
Roche

Angiogenesis Meeting 2023

Virtual IR event

13 February 2023

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2 legislative and regulatory developments and economic conditions;
3 delay or inability in obtaining regulatory approvals or bringing products to market;
4 fluctuations in currency exchange rates and general financial market conditions;
5 uncertainties in the discovery, development or marketing of new products or new uses of existing products, including without limitation negative results of clinical trials or research projects, unexpected side-effects of pipeline or marketed products;
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Welcome

Bruno Eschli |
Head of Investor Relations

Agenda

Welcome

Bruno Eschli, Head of Investor Relations

Roche ophthalmology strategy

Nilesh Mehta, Franchise Head Ophthalmology, Global Product Strategy

Roche ophthalmology pipeline

Christopher Brittain, Global Head of Ophthalmology, Product Development

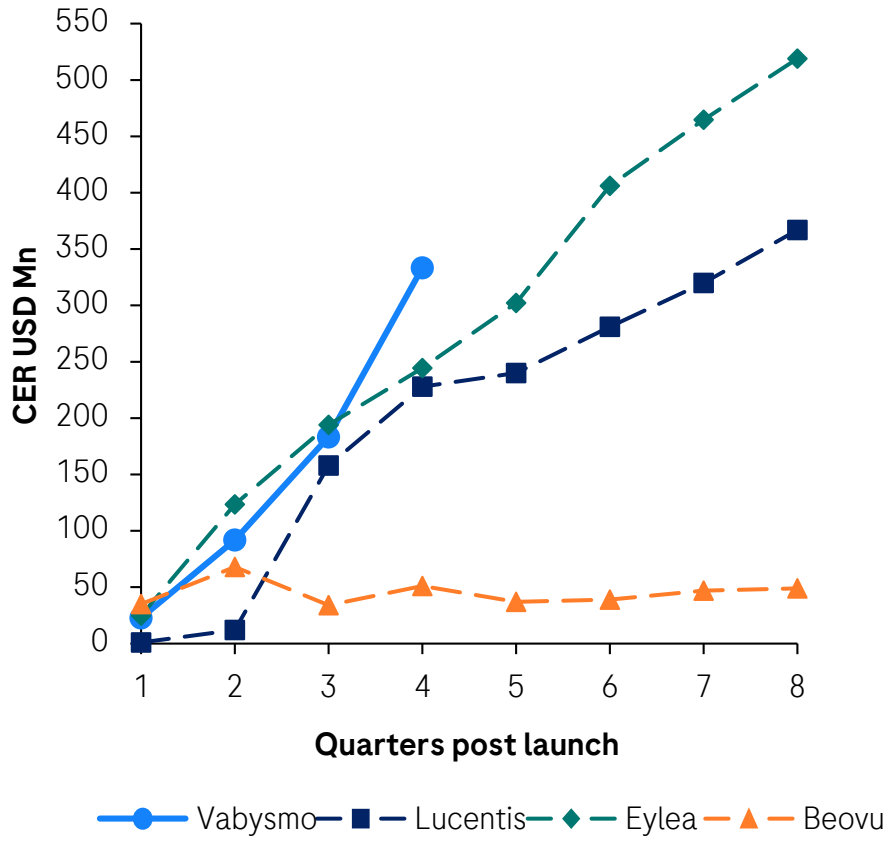
Key data presented at Angiogenesis

Veeral Sheth, MD, Retina Specialist and Clinical Investigator

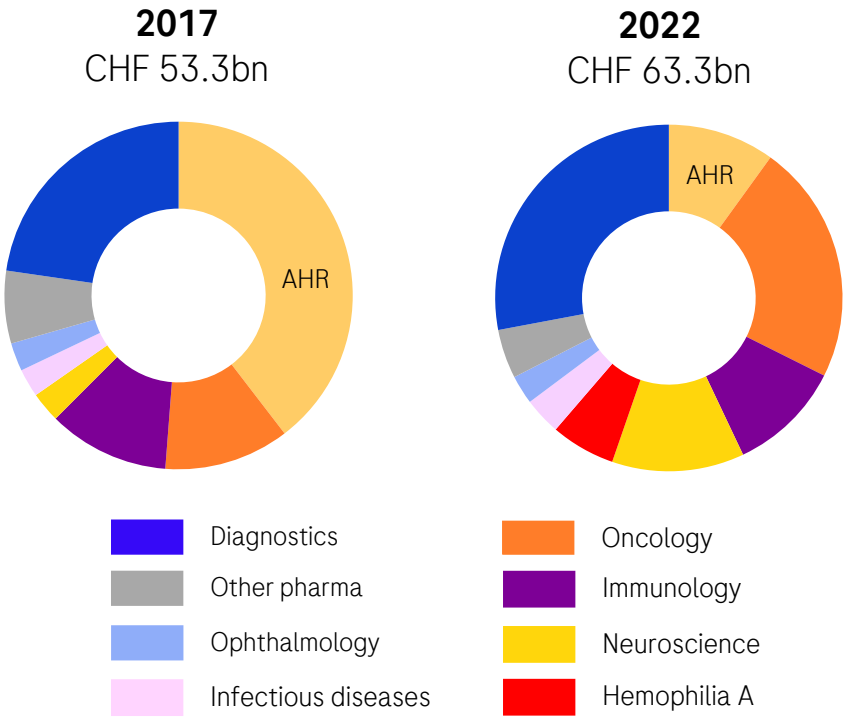
Q&A

Vabysmo launch among strongest in ophthalmology

Global Product Revenues



Diversification of Roche business



Source: Evaluate Feb 2023

Ophthalmology franchise strategy

Nilesh Mehta **|**
Global Franchise Head, Ophthalmology

Ophthalmology franchise: significant progress made in 2022

VABYSMO

susvimo™ ranibizumab injection 100 mg/mL For Ocular Implant

Strong global launch of Vabysmo

- More than 450k vials shipped globally in first 11 months of launch
- Two year follow-up data for Vabysmo presented for nAMD and DME

Pipeline development: four positive Ph 3 trials in past 12m

- Positive Ph III readouts for Vabysmo in BRVO/CRVO (BALATON/COMINO)
- Positive Ph III readouts for Susvimo in DME and DR (PAGODA/PAVILLION)
- Nine Positive Ph III readouts combined across Susvimo and Vabysmo

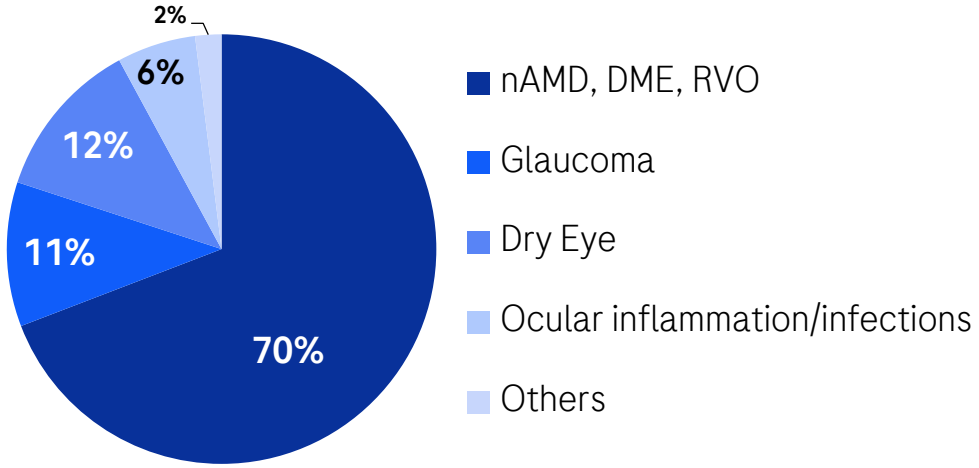
Significant progress made in ophthalmology pipeline

- Anti-IL-6: Ph III (MEERKAT/SANDCAT) trials in UME initiated
- Advanced OpRegen to Ph IIa in Geographic Atrophy

nAMD=neovascular age-related macular degeneration; DME=diabetic macular edema; UME=uveitic macular edema; DR=diabetic retinopathy; BRVO=branch retinal vein occlusion; CRVO=central retinal vein occlusion

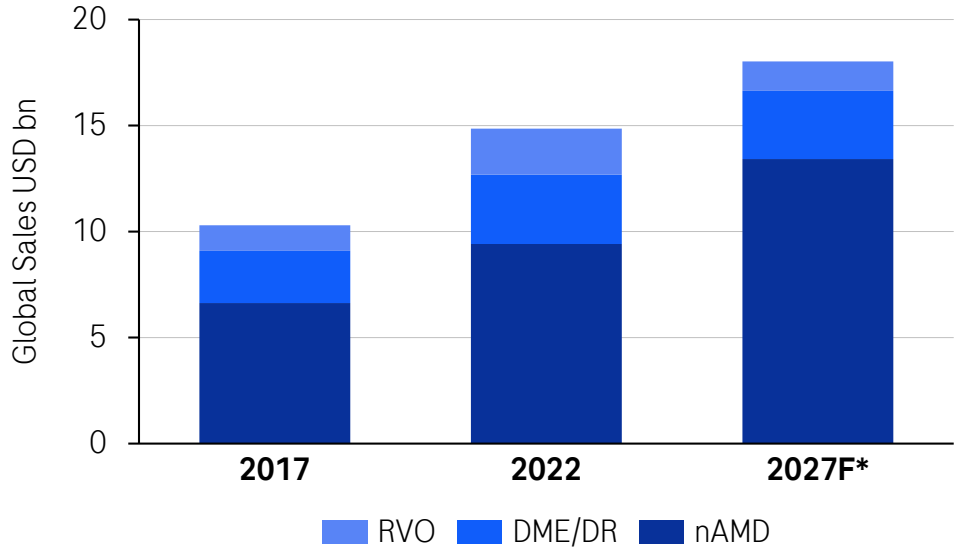
Retinal diseases are the fastest growing segment of the ophthalmology market

Ophthalmology market[1]



- Retinal vascular diseases remain leading causes of vision loss

Global retina market ~15 bn USD and growing[1]



- Incidence and prevalence of common retinal diseases are increasing due to ageing and Type 2 Diabetes[2]

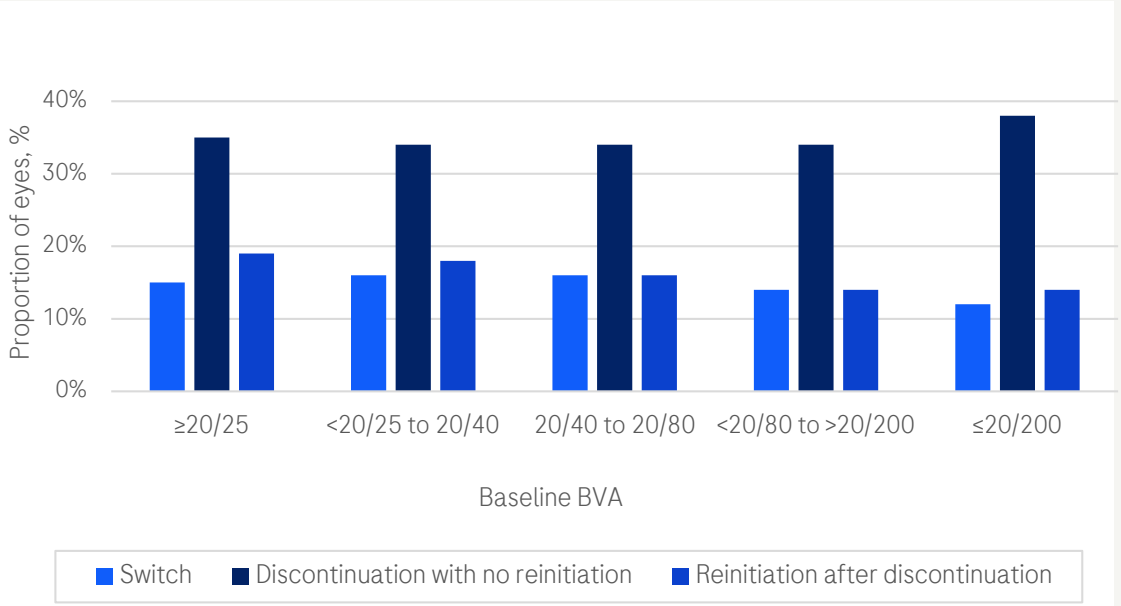
Source: Evaluate Pharma

[1] Evaluate Pharma Feb 2023; [2] Rosenblatt T et al., Ophthalmic Surg Lasers Imaging Retina. 2021 Jan 1;52(1):29-36, National Eye Institute. Facts About Diabetic Eye Disease; *2027 Evaluate forecast, does not yet include Vabysmo in RVO; DME=diabetic macular edema; DR=diabetic retinopathy; nAMD=neovascular age-related macular degeneration; RVO=retinal vein occlusion

Significant unmet need remains in retinal disease

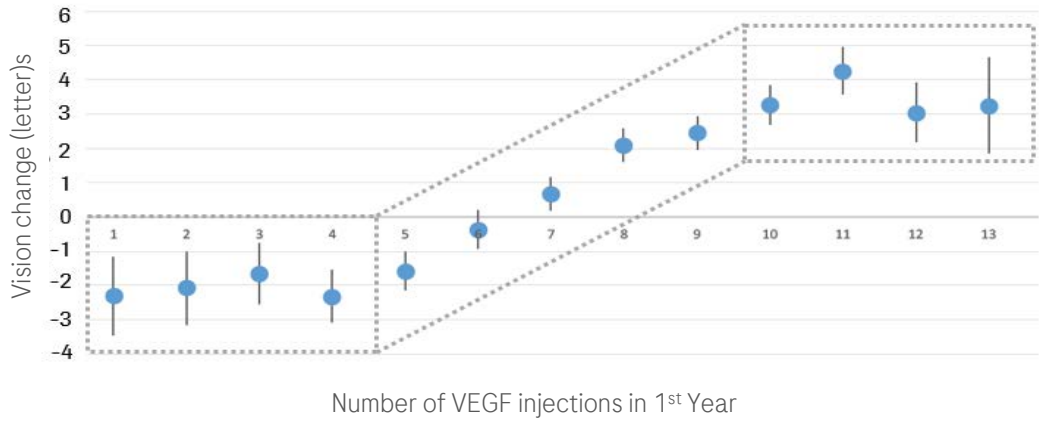
Discontinuation, undertreatment and suboptimal vision with aVEGF monotherapy

DME treatment discontinuation/switch: 6yr follow-up data from the IRIS ophthalmology registry[1]



- One third of patients discontinued anti-VEGF IVT therapy in any given year
- Anti-VEGF switching and discontinuation similar across baseline visual acuity

nAMD: Infrequent dosing correlates with poor vision gains in real-world[2]

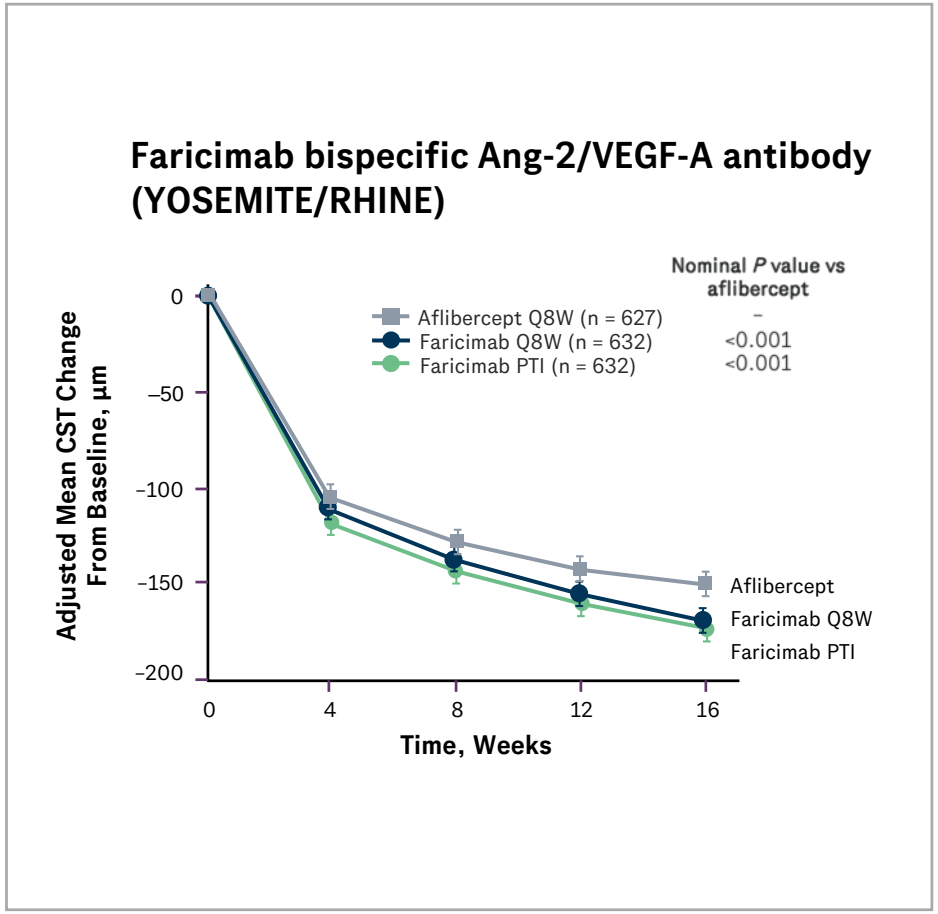


- Real-word data show patients receive as few as 3-7 treatments in the first year, with consistently suboptimal visual outcomes[3]
- Even in clinical trials, only half of patients achieve 20/40 vision, necessitating better efficacy and more than VEGF to achieve superior vision function outcomes

[1] Leng T, et al., ASRS 2022, Long-Term Real-World Treatment Patterns Among Patients With Diabetic Macular Edema Initiating Anti-VEGF: 6-Year Follow-Up Using the IRIS® Registry; [2] Courtesy of T. Brogan/Vestrum Health, presented by Dr. D. Williams at ASRS 2018; [3] Blinder KJ et al., Clin Ophthalmol 2017;11:393–401; Holekamp NM et al., Am J Ophthalmol 2018;191:83–91; Cantrell R et al., Ophthalmology 2019; BVA=baseline visual acuity; DME=diabetic macular edema; nAMD=neovascular age-related macular degeneration, IVT=intravitreal; VEGF=vascular endothelial growth factor

Vabysmo 2-year data continue to support excellent launch

Q16W dosing increases to ≥ 60% in nAMD and DME



Dual pathway: Inhibition of Ang-2 and VEGF-A

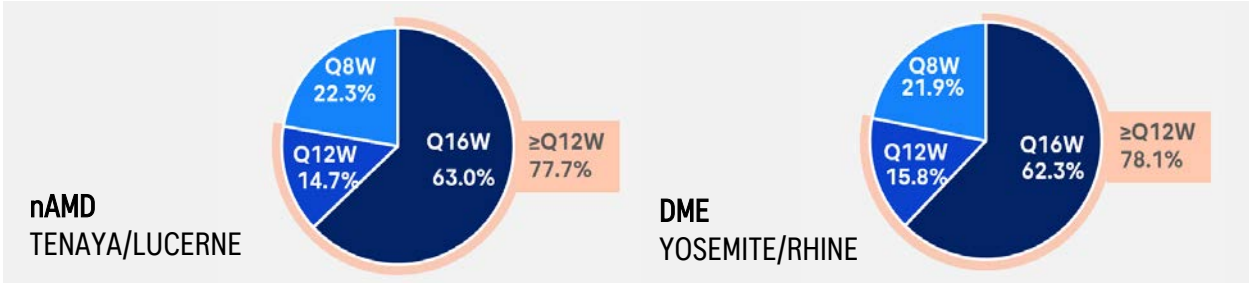
- First bispecific antibody inhibiting two distinct disease pathways by simultaneously binding to Ang-2 and VEGF-A

Strong anatomic data across DME and nAMD

- CST reduction and absence of fluid showed greater retinal drying during the matched loading dose phase in nAMD and throughout the study in DME*
- In the real world retinal specialists use anatomy to inform treatment decisions

Durability: Updated 2-year data continues to strengthen profile

- ~80% of patients reaching Q12W dosing or longer and >60% Q16M dosing in both DME and AMD

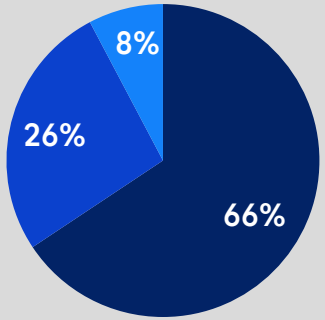


Heier JS et al. AAO 2021; Eichenbaum D.A. et al, ASRS 2022; Khanani A.M. et al., ASRS conference 2022; nAMD=neovascular age-related macular degeneration; DME=diabetic macular edema; RVO=retinal vein occlusion; CST=central subfiled thickness; Ang-2=angiopoietin-2; VEGF-A=vascular endothelial growth factor A; Q16W= every 16 weeks; Q12W=every 12 weeks; Q8W=every 8 weeks; PTI=personalized treatment interval; * CST reduction and absence of fluids were secondary endpoints and unadjusted for multiplicity (nominal P-values)

Vabysmo real world outcomes consistent with Ph III trials*

Case reports of anatomic benefits in patients switching from other VEGF therapies

TRUCKEE (real-world data) results



Patient characteristics:
last prior therapy

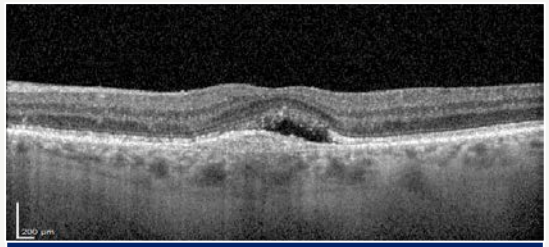
- aflibercept
- Other anti-VEGF treatment
- Treatment naïve

Improvements in anatomy among patients switching from VEGF (n=298):

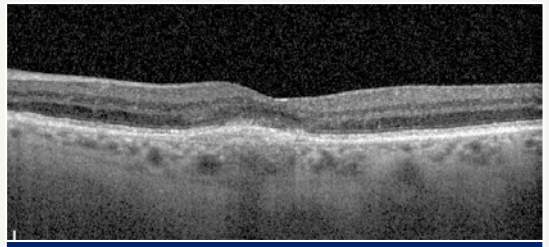
- ✔ CST reduced from 328.0 µM to 302.7 µM (-25.3µM)
- ✔ PED height reduced from 244.5 µM to 185.6 µM (-58.9µM)
- ✔ Intraretinal Fluid (IRF) reduced from 38% to 31% of patients
- ✔ Subretinal Fluid (SRF) reduced from 58% to 37% of patients

Safety: one case of IOI and one case of infectious endophthalmitis was reported in 491 patients with 1,231 injections

Case example: SRF response to Vabysmo

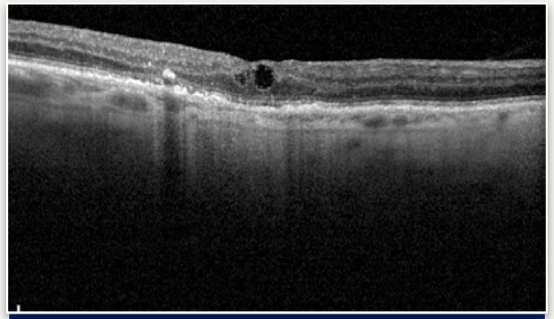


BCVA: 20/60
CST: 387 µM
Previous: monthly aflibercept injections

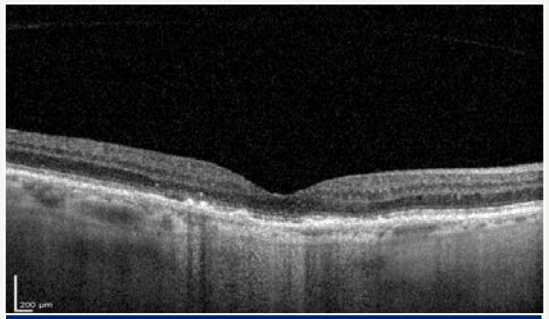


Follow-up: 35 days
BCVA: 20/40
CST: 303 µM

Case example: response to Vabysmo in patient with IRF



BCVA: 20/200
CST: 326 µM
C/o severe injection exhaustion

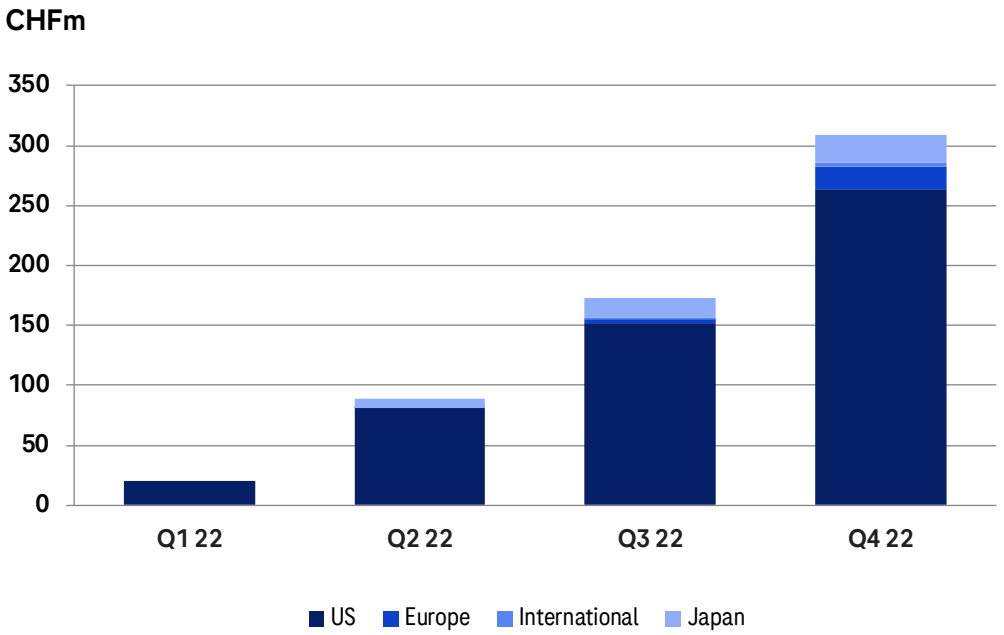


Follow-up: 70 days
BCVA: 20/80
CST: 236 µM

Bhandari AAO 2022; *This study was not sponsored by, and is independent of Genentech/Roche, data from presented interim analysis; nAMD=neovascular age-related macular degeneration; VEGF=vascular endothelial growth factor; BCVA=best corrected visual acuity; CST=central subfield thickness; SEM=standard error of mean; PED=pigment epithelial detachment; SRF=subretinal fluid; IRF=intraretinal fluid; RWD=Real world data; IOI=intraocular inflammation

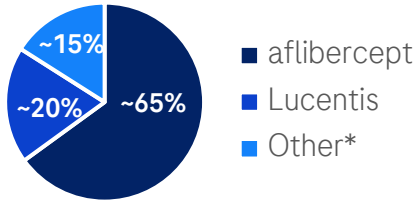
Vabysmo global growth drivers

Healthcare systems recognize importance of durability to overall outcomes and costs



US: Uptake accelerating with establishment of permanent J-code (Oct 1)

- Increasing use among earlier line patients and DME patients (2 year DME data added to US label)
- Patients are primarily switches coming from aflibercept



>450k vials shipped globally in first 11m of launch

- >50 countries approved (EU: approval Sep 2022)
- Rapid launch uptake in Japan & UK (NICE reimbursement 1 week after approval, listed as 1L therapy for nAMD at Moorfields Eye Hospital, London)

Broaden to additional indications, formulations

- Ph III (COMINO / BALATON) in RVO to be filed with health authorities in 2023
- Prefilled syringe under development

*Includes treatment-naive Avastin and brolucizumab switch patients; nAMD=neovascular age-related macular degeneration; DME=diabetic macular edema; RVO=retinal vein occlusion; NICE=National Institute for Health and Care Excellence

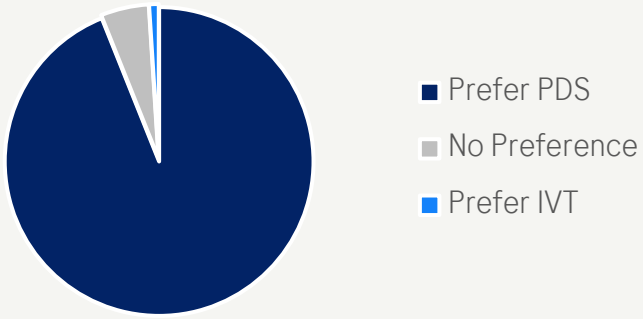
Susvimo

Fully committed to Port Delivery System platform

Susvimo will be targeted to patients who wish to achieve optimal vision with the fewest treatments

2x
per year

93% of patients prefer Susvimo to IVT injections[1]



Global launch expected to resume in ~1 year

- Roche voluntarily recalled Susvimo for nAMD in the US in 2022
- New implantation including ongoing global clinical trials have been paused
- Since the voluntary recall, significant progress has been made to understand the nature of the problems associated with septum dislodgement

Continued development for Port Delivery platform

- Synergies of positive data for DME (PAGODA) and DR (PAVILLION):
  - Prevent disease progression in DR
  - Improve vision in DME
  - Extend treatment intervals in DME patients after fluid resolution and only DR remains
- Ph IIIb extended 9 month duration study in nAMD (VELODROME) ongoing
- Developing next generation DutaFab bispecifics, compatible with PDS

[1] Holekamp N et al. Archway Ph3 Trial of the PDS for nAMD , American Academy of Ophthalmology, 129(3), 2022; IVT=intravitreal injection; PDS=port delivery system; Q6M=every 6 months; DME=diabetic macular edema; DR=diabetic retinopathy; nAMD=neovascular age-related macular degeneration; DutaFabs=dual targeting fragment antigen-binding

Roche ophthalmology pipeline

***Christopher Brittain* |**
Vice President and Global Head of Ophthalmology Product Development

Ophthalmology pipeline

Aiming to alter the trajectory of vision loss as experienced today

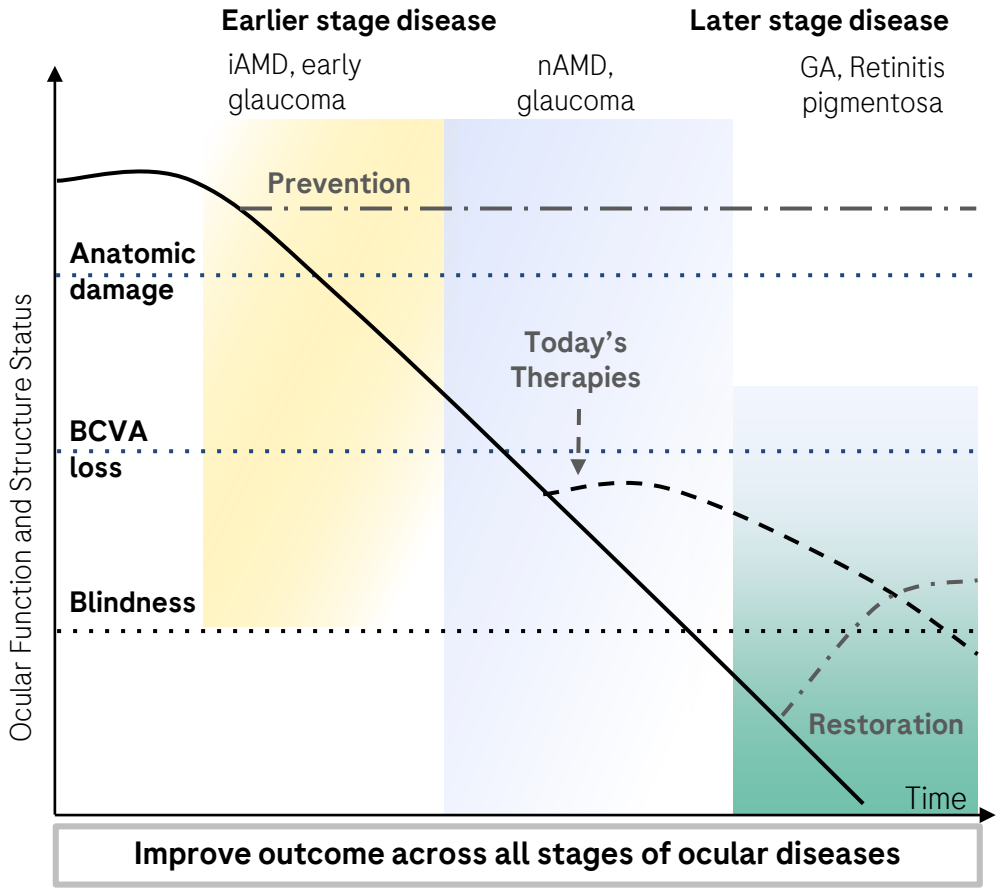
Vision preservation and restoration – technologies and approaches for all disease stages

Earlier stage disease

- Supplement current target approaches: inhibit inflammation & neo-angiogenesis
- Explore clinically useful biomarkers predicting rapid vision loss
- Protect key retinal lineages

Later stage disease

- Replace photosensitive cells once vision is lost
- Continue investment in new therapeutic modalities e.g. cell therapy and gene therapy/optogenetics



nAMD=neovascular age-related macular degeneration; iAMD=intermediate age related macular degeneration; GA=geographic atrophy; BCVA=Best-corrected visual acuity

Ophthalmology R&D focus areas

Improving patient outcomes and reducing treatment burden

Biomarkers enabling PHC

Biomarker identification

- Integration of omics, clinical and imaging data
- Real world data & natural history
- Improved disease understanding
- New drug targets
- Optimized treatment regimen

AI/ML

- Clinical decision support

Remote vision monitoring

- Flexibility/compliance with longer duration treatments

Key partnerships

olink PROTEOMICS · DRCR.net · macustar

Novel MOAs, New Indications

Novel MOAs

- Vabysmo first dual pathway inhibitor (VEGF/Ang-2)
- Addressing retinal inflammation (IL-6)
- Complement pathway (ASO-Factor B)

New indications

- UME, GA, DR, Glaucoma

Potential for combination therapies

- Characterizing disease pathways, e.g. angiogenesis, inflammation, fibrosis and ischemia

Key partnerships

IONIS · SEMA

Extended durability, Future technologies

Long acting delivery

- Port Delivery System
- DutaFabs

Cell therapy

- Retinal pigment epithelium cell therapy for patients with GA
- Ph I/II study ongoing, with FDA Fast Track Designation granted

Gene therapy

- AAV engineering platform technology to target specific cell types
- Development of AAV capsids for intravitreal targets

Key partnerships

AVISTA Rx · LINEAGE CELL THERAPEUTICS

PHC=personalized healthcare; AI=artificial intelligence; ML=machine-learning; MOA=mode of action; Ang-2=angiopoietin-2; VEGF=Vascular endothelial growth factor; ASO=antisense oligonucleotide; DutaFabs=dual targeting fragment antigen-binding; IL-6=inter-leukin 6; AAV=adeno-associated virus; DR: diabetic retinopathy; GA=geographic atrophy; UME=uveitic macular edema

Ophthalmology pipeline gaining momentum

Further improving the standard of care and expanding in new indications

Ph I (5 NME)		
RG6351	**NME**	Retinal disease
RG6209	**NME**	Retinal disease
RG6312	**NME**	GA
RG7921	**NME**	nAMD
RG6120	**VEGF-Ang2 DutaFab**	nAMD

Ph II (3 NMEs, 1 AI)		
RG6179	**Anti-IL-6**	DME
RG7774	**Vicasinabin (CB2 agonist)**	DR
RG6299	**IONIS-FB-LRx[2]**	GA
RG6501	**OpRegen[1]**	GA

Ph III (1 NME, 4 AIs)		
RG7716	**Vabysmo**	BRVO
RG7716	**Vabysmo**	CRVO
RG6321	**Susvimo**	DME
RG6321	**Susvimo**	DR
RG6179	**Anti-IL-6**	UME

Launched (2 NMEs, 1AI)			
RG7716	**Vabysmo**	nAMD	✓
RG7716	**Vabysmo**	DME	✓
RG6321	**Susvimo**	nAMD	✓

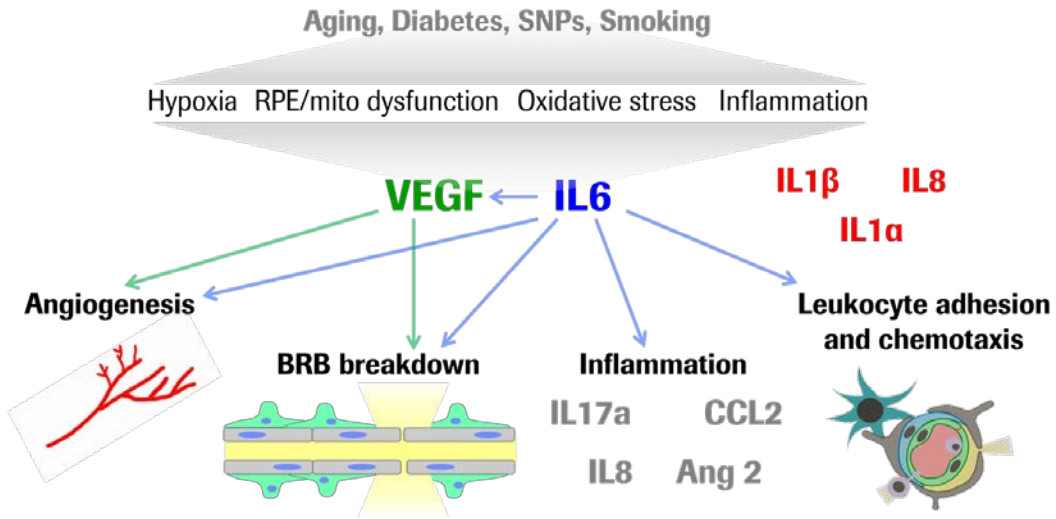
Antibody
DutaFab
Port delivery system
Antisense oligonucleotide
Stem cell therapy
Small molecule

nAMD
DME/UME
GA
DR
RVO
Retinal disease
FDA approval

[1] In collaboration with Lineage Cell Therapeutics (LCTX); [2] In collaboration with Ionis; nAMD=neovascular age-related macular degeneration; DME=diabetic macular edema; UME=Uveitic macular edema; DR=diabetic retinopathy; BRVO=branch retinal vein occlusion; CRVO=central retinal vein occlusion; GA=geographic atrophy; NME=new molecular entity; AI=additional indication; DutaFabs=dual targeting fragment antigen-binding; VEGF=vascular endothelial growth factor; Ang-2=angiopoietin-2; IL-6=inter-leukin; CB2=cannabinoid type 2

Novel anti-IL-6 mAb: Addressing the inflammation cascade in retinal diseases

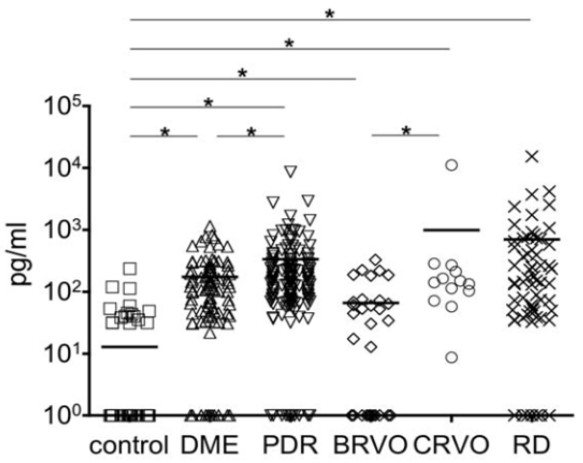
IL-6: Involved in many pathways, including inflammation



- Inflammation is a sub-optimally treated pathway in a number of ocular diseases

IL-6: Upregulated in retinal diseases

Concentration of IL-6 in the vitreous cavity of patients; mean (range) in pg/ml[1]



	IL-6 concentration pg/ml
Control	12.1 (<30-206.8)
DME	174 (<30-1152)
PDR	330.1 (<30-8630)
BRVO	65.6 (<30-326)
CRVO	985.4 (<30-11103)
RRD	701.6 (<30-15381)

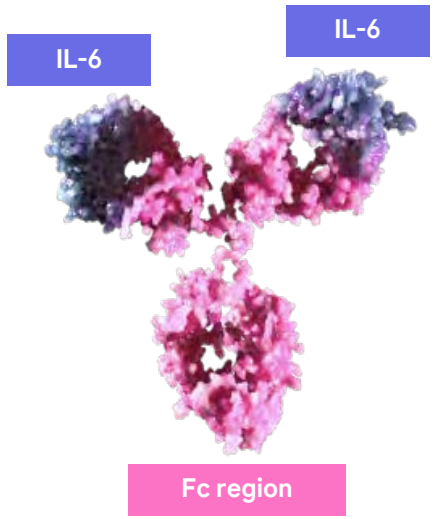
- IL-6 levels significantly increased vs control in vitreous fluids of people with retinal diseases

Anti-IL-6 mAb=RG6179; [1] Yoshimura T, Sonoda K-H, Sugahara M, Mochizuki Y, Enaida H, et al. (2009) Comprehensive Analysis of Inflammatory Immune Mediators in Vitreoretinal Diseases. PLoS ONE 4(12): e8158. doi:10.1371/journal.pone.0008158; IL-6=interleukin-6; VEGF=vascular endothelial growth factor; DME=diabetic macular edema; RPE=retinal pigment epithelium; BRB=blood-retinal barrier; PDR=proliferative diabetic retinopathy; BRVO=branch retinal vein occlusion; CRVO=central retinal vein occlusion; RRD=rhegmatogenous retinal detachment; RD=retinal detachment

Novel anti-IL-6 mAb in DME and UME

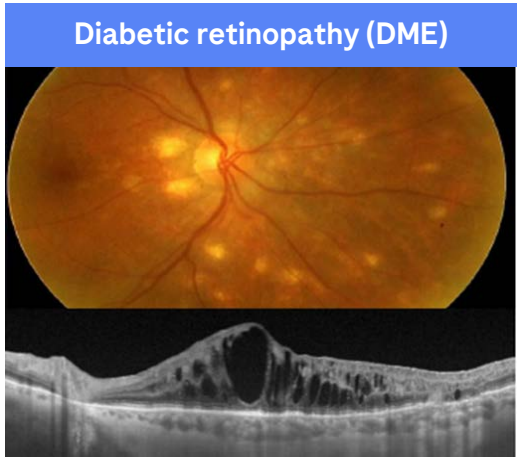
Ph III study in UME first patient in achieved in January

MoA

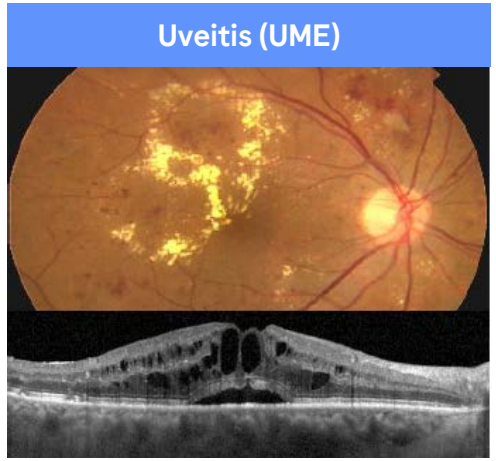


- Anti-IL-6 mAb (RG6179) binds IL-6 and inhibits all known forms of IL-6 signaling
- Specifically designed for intraocular use and optimized for a rapid systemic clearance

Macular edema is a common end stage complication in retinal diseases
High unmet need in patients with DME and UME



Caused by long-term hyperglycaemia



Caused by intraocular inflammation

Disruption of the blood-retinal barrier precedes fluid accumulation in the macular retina in both DME and UME

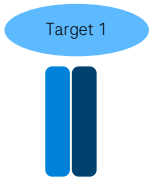
- UME is a vision threatening complication of uveitis, with about 1/3 of patients being affected
- DME is a vision threatening condition and the most common cause of visual loss in patients with diabetes mellitus[1,2]
- Early clinical data in UME encouraging; to be presented at medical congress in 2023
- Ph II studies in DME (BARDENAS, ALLUVIUM) ongoing

[1] Musat O, Cernat C, Labib M, et al. Diabetic Macular Edema. Romanian J Ophthalmol. 2015;59(3):133-6.; [2] Calvo P, Abadia B, Ferreras A, et al. Diabetic macular edema: options for adjunct therapy. Drugs. 2015;75(13):1461-9;
DME=diabetic macular edema; UME=uveitic macular edema; IOP=intraocular pressure; MoA=mode of action; IL-6=interleukin-6

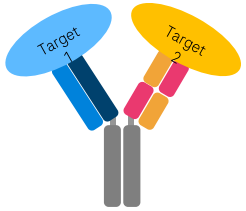
DutaFabs have the potential for long duration of action and enhanced efficacy

DutaFabs: next generation bispecifics

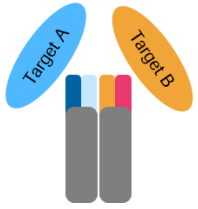
Monospecific Fab
e.g. Lucentis



Bispecific mAb
e.g. Vabysmo

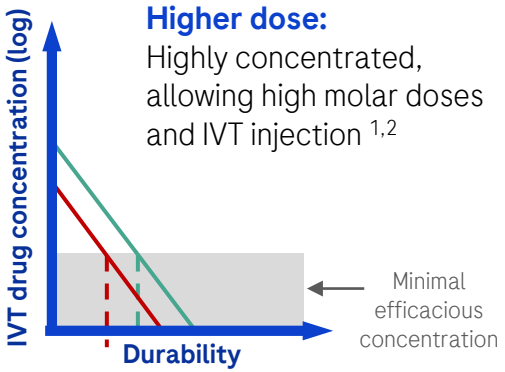


DutaFab bispecific Fab
e.g. VEGF/Ang-2 DutaFab (RG6120)

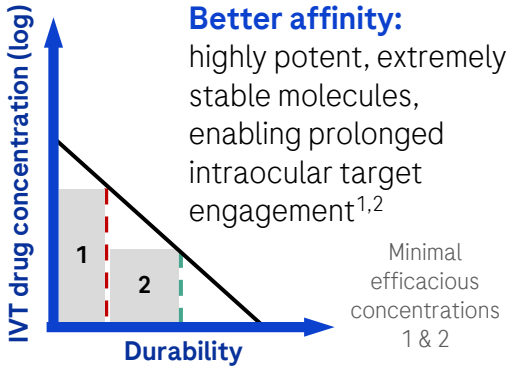


Single antigen-binding fragment binding two targets

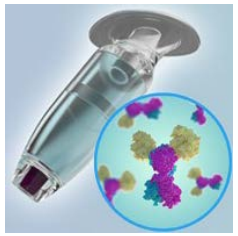
Designed for increased durability
Future development opportunities with the port delivery system



Higher dose:
Highly concentrated, allowing high molar doses and IVT injection [1,2]



Better affinity:
highly potent, extremely stable molecules, enabling prolonged intraocular target engagement [1,2]



Sustained release:
compatible with the port delivery system owing to their size and ability to be highly concentrated

- DutaFabs are a novel bispecific Fab format significantly smaller than bispecific antibodies, size similar to Fabs e.g. Lucentis
- DutaFabs are compatible with the port delivery system enabling increased durability beyond Q6M[2]
- There are several DutaFabs in preclinical and clinical development, e.g. VEGF-Ang2 DutaFab (RG6120) currently investigated in nAMD (Ph I ongoing)

[1] Roche. Data on file. Bispecific Antibody Technologies to improve Clinical Efficacy and Duration of Action for Ophthalmology. I2O Summit 2019; [2] Roche. Data on file. 2020; DutaFabs=dual targeting fragment antigen-binding; VEGF=vascular endothelial growth factor; Ang-2=angiopoietin-2; mAb=monoclonal antibody; IVT=Intravitreal; Q6M=every 6 months; nAMD=neovascular age-related macular degeneration

Geographic atrophy (GA): A multifactorial and irreversible disease

Extensive development program covering different MoAs and platform technologies

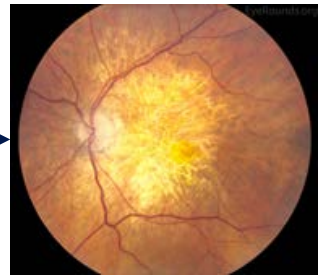
Pathogenesis of GA remains unclear, key risk factors identified

Environmental risks
(e.g. smoking, diet)

Genetic risks
(e.g. Complement, HTRA)

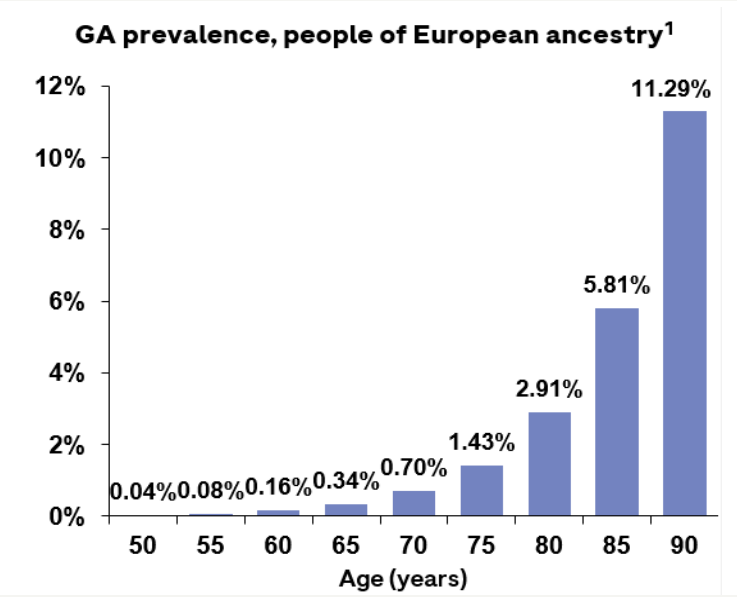
Oxidative stress
(e.g. reactive oxygen species, lipid deposition, photoreceptor debris)

Overactive complement system & chronic inflammation



Symptoms
- Blind spots
- Loss of contrast sensitivity
- Decreased reading speed
- Decreased function in dim lighting

>5 mn people globally affected by GA

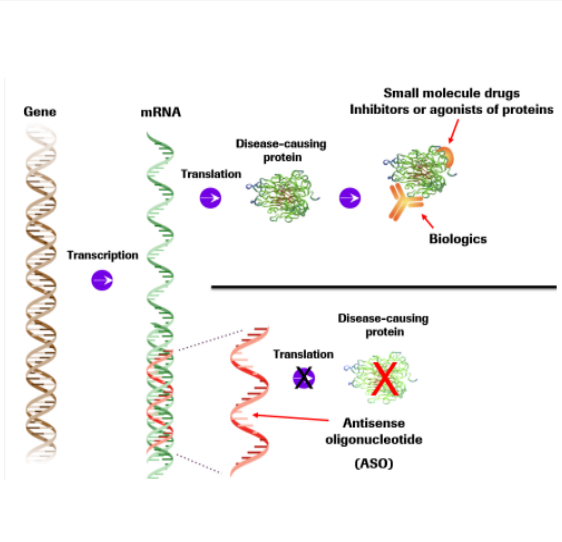


- GA can have a devastating effect on patients' visual function and quality of life, however there are currently limited treatment options

[1] Wong WL, et al. Lancet Glob Health. 2014;2:e106–16; GA=geographic atrophy, MoA=mode of action

ASO factor B in GA: Targeting hyperactive alternative complement pathway via SC delivery

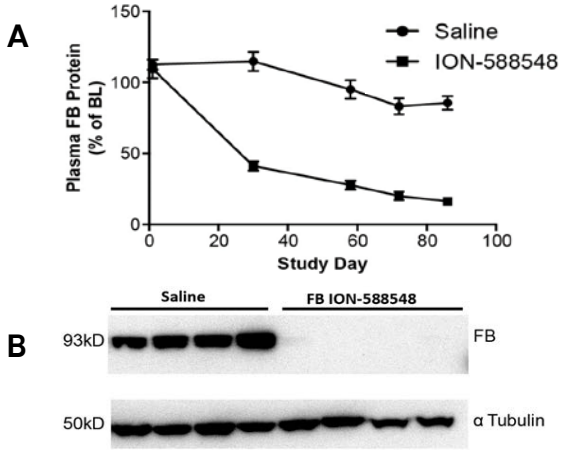
MoA



- Complement Factor B (CFB): key component of alternative complement pathway; associated with complement hyperactivity seen in GA
- Inhibits CFB gene expression and reduces the production of factor B protein

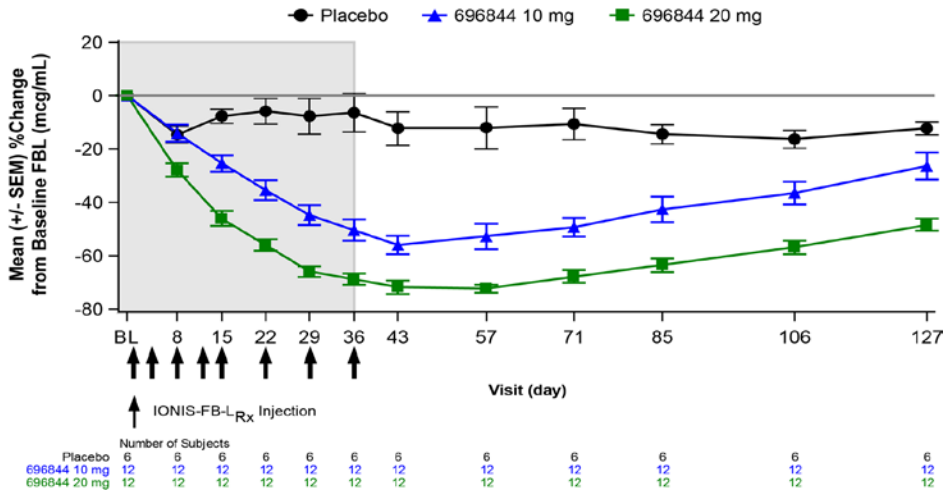
Preclinical and Ph1 results

Preclinical results in monkeys[1]



Systemic (A) and ocular (B) ASO FB protein knockdown achieved with RG6299 SC

Ph1: Significant dose-dependent reductions in plasma FB levels[2]



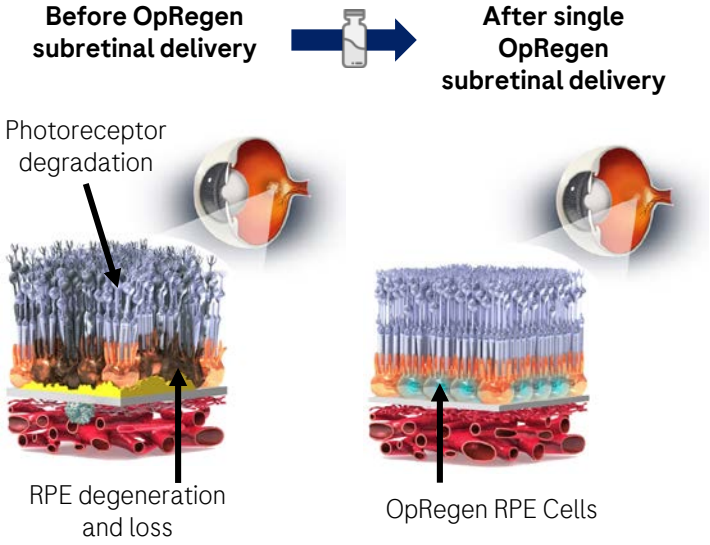
- Advantages of RG6299:
  - Potential for systemic Q4W SC administration and simultaneous treatment of bilateral GA and self-administration at home
  - More suitable option for treatment of early stage disease (e.g. iAMD)
- Ph2 GOLDEN multiple dose study assessing safety and efficacy ongoing*

*Managed by IONIS; 1. Grossman et al., Mol Vis 2017; 2. Guymer RG, et al. Presented at EURETINA 2020; ASO=antisense oligonucleotide; MoA=Mode of action; FB=Factor B; GA=geographic atrophy; CFB=Complement factor B; iAMD=intermediate age related macular degeneration; SC=Subcutaneous; ASO factor B in-licenced from IONIS pharmaceuticals

OpRegen in GA: Replenishing the retinal pigment epithelium

Encouraging early clinical data presented at ARVO 2022

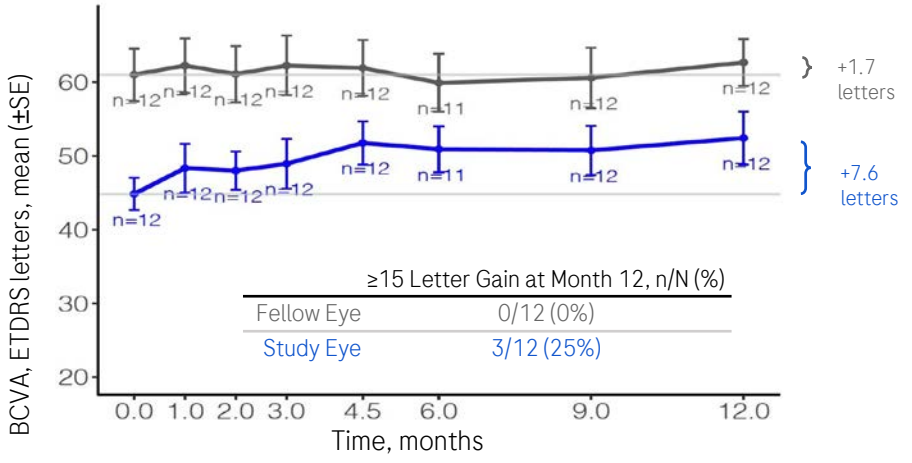
Potential to counteract RPE cell loss in GA

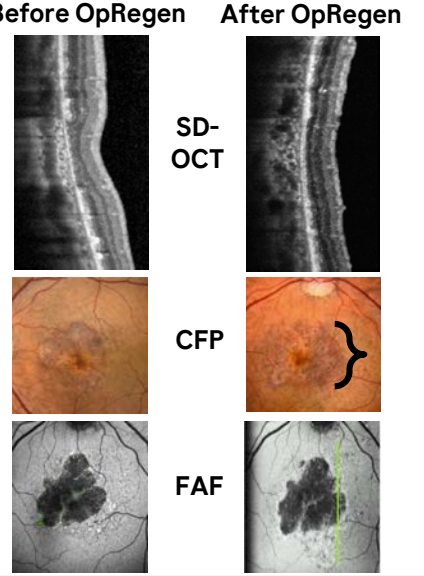


- OpRegen (RG6501) has the potential to counteract RPE cell loss in areas of GA by supporting retinal structure and function
- Launched Ph IIa trial, continuing to optimize subretinal surgical delivery

Ph I/IIa data: Outer retinal structure and visual function improvements in patients with impaired vision[1]

Cohort 4 (n=12):
Patients with bilateral GA secondary to AMD with BCVA ≥20/250 and ≤20/64 and GA area ≥4 and ≤11mm2





- Preliminary evidence of outer retinal structure and visual function improvements with OpRegen was observed in patients with GA and impaired vision (Cohort 4 [n=12])
- Average 7.6 letter gain and 25% of patients with ≥15 Letter gain in Cohort 4
- OpRegen well tolerated in PhI/IIa GA study with an acceptable safety profile and mostly mild AEs

In collaboration with Lineage Cell Therapeutics, Inc. (LCTX); 1. Ho AC, et al. Presented at ARVO 2022; RPE=Retinal pigment epithelium; GA=Geographic atrophy; AMD=Age-related macular degeneration; BCVA=Best-corrected visual acuity; ETDRS=Early treatment of diabetic retinopathy study; SD-OCT=Spectral-domain optical coherence tomography; CFP=Color fundus photography; FAF=Fundus autofluorescence; AEs=Adverse events

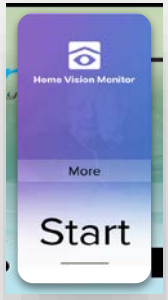
PHC solutions support the Roche ophthalmology vision while delivering patient benefits and value for Roche

Remote Vision Monitoring Apps

Accessible, effective and low cost tracking of disease activity to provide confidence between treatment intervals and reduce treatment burden

Home Vision Monitor®

- FDA-cleared medical device
- App implements a vision function test accurate at detecting significant changes in vision function
- Results are sent automatically to the prescribing physician
- Release of next version expected in H2 2023



Prevent vision loss by identifying **high-risk patients** early

Predict or mitigate treatment burden

Inform on variable **treatment outcomes**

Personalize treatment for more **efficient utilization** of **health system**

AI-powered Retinal Imaging Algorithms

Segmentation and disease or treatment prediction to inform disease activity and personalized management

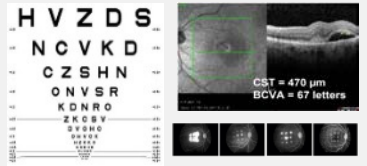
Utilize analytics and large scale data to answer questions of prime clinical importance

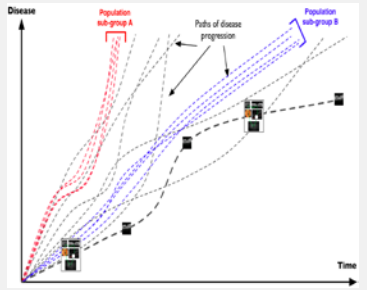
Verana Health

INSIGHT Health Data Research Hub

inoveon

CATT





Key clinical data presented at Angiogenesis

Veeral Sheth, MD |
Retina Specialist and Clinical Investigator

Disclosures

Speaker: Genentech, Alimera, Apellis

Consultant: Genentech, Novartis, Alimera, EyePoint, IvericBio, Graybug, Apellis, Regeneron, Vial

Contracted research: Allergan, Opthea, Oxurion, Recens Medical, Roche, Regenxbio, Eyepoint, Genentech, Ionis, Novartis, Regeneron, Santen, SamChungDang, IvericBio, Gyroscope, Chengdu Kanghong, SalutarisMD, NGM Biopharmaceuticals, Alimera Sciences, Outlook, 4D Molecular Therapeutics, Ashvattha Therapeutics, Olix pharmaceuticals, Janssen, OcuTerra

Overview of key clinical data presentations at Angiogenesis

Vabysmo in RVO

Results from the Phase III BALATON and COMINO trials

Susvimo in Diabetic Macular Edema

Results from the Phase III Pagoda Trial

Diabetic Retinopathy

Results from the Phase III Pavilion Trial

Faricimab in RVO: Results From the BALATON and COMINO Phase 3 Studies

Ramin Tadayoni, MD, PhD[1]

Liliana P. Paris, MD, PhD[2]; Francis Abreu, PhD[2]; Pablo Arrisi, PhD[3]; Karen Basu, PhD[4]; Zdenka Haskova, MD, PhD[2]; Ying Liu, PhD[2]; Anne-Cecile Retiere, PharmD[3]; Jeffrey R. Willis, MD, PhD[2]; Aachal Kotecha, PhD[3]

[1] University Paris Cité, Lariboisière and Rothschild Foundation hospitals, Paris, France
[2] Genentech, Inc., South San Francisco, CA, USA
[3] Roche Products Ltd., Welwyn Garden City, UK
[4] Roche Products (Ireland), Dublin, Ireland

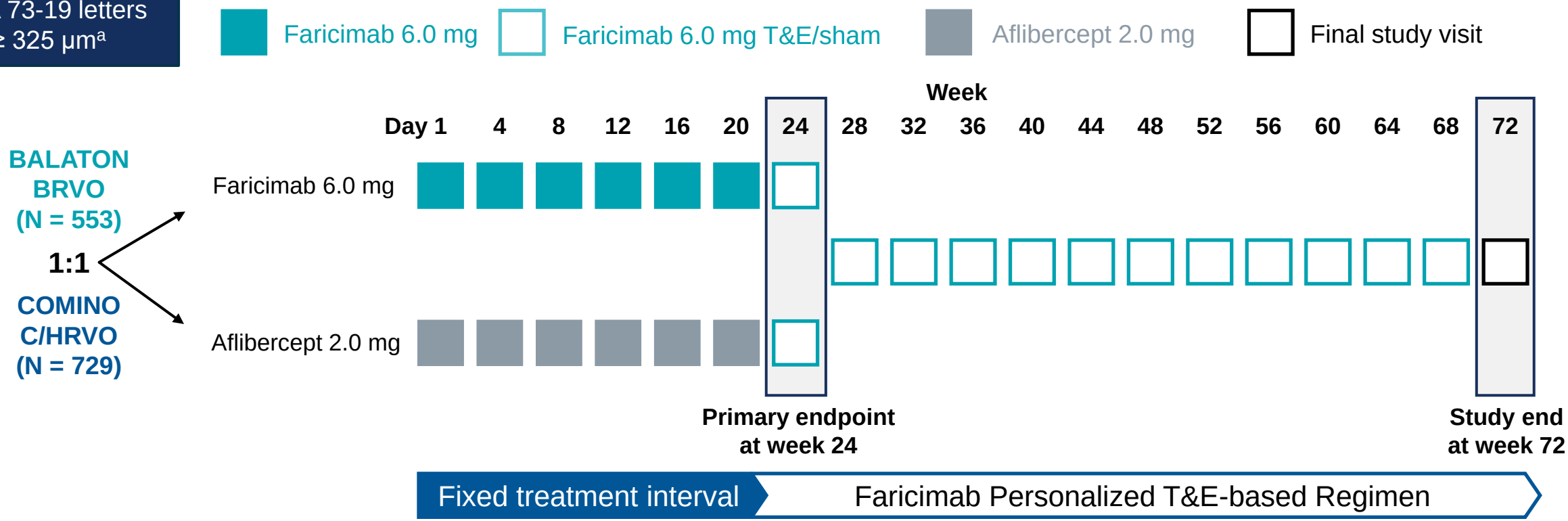
Presented at the Angiogenesis, Exudation, and Degeneration 2023 Virtual Congress | February 10–11, 2023

BALATON
COMINO

BALATON and COMINO
Phase 3, Randomized, Double-Masked, Multicenter Trials Designed to Evaluate the Efficacy and Safety of Faricimab vs Aflibercept

Key Inclusion criteria
- Age ≥18 years
- Treatment-naive macular edema due to RVO
- BCVA 73-19 letters CST ≥ 325 µm[a]

Primary endpoint: Change from baseline in BCVA[b] at week 24 (faricimab vs aflibercept)

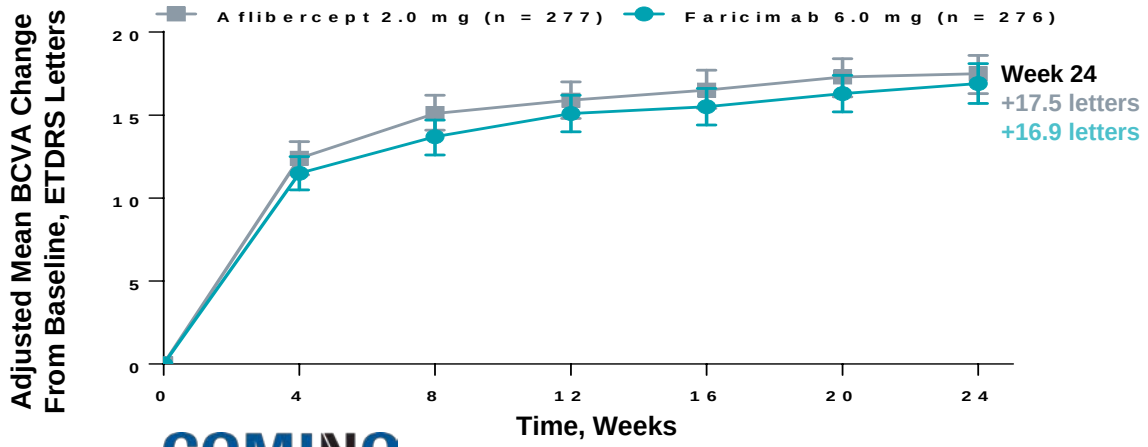


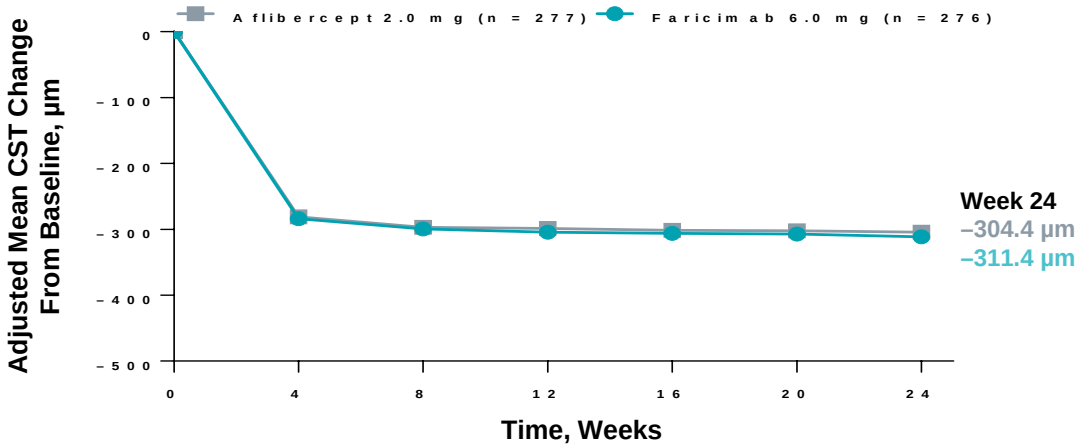
[a] CST ≥ 325 µm (Spectralis SD-OCT) or ≥ 315 µm (Cirrus SD-OCT or Topcon SD-OCT) at screening.
[b] BCVA was measured using the Early Treatment Diabetic Retinopathy Study visual acuity chart at a starting distance of 4 m.
BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; CST, central subfield thickness; HRVO, hemiretinal vein occlusion; RVO, retinal vein occlusion; SD-OCT, spectral domain optical coherence tomography; T&E, treat-and-extend.

Faricimab Achieved Robust Vision Gains and Reductions in CST Across Studies: Results Were Comparable Between Treatment Arms in Both Trials

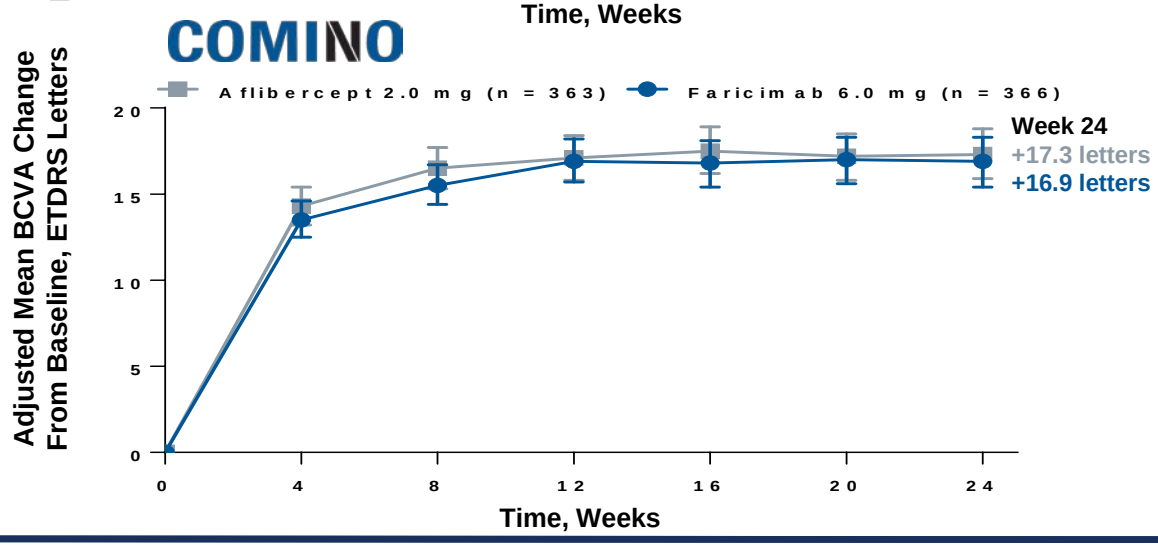
ITT Population

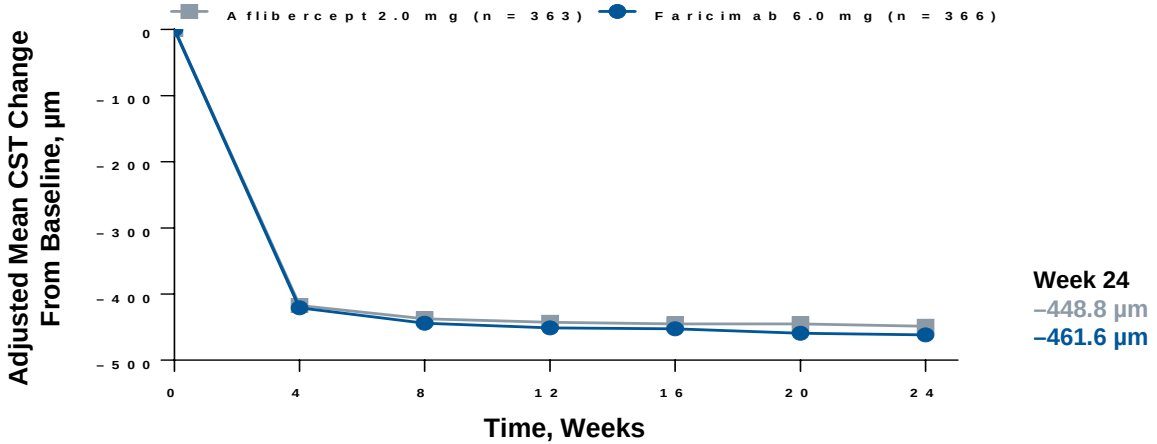
BALATON





COMINO



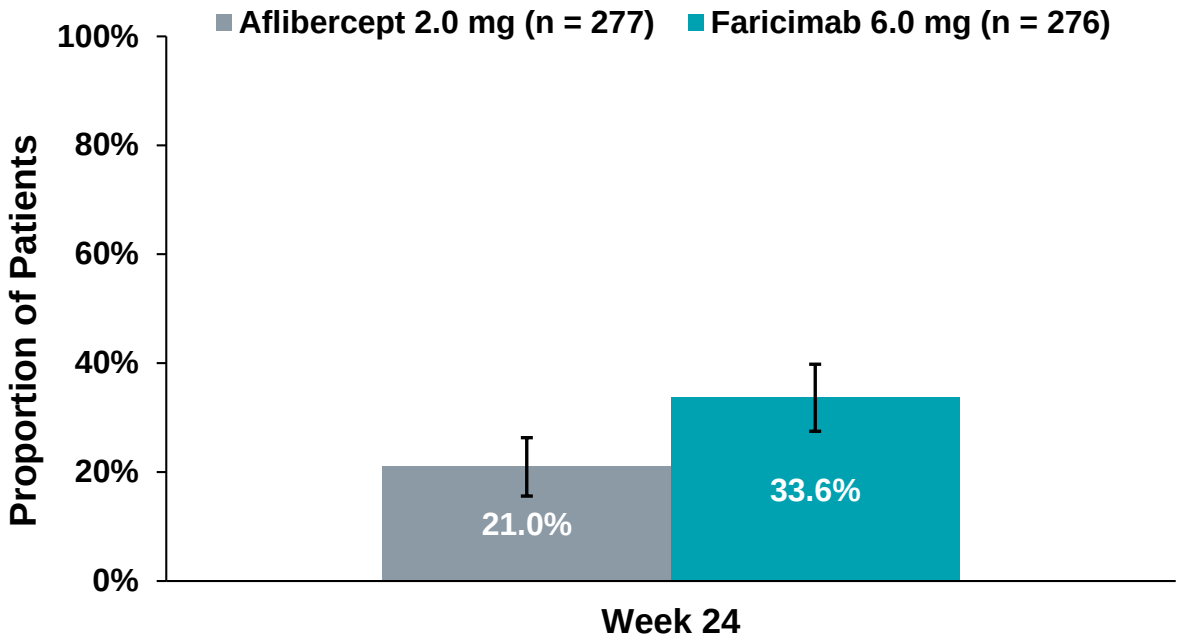


All observed values are used regardless of the occurrence of the intercurrent events. Results are based on a mixed model repeated measures analysis in the ITT population. 95.03% CIs are shown. . CST is measured as ILM-BM, as graded by central reading center. BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; BM, Bruch's membrane; CST, central subfield thickness; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; HRVO, hemiretinal vein occlusion; ITT, intent-to-treat.

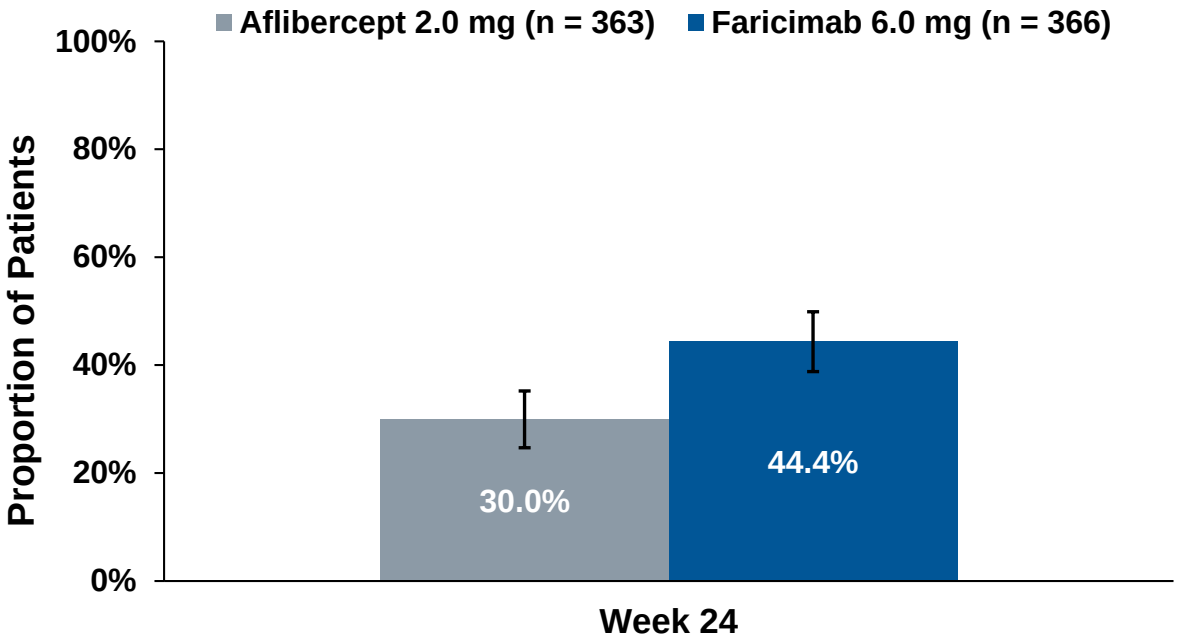
More Patients Achieved Absence of Macular Leakage[a] With Faricimab vs Aflibercept at Week 24

ITT Population

BALATON (BRVO)



COMINO (H/CRVO)



[a] Macular leakage area within ETDRS grid was assessed by the reading center based on FA images obtained at baseline and predefined follow-up intervals, Absence is defined as area of leakage within the macula of 0 mm^2 per FA. The prespecified exploratory analysis only included patients with evaluable FA data (BALATON: aflibercept, n = 224; faricimab, n = 229; COMINO: aflibercept, n = 297; faricimab, n = 311). All observed values are used regardless of the occurrence of the intercurrent events. Results are based on a descriptive summary in the ITT population. 95.03% CIs are shown.

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fluorescein angiography; HRVO, hemiretinal vein occlusion; ITT, intent-to-treat.

BALATON COMINO

Faricimab Was Well Tolerated, With a Safety Profile Similar to That of Aflibercept

AEs Through Week 24, Patients With ≥ 1 AE, n (%)	BALATON (BRVO)		COMINO (H/CRVO)	
	Aflibercept 2.0 mg n = 274	Faricimab 6.0 mg n = 276	Aflibercept 2.0 mg n = 361	Faricimab 6.0 mg n = 365
Ocular AEs	56 (20.4%)	45 (16.3%)	100 (27.7%)	84 (23.0%)
Serious ocular AEs	2 (0.7%)	3 (1.1%)	12 (3.3%)	9 (2.5%)
Ocular AEs of special interest	2 (0.7%)	1 (0.4%)	12 (3.3%)	8 (2.2%)
Intraocular inflammation events	0	1 (0.4%)*	4 (1.1%)	8 (2.2%)
Vitritis	0	0	0	3 (0.8%)
Iritis	0	0	2 (0.6%)	2 (0.5%)
Uveitis	0	0	1 (0.3%)	2 (0.5%)[a]
Noninfectious endophthalmitis	0	0	1 (0.3%)	0
Iridocyclitis	0	0	0	1 (0.3%)
Endophthalmitis events	0	0	1 (0.3%)	0
Retinal vasculitis events	0	0	0	0
Retinal artery occlusion/embolism[b]	0	0	2 (0.6%)	3 (0.8%)
Serious nonocular AEs	16 (5.8%)	9 (3.3%)	23 (6.4%)	22 (6.0%)
APTC events	4 (1.5%)	3 (1.1%)	5 (1.4%)	4 (1.1%)
AEs leading to treatment discontinuation through week 24	1 (0.4%)	1 (0.4%)	3 (0.8%)	3 (0.8%)

* Verbatim term “noninflammatory vitreous cells”.

[a] A single patient serious AE associated with a > 30-letter loss. [b] One retinal artery embolism in the aflibercept arm. Percentages are based on the n in the column headings. Results are presented based on the safety evaluable population; includes AEs with onset prior to week 24 (injection date or dose hold date for week 24). Multiple occurrences of the same AE in 1 individual are counted only once, except for the "Total number of AEs" and “Total number of serious AEs” rows in which multiple occurrences of the same AE are counted separately. Total number of AEs and serious AEs includes nonocular and ocular events in the study or fellow eye.
AE, adverse event; APTC, Antiplatelet Trialists’ Collaboration; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; HRVO, hemiretinal vein occlusion.

BALATON COMINO

Port Delivery System With Ranibizumab in Patients With Diabetic Macular Edema: Primary Analysis Results of the Phase 3 Pagoda Trial

Arshad M. Khanani, MD, MA, FASRS[1]

Varun Malhotra, MD, MBA[2]; Paul Latkany, MD[2]; Shamika Gune, MD[2]; Stephanie DeGraaf, PhD[2]; Ashwini Bobbala, MS[2]; Mel Rabena, BA[2]; Carlos Quezada-Ruiz, MD, FASRS[2,3]

On behalf of the Pagoda Investigators

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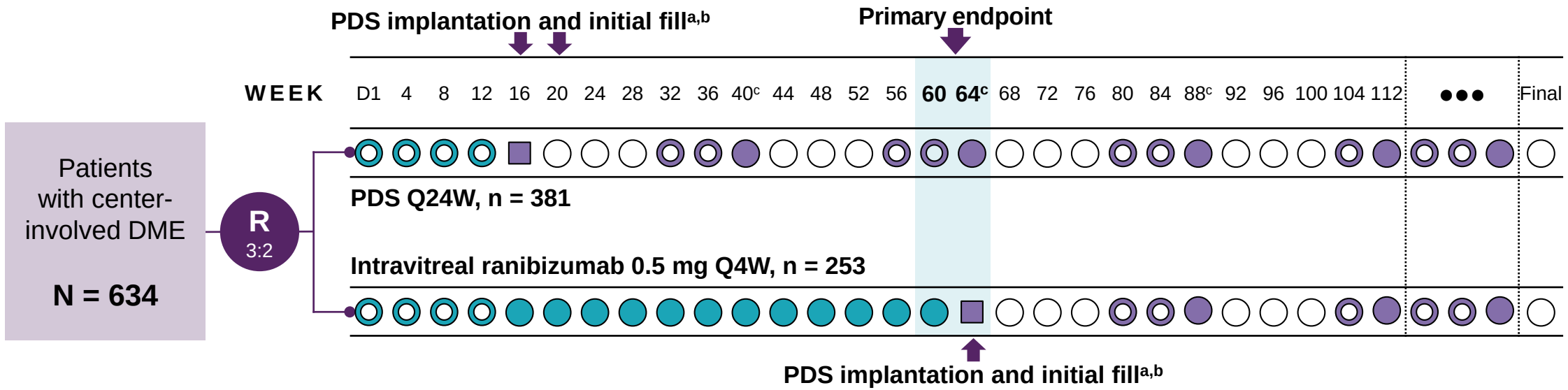
[2] Genentech, Inc., South San Francisco, CA, USA

[3] Clinica de Ojos Garza Viejo. San Pedro Garza Garcia, Nuevo Leon, Mexico

Presented at Bascom Palmer Eye Institute Angiogenesis, Exudation, and Degeneration 2023

Virtual | February 10–11, 2023

Pagoda Phase 3 Trial: Designed to Evaluate Efficacy, Safety, and Pharmacokinetics of PDS Q24W for DME



- Intravitreal ranibizumab 0.5 mg loading dose
- Intravitreal ranibizumab 0.5 mg
- PDS implantation and initial fill
- Patients assessed for supplemental treatment
- PDS refill-exchange
- Visit with no refill-exchange or intravitreal ranibizumab

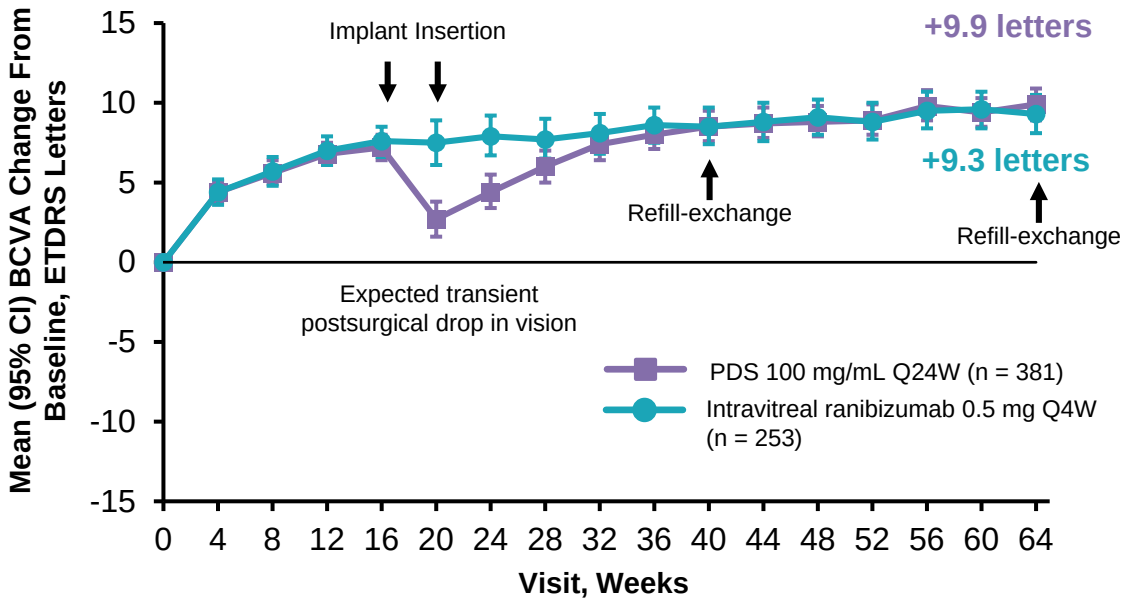
Primary Endpoint

Noninferiority of PDS Q24W compared with monthly intravitreal ranibizumab 0.5 mg injections based on change in BCVA score from baseline averaged over weeks 60 and 64

Pagoda, NCT04108156. Every 24-week interval consists of visits X, Y, and Z, with an 8-week interval between each visit until the final visit at end of study: visit X: 8 weeks post refill-exchange; visit Y: 16 weeks post refill-exchange; visit Z: PDS refill-exchange.
[a] Within 21–35 days since last intravitreal injection; additional visits for safety assessments 1 and 7 days after implantation. [b] If week 16 (PDS Q24W arm) or week 64 (ranibizumab 0.5 mg Q4W arm) is not possible; additional loading dose required at week 16 or week 64; implant insertion procedure must happen within 28 ± 7 days since last intravitreal injection; additional visits for safety assessments 1 and 7 days after implantation. [c] Delayed PDS implantation and initial fill, if applicable. Protocol updates in response to COVID-19 pandemic include patients to continue on monthly ranibizumab and undergo implantation at first allowable opportunity (week 40, 64, 88, etc); minimum 4 loading doses required before implantation (and the last injection within 21–35 days of implantation); safety assessment visits required at days 1 and 7 after implantation; implantation may be delayed 4 weeks, from week 40 to 44 or 64 to 68, under extenuating circumstances, similar to the implant delay allowed at week 20.
BCVA, best-corrected visual acuity; COVID-19, coronavirus disease 2019; D, day; DME, diabetic macular edema; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks; R, randomization.

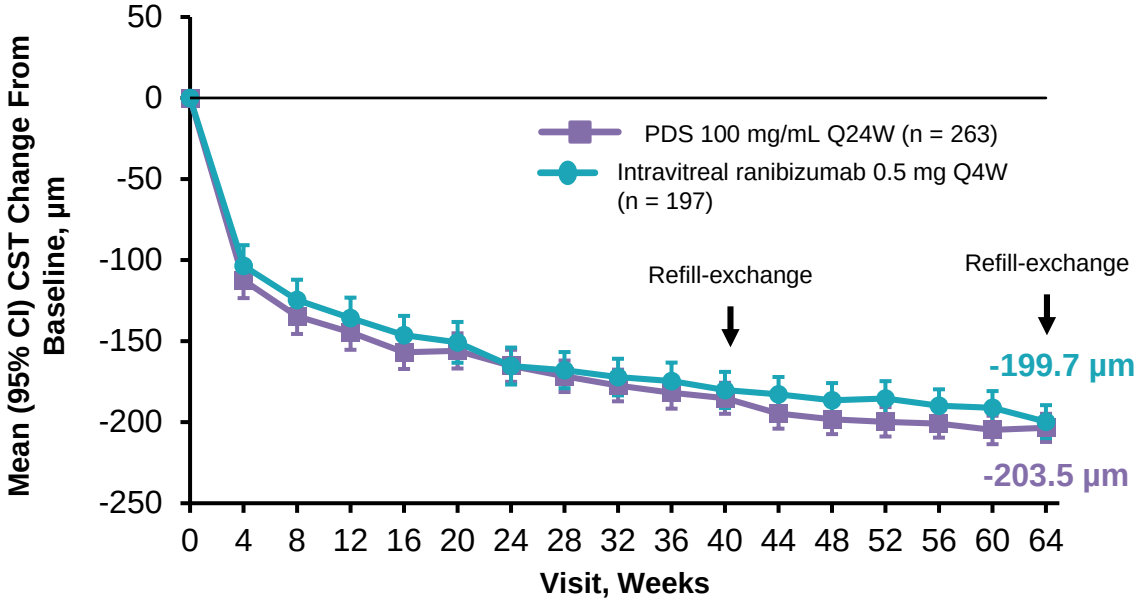
PDS Q24W Resulted Vision Gains and CST Reduction Comparable to Monthly Ranibizumab Through Week 64

Adjusted Mean BCVA Change From Baseline, Efficacy Population



n =	380	370	369	362	357	348	344	343	342	334	341	334	332	331	338	336	333
n =	253	251	243	241	238	237	241	235	234	230	222	232	231	224	228	227	217

Adjusted Mean CST Change From Baseline, mITT Population[a]

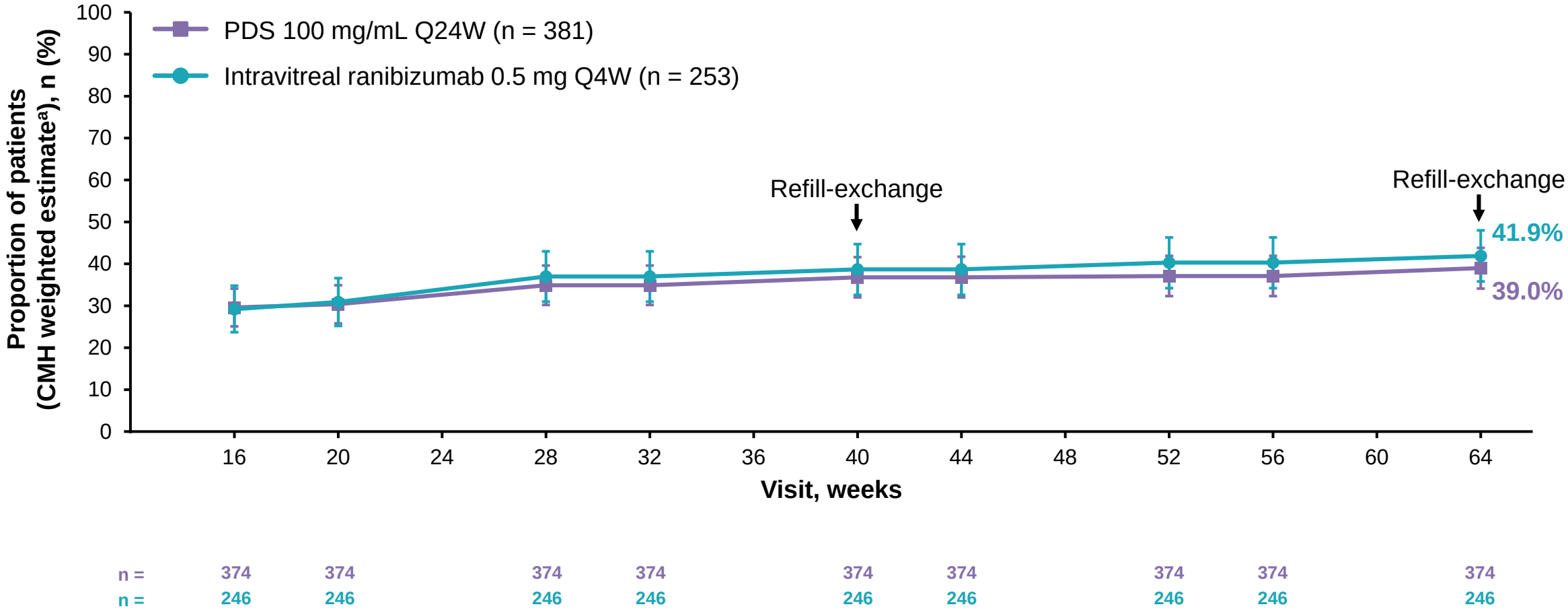


n =	263	258	256	256	260	247	249	247	250	251	254	245	244	244	249	247	247
n =	197	195	189	185	185	184	188	181	181	175	168	177	178	175	175	177	168

Pagoda, NCT04108156. a The mITT population comprised of all patients who had their PDS implant insertion at Week 16 or Week 20 and all patients in the intravitreal arm who received treatment, with the exclusion of all patients in the randomization blocks which included at least one patient in the PDS arm non-compliant to the protocol-defined PDS insertion schedule due to Sponsor-initiated surgery pause.
BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; CI, confidence interval; CST, center subfield thickness; mITT, modified intention to treat population; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.

PDS Q24W Resulted in Clinically Meaningful DRSS Improvements Over Time

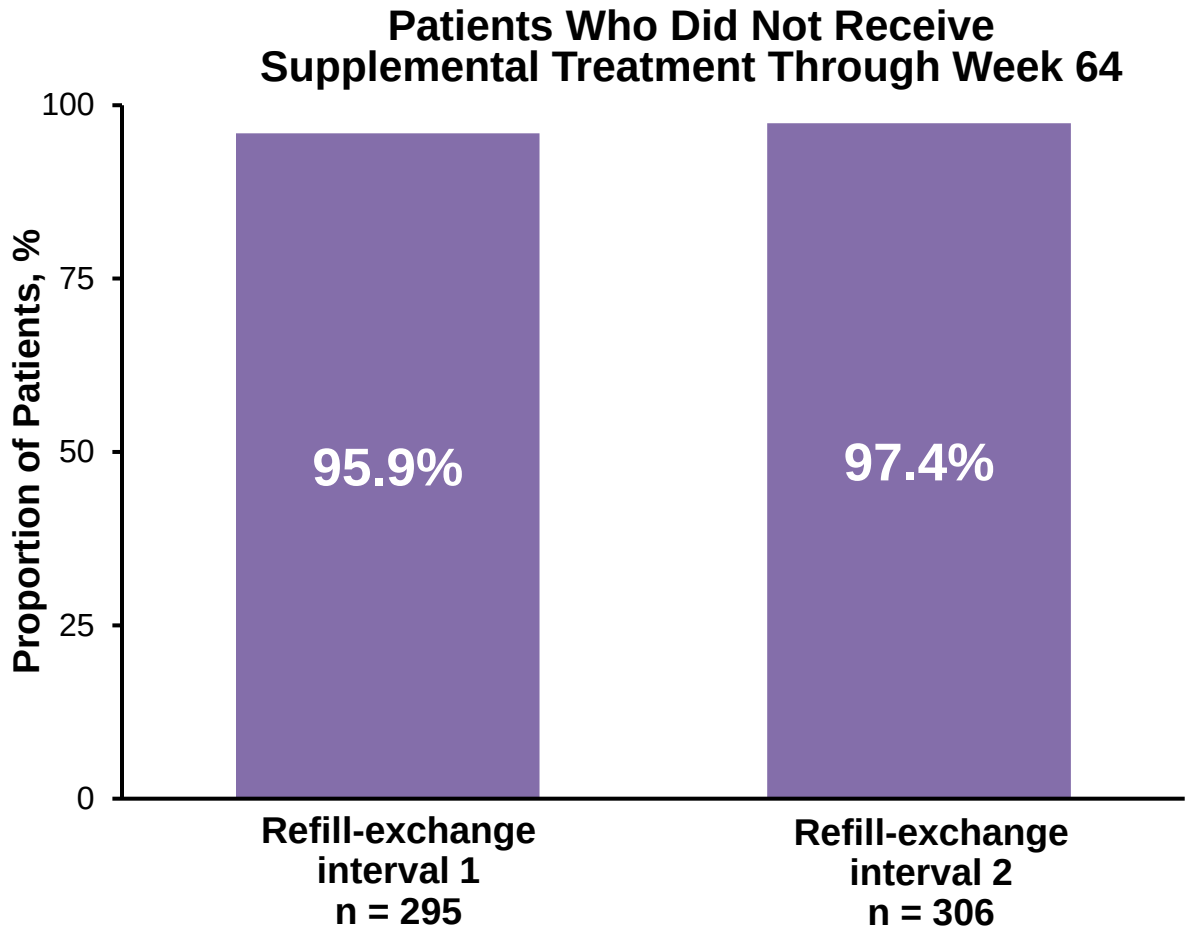
Proportion of Patients with a ≥ 2-Step Improvement from Baseline on ETDRS-DRSS in Study Eye Over Time Through Week 64, Efficacy Population



Pagoda, NCT04108156. Efficacy population. [a]The weighted estimate is based on CMH method stratified by baseline BCVA (≥ 64 vs. < 64 letters), prior intravitreal anti-VEGF treatment for DR with or without DME (yes vs. no), and DR severity (NPDR vs. PDR). Horizontal bars represent 95% CI. 95% CI is a rounding of 95.05% CI.

BCVA, best-corrected visual acuity; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; DME, diabetic retinopathy with diabetic macular edema; DR, diabetic retinopathy without diabetic macular edema; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks; VEGF, vascular endothelial growth factor.

>95% of PDS Q24W Patients Did Not Receive Supplemental Treatment Through Each Refill-Exchange Interval



Supplemental Treatment Criteria, Assessed at 2 Visits Before Refill-Exchange
Decrease of ≥ 15 letters from the best-recorded BCVA in the study due to the presence of DME
OR
Decrease of ≥10 letters from the day 1 visit BCVA score, due to the presence of DME
OR
Increase of ≥ 150 µm in CST on SD-OCT from the lowest CST measurement in the study, due to the presence of DME
OR
Development of high-risk PDR[a]

Pagoda, NCT04108156. Efficacy population.

[a] Development of high-risk PDR, as defined by any of the following criteria: Any vitreous or preretinal haemorrhage, neovascularization at disc ≥ 1/3 disc area, neovascularization elsewhere ≥ 1/2 disc area within an area equivalent to the mydriatic ETDRS 7 fields.

BCVA, best-corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; PDR, proliferative diabetic retinopathy; PDS, Port Delivery System with ranibizumab; Q24W, every 24 weeks. SD-OCT, spectral-domain optical coherence tomography.

Ocular AESIs Were Well Understood and Manageable

No Cases of Endophthalmitis or Retinal Detachment Were Reported in the PDS Q24W Arm After Implantation Through Week 64

Ocular AESIs in the Study Eye Through Week 64, Safety Population

	PDS 100 mg/mL Q24W (n = 320)		Intravitreal Ranibizumab 0.5 mg Q4W (n = 314)	
	Overall		Overall	
	All	Serious	All	Serious
Total number of AE, n	110	12	34	2
Total number of patients with ≥ 1 AE, n (%)	88 (27.5)	9 (2.8)	28 (8.9)	2 (0.6)
Cataract	35 (10.9)	1 (0.3)	23 (7.3)	1 (0.3)
Conjunctival bleb	25 (7.8)	4 (1.3)	0	0
Conjunctival erosion	6 (1.9)	5 (1.6)	0	0
Conjunctival retraction	4 (1.3)	1 (0.3)	0	0
Implant dislocation*	1 (0.3)	1 (0.3)	0	0
Endophthalmitis	0	0	1 (0.3)	1 (0.3)
Hyphema	6 (1.9)	0	0	0
Retinal detachment	0	0	0	0
Vitreous hemorrhage	31 (9.7)	1 (0.3)	5 (1.6)	0

One case of septum dislodgement was reported as a device deficiency in the PDS arm through week 64

* "Implant dislocation" is reported in MedDRA as "device dislocation".

Pagoda, NCT04108156. Safety population.
AE, adverse event; AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.

Port Delivery System With Ranibizumab in Patients With Diabetic Retinopathy: Primary Analysis Results of the Phase 3 Pavilion Trial

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On behalf of the Pavilion Investigators

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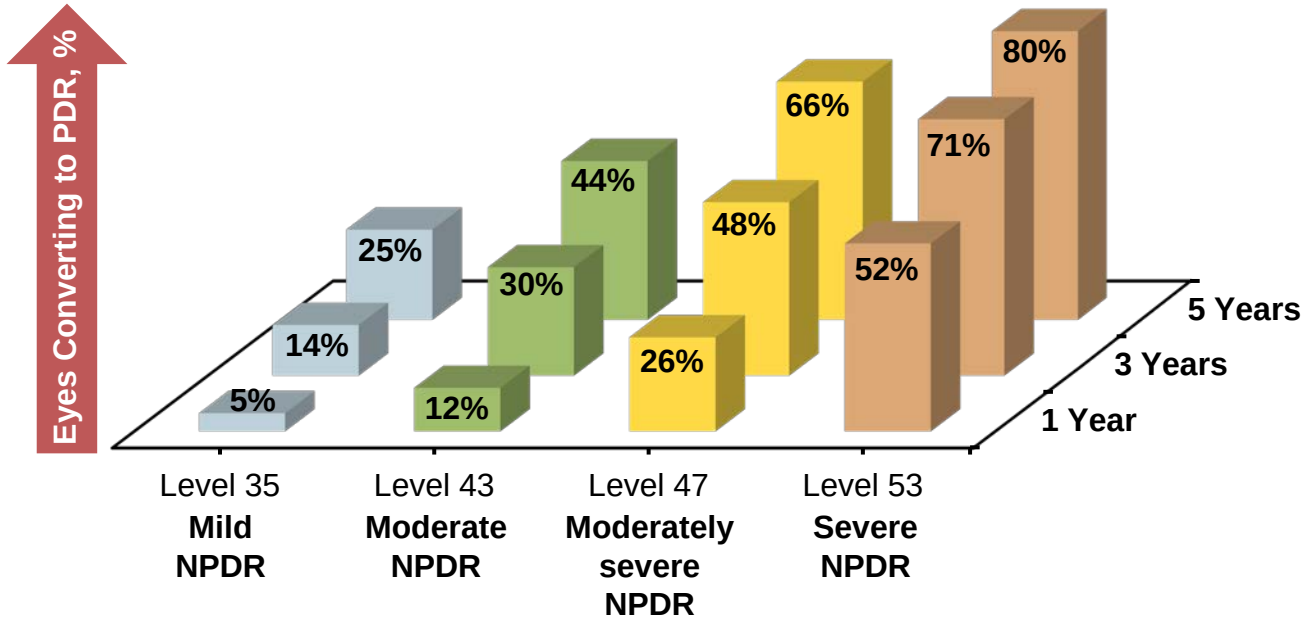
Presented at Bascom Palmer Eye Institute Angiogenesis, Exudation, and Degeneration 2023

Virtual | February 10–11, 2023

Risk of Developing Vision-Threatening Forms of DR Increases With Disease Severity

- DR affects over **one-third** of all people with diabetes, and is a **leading cause of vision loss** in adults worldwide[1–3]
- Patients with **moderately severe** to **severe NPDR** are at **high risk of progression to PDR and vision loss**[4]
- Current DR treatment guidelines generally recommend treatment upon onset of PDR and/or CI-DME[5]
- Observation with no treatment is currently a common practice for DR, given the treatment burden[5]

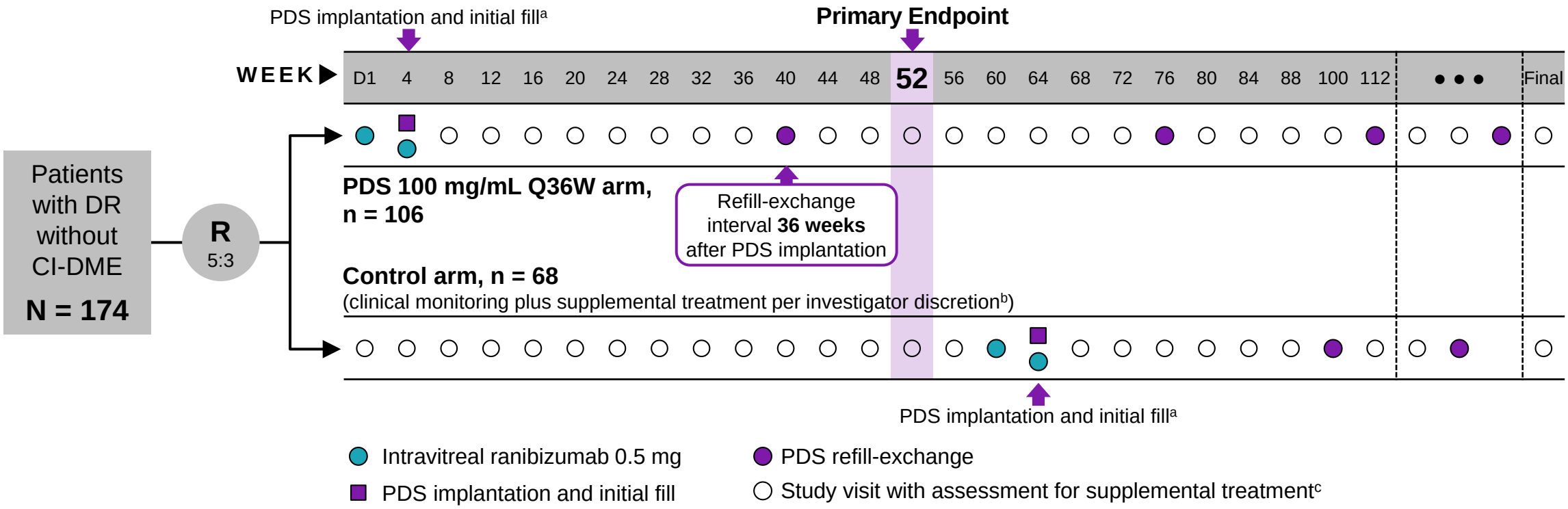
Progression of DR to PDR[4]



There is an unmet need for treatment options that prevent the progression of NPDR to PDR and development of vision-threatening complications, including DME

1. Flaxel CJ et al. *Ophthalmology*. 2020;127(1):P66-P145. 2. Yau JWY et al; Meta-Analysis for Eye Disease (META-EYE) Study Group. *Diabetes Care*. 2012;35(3):556-564. 3. Flaxman SR et al; Vision Loss Expert Group of the Global Burden of Disease Study. *Lancet Glob Health*. 2017;5(12):e1221-e1234. 4. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1991;98(5 suppl):823-833. 5. American Academy of Ophthalmology PPP Retina/Vitreous Committee. Diabetic Retinopathy PPP 2019, October 2019. Accessed January 2023. https://www.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp.
CI-DME, center-involved diabetic macular edema; DME, diabetic macular edema; DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Pavilion Phase 3 Trial: Designed to Evaluate Efficacy, Safety, and Pharmacokinetics of PDS Q36W for DR



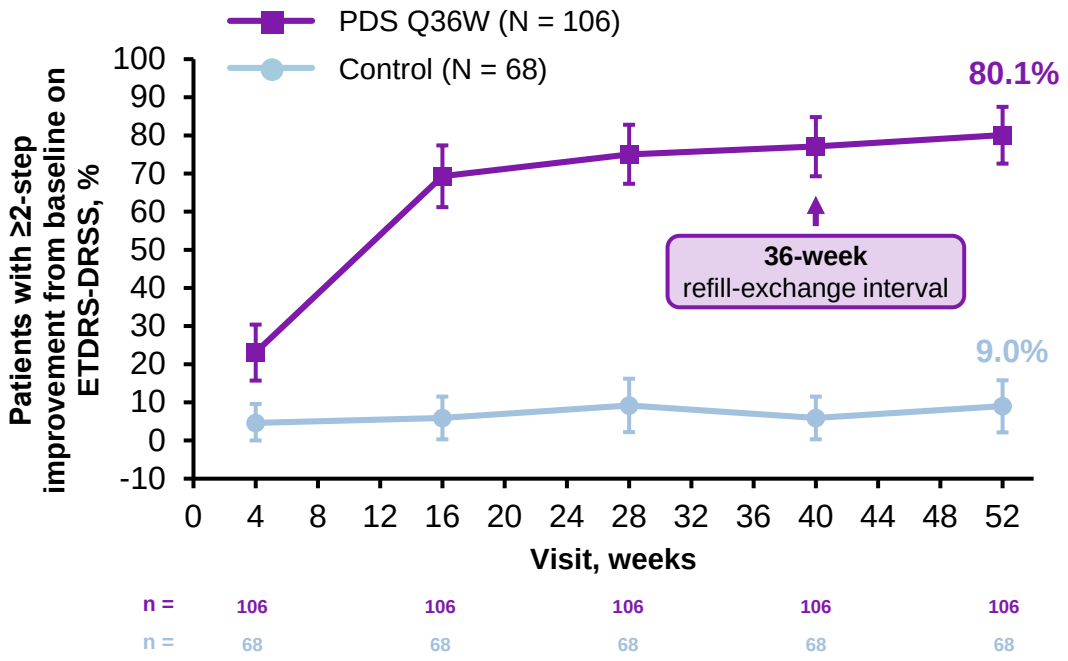
Primary Endpoint

Superior efficacy of PDS Q36W compared with control, based on proportion of patients with ≥ 2-step improvement from baseline on the ETDRS-DRSS at week 52

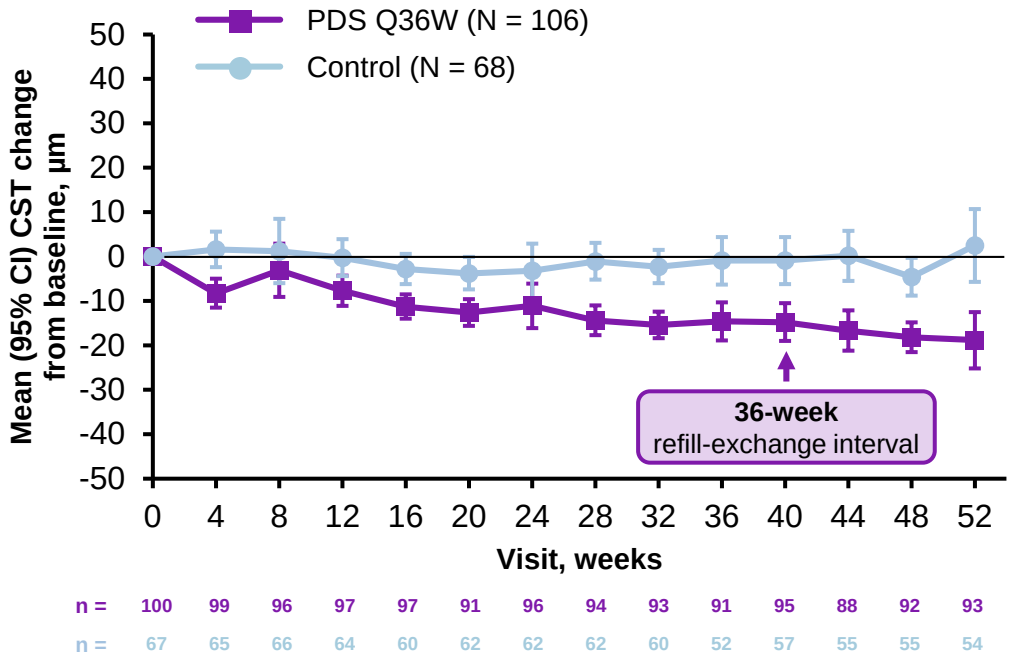
Pavilion, NCT04503551. [a] Additional visits for safety assessments 1 and 7 days after implant insertion procedure. [b] Observation only, plus supplemental treatment with intravitreal ranibizumab 0.5 mg per investigator discretion. Study visits Q4W for comprehensive clinical monitoring; no mandatory treatment per protocol; standard of care allowed until patients receive the PDS implant. [c] Patients were eligible to receive supplemental treatment with intravitreal ranibizumab 0.5 mg at each Q4W visit before week 60 (control), or at any non–refill-exchange visit (PDS Q36W) if any of the following criteria were met in the study eye as assessed by investigator: i) presence of CI-DME (CST ≥ 325 µm on SD-OCT; ii) development of PDR or ASNV.
ASNV, anterior segment neovascularization; CI-DME, center-involved diabetic retinopathy with diabetic macular edema; D, day; DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q36W, every 36 weeks; R, randomization; SD-OCT, spectral-domain optical coherence tomography.

A Greater Proportion of Patients Achieved ≥ 2-step Improvement on ETDRS-DRSS; Retinal Anatomy Maintained Through Week 52

Adjusted Proportion of Patients With ≥ 2-step Improvement From Baseline on ETDRS-DRSS Over Time, ITT population



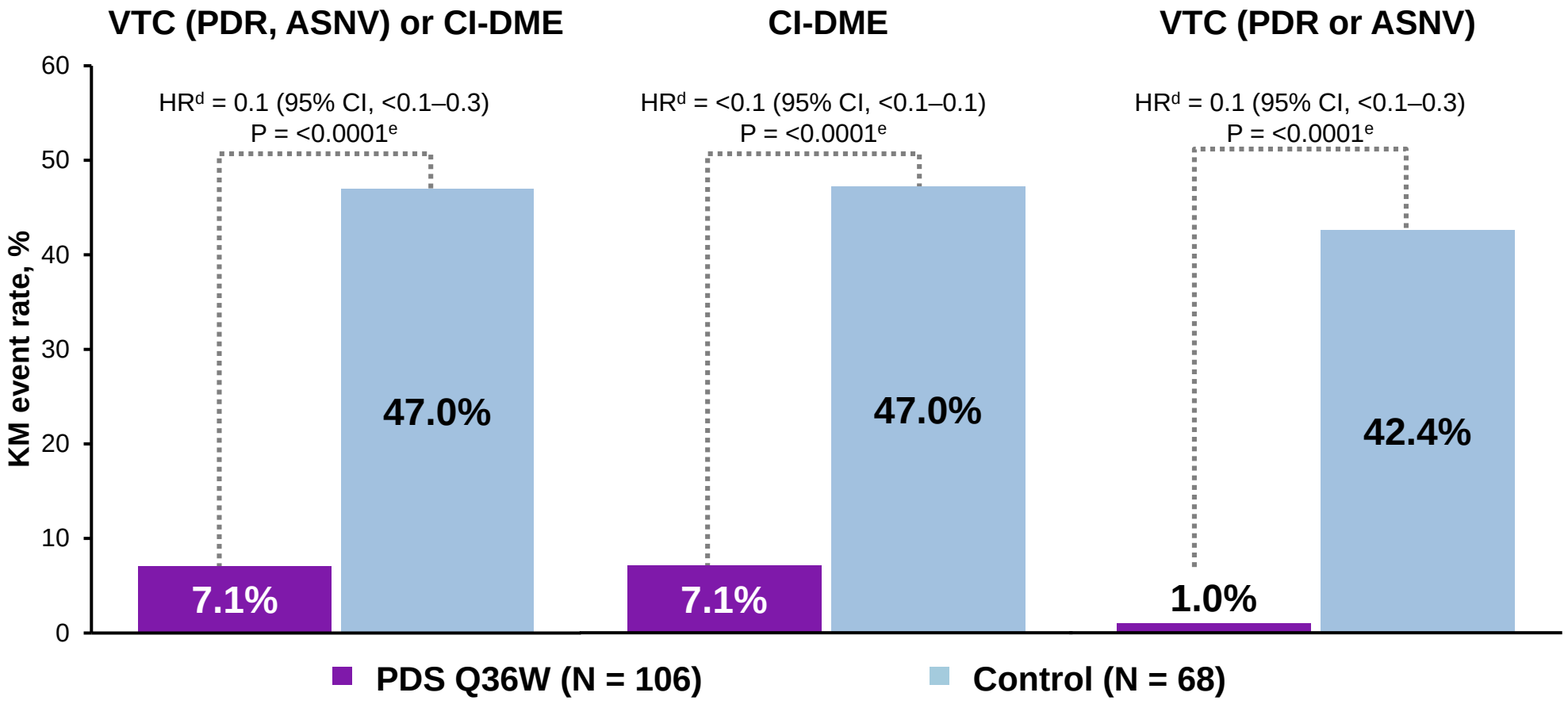
Adjusted Mean CST Change From Baseline Through Week 52, ITT Population



Pavilion, NCT04503551. CMH method (main estimand strategy): analysis was stratified by baseline ETDRS-DRSS level (47 vs. 53) and baseline intraretinal or subretinal fluid status (present vs. absent). The Type 1 error for the CIs adjusted for interim safety monitoring. MMRM method: the model adjusted for treatment group, visit, treatment-by-visit interaction, baseline CST score (continuous), baseline ETDRS-DRSS level (47 vs. 53), baseline intraretinal or subretinal fluid status (present vs. absent). The Type 1 error adjusted for interim safety monitoring. 95% CI is a rounding of 95.04% CI. All observed data are included in the analysis regardless of whether or not a patient has experienced an intercurrent event. Missing data are implicitly imputed by the MMRM model, assuming a missing at random mechanism.
CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CST, center subfield thickness; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intention to treat; PDS, Port Delivery System with ranibizumab; Q36W, every 36 weeks.

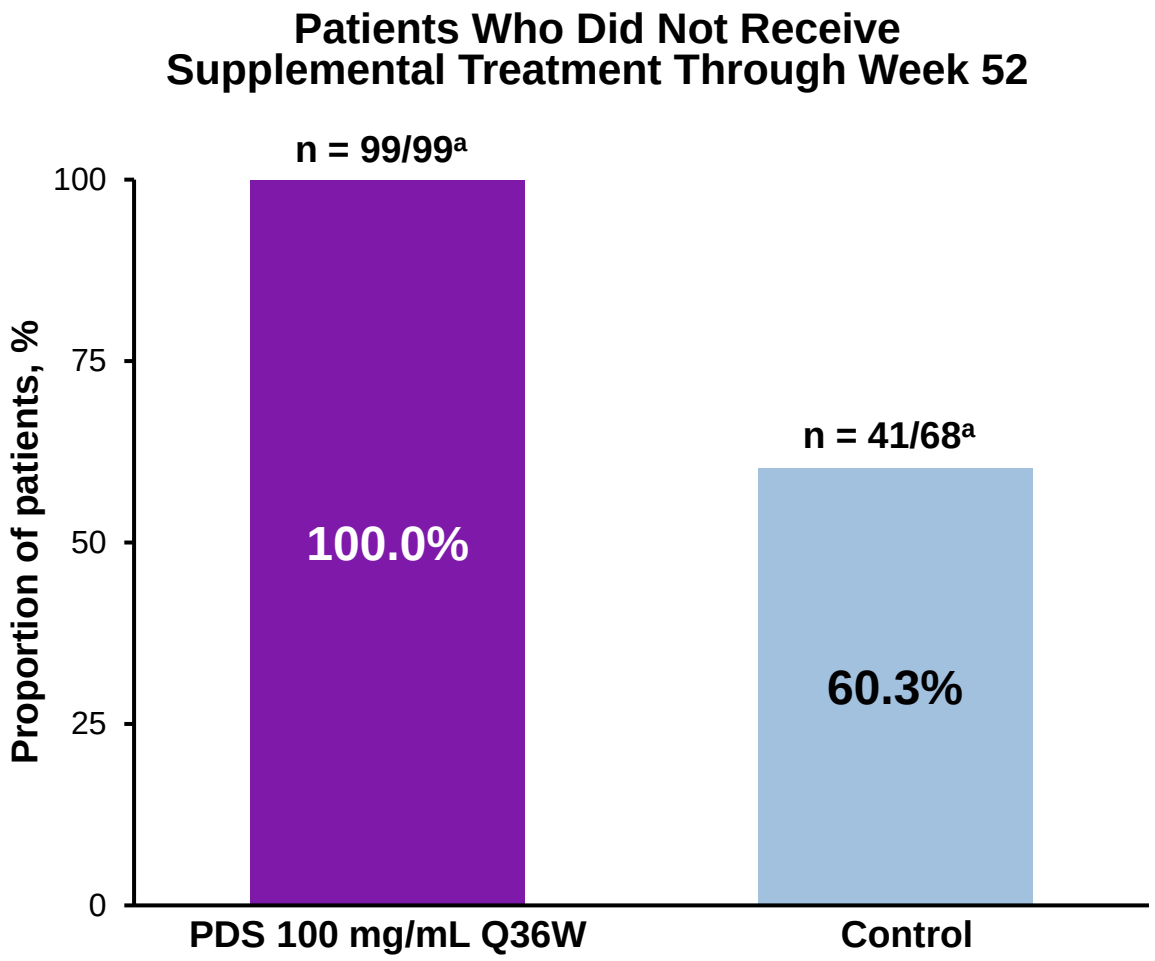
PDS Q36W Resulted in Fewer Patients Developing Vision-Threatening Complications or CI-DME

Rate of Patients Developing a Vision-Threatening Complication (PDR or ASNV) or CI-DME[b] Through Week 52, ITT Population



Pavilion, NCT04503551. Main estimand strategy: supplemental treatment, prohibited therapy, or PRP is considered to be an event. The Type 1 error adjusted for interim safety monitoring (95.04% CI is presented). Analysis was stratified by baseline ETDRS-DRSS level (47 vs. 53) and baseline intraretinal or subretinal fluid status (present vs. absent).[a] Protocol-defined (CST <325 µm). [b] Cox proportional hazards regression. [c] Log-rank test.
ASNV, anterior segment neovascularization; CI, confidence interval; CI-DME, center-involved diabetic retinopathy with diabetic macular edema; CST, central subfield thickness; HR, hazard ratio; ITT, intention to treat; KM, Kaplan-Meier; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; PDS, Port Delivery System with ranibizumab; Q36W, every 36 weeks; VTC, vision-threatening complication.

100% of Patients Treated With PDS Q36W Did Not Receive Supplemental Treatment Through Week 52



Supplemental Treatment Criteria
Presence of CI-DME, defined as CST ≥325 µm on SD-OCT as assessed by investigator
OR
Development of PDR or ASNV, as assessed by investigator

Pavilion, NCT04503551. [a] Number of patients who were assessed for the need of supplemental treatment at least once.
ASNV, anterior segment neovascularization; CI-DME, center-involved diabetic retinopathy with diabetic macular edema; CST, central subfield thickness; PDR, proliferative diabetic retinopathy; PDS, Port Delivery System with ranibizumab; Q36W, every 36 weeks; SD-OCT, spectral-domain optical coherence tomography.

Majority of Ocular AESIs Through Week 52 Were Non-Serious

No Cases of Endophthalmitis or Implant Dislocation Were Reported Through Week 52

Ocular AESIs in the Study Eye Through Week 52

	PDS 100 mg/mL Q36W (n = 105)	
	Overall*	
	All	Serious
Overall total number of AEs, n	**22**	**2**
Total number of patients with ≥ 1 AE, n (%)	**17 (16.2)**	**2 (1.9)**
Cataract	7 (6.7)	0
Conjunctival bleb	2 (1.9)	0
Conjunctival erosion	1 (1.0)	0
Conjunctival retraction	2 (1.9)	0
Endophthalmitis	0	0
Hyphema	2 (1.9)	0
Implant dislocation†	0	0
Retinal detachment	1 (1.0)	1 (1.0)
Vitreous hemorrhage	6 (5.7)	1 (1.0)

* Overall period: day of first loading dose through week 52

† "Implant dislocation" is reported in MedDRA as "device dislocation"

Pavilion, NCT04503551. Safety population. For frequency counts of "Total number of AEs" rows, multiple occurrences of the same AE in an individual are counted separately.
AE, adverse event; AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; PDS, Port Delivery System with ranibizumab; Q36W, every 36 weeks.

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