IRF, intraretinal fluid; SRF, subretinal fluid. SD, standard deviation

Primary Endpoint: Proportion of Subjects Who Maintain Visual Acuity*

SOL-1

Statistically significant higher proportion of subjects maintained visual acuity* with OTX-TKI vs. aflibercept 2 mg at Week 36



	OTX-TKI (0.45 mg) n = 170	Aflibercept (2 mg) n = 172
Proportion of Subjects	**74.1%**	**55.8%**
Risk difference vs. aflibercept 2 mg 95% CI *P* value	17.5% (7.7, 27.4) ***0.0006***	
Observed difference vs. aflibercept 2 mg	18.3%	

OCULAR THERAPEUTIX Retina experience redefined™

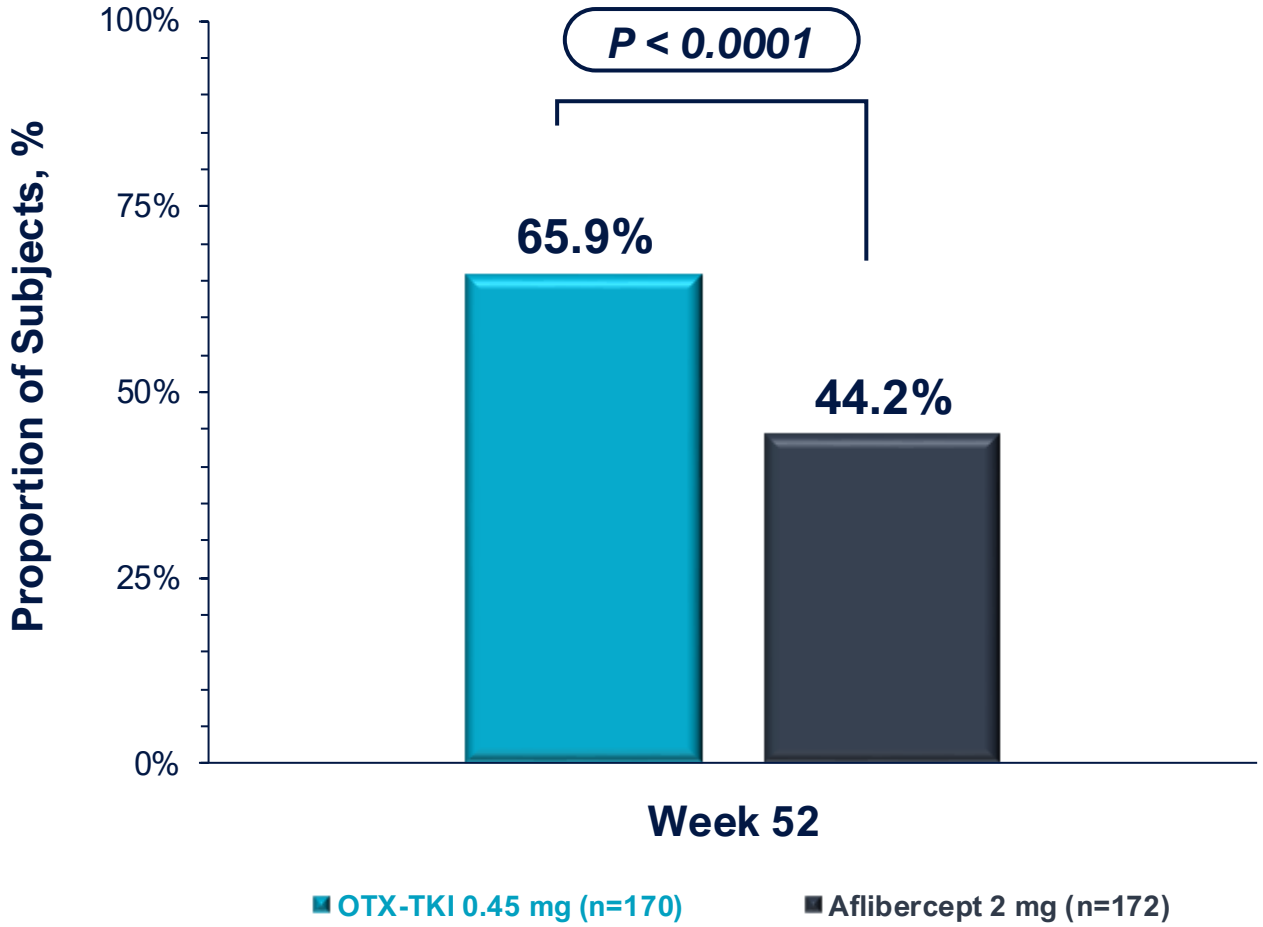
*Defined as proportion of subjects who maintain visual acuity, a loss of <15 ETDRS letters of BCVA from baseline, at Week 36
Predefined statistical rules were applied to adjust for treatment discontinuation or deviation as per the pre-specified statistical analysis plan. Full analysis set
BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; SD, standard deviation

OTX-TKI 0.45 mg (n=170)
Aflibercept 2 mg (n=172)

Key Secondary: Proportion of Subjects Who Maintain Visual Acuity*

SOL-1

Treatment benefit continued through 52 weeks with high statistical significance



	OTX-TKI (0.45 mg) n = 170	Aflibercept (2 mg) n = 172
Proportion of Subjects	**65.9%**	**44.2%**
Risk difference vs. aflibercept 2 mg 95% CI *P* value	21.1% (10.8, 31.4) ***<0.0001***	
Observed difference vs. aflibercept 2 mg	21.7%	

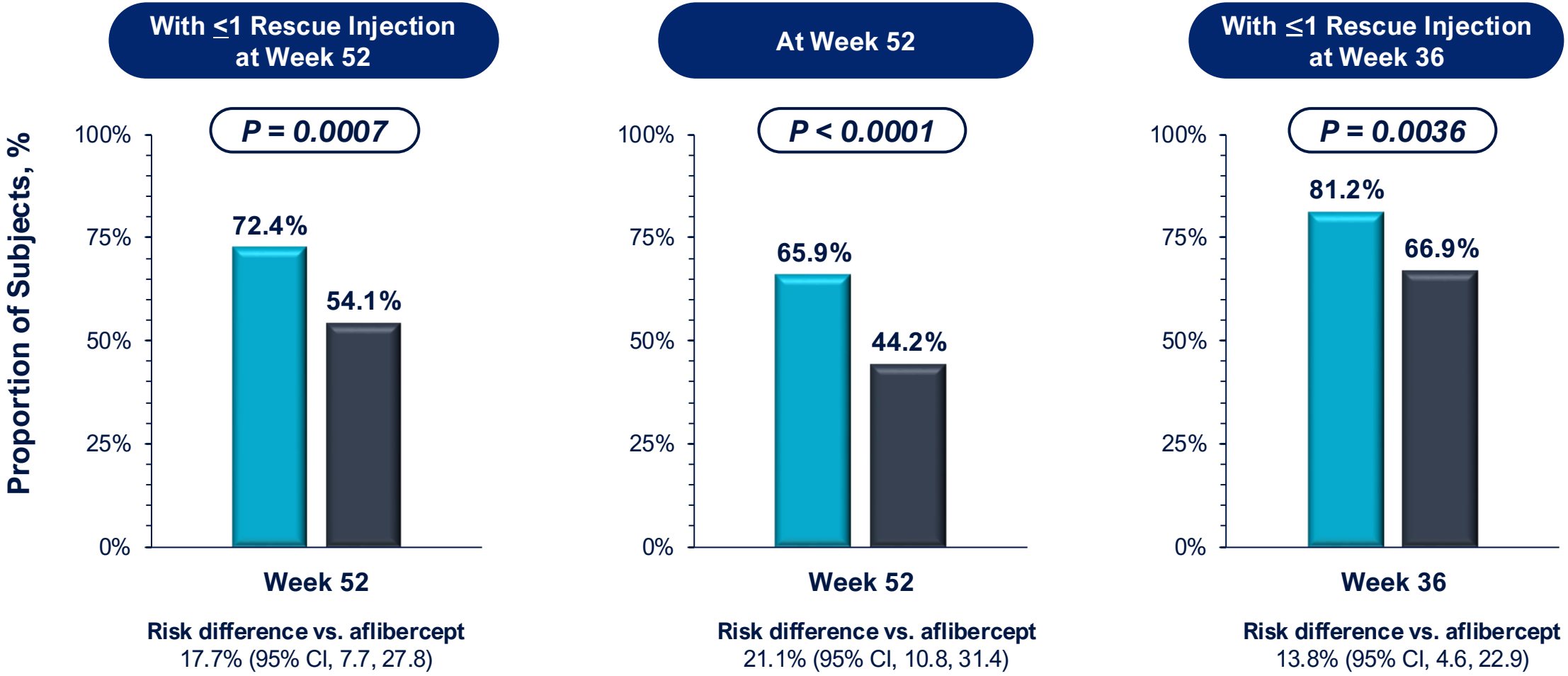
OCULAR THERAPEUTIX Retina experience redefined™

*Defined as proportion of subjects who maintain visual acuity, a loss of <15 ETDRS letters of BCVA from baseline, at Week 52
Predefined statistical rules were applied to adjust for treatment discontinuation or deviation as per the pre-specified statistical analysis plan
Full analysis set
ETDRS, Early Treatment Diabetic Retinopathy Study; BCVA, best corrected visual acuity; CI, confidence interval. Full analysis set.

Key Secondary: Proportion of Subjects Who Maintain Visual Acuity*

SOL-1

Key secondary endpoints achieved in accordance with the prespecified hierarchy

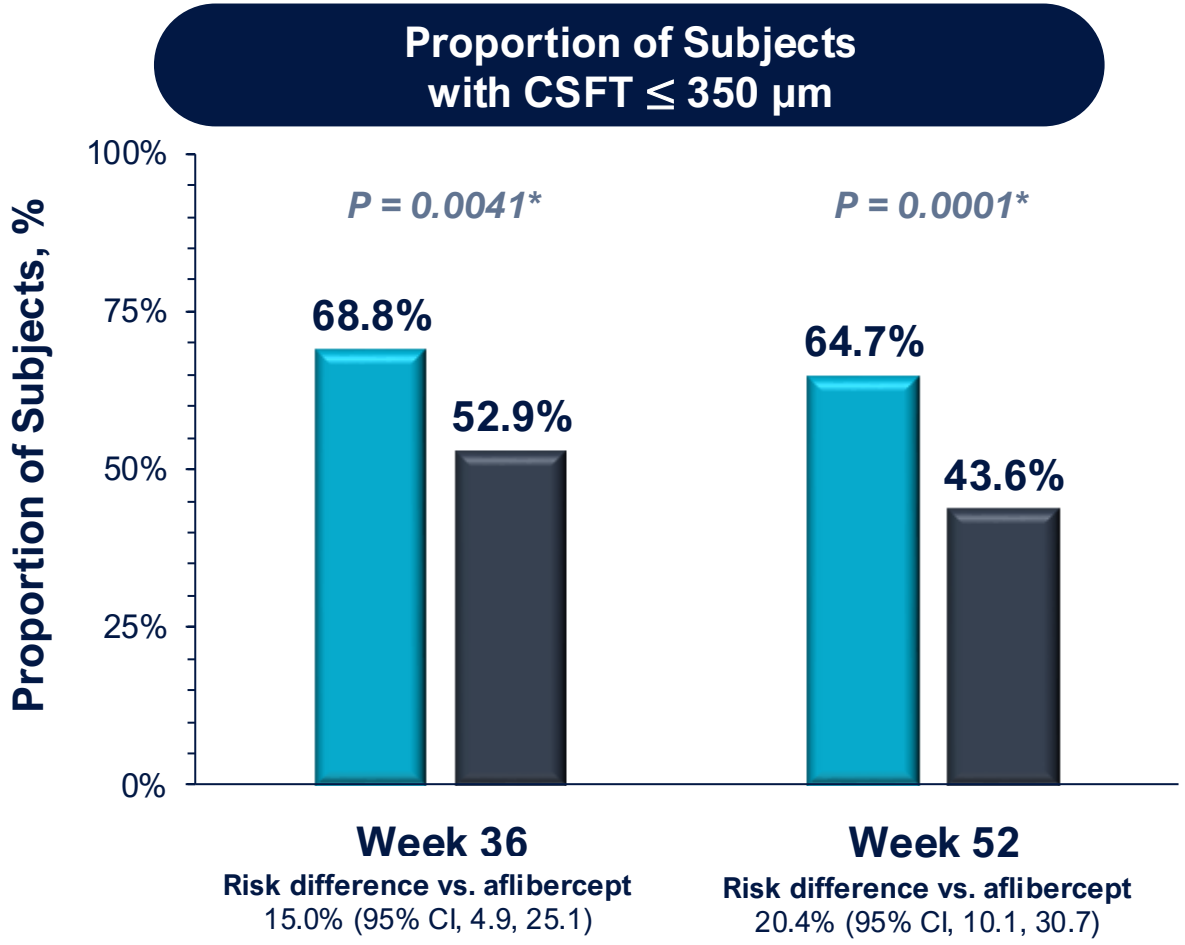


*Defined as proportion of subjects who maintain visual acuity, a loss of <15 ETDRS letters of BCVA from baseline
Predefined statistical rules were applied to adjust for treatment discontinuation or deviation as per the pre-specified statistical analysis plan
Full analysis set
BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; CI, confidence interval

OCULAR THERAPEUTIX Retina experience redefined™

Secondary Endpoint

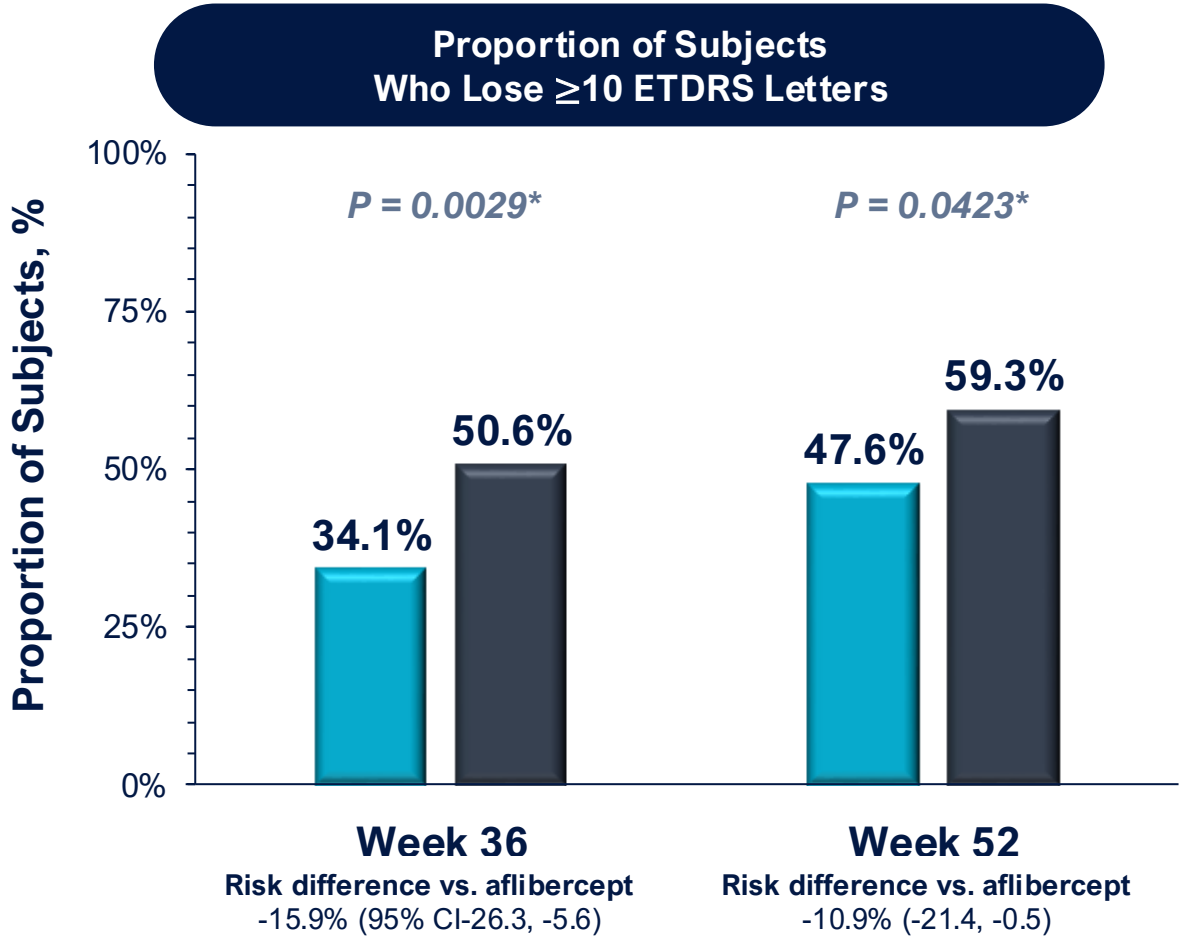
Significantly improved anatomic control with OTX-TKI



Full analysis set; Pre-specified secondary endpoint
ETDRS, early treatment diabetic retinopathy study, best corrected visual acuity; CI, confidence interval
CSFT, central subfield thickness, measured from the internal limiting membrane to the retinal pigment epithelium
CI, confidence interval; *Nominal p-value

Secondary Endpoint

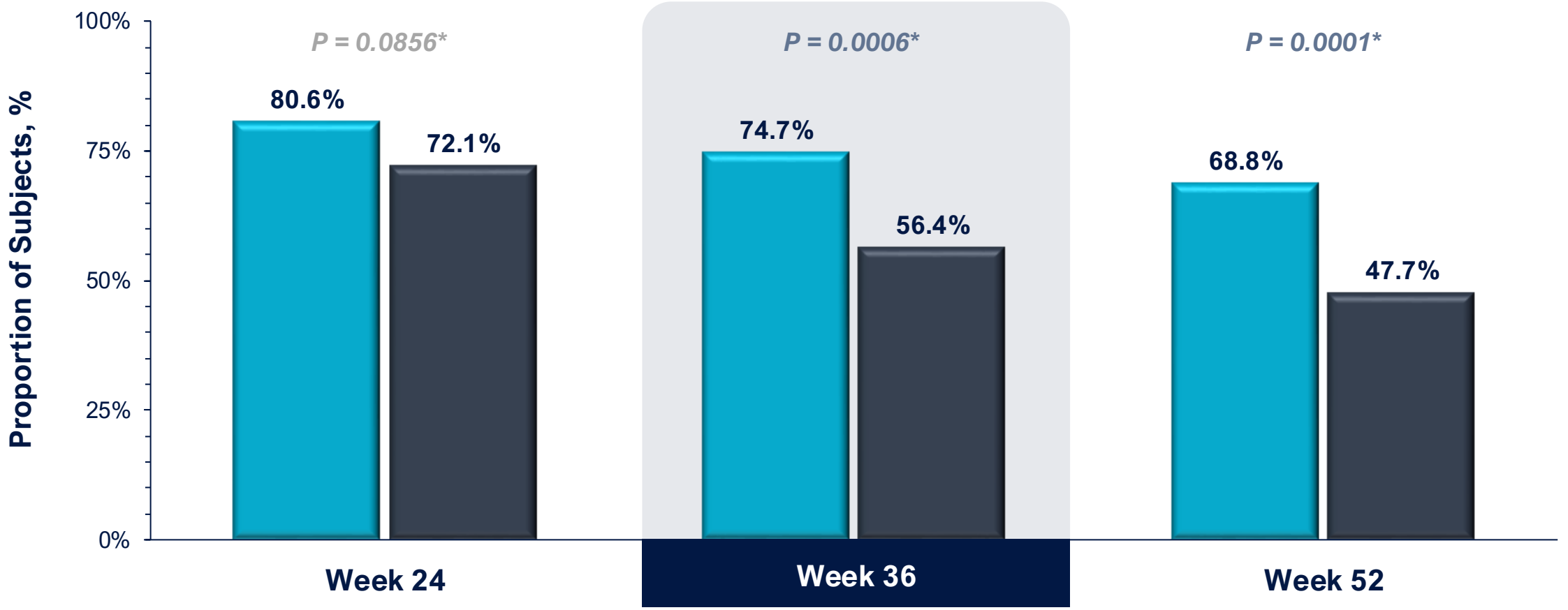
Significantly decreased rates of vision loss with OTX-TKI



Full analysis set; Pre-specified secondary endpoint
ETDRS, early treatment diabetic retinopathy study; BCVA, best corrected visual acuity; CI, confidence interval
CI, confidence interval; *Nominal p-value

Proportion of Rescue Free Subjects

Significant reduction in need for rescue treatment through week 52

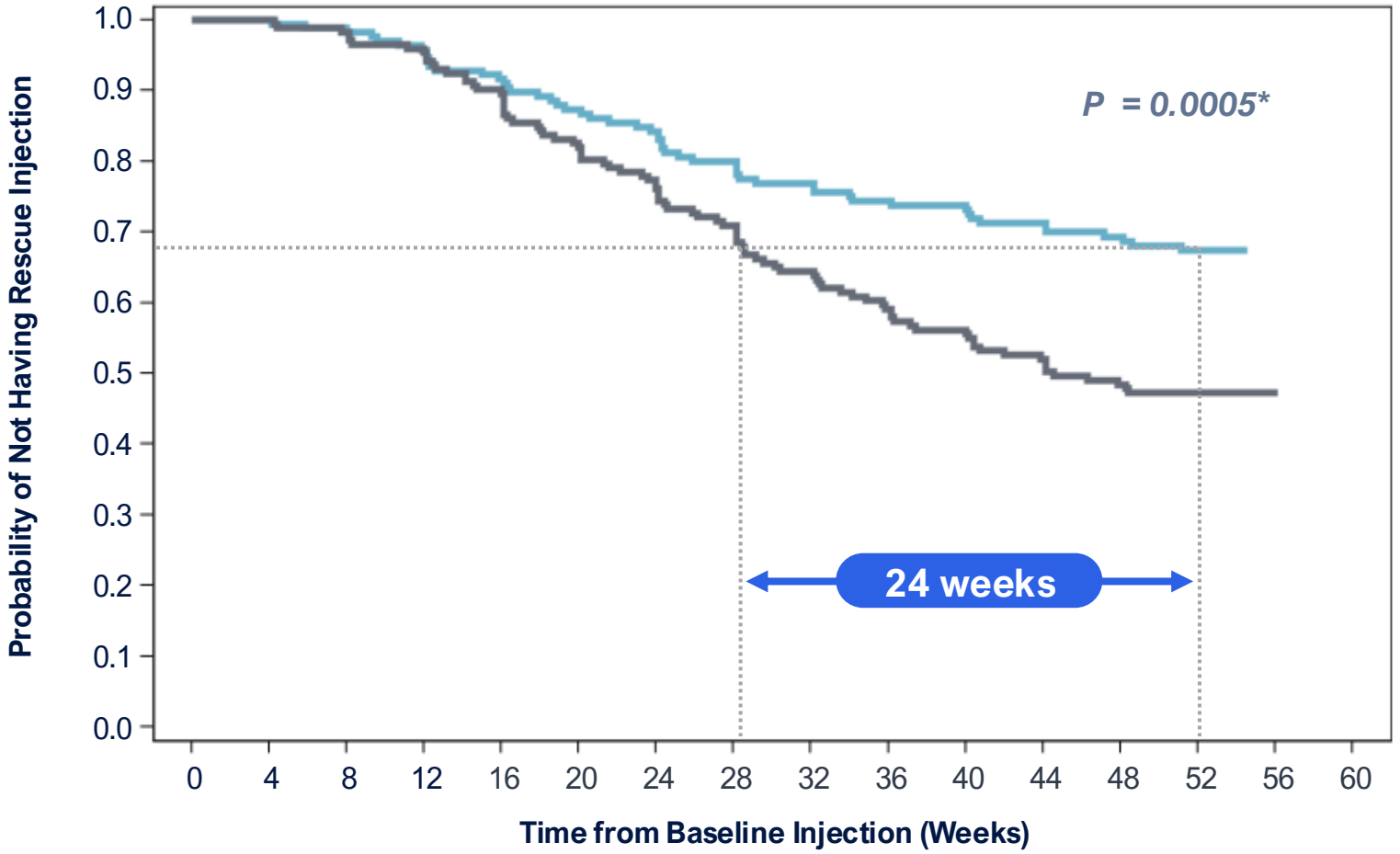


Rescue-free subjects include those who did not require rescue injections as specified by the protocol
Post-hoc analysis; Full analysis set; *Descriptive p-values

Secondary Endpoint: Time to First Rescue Treatment

SOL-1

OTX-TKI meaningfully extended durability, significantly delaying first rescue injection



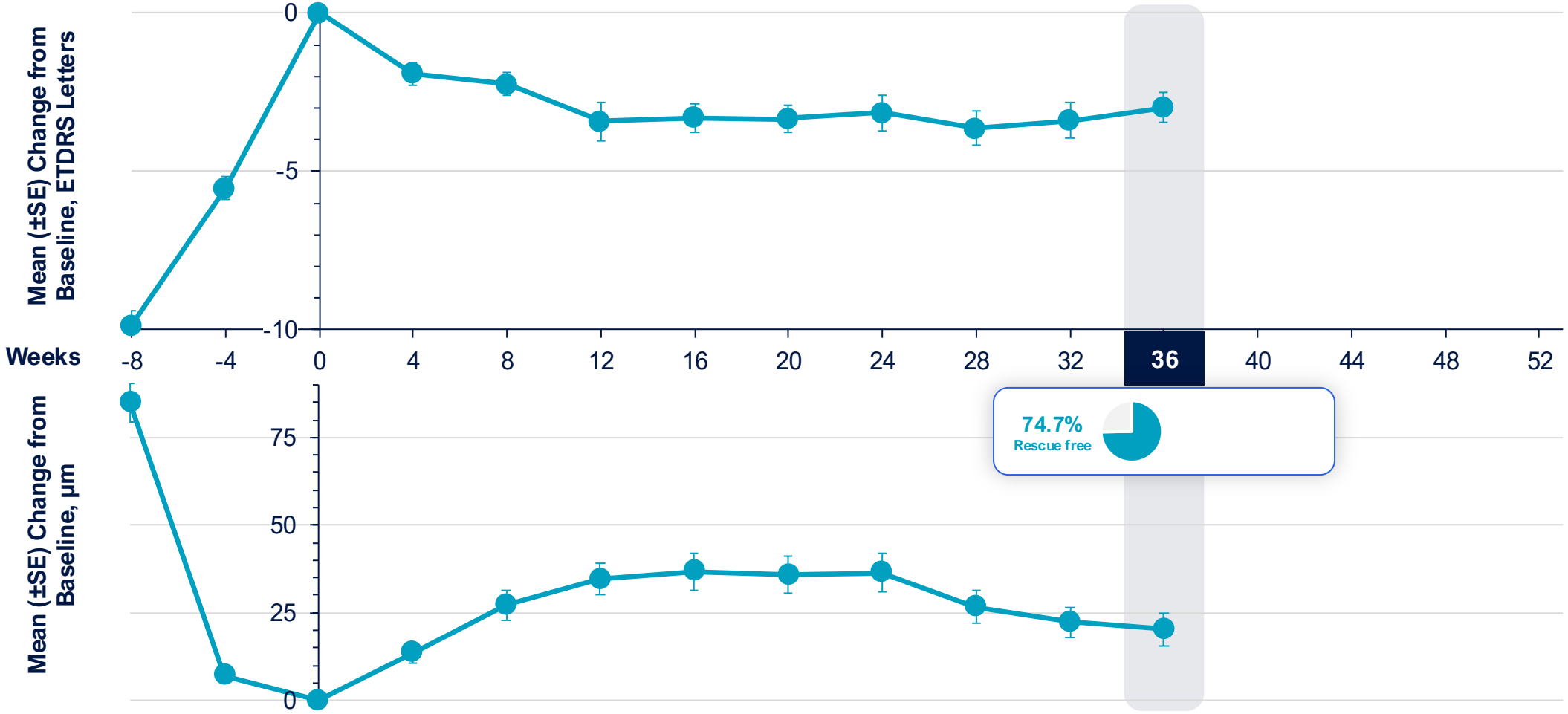
Rescue-free subjects include those who did not require rescue injections as specified by the protocol
*Nominal P value

OCULAR THERAPEUTIX Retina experience redefined™

Mean Change in BCVA and CSFT Over Time

SOL-1

75% of OTX-TKI subjects were rescue-free with maintenance of visual acuity and anatomy at Week 36



Full analysis set. Only data up to Week 52 is included in the analyses.
For subjects who received any rescue injections, their observed CSFT values after the 1st rescue injection are set to missing Baseline measurements are the last non-missing measurement prior to the study drug injection on Day 1.
BCVA, best corrected visual acuity; CSFT; central subfield thickness, measured from the internal limiting membrane to the retinal pigment epithelium; ETDRS, Early Treatment Diabetic Retinopathy Study; SE, standard error

OCULAR THERAPEUTIX Retina experience redefined™

Mean Change in BCVA and CSFT Over Time

SOL-1

75% of OTX-TKI subjects were rescue-free with maintenance of visual acuity and anatomy at Week 36

OCULAR THERAPEUTIX Retina experience redefined™

Full analysis set. Only data up to Week 52 is included in the analyses.
For subjects who received any rescue injections, their observed CSFT values after the 1st rescue injection are set to missing.Baseline measurements are the last non-missing measurement prior to the study drug injection on Day 1.
BCVA, best corrected visual acuity; CSFT; central subfield thickness, measured from the internal limiting membrane to the retinal pigment epithelium; ETDRS, Early Treatment Diabetic Retinopathy Study; SE, standard error

Mean Change in BCVA and CSFT Over Time

SOL-1

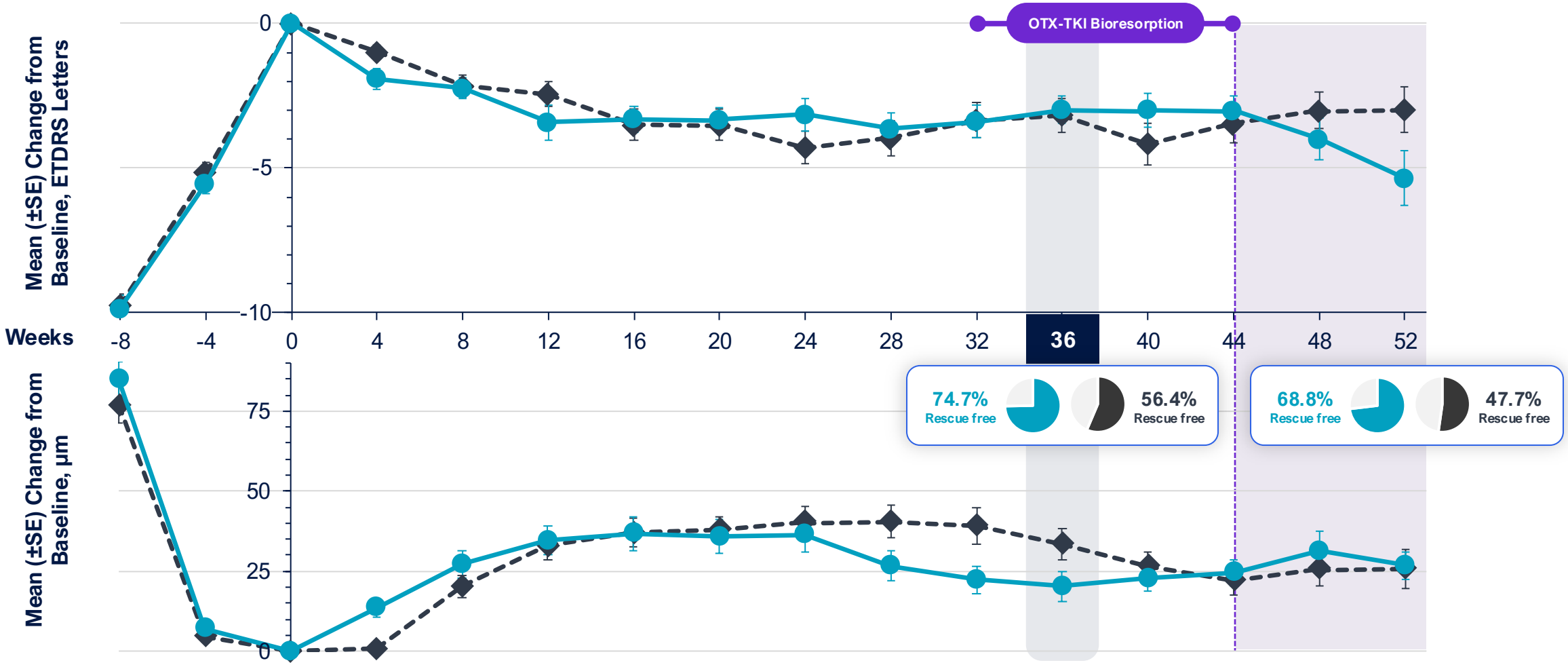
75% of OTX-TKI subjects were rescue-free with maintenance of visual acuity and anatomy

Full analysis set. Only data up to Week 52 is included in the analyses.
For subjects who received any rescue injections, their observed CSFT values after the 1st rescue injection are set to missing Baseline measurements are the last non-missing measurement prior to the study drug injection on Day 1.
BCVA, best corrected visual acuity; CSFT; central subfield thickness, measured from the internal limiting membrane to the retinal pigment epithelium; ETDRS, Early Treatment Diabetic Retinopathy Study; SE, standard error

OCULAR THERAPEUTIX Retina experience redefined™

Mean Change in BCVA and CSFT Over Time

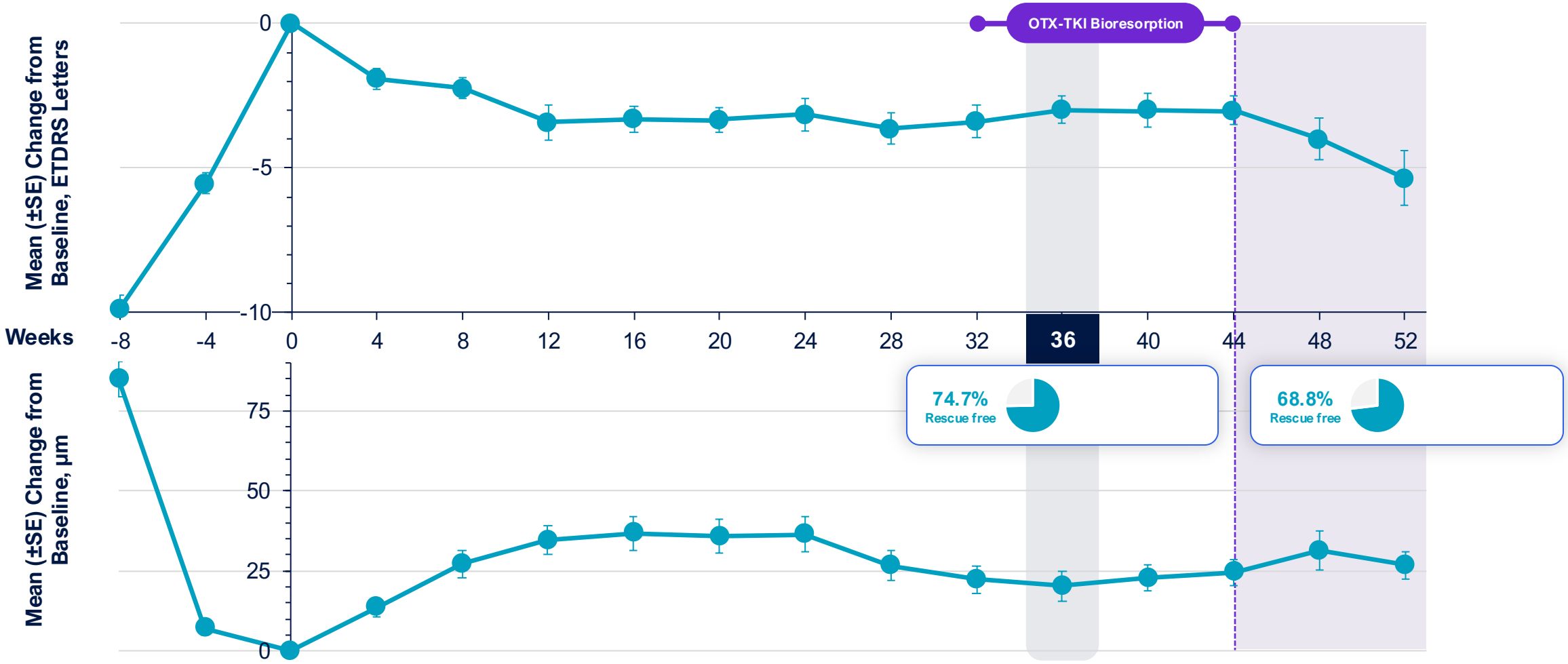
75% of OTX-TKI subjects were rescue-free with maintenance of visual acuity and anatomy



Full analysis set. Only data up to Week 52 is included in the analyses.
For subjects who received any rescue injections, their observed CSFT values after the 1st rescue injection are set to missing Baseline measurements are the last non-missing measurement prior to the study drug injection on Day 1.
BCVA, best corrected visual acuity; CSFT; central subfield thickness, measured from the internal limiting membrane to the retinal pigment epithelium; ETDRS, Early Treatment Diabetic Retinopathy Study; SE, standard error

Mean Change in BCVA and CSFT Over Time

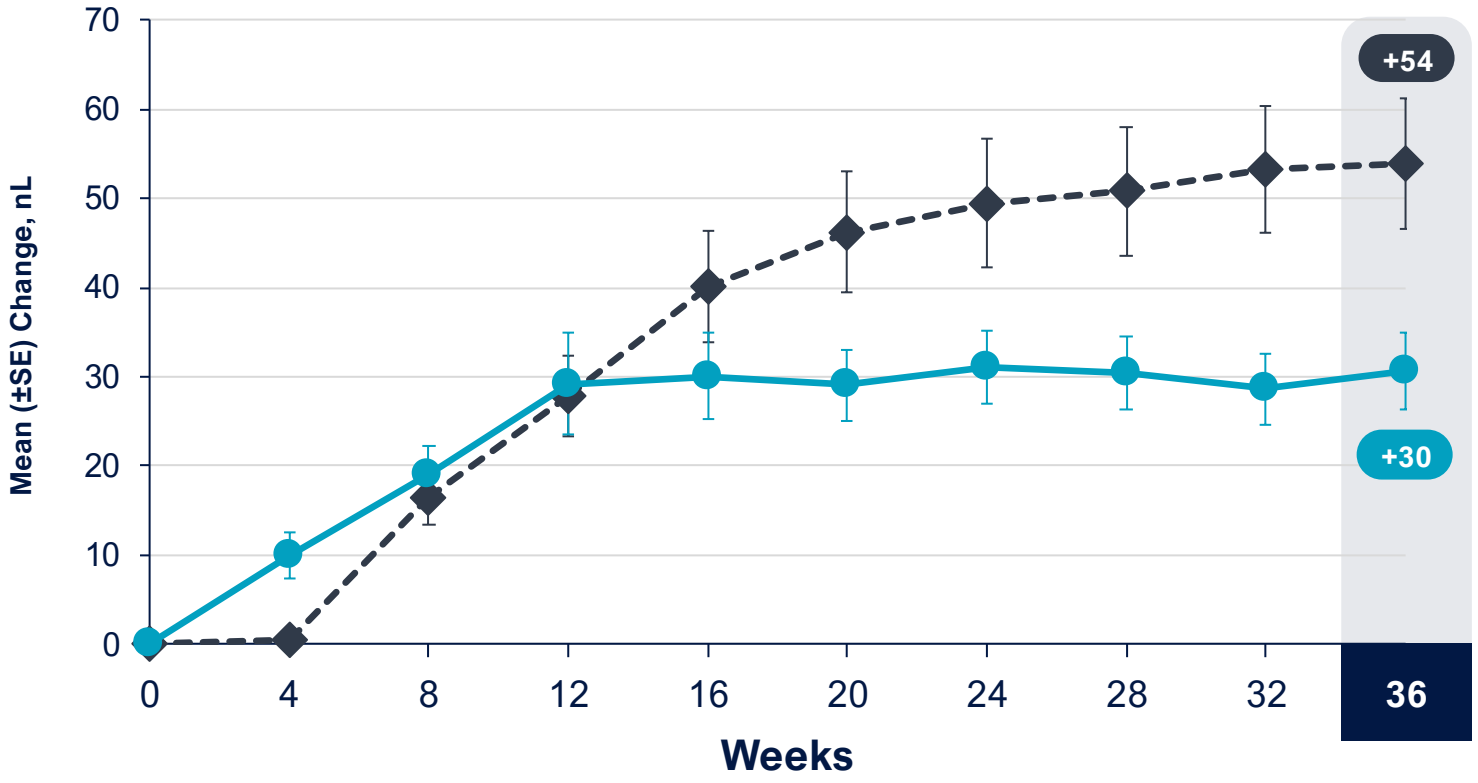
75% of OTX-TKI subjects were rescue-free with maintenance of visual acuity and anatomy



Full analysis set. Only data up to Week 52 is included in the analyses.
For subjects who received any rescue injections, their observed CSFT values after the 1st rescue injection are set to missing Baseline measurements are the last non-missing measurement prior to the study drug injection on Day 1.
BCVA, best corrected visual acuity; CSFT; central subfield thickness, measured from the internal limiting membrane to the retinal pigment epithelium; ETDRS, Early Treatment Diabetic Retinopathy Study; SE, standard error

Mean Change in Intra-Retinal and Sub-Retinal Total Fluid Volume

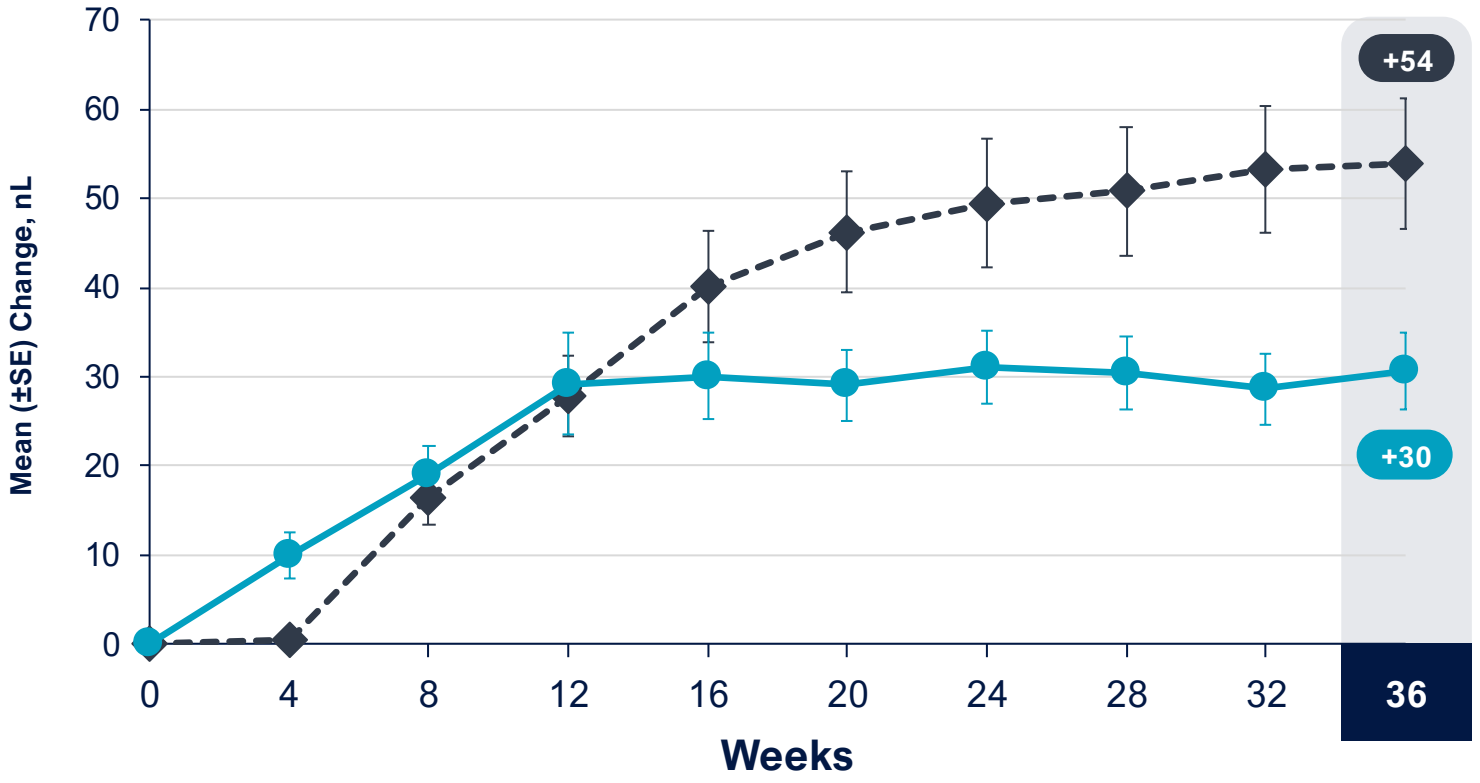
OTX-TKI delivered robust, durable IRF and SRF control



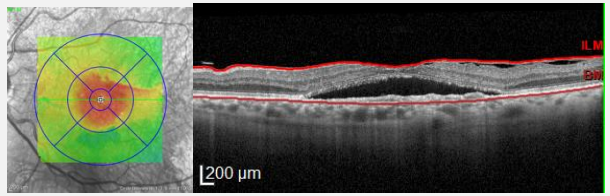
Pre-specified exploratory analysis
SE, standard error. Full analysis set

Mean Change in Intra-Retinal and Sub-Retinal Total Fluid Volume

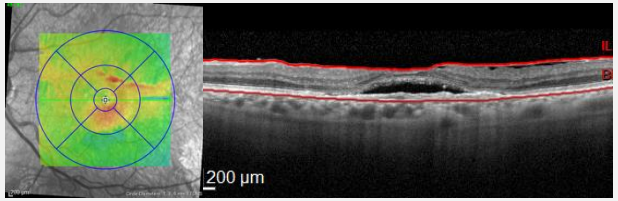
OTX-TKI delivered robust, durable IRF and SRF control



Total Fluid Volume: 60 nL



Total Fluid Volume: 30 nL



OTX-TKI 0.45 mg (n=170)

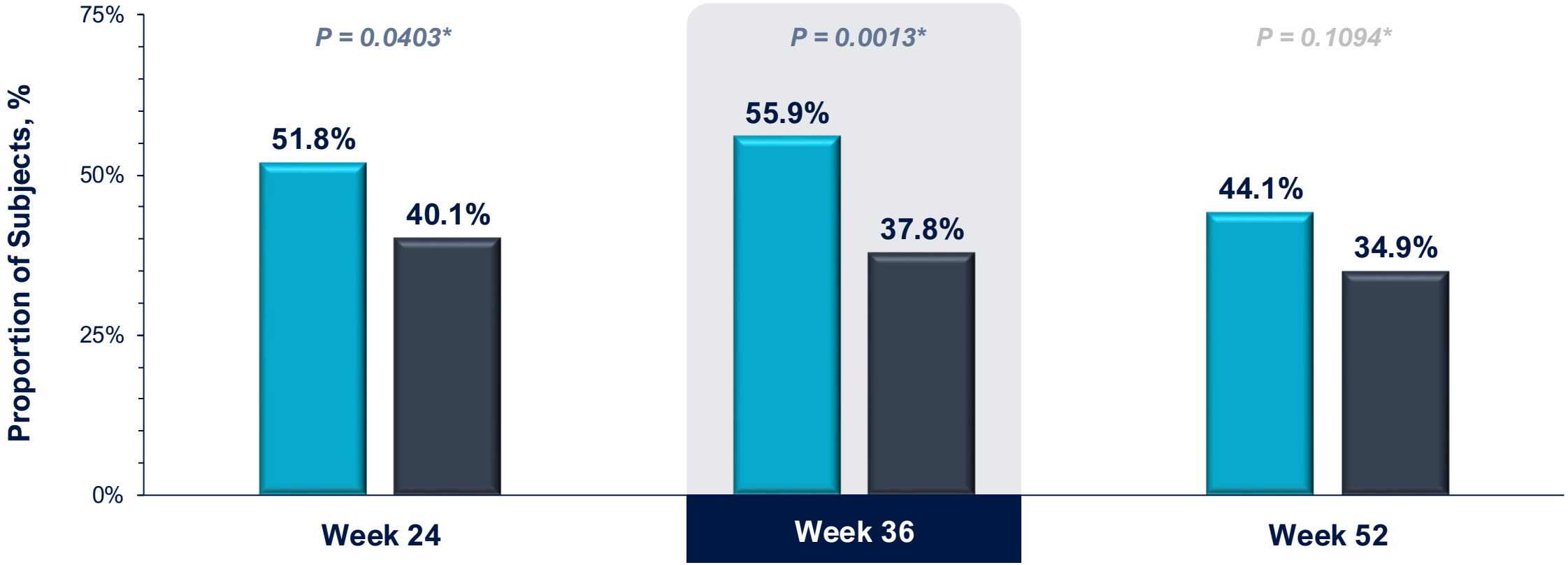
Aflibercept 2 mg (n=172)

Pre-specified exploratory analysis
SE, standard error. Full analysis set

Proportion of Subjects with ≤30 µm Increase in CSFT vs Baseline

SOL-1

Superior fluid control in OTX-TKI arm



Risk difference vs. aflibercept
11.0% (95% CI, 0.6, 21.5)

80.6% Rescue free | 72.1% Rescue free

Risk difference vs. aflibercept
17.1% (95% CI, 6.8, 27.4)

74.7% Rescue free | 56.4% Rescue free

Risk difference vs. aflibercept
8.4% (95% CI, -1.8, 18.7)

68.8% Rescue free | 47.7% Rescue free

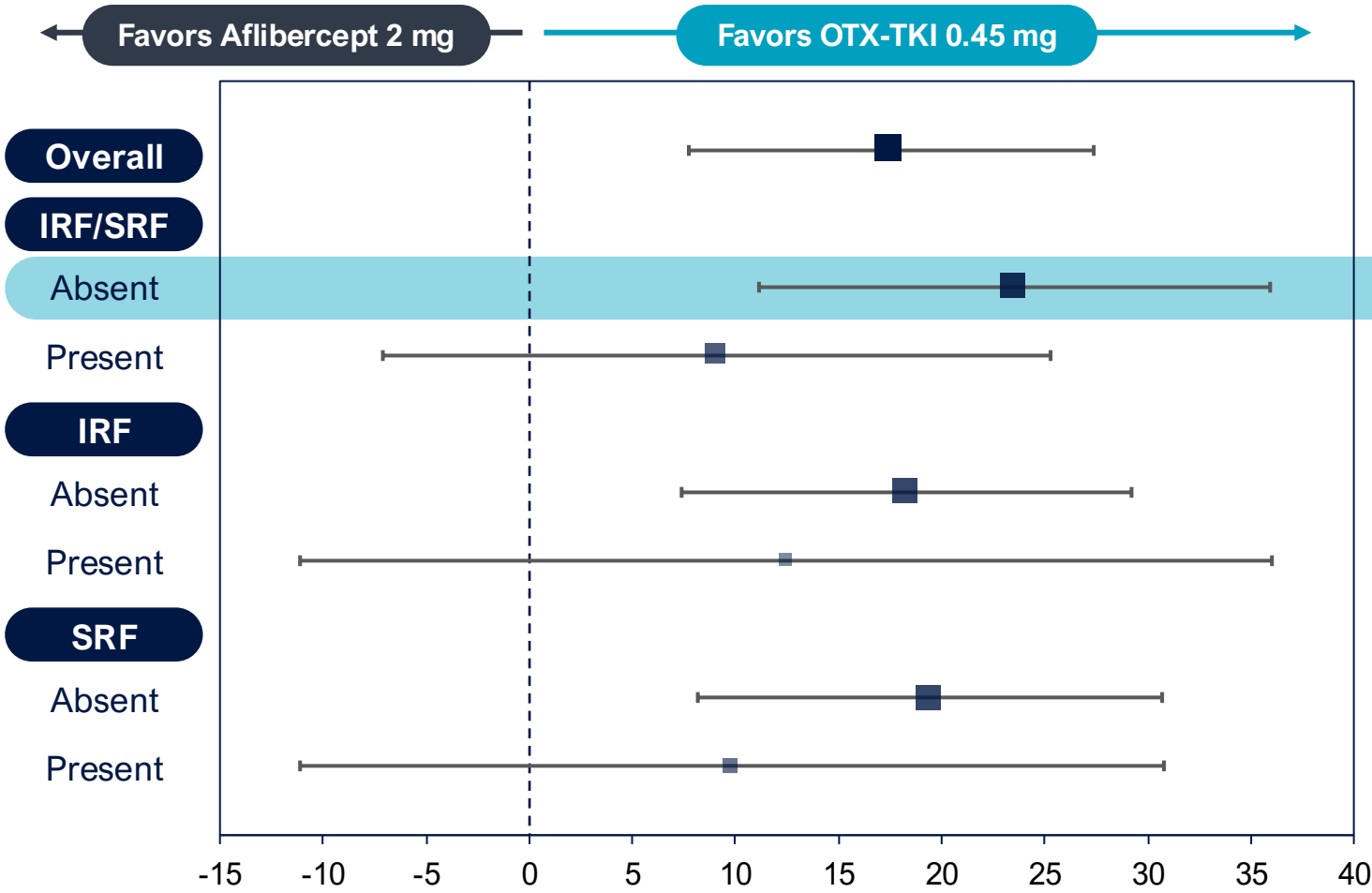
OCULAR THERAPEUTIX Retina experience redefined™

Full analysis set. Post hoc analysis; *Descriptive p-value
CSFT; central subfield thickness, measured from the internal limiting membrane to the retinal pigment epithelium; CI, confidence interval

OTX-TKI 0.45 mg (n=170)
Aflibercept 2 mg (n=172)

Effect of Baseline Fluid Status and Maintaining Vision* at Week 36

Subjects who were dry at baseline, maintained vision* with OTK-TKI

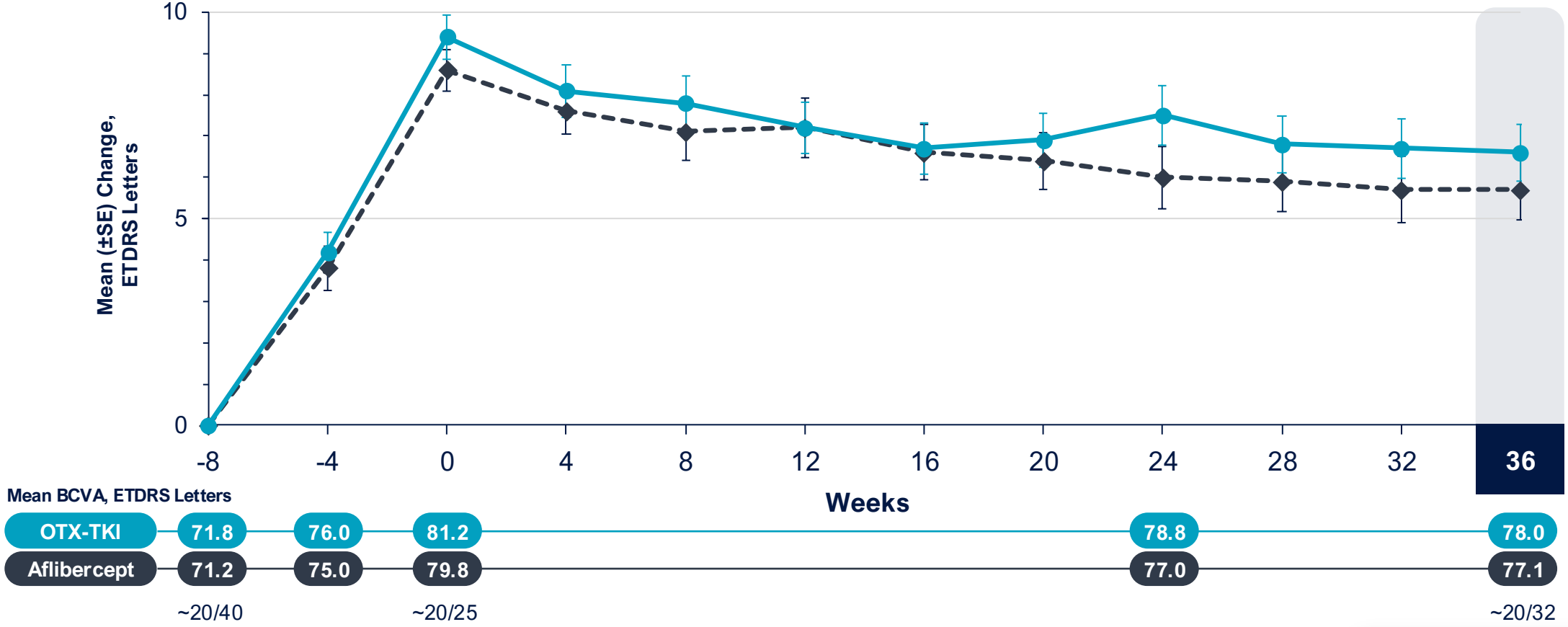


	OTX-TKI	Aflibercept	Risk Difference (95% CI)
Overall	74.1%	55.8%	17.5 (7.7, 27.4)
IRF/SRF			
Absent	80.4%	56.0%	23.5 (11.1, 35.9)
Present	63.5%	55.6%	9.1 (-7.1, 25.3)
IRF			
Absent	77.2%	57.4%	18.3 (7.4, 29.2)
Present	61.8%	50.0%	12.4 (-11.1, 36.0)
SRF			
Absent	76.6%	56.5%	19.4 (8.2, 30.7)
Present	63.6%	54.2%	9.8 (-11.1, 30.8)

*Defined as proportion of subjects who maintain visual acuity, a loss of <15 ETDRS letters of BCVA from baseline
Predefined statistical rules were applied to adjust for treatment discontinuation or deviation as per the prespecified statistical analysis plan
BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; IRF, intraretinal fluid; SRF, subretinal fluid

Visual Outcomes in Rescue-free Subjects through Week 36

75% of OTX-TKI subjects were rescue-free vs 56% of aflibercept subjects

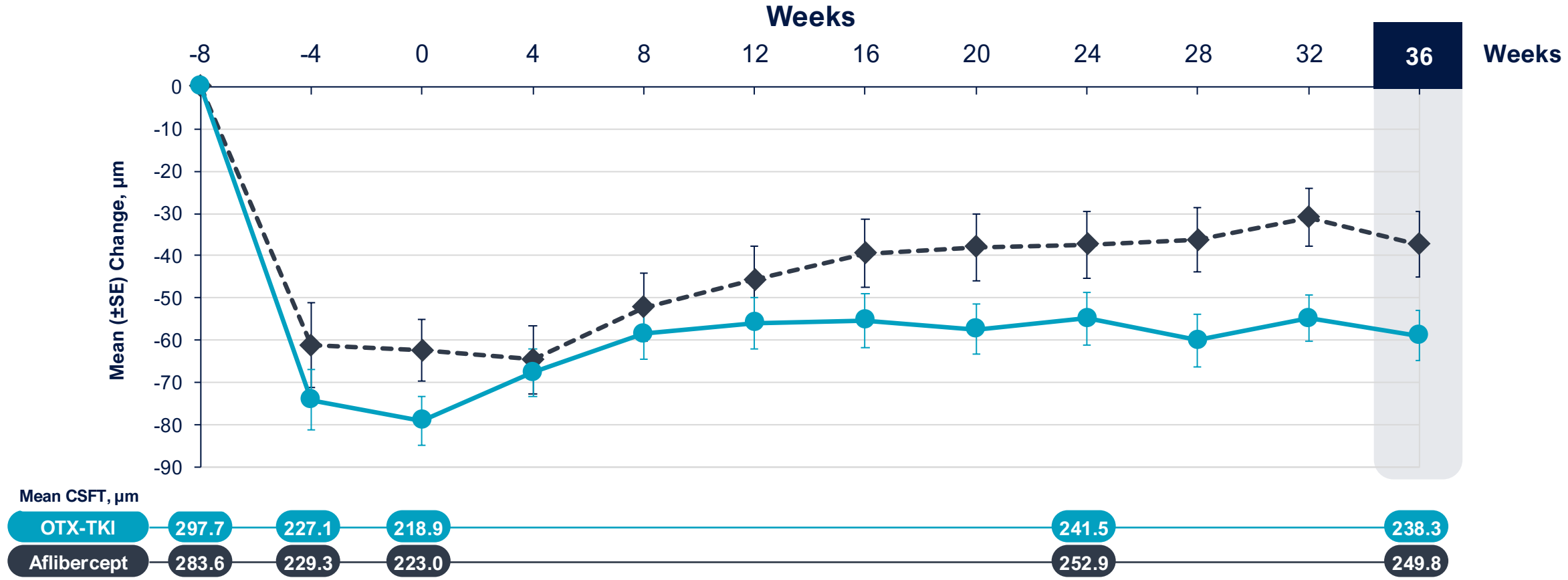


Rescue-free subjects include those who did not require rescue injections as specified by the protocol
BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; SE, standard error

OCT Outcomes in Rescue-free Subjects through Week 36

SOL-1

Better disease control demonstrated in a greater proportion of OTX-TKI subjects



Rescue-free subjects include those who did not require rescue injections as specified by the protocol
CSFT; central subfield thickness, measured from the internal limiting membrane to the retinal pigment epithelium; SE, standard error

OCULAR THERAPEUTIX Retina experience redefined™

SOL-1: Key Efficacy Outcomes

SOL-1

Superior Visual Outcomes

74% of OTX-TKI subjects maintained vision* to Week 36

Two-thirds of OTX-TKI subjects maintained vision* to Week 52

Superior Anatomic Control

56% of OTX-TKI subjects had ≤30 µm increase in fluid to Week 36

Robust intraretinal and subretinal fluid control

Durable CSFT control up to Week 52

Superior Rescue-Free Rates

75% of OTX-TKI subjects rescue-free to Week 36

Reduced cumulative rescue injection burden up to Week 52

Significantly reduced risk of requiring rescue over time up to Week 52

OTX-TKI is a novel, first-in-class, sustained delivery platform with 9-12 month durability

OCULAR THERAPEUTIX Retina experience redefined™

*Defined as proportion of subjects who maintain visual acuity, a loss of <15 ETDRS letters of BCVA from baseline at Week 36
Predefined statistical rules were applied to adjust for treatment discontinuation or deviation as per the prespecified statistical analysis plan
BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study

SOL-1

Safety Results

Treatment Tolerability through Week 52

Patricio G. Schlottmann, MD

OCULAR THERAPEUTIX Retina experience redefined

Safety Summary: Non-Ocular Events

No treatment or procedure related SAEs

Subjects with Non-Ocular AEs Through Week 52, n (%)	OTX-TKI 0.45 mg n = 170	Aflibercept 2 mg n = 172
Non-ocular AEs		
≥ 1 AE	84 (49.4)	73 (42.4)
≥ 1 SAE	19 (11.2)	21 (12.2)
≥ 1 treatment-related AE	0	0
≥ 1 treatment-related SAE	0	0
≥ 1 study procedure-related AE	1 (0.6)	0
≥ 1 study procedure-related SAE	0	0
AE leading to study discontinuation	3 (1.8)	3 (1.7)
AE leading to death*	2 (1.2)	1 (0.6)

*Stroke (day 103); worsening of metastatic melanoma (day 319); lung cancer metastatic (day 503)
AE, adverse event; SAE, serious AE

Safety Summary: Ocular Events in the Study Eye

No treatment or procedure related SAEs

Subjects with Ocular AEs Through Week 52, n (%)	OTX-TKI 0.45 mg n = 170	Aflibercept 2 mg n = 172
Ocular AEs in the study eye		
≥ 1 AE	90 (52.9)	58 (33.7)
≥ 1 SAE*	1 (0.6)	0
≥ 1 treatment-related AE	15 (8.8)	1 (0.6)
≥ 1 treatment-related SAE	0	0
≥ 1 study procedure-related AE	15 (8.8)	7 (4.1)
≥ 1 study procedure-related SAE	0	0
Ocular AE leading to study discontinuation	0	0

AE, adverse event; SAE, serious AE
*Severe vision loss due to 3+ PSC cataract, 78 ETDRS letters at baseline, recovered to 70 ETDRS letters after cataract surgery
PSC, posterior subcapsular cataract; ETDRS, early treatment diabetic retinopathy study

Ocular Adverse Events in the Study Eye

SOL-1

OTX-TKI was generally well tolerated

Subjects with Ocular AEs (> 2%) Through Week 52, n (%)	OTX-TKI 0.45 mg n = 170	Aflibercept 2 mg n = 172
Vitreous floaters	21 (12.4)	2 (1.2)
Cataract	12 (7.1)	5 (2.9)
Conjunctival hemorrhage	11 (6.5)	5 (2.9)
Retinal hemorrhage	10 (5.9)	17 (9.9)
Dry eye	7 (4.1)	2 (1.2)
Vitreous detachment	7 (4.1)	3 (1.7)
Punctate keratitis	6 (3.5)	0
Vitreous opacities	6 (3.5)	0
Eye pain	5 (2.9)	1 (0.6)
Anterior chamber opacity	4 (2.4)	0
Posterior capsule opacification	4 (2.4)	6 (3.5)

There were no cases of endophthalmitis, occlusive or non-occlusive retinal vasculitis

OCULAR THERAPEUTIX Retina experience redefined™

AE, adverse event

Safety Across nAMD Trials

OTX-TKI relative to other therapeutic agents

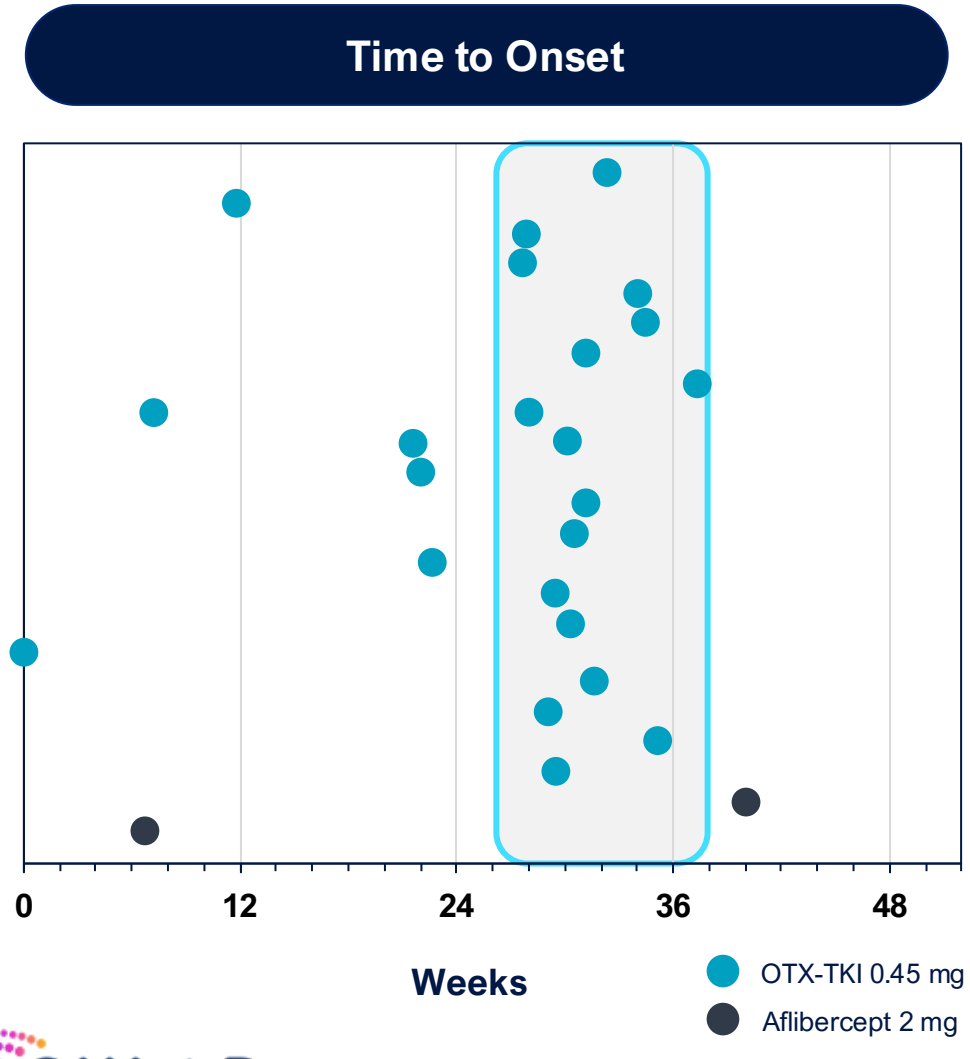
	SOL-1		DAVIO2[1]	Prescribing Information			
	OTX-TKI (0.45 mg) n=170	Aflibercept (2 mg) n=172	EYP-1901 (3 mg) n=52	Aflibercept[2] (2 mg)	Aflibercept[3] (8 mg)	Ranibizumab[4] (0.5 mg)	Faricimab[5] (6 mg)
Vitreous floaters	12.4%	1.2%	11.5%	6%	4%	19%	3%
Cataract	7.1%	2.9%	9.6%	7%	4%	11%	3%
Vision Blurred	0.0%	1.7%	N/A	2%	6%	13%†	<1%
Visual Acuity Reduced	1.2%	0.6%	15.4%	N/A	N/A	N/A	<1%
Endophthalmitis	0%	0%	5.8%	<1%	0%	<0.1%	<1%

*Event rates in Q16W (every 16 weeks) arm;
†Includes both vision blur or vision disturbance

1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05381948. Accessed February 24, 2026. 2.EYLEA® package insert. Tarrytown, NY: Regeneron Pharmaceuticals, Inc. 2024 3.EYLEA HD® package insert. Tarrytown, NY: Regeneron Pharmaceuticals, Inc. 2025 4.LUCENTIS® package insert. San Francisco, CA: Genentech, Inc. 2018 5. VABYSMO® package insert. San Francisco, CA: Genentech, Inc. July 2024

Evaluation of Vitreous Floaters

Appearance of floaters likely corresponds to hydrogel dissolution and drug elution



	OTX-TKI 0.45 mg n = 23*	Aflibercept 2 mg n = 2
Time to onset, days		
Mean (SD)	187.9 (64.0)	164.5 (164.8)
Median	207.0	164.5
BCVA change from prior visit before onset of floaters, ETDRS letters		
Mean change (SD)	-0.4 (5.0)	-5.5 (6.4)
Median change	0.0	-5.5

- All cases were mild to moderate in severity with minimal impact on vision
- No evidence of IOI
- No case observed to be associated with cataract formation

OCULAR THERAPEUTIX Retina experience redefined™

*23 events, 21 subjects
OTK-TKI: Mean change from baseline (SD) in BCVA, -3.3 (8.2) ETDRS letters; median change from baseline, -1.0 ETDRS letters
SD, standard deviation; BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; AE, adverse events; IOI, intraocular inflammation

Evaluation of Intraocular Inflammation (IOI)

Cases were mild/moderate in severity and resolved with topical treatment

- Nine events observed in 7 subjects in the OTX-TKI arm
- **All cases mild or moderate** in severity:
  - 8 events treated with topical corticosteroids and resolved
  - 1 event (vitreous cells), mild in severity, resolved without treatment

MedDRA AE Event	Number of Subjects	Classified as*
AC inflammation **Eye inflammation** **Iridocyclitis**	1 1 1	**Iritis**
Iritis **Uveitis**	2 1 (bilateral)	**Uveitis**
Vitreal cells	1	**Vitreous cells**

There were no cases of endophthalmitis, occlusive or non-occlusive retinal vasculitis, confirmed by wide-field fluorescein angiography in uveitis cases (Reading Center graded)

AC, anterior chamber

SOL-1: Safety Summary

OTX-TKI was generally well tolerated through Week 52

Vitreous Floaters

Timing likely corresponds with hydrogel dissolution and drug elution

No visual acuity impact

Not observed to be associated with IOI or cataracts

Intraocular Inflammation

Mild or moderate in severity per investigator

All resolved with topical treatment or observation

There were no cases of endophthalmitis, occlusive or non-occlusive retinal vasculitis

SOL-1

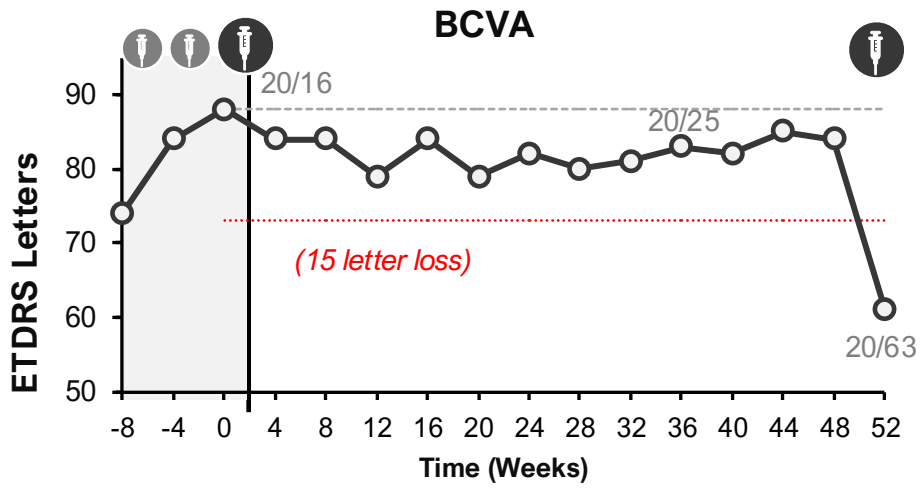
Clinical Evidence

Representative Cases

Mark R. Barakat, MD

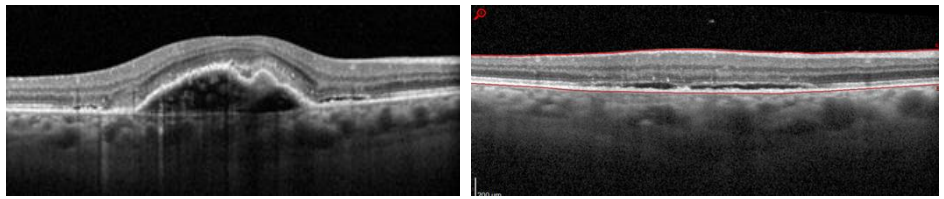
OCULAR THERAPEUTIX Retina experience redefined

Aflibercept Case 1



-8 Weeks

BCVA: 74 Ltrs **CSFT:** 227 µm



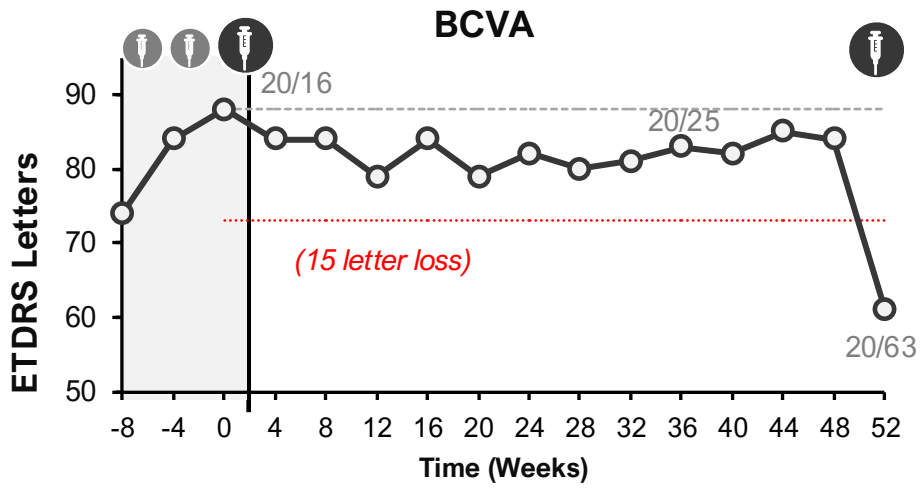
Screening Aflibercept (2mg)

Study Aflibercept (2 mg)

OCULAR THERAPEUTIX Retina experience redefined™

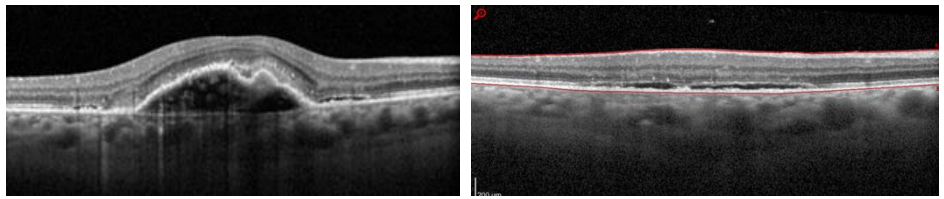
Case study of one subject; individual results may vary
BCVA, best corrected visual acuity; CSFT, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Ltrs, letters

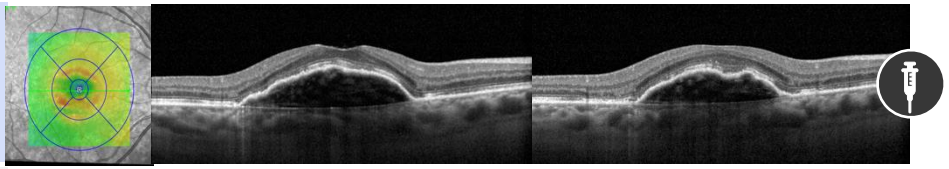
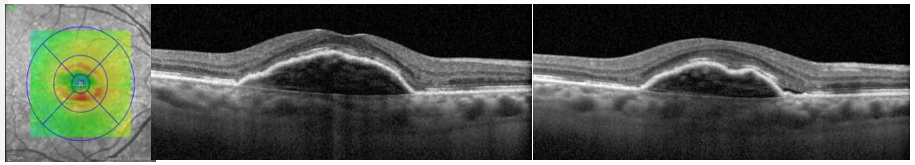
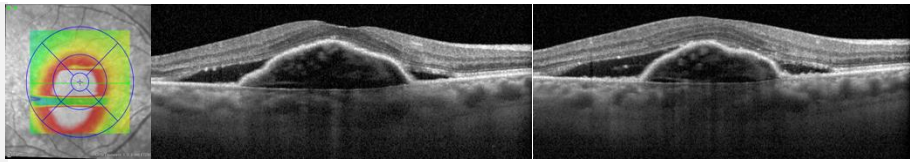
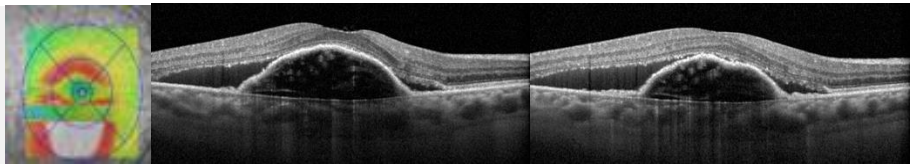
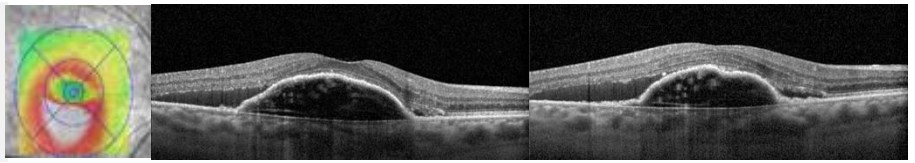
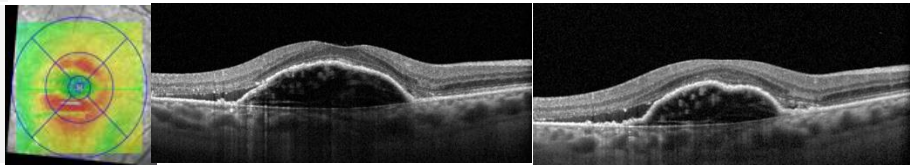
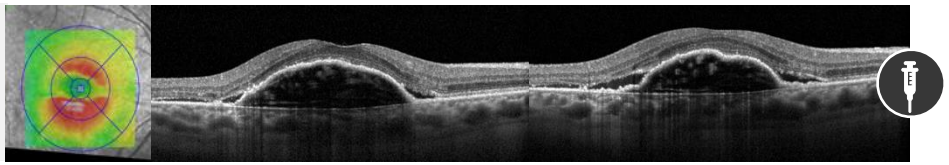
Aflibercept Case 1



-8 Weeks

BCVA: 74 Ltrs **CSFT:** 227 µm



Baseline	**BCVA:** 88 Ltrs *Snellen: 20/16* **CSFT:** 210 µm	
Week 4	**BCVA (Δ):** 84 (-4) Ltrs **CSFT (Δ):** 213 (+3) µm	
Week 12	**BCVA (Δ):** 79 (-9) Ltrs **CSFT (Δ):** 208 (-2) µm	
Week 24	**BCVA (Δ):** 82 (-6) Ltrs **CSFT (Δ):** 209 (-1) µm	
Week 36	**BCVA (Δ):** 83 (-5) Ltrs *Snellen: 20/25* **CSFT (Δ):** 207 (-3) µm	
Week 48	**BCVA (Δ):** 84 (-4) Ltrs **CSFT (Δ):** 203 (-7) µm	
Week 52	**BCVA (Δ):** 61 (-27) Ltrs *Snellen: 20/63* **CSFT (Δ):** 204 (-6) µm	

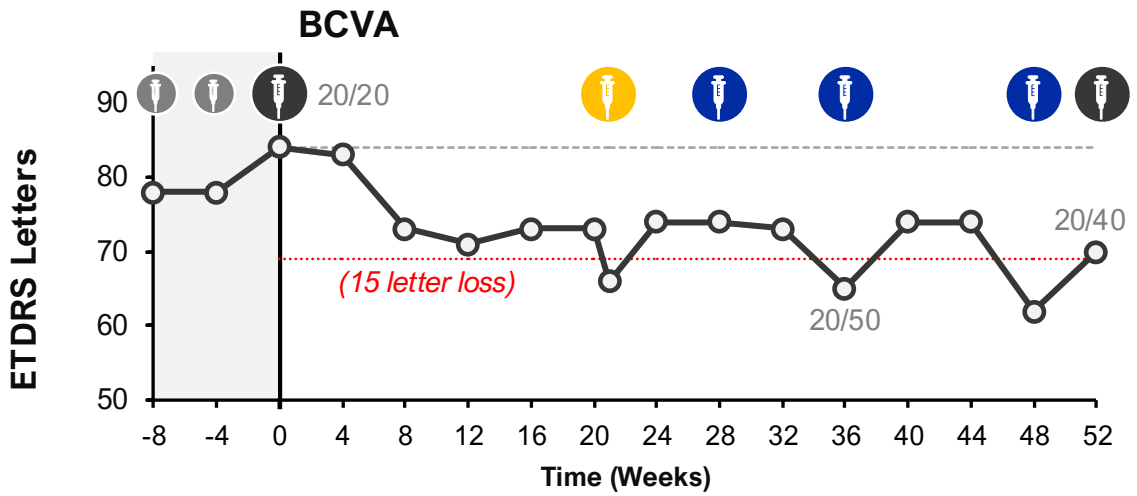
Screening Aflibercept (2mg)

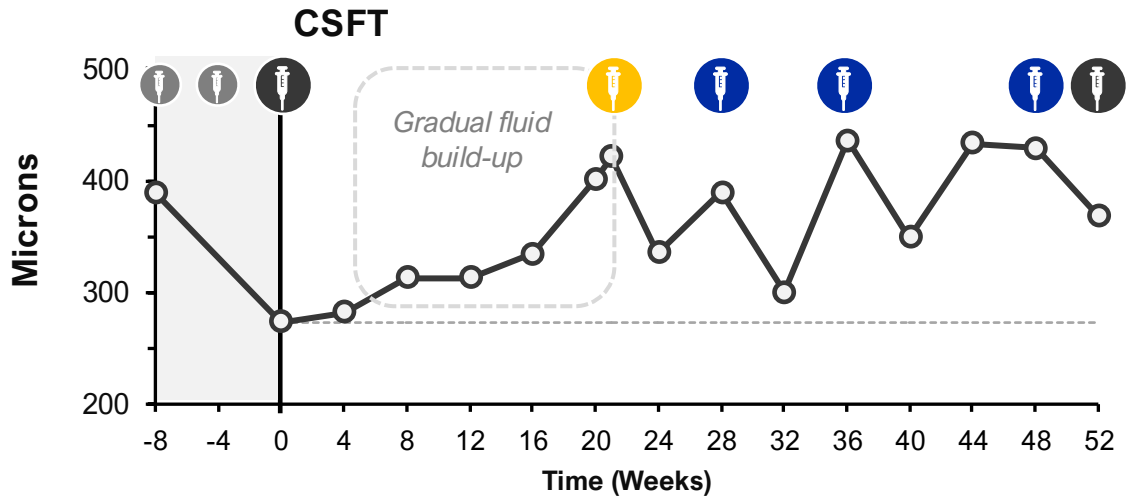
Study Aflibercept (2 mg)

OCULAR THERAPEUTIX Retina experience redefined™

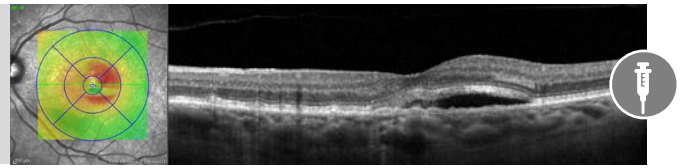
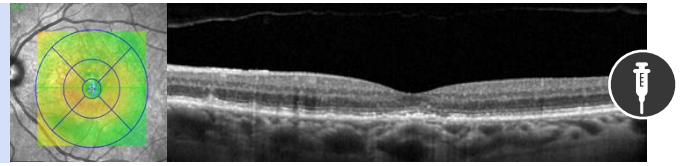
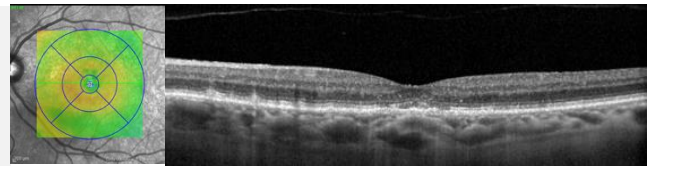
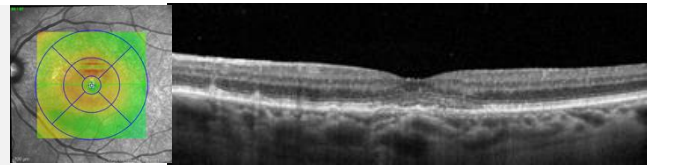
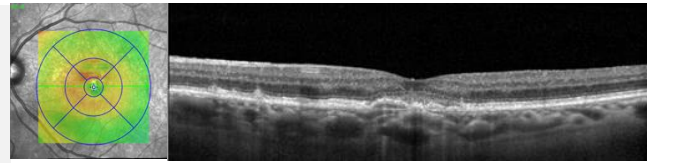
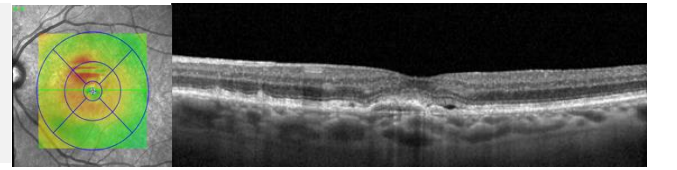
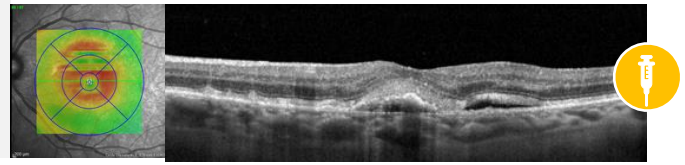
Case study of one subject; individual results may vary
BCVA, best corrected visual acuity; CSFT, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Ltrs, letters

Aflibercept Case 2





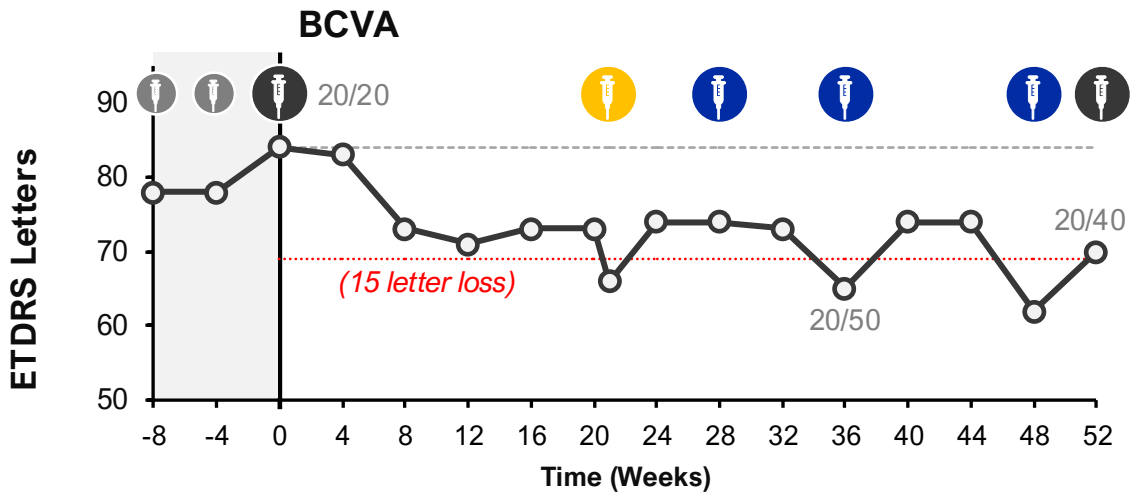
Screening Aflibercept (2mg)
Study Aflibercept (2 mg)
Per-Protocol Rescue Aflibercept (2mg)
Investigator Discretion Rescue

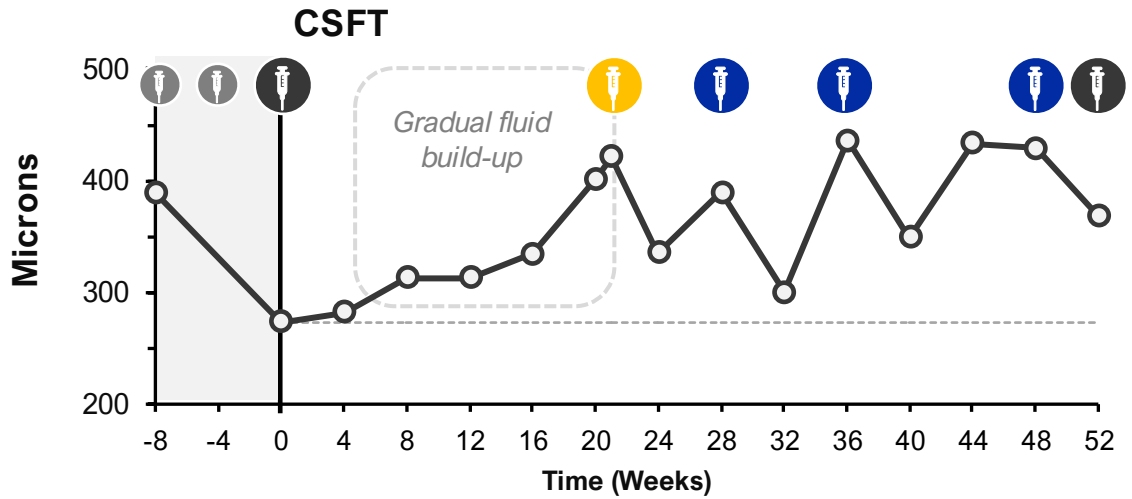
-8 Weeks	**BCVA:** 78 Ltrs **CSFT:** 389 µm	
Baseline	**BCVA:** 84 Ltrs *Snellen: 20/20* **CSFT:** 273 µm	
Week 4	**BCVA (Δ):** 83 (-1) Ltrs **CSFT (Δ):** 282 (+9) µm	
Week 8	**BCVA (Δ):** 73 (-11) Ltrs **CSFT (Δ):** 313 (+40) µm	
Week 12	**BCVA (Δ):** 71 (-13) Ltrs **CSFT (Δ):** 313 (+40) µm	
Week 16	**BCVA (Δ):** 73 (-11) Ltrs **CSFT (Δ):** 334 (+61) µm	
Week 21 *unscheduled*	**BCVA (Δ):** 66 (-18) Ltrs **CSFT (Δ):** 421 (+148) µm	

OCULAR THERAPEUTIX Retina experience redefined™

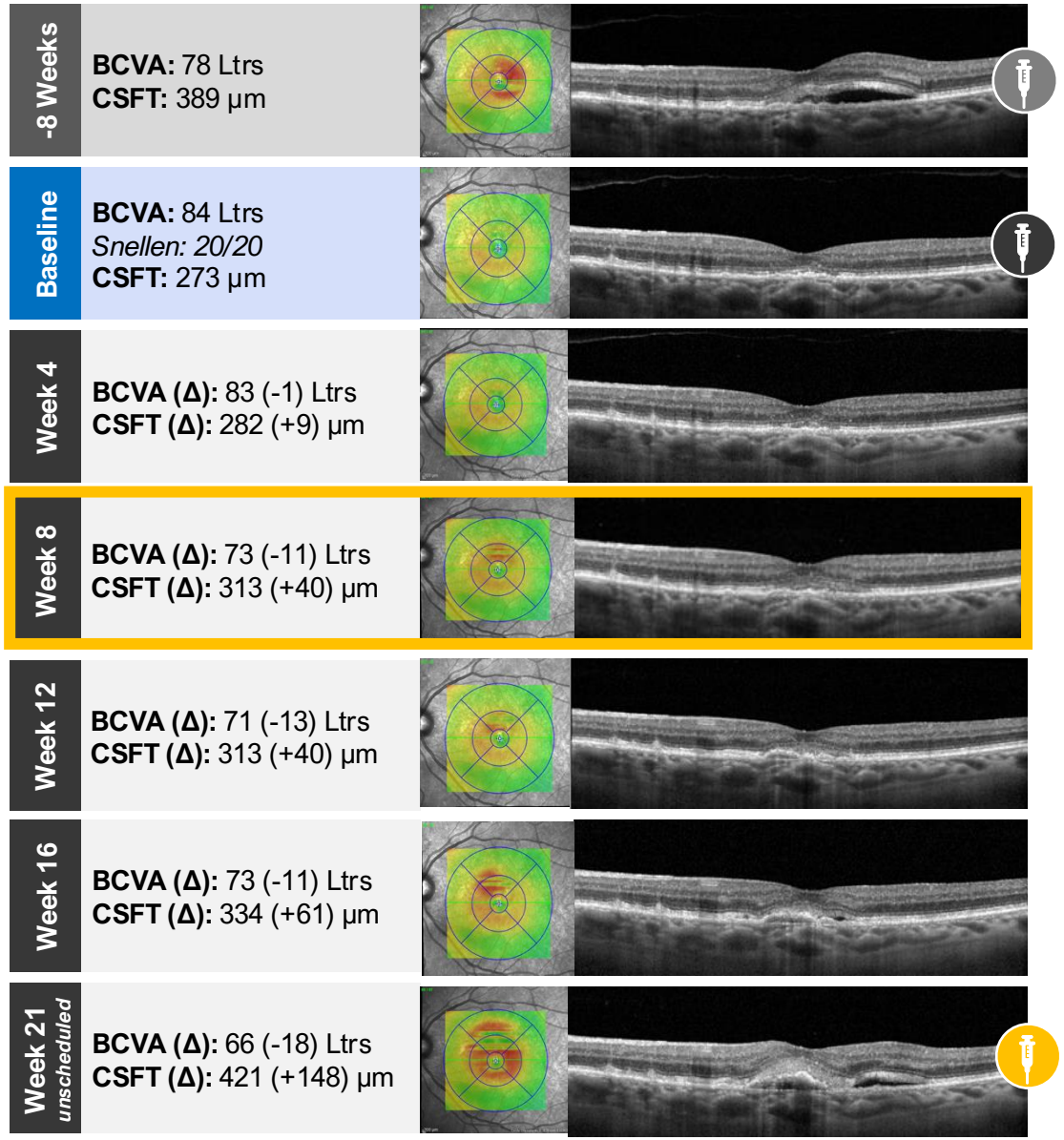
Case study of one subject; individual results may vary
BCVA, best corrected visual acuity; CSFT, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Ltrs, letters

Aflibercept Case 2





Screening Aflibercept (2mg)
Study Aflibercept (2 mg)
Per-Protocol Rescue Aflibercept (2mg)
Investigator Discretion Rescue



OCULAR THERAPEUTIX Retina experience redefined™

Case study of one subject; individual results may vary
BCVA, best corrected visual acuity; CSFT, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Ltrs, letters

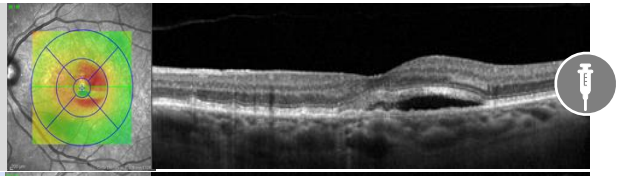
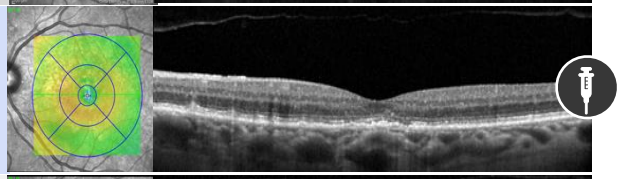
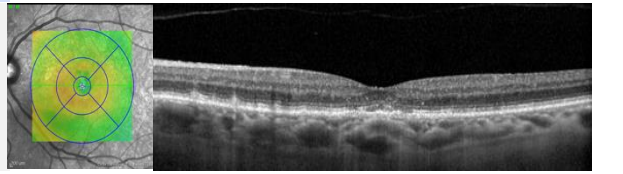
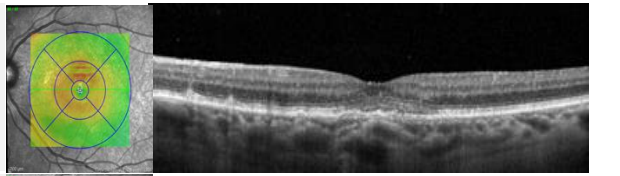
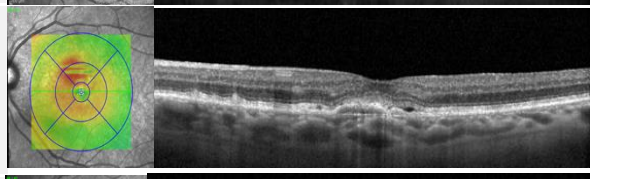
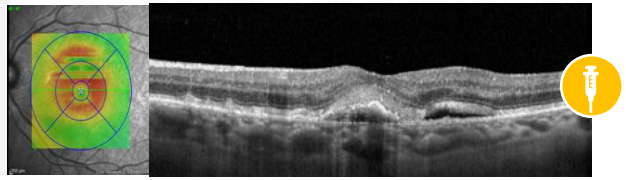
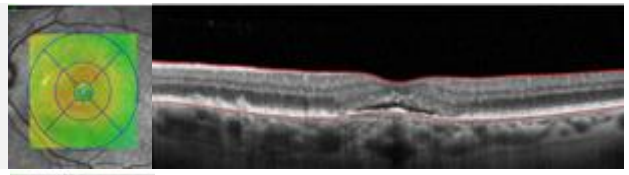
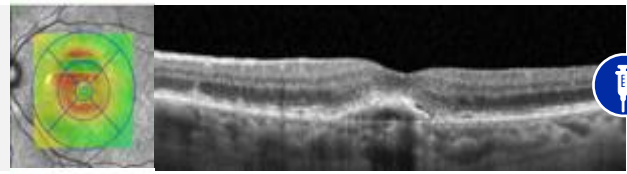
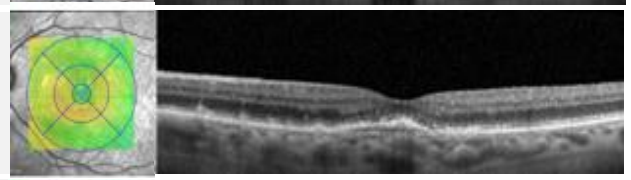
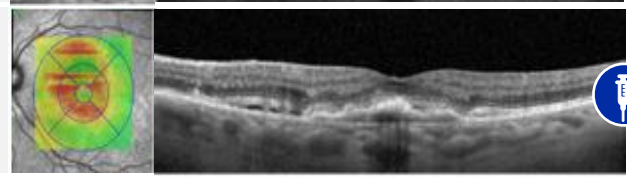
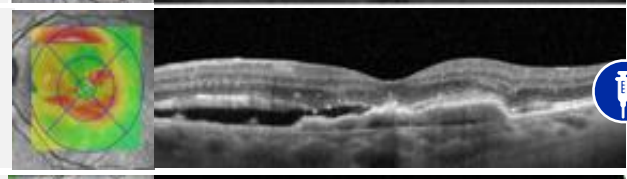
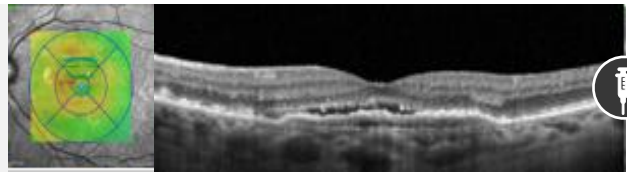
Aflibercept Case 2

Screening Aflibercept (2mg)

Study Aflibercept (2 mg)

Per-Protocol Rescue Aflibercept (2mg)

Investigator Discretion Rescue

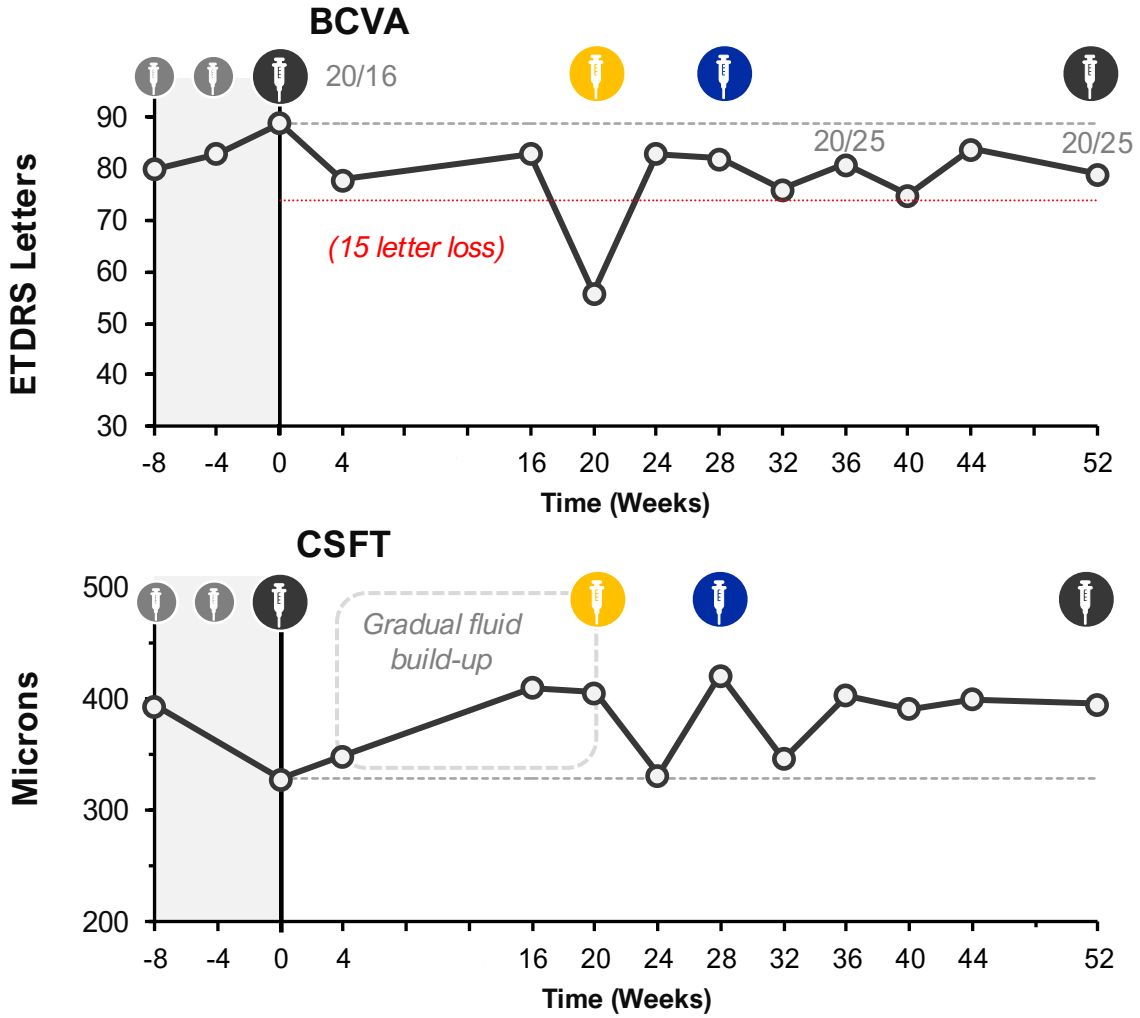
-8 Weeks	**BCVA:** 78 Ltrs **CSFT:** 389 µm	
Baseline	**BCVA:** 84 Ltrs *Snellen: 20/20* **CSFT:** 273 µm	
Week 4	**BCVA (Δ):** 83 (-1) Ltrs **CSFT (Δ):** 282 (+9) µm	
Week 8	**BCVA (Δ):** 73 (-11) Ltrs **CSFT (Δ):** 313 (+40) µm	
Week 16	**BCVA (Δ):** 73 (-11) Ltrs **CSFT (Δ):** 334 (+61) µm	
Week 21 *unscheduled*	**BCVA (Δ):** 66 (-18) Ltrs **CSFT (Δ):** 421 (+148) µm	
Week 24	**BCVA (Δ):** 74 (-10) Ltrs **CSFT (Δ):** 335 (+62) µm	
Week 28	**BCVA (Δ):** 74 (-10) Ltrs **CSFT (Δ):** 389 (+116) µm	
Week 32	**BCVA (Δ):** 73 (-11) Ltrs **CSFT (Δ):** 300 (+27) µm	
Week 36	**BCVA (Δ):** 65 (-19) Ltrs *Snellen: 20/50* **CSFT (Δ):** 436 (+163) µm	
Week 48	**BCVA (Δ):** 62 (-22) Ltrs **CSFT (Δ):** 429 (+156) µm	
Week 52	**BCVA (Δ):** 70 (-14) Ltrs *Snellen: 20/40* **CSFT (Δ):** 369 (+96) µm	

OCULAR THERAPEUTIX Retina experience redefined™

Case study of one subject; individual results may vary

BCVA, best corrected visual acuity; CSFT, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Ltrs, letters

Aflibercept Case 3

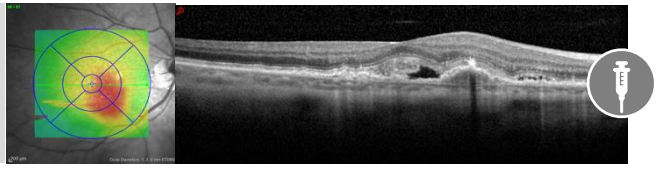
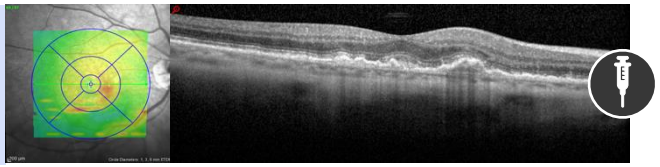
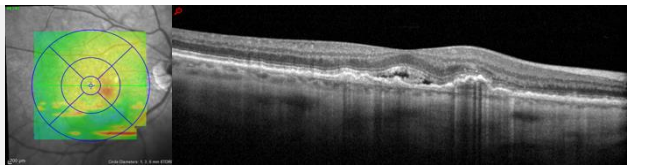
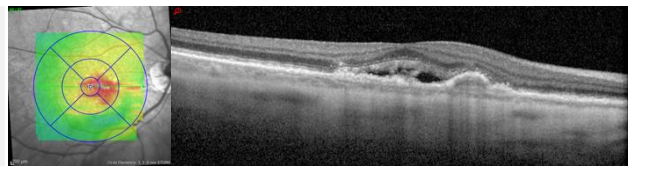
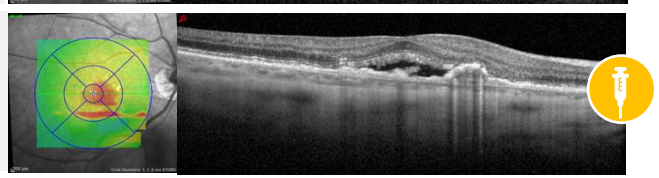
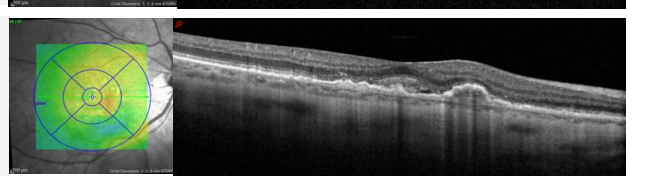
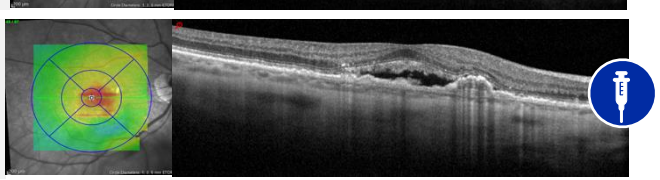
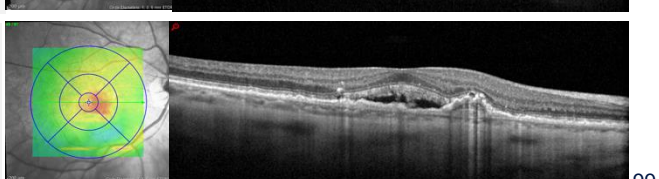


Screening Aflibercept (2mg)

Study Aflibercept (2 mg)

Per-Protocol Rescue Aflibercept (2mg)

Investigator Discretion Rescue

-8 Weeks	**BCVA:** 80 Ltrs **CSFT:** 394 µm	
Baseline	**BCVA:** 89 Ltrs *Snellen: 20/16* **CSFT:** 328 µm	
Week 4	**BCVA (Δ):** 78 (-11) Ltrs **CSFT (Δ):** 349 (+21) µm	
Week 16	**BCVA (Δ):** 83 (-6) Ltrs **CSFT (Δ):** 410 (+82) µm	
Week 20	**BCVA (Δ):** 56 **(-33)** Ltrs **CSFT (Δ):** 406 (+78) µm	
Week 24	**BCVA (Δ):** 83 (-6) Ltrs **CSFT (Δ):** 332 (+4) µm	
Week 28	**BCVA (Δ):** 82 (-7) Ltrs **CSFT (Δ):** 421 (+93) µm	
Week 36	**BCVA (Δ):** 81(-8) Ltrs *Snellen: 20/25* **CSFT (Δ):** 403 (+75) µm	

OCULAR THERAPEUTIX Retina experience redefined™

Subject missed W8/W12/W48 Visits
Case study of one subject; individual results may vary
BCVA, best corrected visual acuity; CSFT, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Ltrs, letters

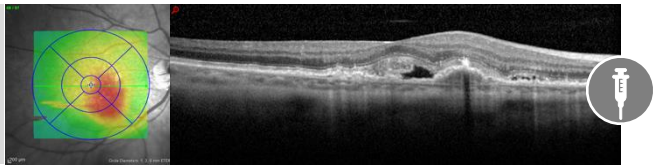
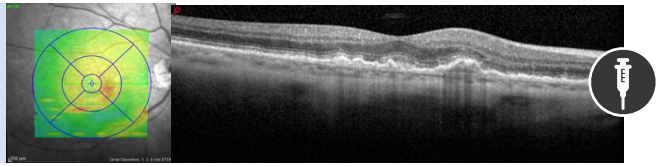
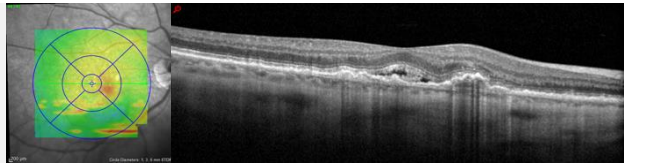
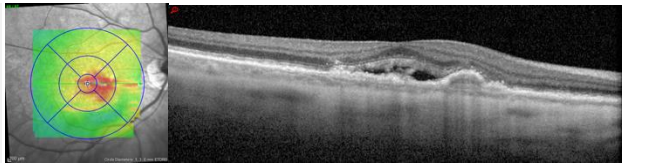
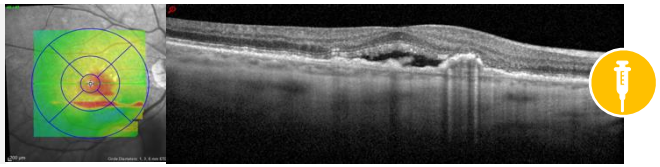
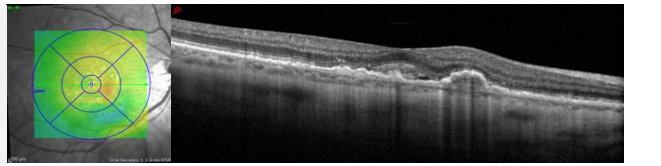
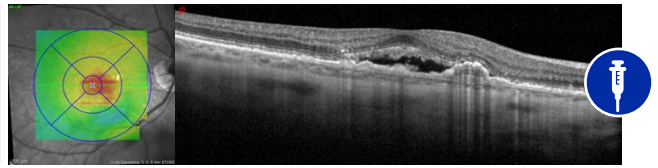
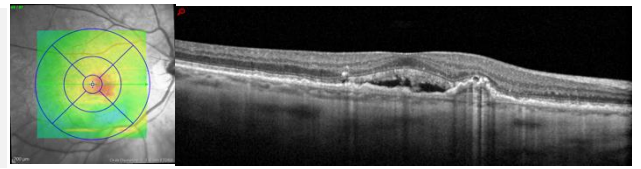
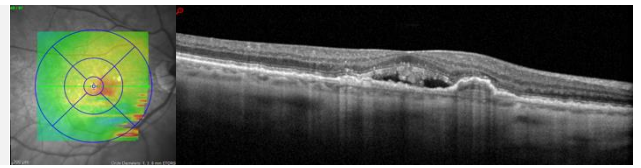
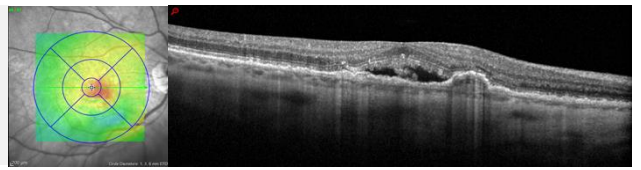
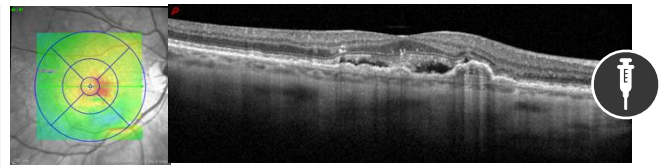
Aflibercept Case 3

Screening Aflibercept (2mg) injection

Study Aflibercept (2 mg) administration

Per-Protocol Rescue Aflibercept (2mg)

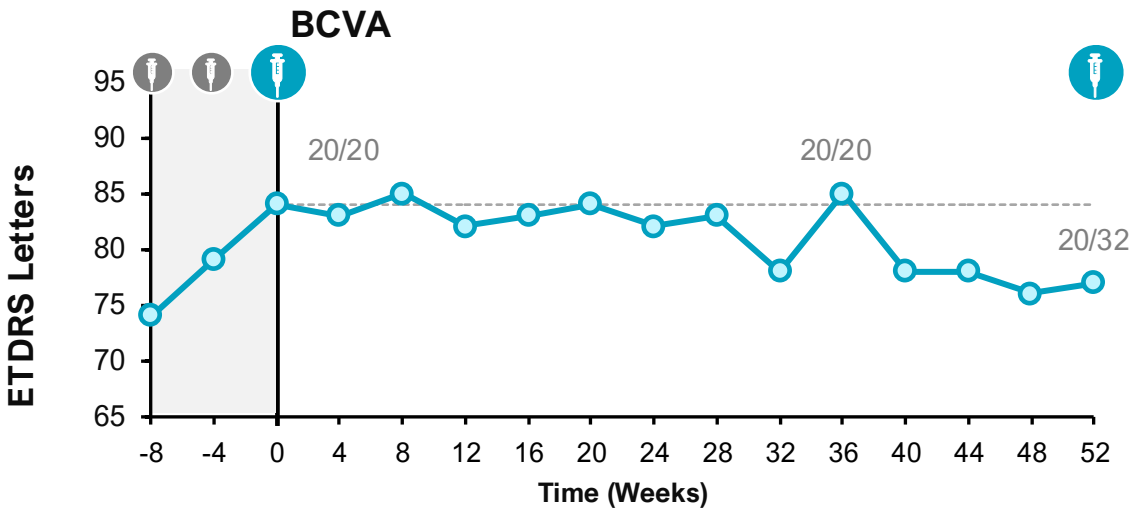
Investigator Discretion Rescue

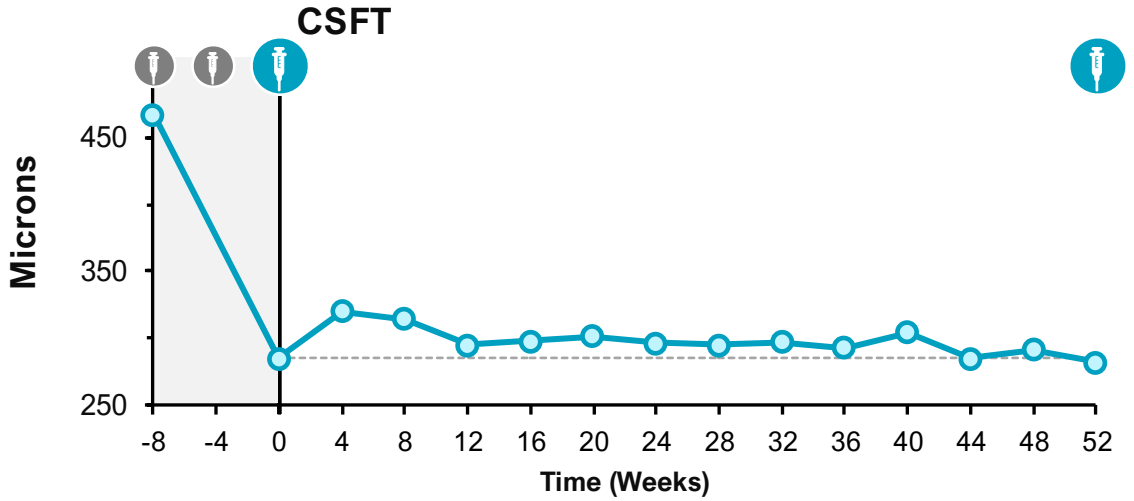
-8 Weeks	**BCVA:** 80 Ltrs **CSFT:** 394 µm	
Baseline	**BCVA:** 89 Ltrs *Snellen: 20/16* **CSFT:** 328 µm	
Week 4	**BCVA (Δ):** 78 (-11) Ltrs **CSFT (Δ):** 349 (+21) µm	
Week 16	**BCVA (Δ):** 83 (-6) Ltrs **CSFT (Δ):** 410 (+82) µm	
Week 20	**BCVA (Δ):** 56 (-33) Ltrs **CSFT (Δ):** 406 (+78) µm	
Week 24	**BCVA (Δ):** 83 (-6) Ltrs **CSFT (Δ):** 332 (+4) µm	
Week 28	**BCVA (Δ):** 82 (-7) Ltrs **CSFT (Δ):** 421 (+93) µm	
Week 36	**BCVA (Δ):** 81(-8) Ltrs *Snellen: 20/25* **CSFT (Δ):** 403 (+75) µm	
Week 40	**BCVA (Δ):** 75 (-14) Ltrs **CSFT (Δ):** 391 (+63) µm	
Week 44	**BCVA (Δ):** 84 (-5) Ltrs **CSFT (Δ):** 400 (+72) µm	
Week 52	**BCVA (Δ):** 79 (-10) Ltrs *Snellen: 20/25* **CSFT (Δ):** 395 (+67) µm	

OCULAR THERAPEUTIX Retina experience redefined™

Subject missed W8/W12/W48 Visits
Case study of one subject; individual results may vary
BCVA, best corrected visual acuity; CSFT, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Ltrs, letters

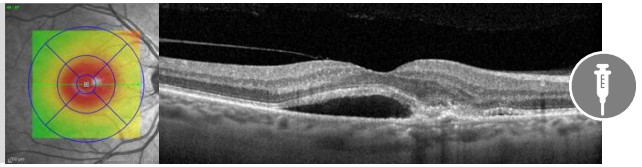
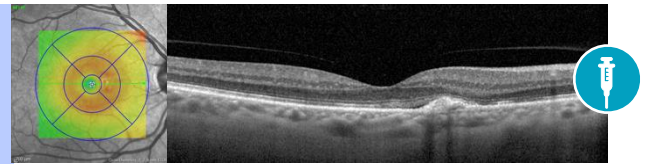
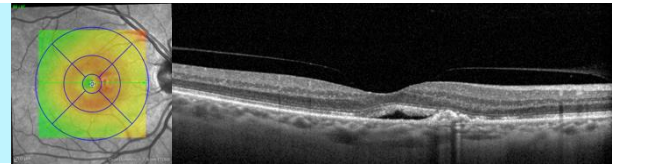
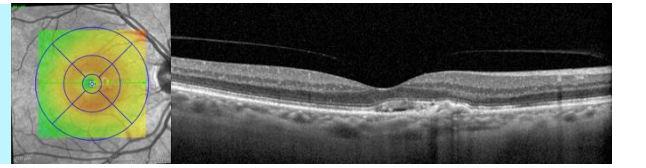
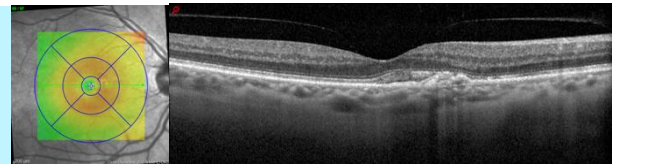
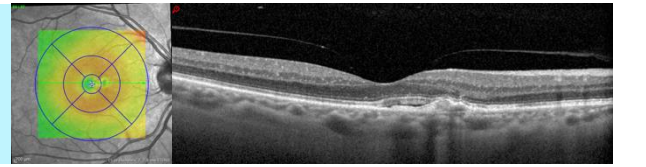
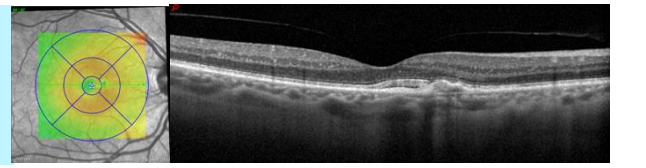
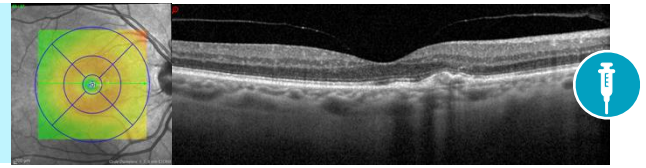
OTX-TKI Case 1





Screening
Aflibercept (2mg)

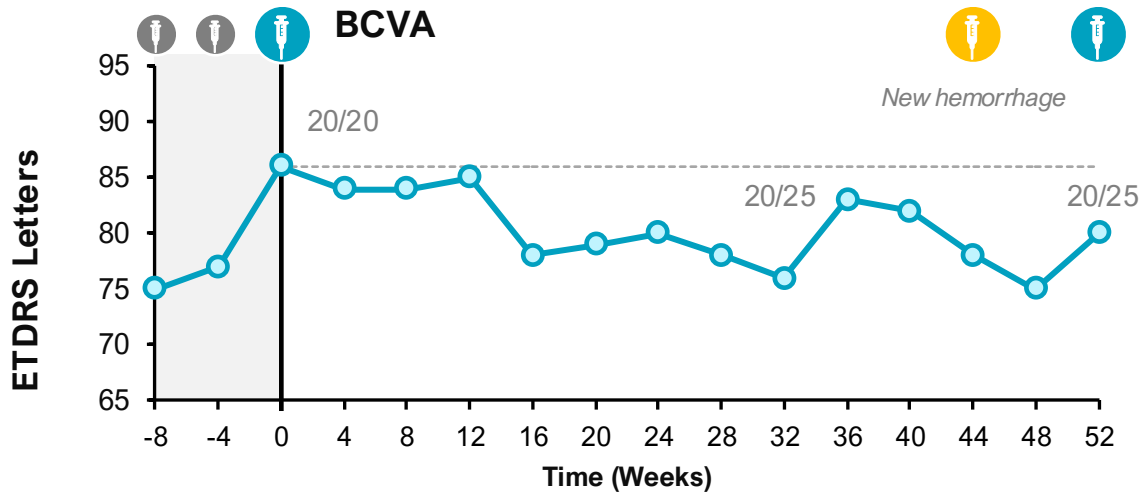
OTX-TKI
(0.45mg)

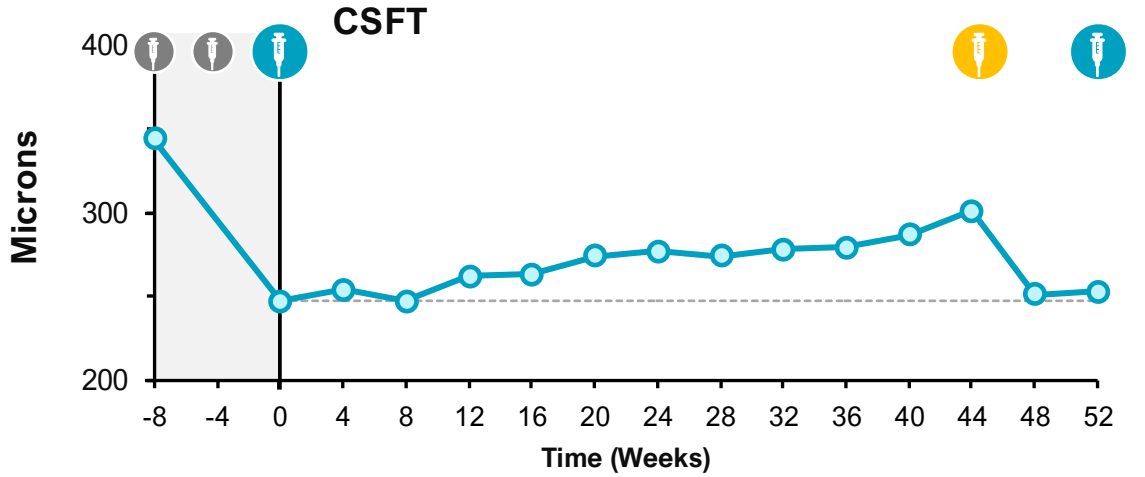
-8 Weeks	**BCVA:** 74 Ltrs (-10) **CSFT:** 467 µm	
Baseline	**BCVA:** 84 Ltrs *Snellen: 20/20* **CSFT:** 285 µm	
Week 4	**BCVA (Δ):** 83 (-1) Ltrs **CSFT (Δ):** 320 (+35) µm	
Week 12	**BCVA (Δ):** 82 (-2) Ltrs **CSFT (Δ):** 295 (+10) µm	
Week 24	**BCVA (Δ):** 82 (-2) Ltrs **CSFT (Δ):** 296 (+11) µm	
Week 36	**BCVA (Δ):** 85 (+1) Ltrs *Snellen: 20/20* **CSFT (Δ):** 293 (+8) µm	
Week 44	**BCVA (Δ):** 78 (-6) Ltrs **CSFT (Δ):** 285 (0) µm	
Week 52	**BCVA (Δ):** 77 (-7) Ltrs *Snellen: 20/32* **CSFT (Δ):** 282 (-3) µm	

OCULAR THERAPEUTIX Retina experience redefined™

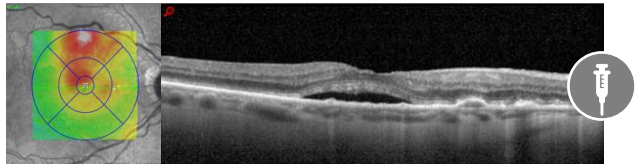
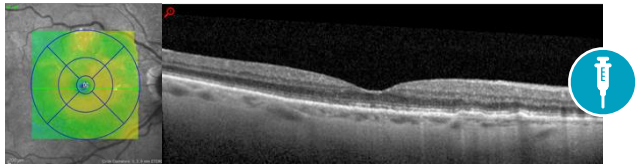
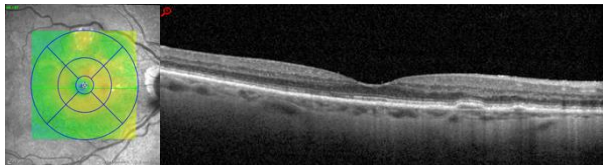
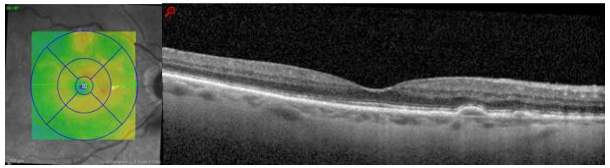
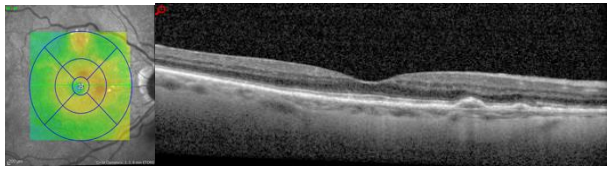
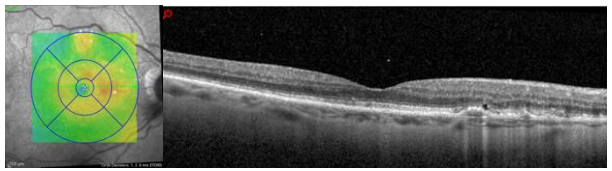
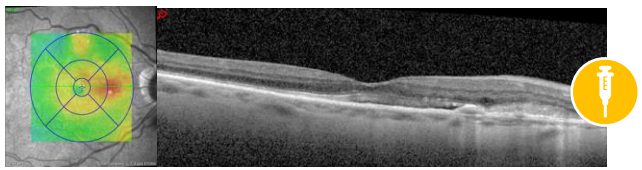
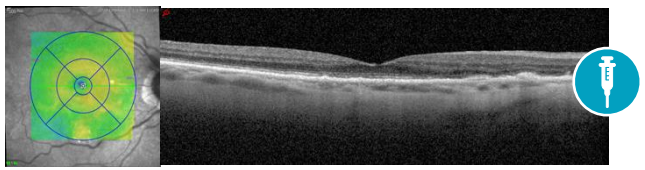
Case study of one subject; individual results may vary
BCVA, best corrected visual acuity; CSFT, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Ltrs, letters

OTX-TKI Case 2





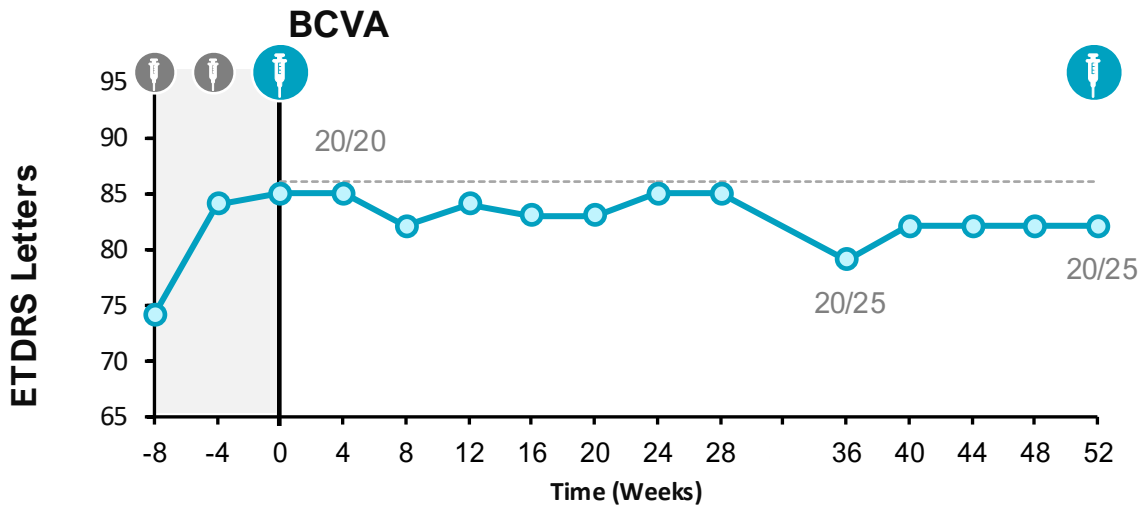
Screening Aflibercept (2mg)
OTX-TKI (0.45mg)
Per-Protocol Rescue Aflibercept (2mg)

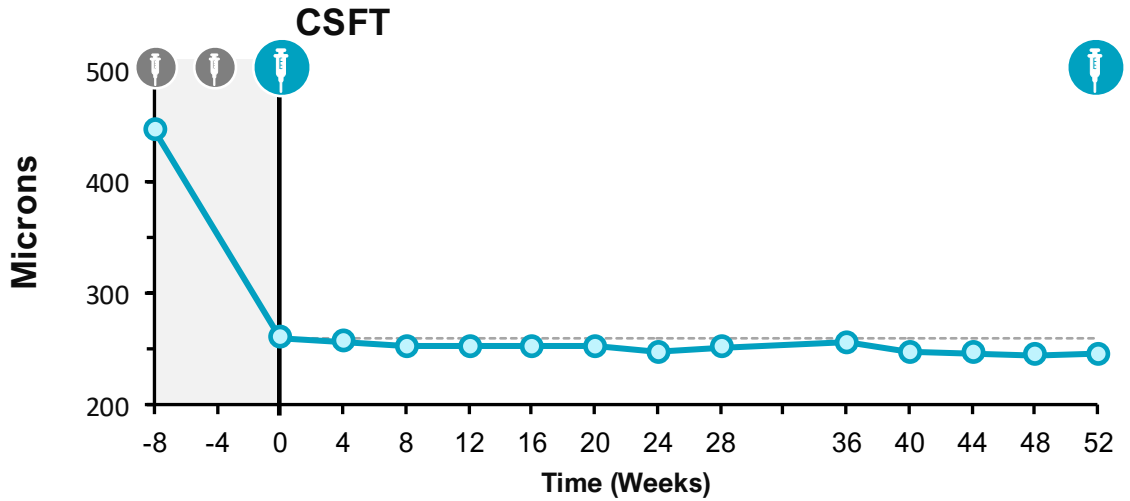
-8 Weeks	**BCVA:** 75 Ltrs **CSFT:** 344 µm	
Baseline	**BCVA:** 86 Ltrs *Snellen: 20/20* **CSFT:** 247 µm	
Week 4	**BCVA (Δ):** 84 (-2) Ltrs **CSFT (Δ):** 254 (+7) µm	
Week 12	**BCVA (Δ):** 85 (-1) Ltrs **CSFT (Δ):** 262 (+15) µm	
Week 24	**BCVA (Δ):** 80 (-6) Ltrs **CSFT (Δ):** 277 (+30) µm	
Week 36	**BCVA (Δ):** 83 (-3) Ltrs *Snellen: 20/25* **CSFT (Δ):** 279 (+32) µm	
Week 44	**BCVA (Δ):** 78 (-8) Ltrs **CSFT (Δ):** 301 (+54) µm	
Week 52	**BCVA (Δ):** 80 (-6) Ltrs *Snellen: 20/25* **CSFT (Δ):** 253 (+6) µm	

OCULAR THERAPEUTIX Retina experience redefined™

Case study of one subject; individual results may vary
BCVA, best corrected visual acuity; CSFT, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Ltrs, letters

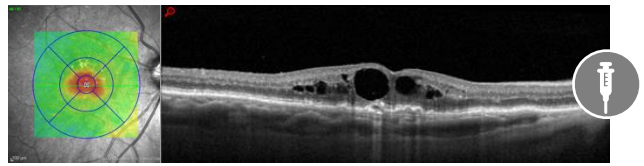
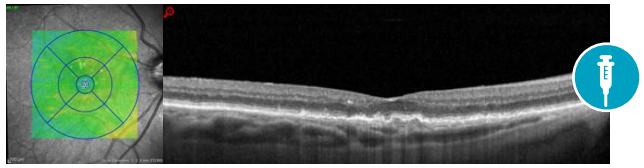
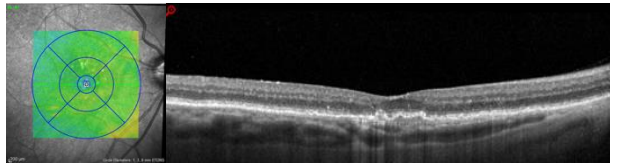
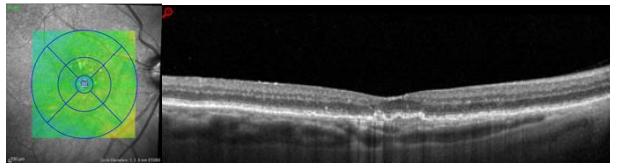
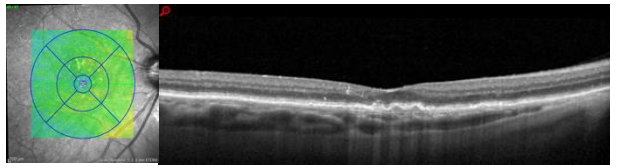
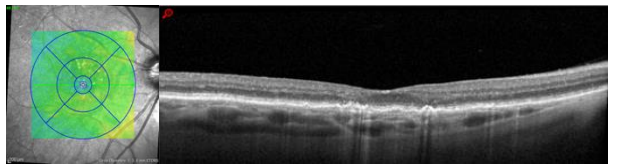
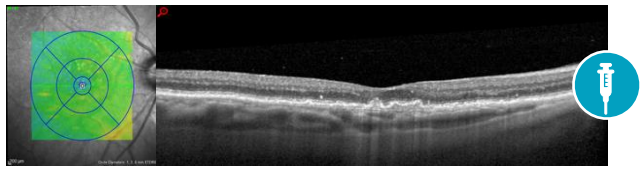
OTX-TKI Case 3





Screening
Aflibercept (2mg)

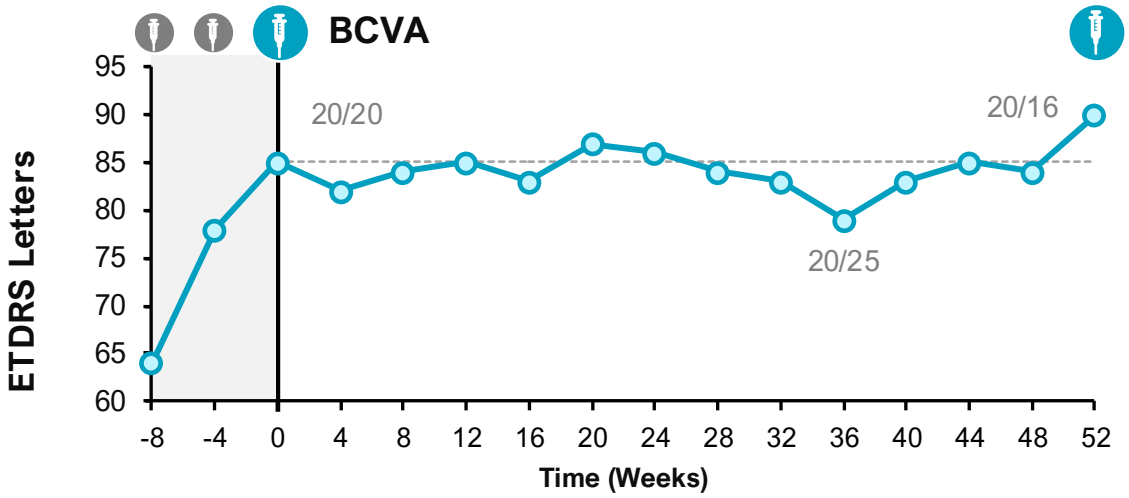
OTX-TKI
(0.45mg)

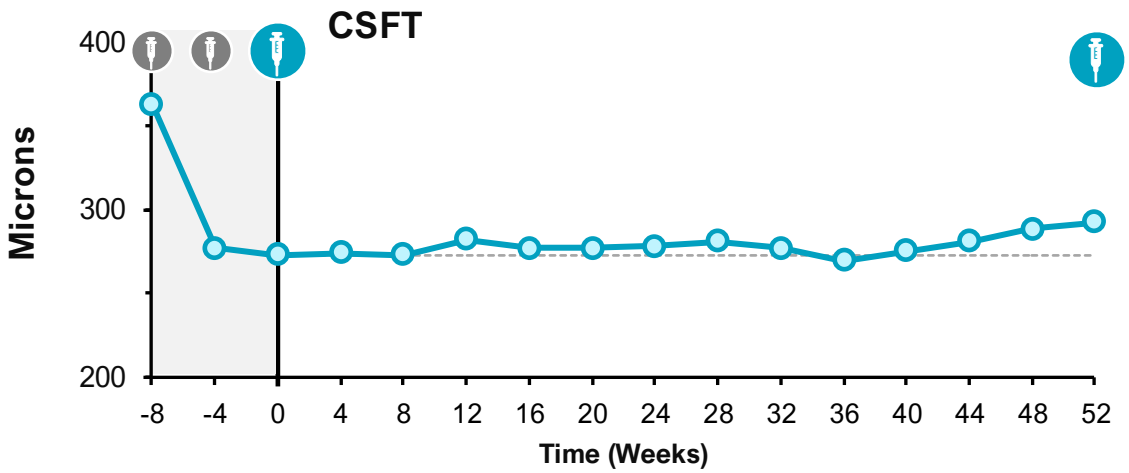
-8 Weeks	**BCVA:** 74 Ltrs **CSFT:** 448 µm	
Baseline	**BCVA:** 85 Ltrs *Snellen: 20/20* **CSFT:** 261 µm	
Week 4	**BCVA (Δ):** 85 (0) Ltrs **CSFT (Δ):** 257 (-4) µm	
Week 12	**BCVA (Δ):** 84 (-1) Ltrs **CSFT (Δ):** 253 (-8) µm	
Week 24	**BCVA (Δ):** 85 (0) Ltrs **CSFT (Δ):** 248 (-13) µm	
Week 36	**BCVA (Δ):** 79 (-6) Ltrs *Snellen: 20/25* **CSFT (Δ):** 256 (-5) µm	
Week 52	**BCVA (Δ):** 82 (-3) Ltrs *Snellen: 20/25* **CSFT (Δ):** 246 (-15) µm	

OCULAR THERAPEUTIX Retina experience redefined™

Subject missed Week 32 visit
Case study of one subject; individual results may vary
BCVA, best corrected visual acuity; CSFT, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Ltrs, letters

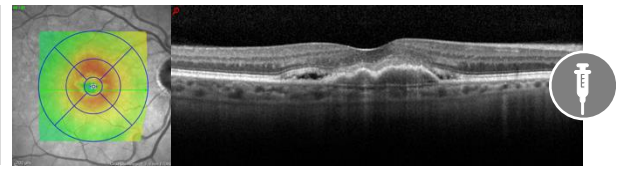
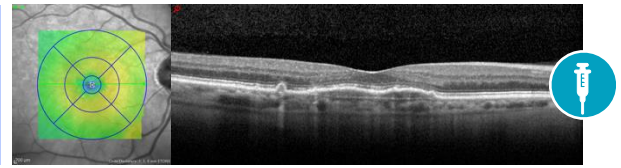
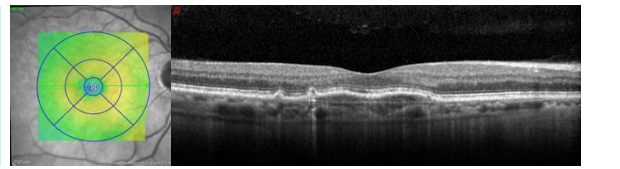
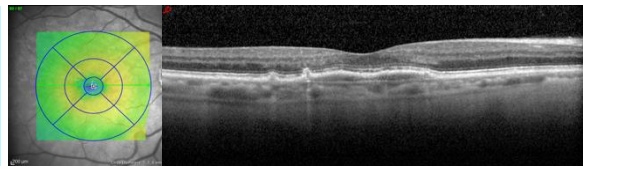
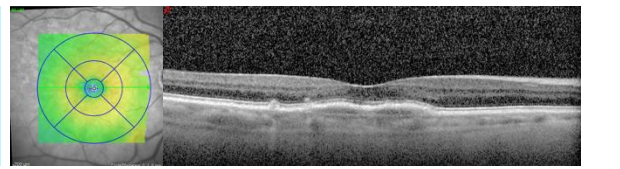
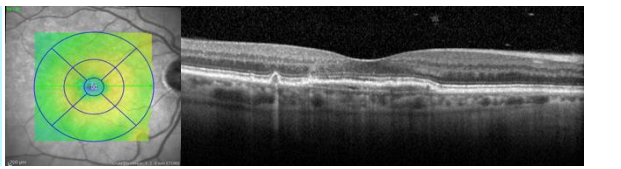
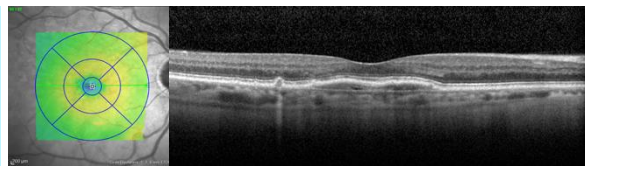
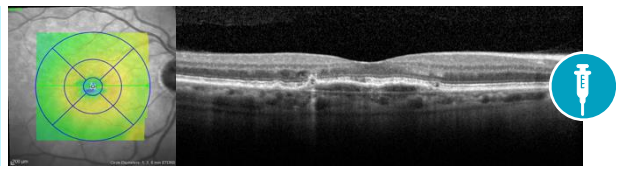
OTX-TKI Case 4





Screening Aflibercept (2mg)

OTX-TKI (0.45mg)

-8 Weeks	**BCVA:** 64 Ltrs **CSFT:** 363 µm	
Baseline	**BCVA:** 85 Ltrs *Snellen: 20/20* **CSFT:** 273 µm	
Week 4	**BCVA (Δ):** 82 (-3) Ltrs **CSFT (Δ):** 274 (+1) µm	
Week 16	**BCVA (Δ):** 83 (-2) Ltrs **CSFT (Δ):** 277 (+4) µm	
Week 24	**BCVA (Δ):** 86 (+1) Ltrs **CSFT (Δ):** 278 (+5) µm	
Week 36	**BCVA (Δ):** 79 (-6) Ltrs *Snellen: 20/26* **CSFT (Δ):** 269 (-4) µm	
Week 44	**BCVA (Δ):** 85 (0) Ltrs **CSFT (Δ):** 281 (+8) µm	
Week 52	**BCVA (Δ):** 90 (+5) Ltrs *Snellen: 20/16* **CSFT (Δ):** 292 (+19) µm	

OCULAR THERAPEUTIX Retina experience redefined™

Case study of one subject; individual results may vary
BCVA, best corrected visual acuity; CSFT, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Ltrs, letters

Key Insights

Interpreting the Data

Adnan Tufail, MBBS, MD

OCULAR THERAPEUTIX Retina experience redefined

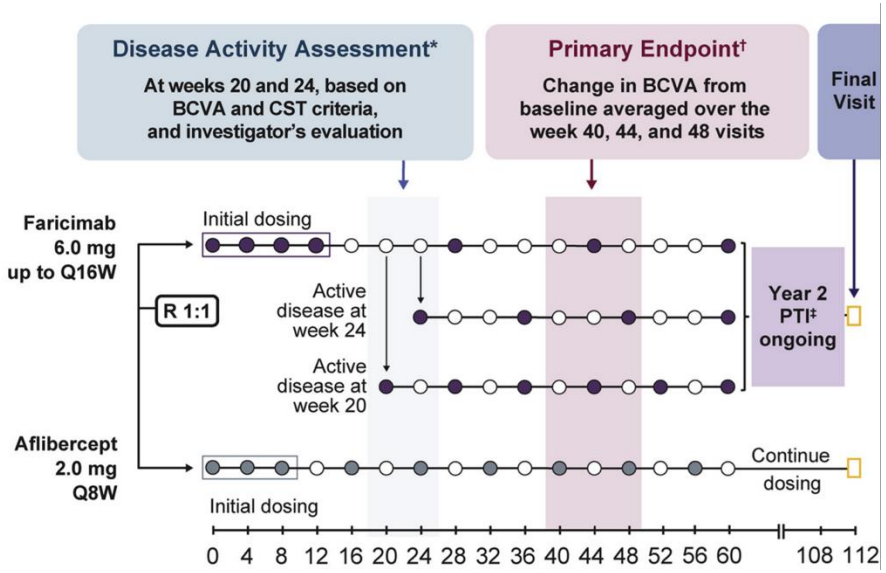
What is the Rationale for the SOL-1 Trial Design?

Clinical trials aimed to get **regulatory approval**

Evidence gap: translating from RCT to real world clinical management

Limitation of recent clinical trial designs

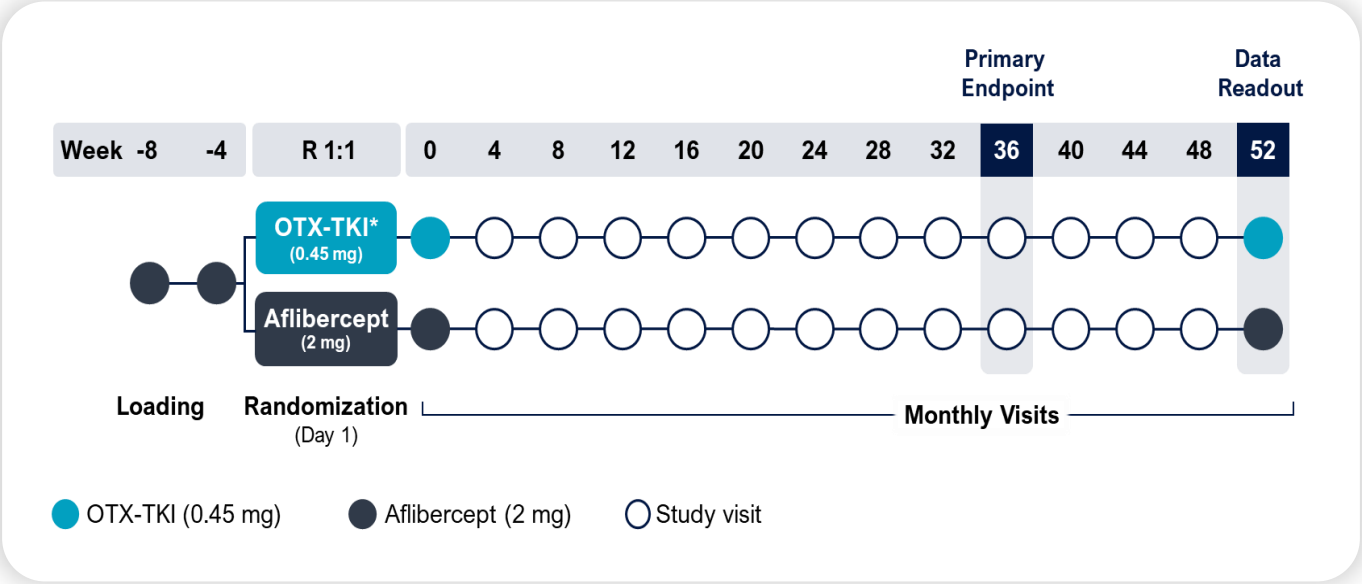
- Suggest extended interval in subgroups
- Investigational drug subgroup extended but not active control
- Cannot claim superior durability, only that a subgroup can mostly remain retreatment free for “x” amount of time
- Non-inferiority
- Results in step therapy



Disruptive Trial Design – Demonstrates Superiority

Only way to show superiority of duration in a meaningful time frame and be compliant with FDA guidance

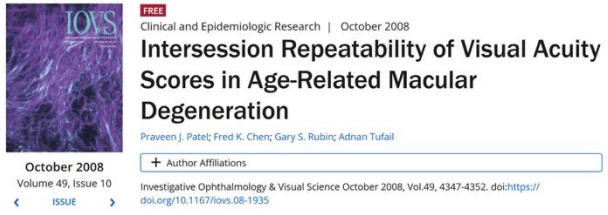
- Proportion of 15-letter events
- Both arms treated identically
- Efficient trial design aligned with FDA with a Special Protocol Agreement (SPA)
- Potentially negates the requirement of step therapy



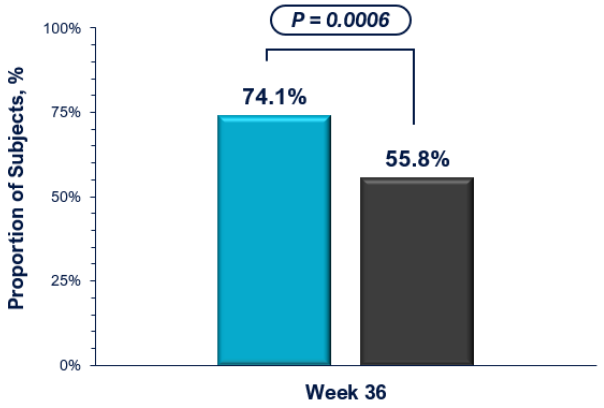
OCULAR THERAPEUTIX Retina experience redefined™

Why was 15-Letter Change Chosen as the Endpoint?

Threshold	Letters	Lines	Clinical Meaning	Regulatory Context
Minimum detectable (good vision)	5	1	Borderline real change; triggers closer follow-up	FDA non-inferiority margin (4.5) in some trials
Minimum clinically important	10	2	Real, patient-perceptible improvement	EMA acceptable endpoint for gains
Moderate loss or gain	**15**	**3**	**Doubling of visual angle; moderate functional impact**	**FDA primary endpoint for wet AMD**
Severe loss	30	6	Quadrupling of visual angle; severe functional impairment	Regulatory threshold for severe vision loss



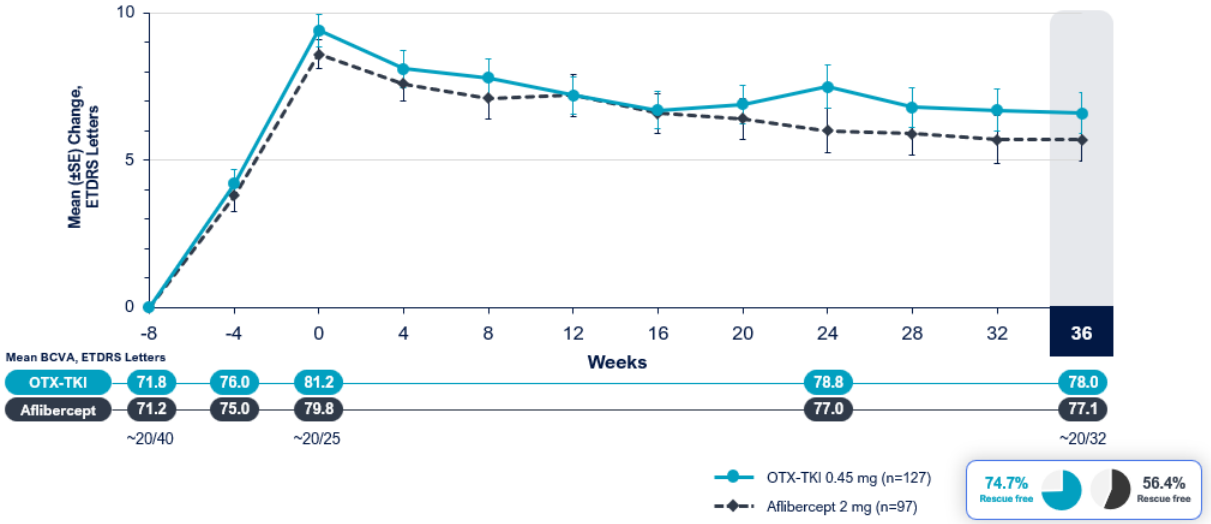
Primary Endpoint: Proportion of Subjects Who Maintain Visual Acuity



OCULAR THERAPEUTIX Retina experience redefined™

SOL-1: Treatment Arms Had Excellent Mean Vision at Baseline
(~70 letters at Screening; – ~80 letters at Baseline)

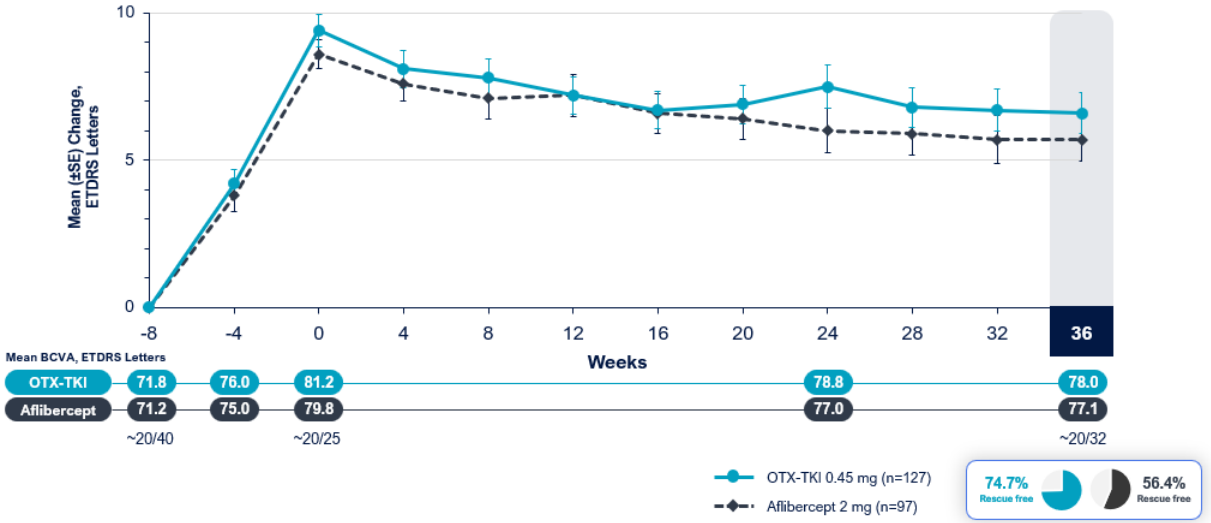
Anti-VEGF trials to date associated with mean VA improvement but low baseline vision (~53-60 letters)



Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration
VIEW 1 and VIEW 2 Study Groups et al. Ophthalmology, Volume 119, Issue 12, 2537- 2548

SOL-1: Treatment Arms Had Excellent Mean Vision at Baseline
(~70 letters at Screening; – ~80 letters at Baseline)

Anti-VEGF trials to date associated with mean VA improvement but low baseline vision (~53-60 letters)



Trial	Arm	Baseline BCVA	Baseline BCVA SD
MARINA	Sham	53.6	14.1
	0.3mg ranibizumab	53.1	12.9
	0.5mg ranibizumab	53.7	12.8
VIEW 1 & 2	Ranibizumab Q4w	53.9	13.4
	Aflibercept 2mg Q4w	54.0	13.6
	Aflibercept 2mg Q8w	53.6	13.5
TENAYA	Faricimab	61.3	12.5
	Aflibercept	61.5	12.9
LUCERNE	Faricimab	58.7	14.0
	Aflibercept	58.9	13.3
PULSAR	Aflibercept 2mg Q8w	58.9	14.0
	Aflibercept HD Q12w	59.9	13.4
	Aflibercept HD Q16w	60.0	12.4

OCULAR THERAPEUTIX Retina experience redefined™

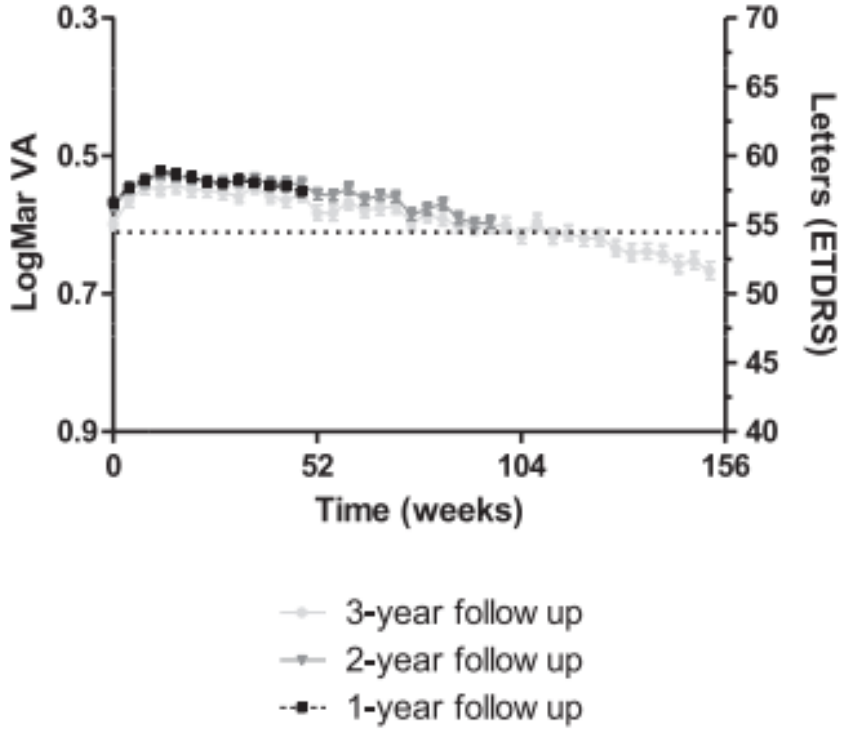
Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration
VIEW 1 and VIEW 2 Study Groups et al. Ophthalmology, Volume 119, Issue 12, 2537- 2548

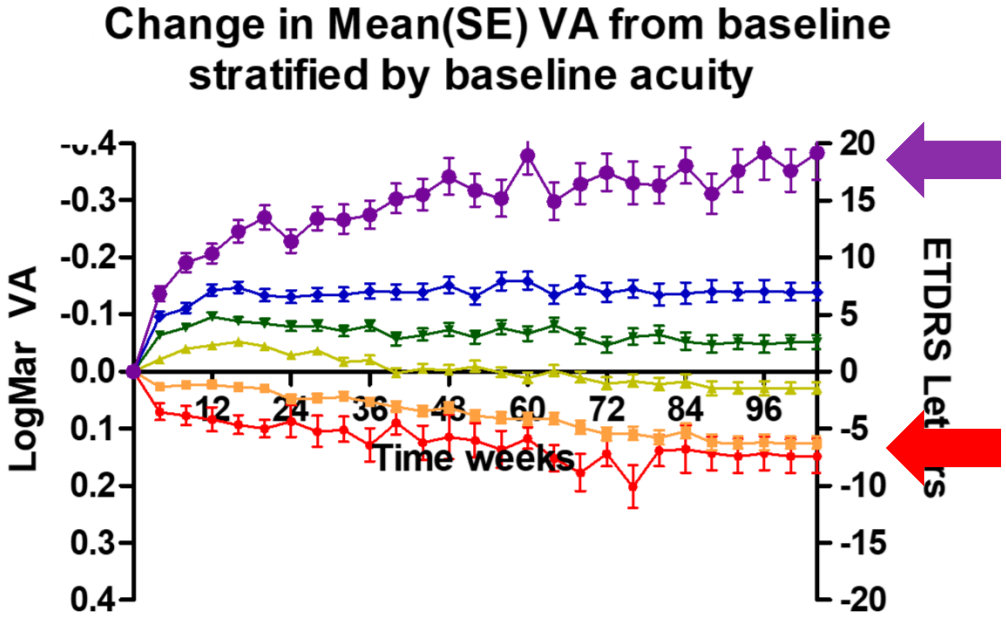
Eyes with Excellent Baseline Acuity Decline on Average in RWE Studies

The Neovascular Age-Related Macular Degeneration Database: Multicenter Study of 92 976 Ranibizumab Injections

Report 1: Visual Acuity

*Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group**

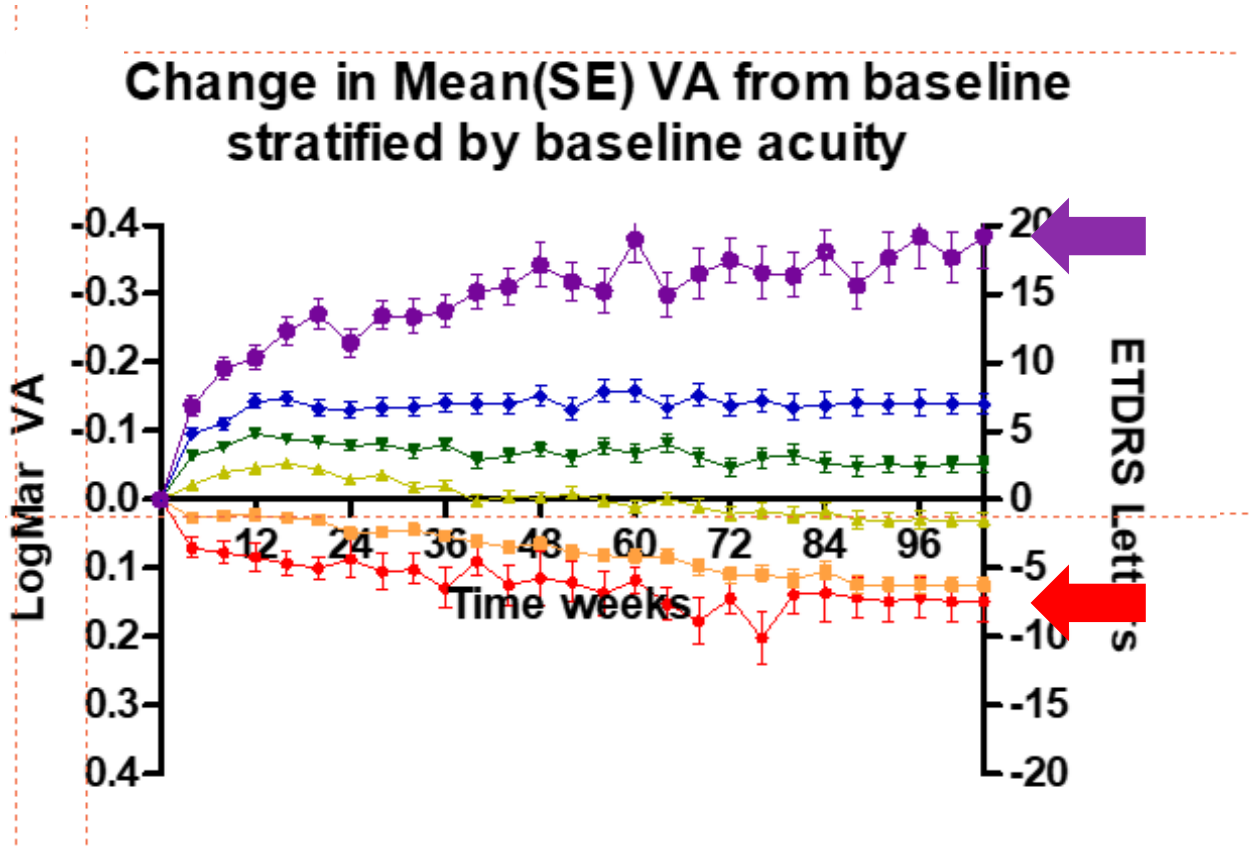


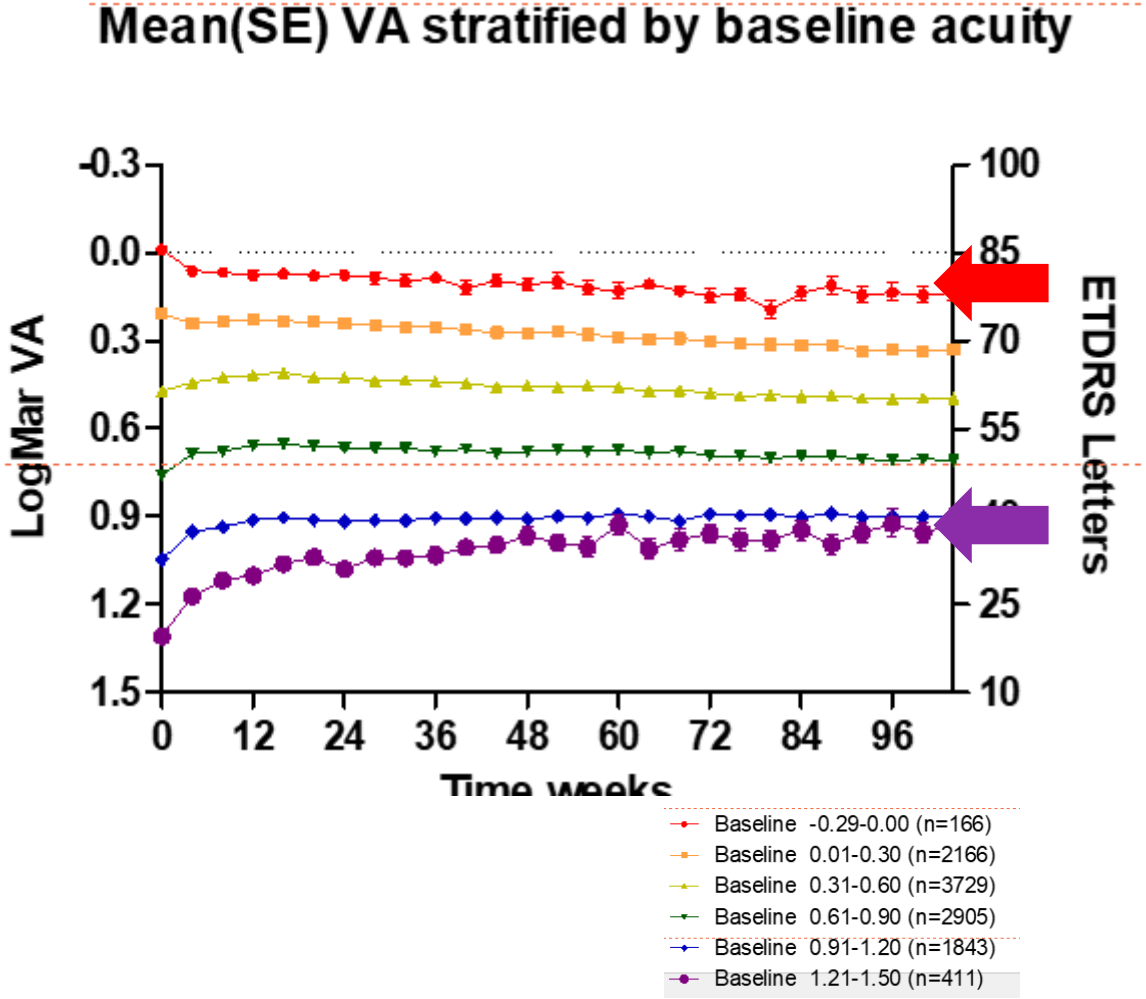


Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group. The neovascular age-related macular degeneration database: multicenter study of 92 976 ranibizumab injections: report 1: visual acuity. Ophthalmology. 2014;121(5):1092-1101.

RWE: Real world evidence

Visual Acuity State and NOT Change is what is Most Meaningful to Patients





Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group. The neovascular age-related macular degeneration database: multicenter study of 92 976 ranibizumab injections: report 1: visual acuity. Ophthalmology. 2014;121(5):1092-1101.

SE, standard error; VA, visual acuity

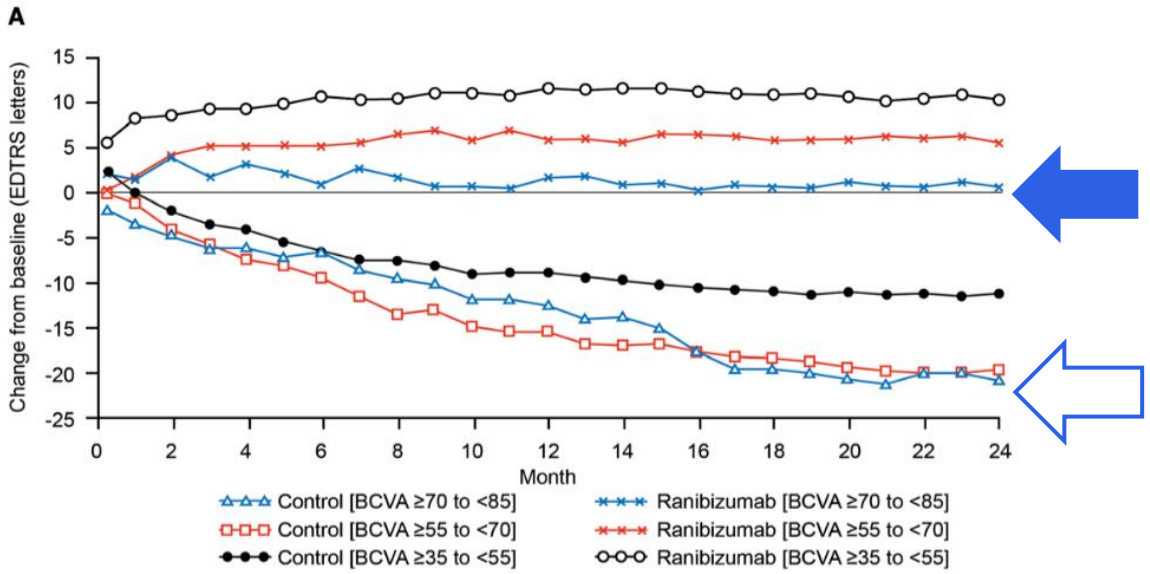
Does Reduced Potential for Visual Acuity Gain Occur in Pivotal Trials?

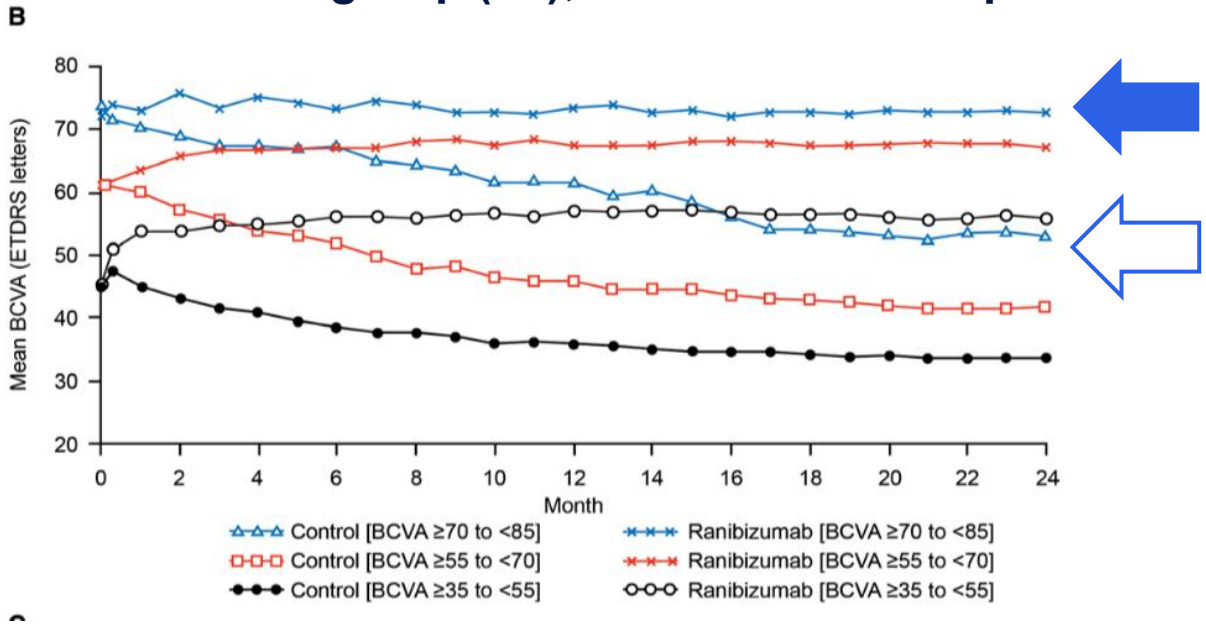
Sub-Analysis of ANCHOR and MARINA

Visual benefit versus visual gain: what is the effect of baseline covariants in the treatment arm relative to the control arm? A pooled analysis of ANCHOR and MARINA

Adnan Tufail [1], Philippe Margaron,[2] Tadhg Guerin,[3] Michael Larsen[4]

In Good VA group (72), 4 letter loss from peak m6





OCULAR THERAPEUTIX Retina experience redefined™

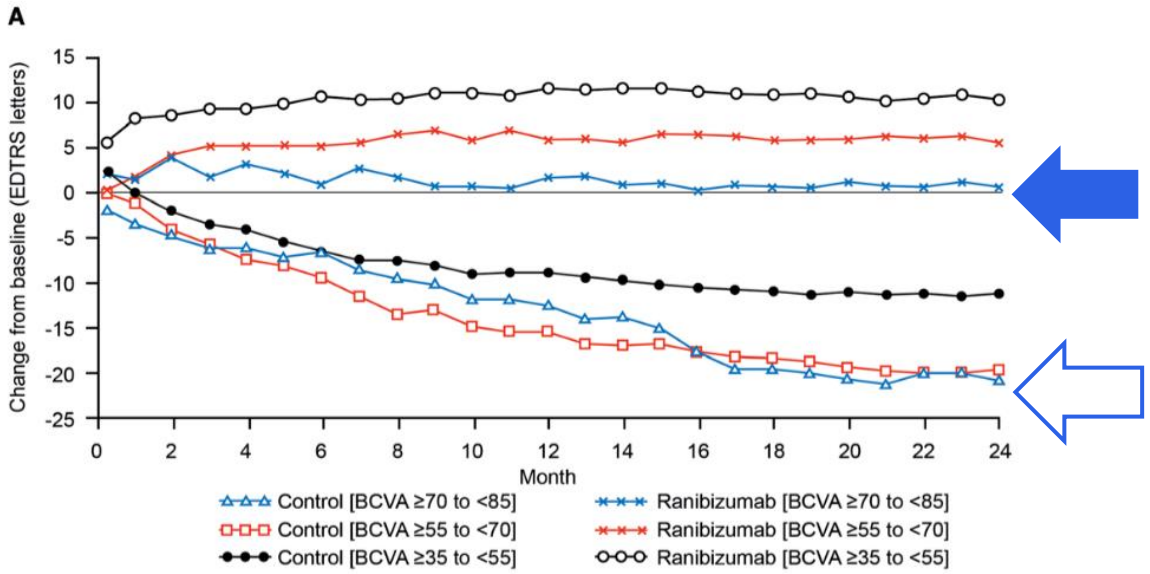
Tufail A, et al.. *Br J Ophthalmol*. 2020;104(5):672-677.

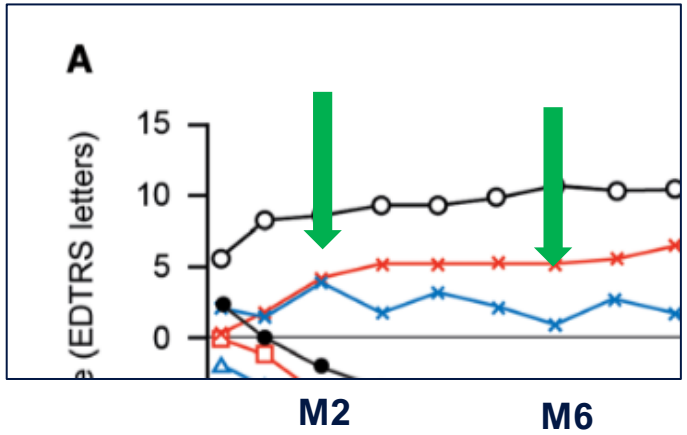
Does Reduced Potential for Visual Acuity Gain Occur in Pivotal Trials?

Sub-Analysis of ANCHOR and MARINA

Visual benefit versus visual gain: what is the effect of baseline covariants in the treatment arm relative to the control arm? A pooled analysis of ANCHOR and MARINA

Adnan Tufail [1], Philippe Margaron,[2] Tadhg Guerin,[3] Michael Larsen[4]





Tufail A, et al.. *Br J Ophthalmol*. 2020;104(5):672-677.

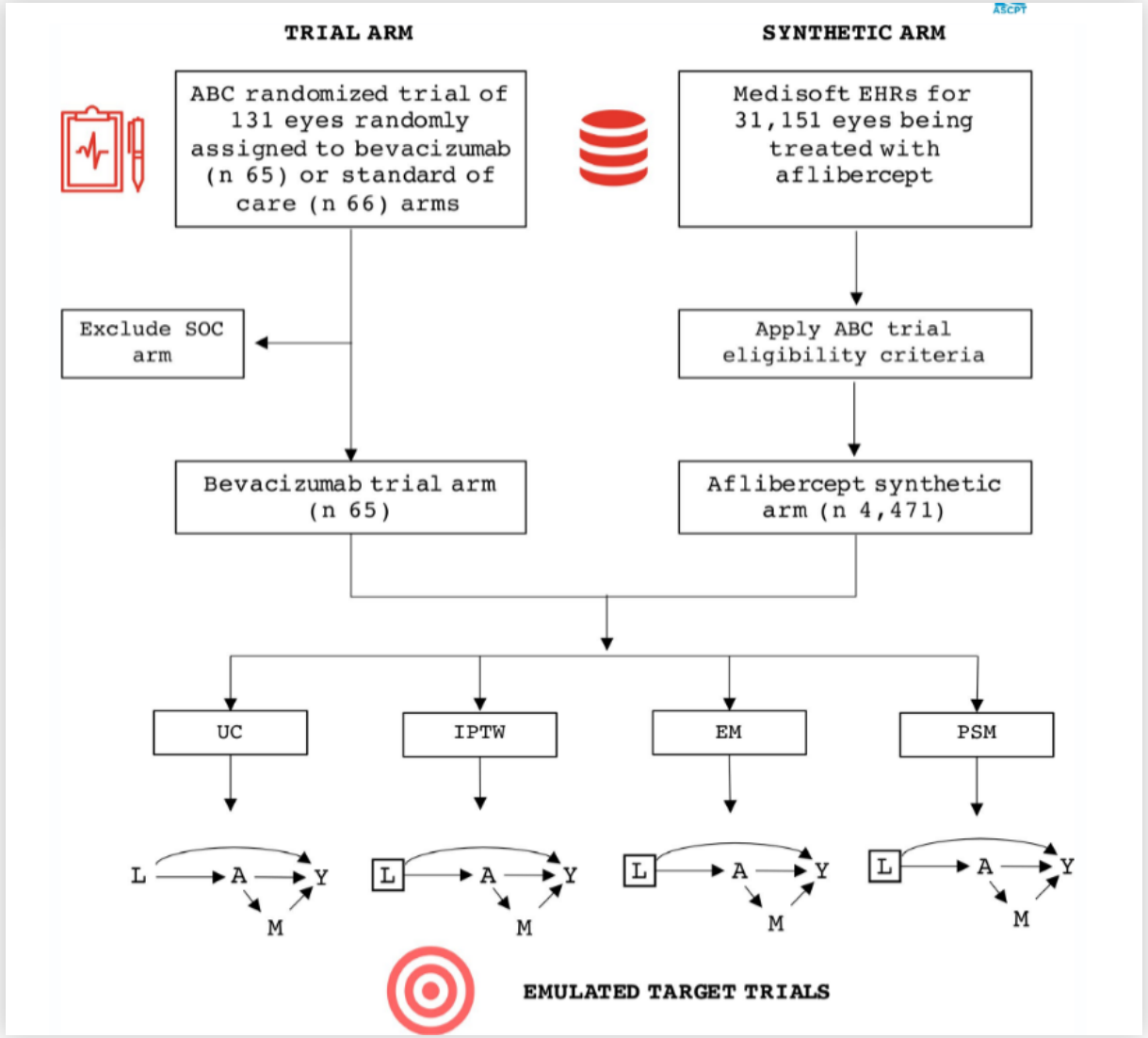
Received: 20 August 2020 | Revised: 4 December 2020 | Accepted: 21 December 2020

DOI: 10.1111/cts.12974

ARTICLE

Contextualizing single-arm trials with real-world data: An emulated target trial comparing therapies for neovascular age-related macular degeneration

Darren S. Thomas[1] | Aaron Y. Lee[2] | Philipp L. Müller[3,4,5] | Roy Schwartz[4,5,6] | Abraham Olvera-Barrios[4,5] | Alasdair N. Warwick[4,7] | Praven J. Patel[6] | Tjebo F.C. Heeren[4,5] | Catherine Egan[4,5,6] | Paul Taylor[1] | Adnan Tufail[4,5,6] | on behalf of the UK AMD EMR Users Group[7]



What does a real-world SOL-1 'eligible' emulated anti-VEGF-treated population with good baseline VA look like (IRIS Registry)?

Step	Criteria	Patients (N)	Patients (%)
1	A first anti-VEGF injection (Injection 1, Week -8) in index period (no prior injection)	866,981	100.00%
2	First injection between January 1, 2017, and March 31, 2024; second injection 4 weeks (± 10 days) after Index date 1; third injection 8 weeks (± 10 days) after Index date 1	274,632	31.68%
3	Diagnosis of nAMD on or after January 1, 2016, to date of Injection 1	263,272	30.37%
4	Screening VA ≥ 54 ETDRS letters within 60 days prior to Index date 1, and either of the following two - Baseline VA ≥ 84 letters - Baseline VA ≥ 10 letters better than Screening BDVA	43,805	5.05%
5	Screening CSFT ≤ 500 µm within 60 days prior to Index date 1, and Baseline CSFT ≤ 350 µm	47,779	5.51%
6	Exclude any cataract surgery in the study eye within 6 months prior to Injection 1	7,058	0.81%
7	Age ≥ 50 on or after January 1, 2016, to date of Injection 1	6,178	0.71%

OCULAR THERAPEUTIX Retina experience redefined™

VEGF, vascular endothelial growth factor; nAMD, neovascular age-related macular degeneration; BDVA, best documented visual acuity; ETDRS, early treatment diabetic retinopathy study; CSFT, central subfield thickness.
Data on File, Ocular Therapeutix

Baseline Characteristics

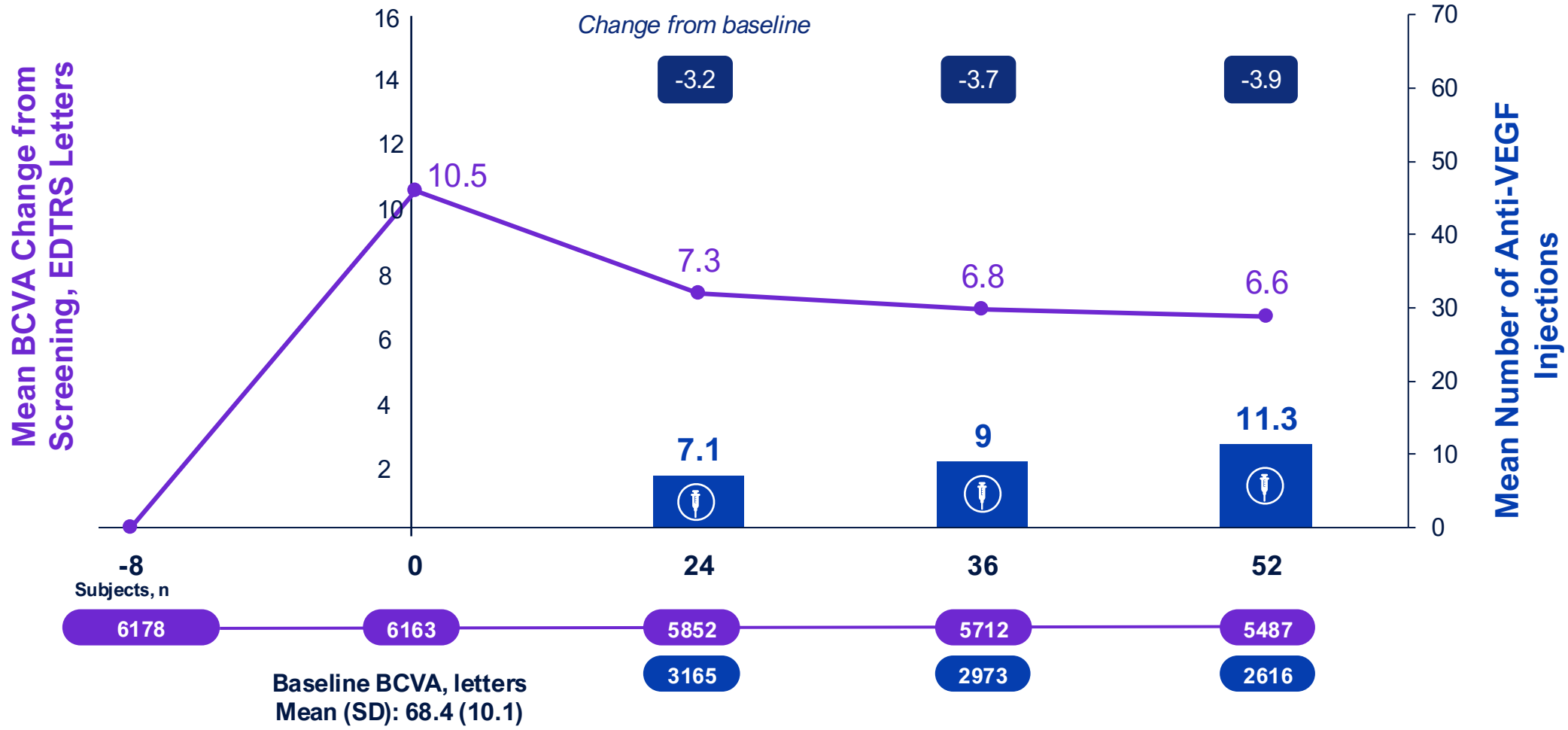
	SOL-1 OTX-TKI N = 172	RWE SOL-1 Emulated N = 6178
Age, years, mean (SD)	75.7 (8.3)	76.6 (7.8)
Sex, female, n (%)	103 (59.9)	3755 (60.8)
VA, ETDRS letters, mean (SD)		
Screening	70.9 (11.3)	68.4 (10.1)
Baseline	80.8 (7.6)	79.0 (6.1)
CSFT, µm, mean (SD)		
Screening	303.6 (72.5)	312.8 (71.3)
Baseline	219.3 (37.1)	257.4 (45.9)

OCULAR THERAPEUTIX Retina experience redefined™

Cohorts 1 and 2 are not mutually exclusive.
SD, standard deviation; VA; best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; CSFT, central subfield thickness.
Data on File, Ocular Therapeutix

SOL-1 ‘Eligible’ Emulated RWE Population

Mean Visual Acuity Change From Screening with Standard of Care Dosing

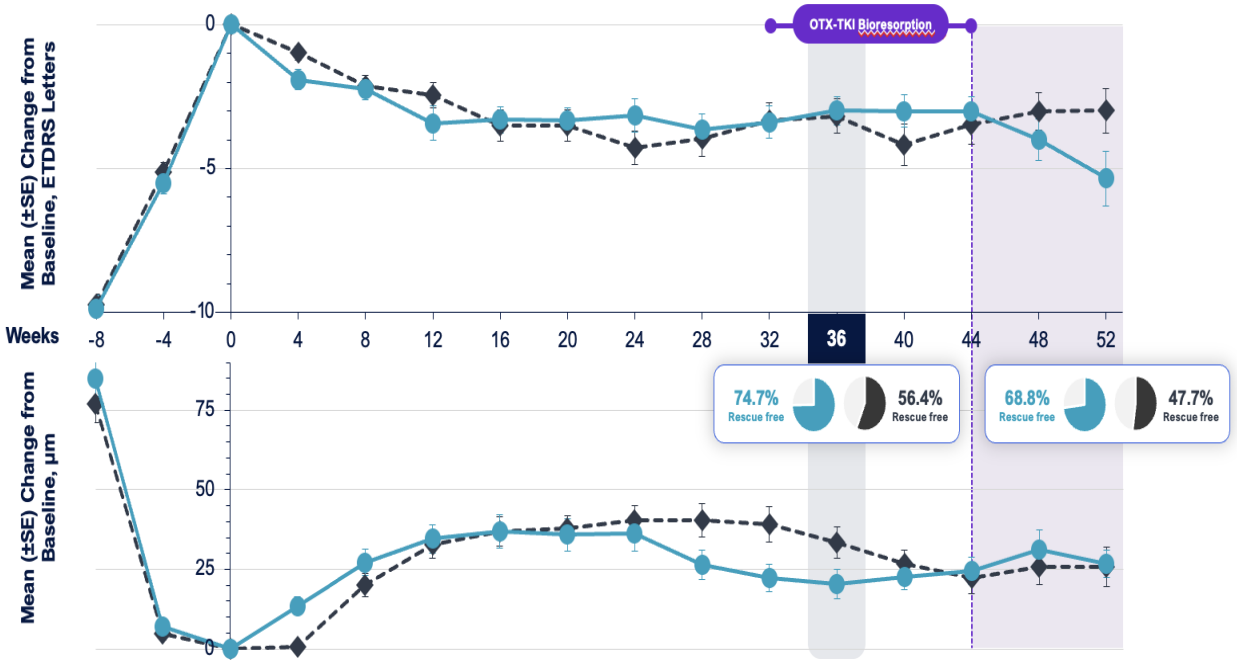


OCULAR THERAPEUTIX Retina experience redefined™

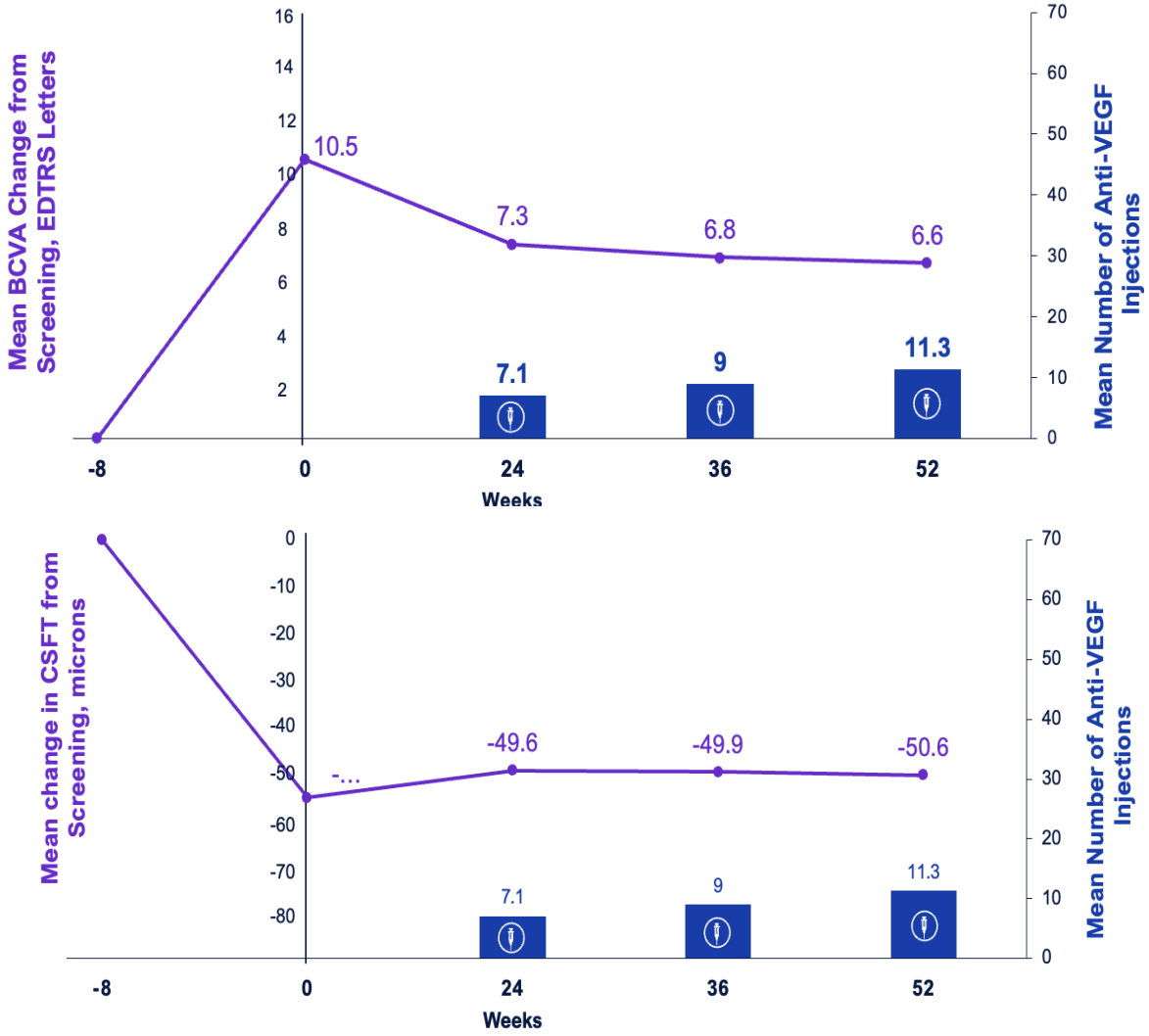
Screening defined as ~60 to 0 days relative to Injection 3.
Data on File. Ocular Therapeutix.
VEGF, vascular endothelial growth factor; SD, standard deviation; real-world evidence.

How Does this Align with Previous Studies?

SOL-1



IRIS Registry – SOL-1 Emulated



OCULAR THERAPEUTIX Retina experience redefined™

Data on File, Ocular Therapeutix

SOL: OTX-TKI Phase 3 Clinical Program in nAMD

Evaluating the efficacy, durability and safety of OTX-TKI in nAMD

Registrational Trials

SOL-1

Phase 3
Superiority Trial

Durability of a single OTX-TKI injection

SOL-R

Phase 3
Non-Inferiority Trial

Repeat dosing every 6 months

Complementary studies designed to provide a comprehensive characterization of OTX-TKI across patient populations

Extension Study

SOL-X

Open-Label Extension

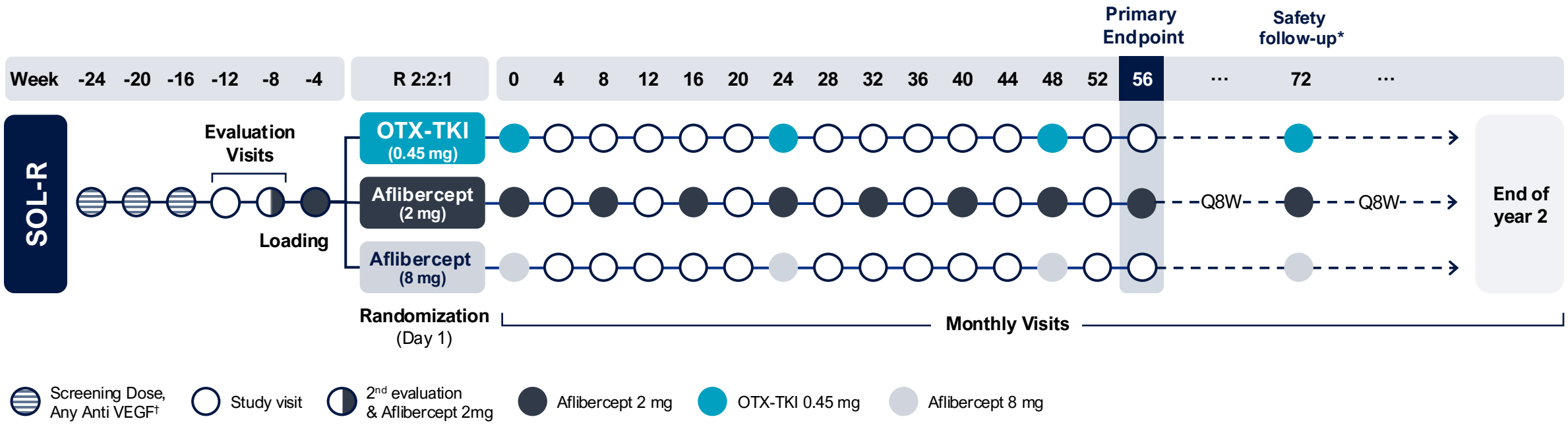
Long-term safety and disease modifying potential of continuous VEGF suppression

Eligible patients who complete year 2 visit in SOL-1 or SOL-R

OCULAR THERAPEUTIX Retina experience redefined

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor

SOL-R: Phase 3 nAMD Study Design



OCULAR THERAPEUTIX Retina experience redefined™

nAMD, neovascular age-related macular degeneration;

Further Insights Utilizing SOL-R Rescue Criteria to the SOL Program

SOL-R Rescue Treatment Criteria

BCVA loss >5 ETDRS letters from best recorded BCVA **AND**
≥75 µm increase in CSFT from lowest measure

OR

New macular hemorrhage that would likely lead to irreversible vision loss if left untreated in the opinion of the investigator after discussion with Medical Monitor

Proportion of subjects receiving rescue treatment in **SOL-1** (OTX-TKI) to Week 24	**19.4%**	→	Estimated proportion of subjects meeting **SOL-R** rescue criteria (OTX-TKI) to week 24	**22.9%**

OCULAR THERAPEUTIX Retina experience redefined™

Key Insights

OTX-TKI SHOWS SUPERIOR

Durability
(rescue-free rates)

Vision Outcomes

Anatomic Control

Future studies should consider superiority trial design

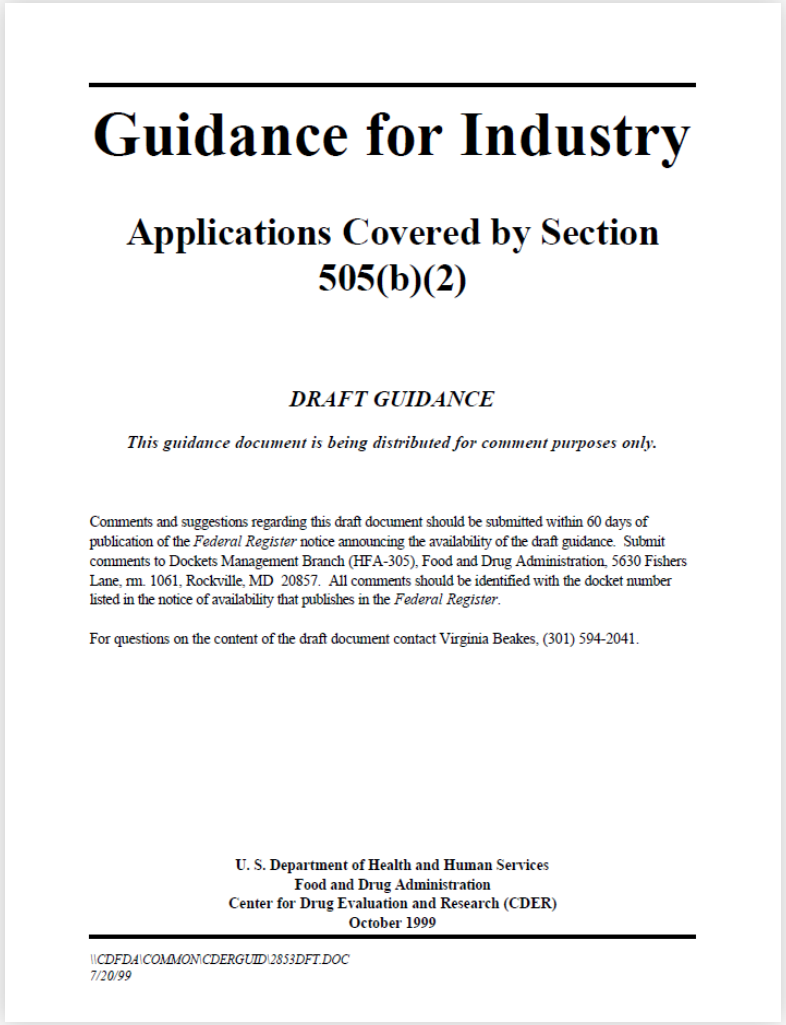
OCULAR THERAPEUTIX Retina experience redefined™

Defined Regulatory Strategy

Jeffrey S. Heier, MD

OCULAR THERAPEUTIX Retina experience redefined

Next Steps: 505(b)(2)



Guidance for Industry

Applications Covered by Section 505(b)(2)

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of the draft document contact Virginia Beakes, (301) 594-2041.

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 1999

\\CDFDA\COMMON\CDERGUID\2853DFT.DOC
7/20/99

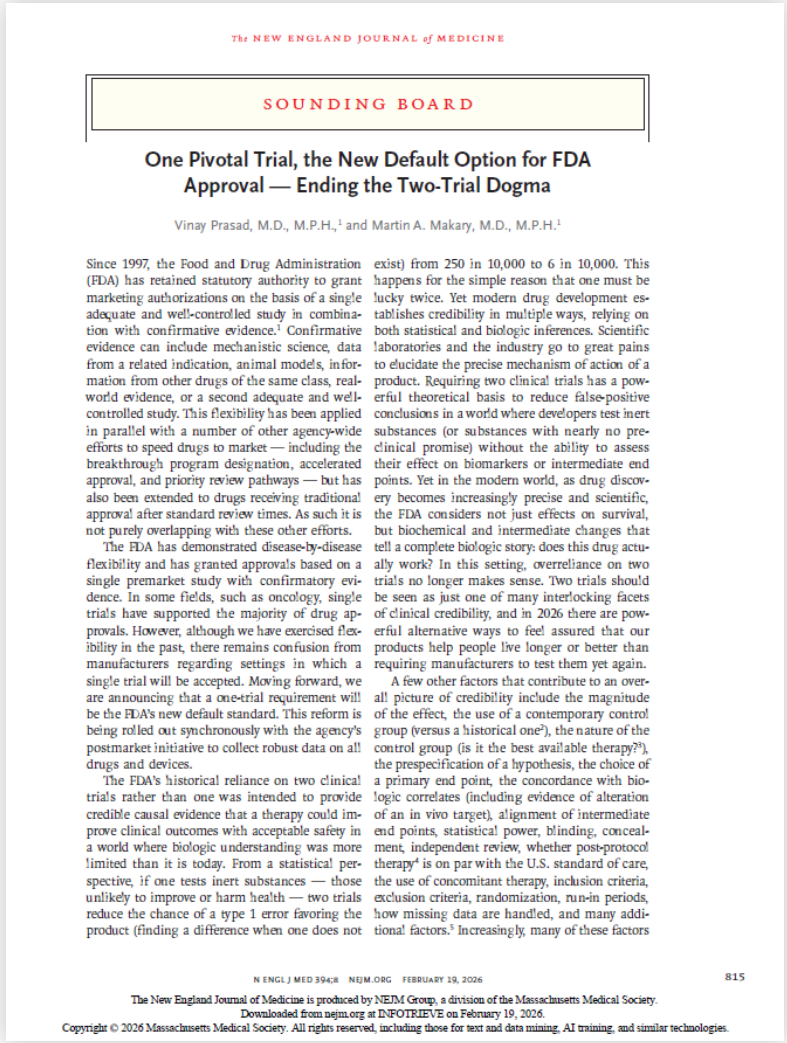
505(b)(2) Pathway

- New drug application for approval of drugs that are similar to, but not identical, to previously approved drugs
- Allows reliance on established safety and efficacy
- **Accelerates approval for new** formulations, dosages, **route of administration** or indications
- Axitinib approved for renal cell carcinoma in 2012

OCULAR THERAPEUTIX Retina experience redefined™

1. U.S. Food and Drug Administration. Applications Covered by Section 505(b)(2). 1999. 2. Inlyta [package insert]. New York, NY: Pfizer Inc; 2012.

One Pivotal Trial for NDA: The New Default



The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

One Pivotal Trial, the New Default Option for FDA Approval — Ending the Two-Trial Dogma

Vinay Prasad, M.D., M.P.H.,[1] and Martin A. Makary, M.D., M.P.H.[1]

Since 1997, the Food and Drug Administration (FDA) has retained statutory authority to grant marketing authorizations on the basis of a single adequate and well-controlled study in combination with confirmative evidence.[1] Confirmative evidence can include mechanistic science, data from a related indication, animal models, information from other drugs of the same class, real-world evidence, or a second adequate and well-controlled study. This flexibility has been applied in parallel with a number of other agency-wide efforts to speed drugs to market — including the breakthrough program designation, accelerated approval, and priority review pathways — but has also been extended to drugs receiving traditional approval after standard review times. As such it is not purely overlapping with these other efforts.

The FDA has demonstrated disease-by-disease flexibility and has granted approvals based on a single premarket study with confirmatory evidence. In some fields, such as oncology, single trials have supported the majority of drug approvals. However, although we have exercised flexibility in the past, there remains confusion from manufacturers regarding settings in which a single trial will be accepted. Moving forward, we are announcing that a one-trial requirement will be the FDA's new default standard. This reform is being rolled out synchronously with the agency's postmarket initiative to collect robust data on all drugs and devices.

The FDA's historical reliance on two clinical trials rather than one was intended to provide credible causal evidence that a therapy could improve clinical outcomes with acceptable safety in a world where biologic understanding was more limited than it is today. From a statistical perspective, if one tests inert substances — those unlikely to improve or harm health — two trials reduce the chance of a type 1 error favoring the product (finding a difference when one does not exist) from 250 in 10,000 to 6 in 10,000. This happens for the simple reason that one must be lucky twice. Yet modern drug development establishes credibility in multiple ways, relying on both statistical and biologic inferences. Scientific laboratories and the industry go to great pains to elucidate the precise mechanism of action of a product. Requiring two clinical trials has a powerful theoretical basis to reduce false-positive conclusions in a world where developers test inert substances (or substances with nearly no preclinical promise) without the ability to assess their effect on biomarkers or intermediate end points. Yet in the modern world, as drug discovery becomes increasingly precise and scientific, the FDA considers not just effects on survival, but biochemical and intermediate changes that tell a complete biologic story: does this drug actually work? In this setting, overreliance on two trials no longer makes sense. Two trials should be seen as just one of many interlocking facets of clinical credibility, and in 2026 there are powerful alternative ways to feel assured that our products help people live longer or better than requiring manufacturers to test them yet again.

A few other factors that contribute to an overall picture of credibility include the magnitude of the effect, the use of a contemporary control group (versus a historical one[2]), the nature of the control group (is it the best available therapy?[3]), the prespecification of a hypothesis, the choice of a primary end point, the concordance with biologic correlates (including evidence of alteration of an in vivo target), alignment of intermediate end points, statistical power, blinding, concealment, independent review, whether post-protocol therapy[4] is on par with the U.S. standard of care, the use of concomitant therapy, inclusion criteria, exclusion criteria, randomization, run-in periods, how missing data are handled, and many additional factors.[5] Increasingly, many of these factors

Factors that contribute to strength of submission

- Statistical significance
- Mechanistic science
- Blinding/masking
- Alignment with the FDA
- Supporting secondary data

OCULAR THERAPEUTIX Retina experience redefined™

Prasad V, Makary MA, *N Engl J Med*. 2026;394(8):815-817

Panel Discussion

OCULAR THERAPEUTIX Retina experience redefined

Faculty

Mark R. Barakat, MD

Founder and Director of Clinical Research, Retina Macula Institute of Arizona, Scottsdale, AZ

Dilsher S. Dhoot, MD

Vitreoretinal Specialist, California Retina Consultants, Santa Barbara, CA

Jeffrey S. Heier, MD

Chief Scientific Officer, Ocular Therapeutix, Inc.

Peter K. Kaiser, MD

Chief Development Officer, Ocular Therapeutix, Inc.

Arshad M. Khanani, MD

Managing Partner, Director of Clinical Research, Director of Fellowship, Sierra Eye Associates, Reno, NV

Patricio G. Schlottmann, MD

Director of Research, Charles Ophthalmic Center, Buenos Aires, Argentina

Adnan Tufail, MBBS, MD

Consultant Ophthalmic Surgeon, Moorsfield Eye Hospital, London, UK

OCULAR THERAPEUTIX Retina experience redefined™

Redefining the Management of Neovascular AMD

February 27, 2026

49th Annual Macula Society Meeting | Coronado, CA

OCULAR THERAPEUTIX

Retina experience redefined™