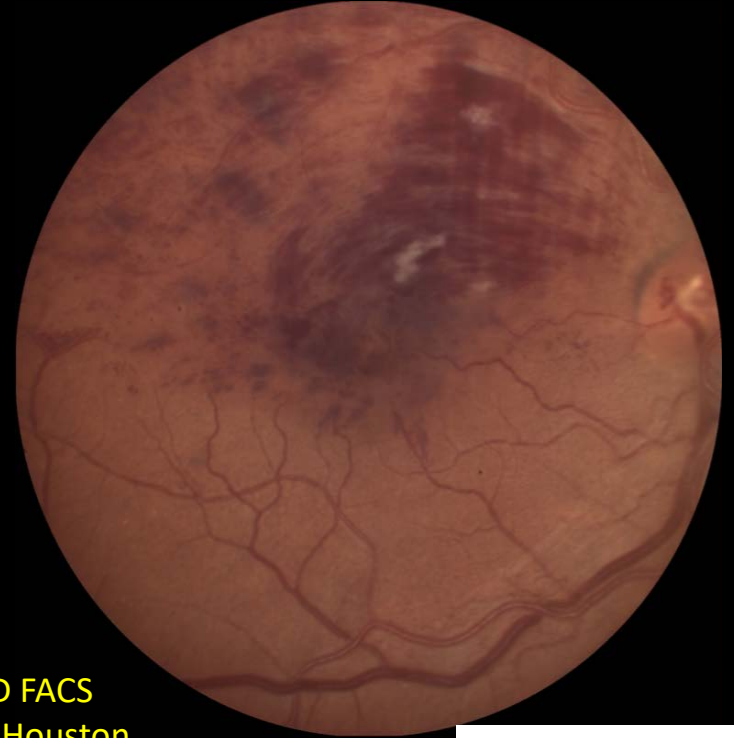
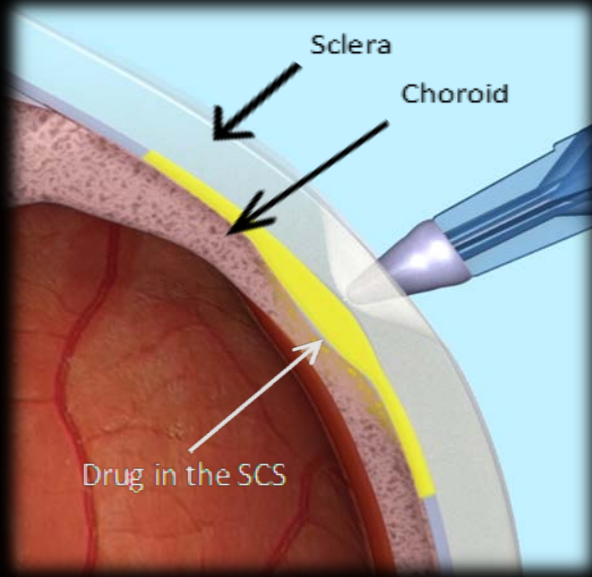


Suprachoroidal Triamcinolone Acetonide with Intravitreal Aflibercept For Retinal Vein Occlusion: Phase 2 Results – TANZANITE study



David M. Brown MD FACS
Retina Consultants of Houston
Blanton Eye Institute, Houston Methodist Hospital
Houston, Texas USA

▪ **Research Grant Funding:**

Alcon/Novartis, Allergan, Clearside Biomedical, Genentech/Roche, NEI/NIH, Ophthotech, PRN, Regeneron/Bayer, Second Sight, Thrombogenics

▪ **Consultant / Scientific Advisory Boards:**

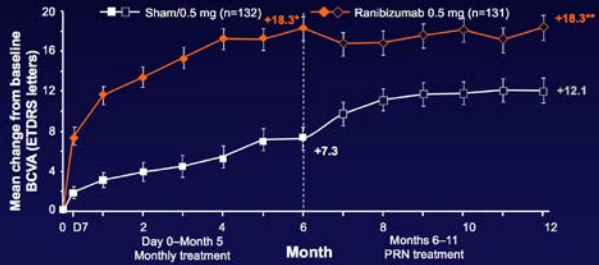
Adverum, Alcon/Novartis, Allergan, Carl Zeiss Meditec, Coda Therapeutics, Clearside Biomedical, Envisia, Janssen, Johnson & Johnson, Genentech/Roche, Heidelberg Engineering, Notal Vision, Ophthotech, OPTOS/Nikon, Optovue, Pfizer, Regeneron/Bayer, RegenxBio, Stealth Biotherapeutics, Thrombogenics

DMB had Full Control of Presentation

Anti-VEGF Improves VA in RVO

BRAVO

BCVA up to Month 12 in patients with macular edema following BRVO

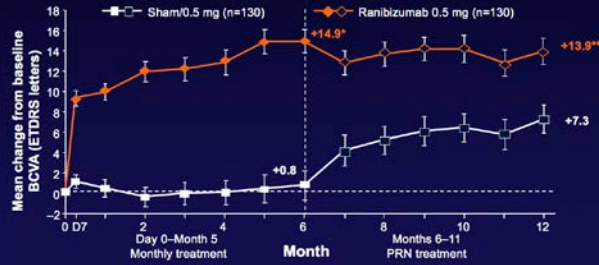


*p<0.0001 vs sham, **p<0.01 vs sham (post-hoc analyses)

Brown D, et al. Ophthalmology 2011;118:1594

CRUISE

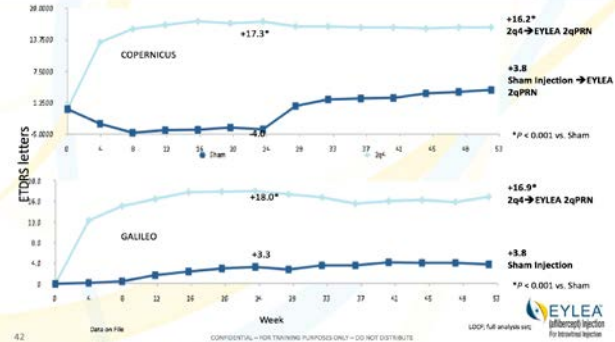
BCVA up to Month 12 in patients with macular edema following CRVO



*p<0.0001 vs sham, **p<0.001 vs sham (post-hoc analysis)

Brown, et al. Ophthalmology 2010

Mean Change in Visual Acuity



*P < 0.001 vs. Sham
EYLEA (aflibercept) injection for intravitreal use
LDOF, full analysis set
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Sustained Benefits from Ranibizumab for Macular Edema Following Branch Retinal Vein Occlusion: 12-Month Outcomes of a Phase III Study

Diaz M, Brown MD, Finkelstein D, et al. Ophthalmology 2011;118:1594

Abstract. Aims: To assess efficacy and safety of intravitreal injections of 0.5 mg of ranibizumab in patients with macular edema following branch retinal vein occlusion (BRVO). Methods: This phase III, randomized, controlled trial compared ranibizumab 0.5 mg intravitreal injection with sham injection in patients with macular edema following BRVO. Results: At baseline, mean BCVA was 12.1 letters in the sham group and 18.3 letters in the ranibizumab group. At 12 months, mean BCVA was 12.1 letters in the sham group and 18.3 letters in the ranibizumab group. Conclusion: Ranibizumab 0.5 mg intravitreal injection significantly improved BCVA in patients with macular edema following BRVO compared with sham injection.

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Ranibizumab for Macular Edema following Central Retinal Vein Occlusion

Six-Month Primary End Point Results of a Phase III Study

Diaz M, Brown MD, Finkelstein D, et al. Ophthalmology 2010

Abstract. Aims: To assess efficacy and safety of intravitreal injections of 0.5 mg of ranibizumab in patients with macular edema following central retinal vein occlusion (CRVO). Methods: This phase III, randomized, controlled trial compared ranibizumab 0.5 mg intravitreal injection with sham injection in patients with macular edema following CRVO. Results: At baseline, mean BCVA was 7.3 letters in the sham group and 14.9 letters in the ranibizumab group. At 6 months, mean BCVA was 7.3 letters in the sham group and 14.9 letters in the ranibizumab group. Conclusion: Ranibizumab 0.5 mg intravitreal injection significantly improved BCVA in patients with macular edema following CRVO compared with sham injection.

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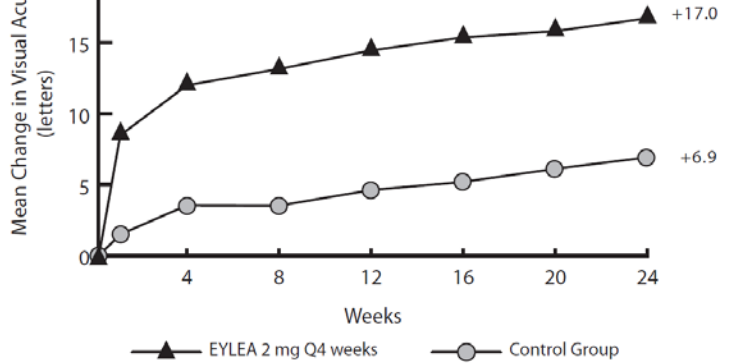
Intravitreal Aflibercept Injection for Macular Edema Due to Central Retinal Vein Occlusion

Two-Year Results from the COPERNICUS Study

Diaz M, Brown MD, Finkelstein D, et al. Ophthalmology 2011;118:1594

Abstract. Aims: To assess the efficacy and safety of intravitreal aflibercept injection (EYLEA) for the treatment of macular edema due to central retinal vein occlusion (CRVO). Methods: This phase III, randomized, controlled trial compared EYLEA 2 mg intravitreal injection with sham injection in patients with macular edema due to CRVO. Results: At baseline, mean BCVA was 3.8 letters in the sham group and 16.9 letters in the EYLEA group. At 24 weeks, mean BCVA was 3.8 letters in the sham group and 16.9 letters in the EYLEA group. Conclusion: EYLEA 2 mg intravitreal injection significantly improved BCVA in patients with macular edema due to CRVO compared with sham injection.

VIBRANT



▲ EYLEA 2 mg Q4 weeks ● Control Group

Retinal Vein Occlusion

Reprinted from *RETINA*, Winter 1981
Vol. 1, No. 1
C.F. E. Lippincott Co. Printed in U.S.A.

CENTRAL RETINAL VEIN OCCLUSION: A Prospective Histopathologic Study of 29 Eyes in 28 Cases

W. RICHARD GREEN, MD, CHI CHAO CHAN, MD,
GROVER M. HUTCHINS, MD, JOSEPH M. TERRY, MD

Abstract: The clinical and histopathologic features of 29 eyes from 28 patients with central retinal vein occlusion (CRVO) are reported. A fresh or recanalized thrombus was observed in each eye. This study considers the temporal aspects of the cases, and it notes the different morphologic features of the occlusion. These observations explain most of the variability of the changes observed in previous reports. We believe these different features represent the various stages in the natural evolution of such a thrombus. The interval between CRVO and histopathologic study in our series ranged from six hours to more than ten years. Local and systemic factors were analyzed and were found to be important in the pathogenesis of thrombus formation. Local diseases with a predisposing effect on CRVO

included glaucoma, papilledema, subdural hemorrhage, optic nerve hemorrhage, and dilation of the optic nerve head. Associated systemic diseases included hyperlipidemia, cardiovascular and cerebrovascular disease, diabetes mellitus, and leukemia with thrombocytopenia.

A fresh thrombus in the CRVO was observed in three (10.3%) and a recanalized thrombus in 26 eyes (89.7%). Endothelial cell proliferation was a conspicuous feature in 14 (48.3%) of the eyes. Chronic inflammation in the area of the thrombus and/or vein wall or perivascular area was observed in 14 (48.3%) of the eyes. Arterial occlusive disease was observed in seven eyes (24.1%). Central macular edema was found in 26 (89.7%) of the eyes. *RETINA* 1:27-55, 1981

The pathology of central retinal vein occlusion (CRVO) has been studied by numerous observers since its first description by Michel¹ in 1878. Various histopathologic features have been described in the central retinal vein (CRV) after thrombosis, including: thrombus or recanalized thrombus²⁻⁵; endothelial cell proliferation^{6,7}; obliterative endophlebitis^{8,9}; phlebitis¹⁰; intimal proliferation^{11,12}; and phlebotomosis.¹³ In experimental animals, a combination of occlusion of both the central retinal artery (CRA) and vein in the orbit was necessary to produce the ophthalmoscopic features of CRVO.¹⁴

We undertook this prospective study in an effort to delineate more clearly the morphologic changes in this condition in human eyes.

Materials and Methods

All eyes submitted to the Eye Pathology Laboratory of the Wilmer Institute in a six-year period (1974-1979) with a clinical history or gross findings of central retinal vein occlusion were included in the study. In one case in which the eyes were obtained postmortem, there was no clinical history or gross findings of CRVO, but a fresh thrombus was observed incidentally in one eye on histopathologic examination.

When necessary, additional clinical information was obtained from the attending ophthalmologist. In each case, serial sections through the optic nerve head were obtained in order to trace the central retinal vein and artery through the optic nerve head and anterior portion of the optic nerve. Sections were stained with the following techniques: hematoxylin-eosin, periodic-acid Schiff, Van de Graaf, Verhoeff-van Gieson, Prussian blue, and phosphotungstic acid-hematoxylin. Flat preparations of portions of the retina of those eyes was made by the tryptic digestion technique.

From the Eye Pathology Laboratory, Wilmer Ophthalmological Institute and the Cardiovascular Pathology Section, Department of Pathology, The Johns Hopkins Medical Institution, Baltimore, Maryland.

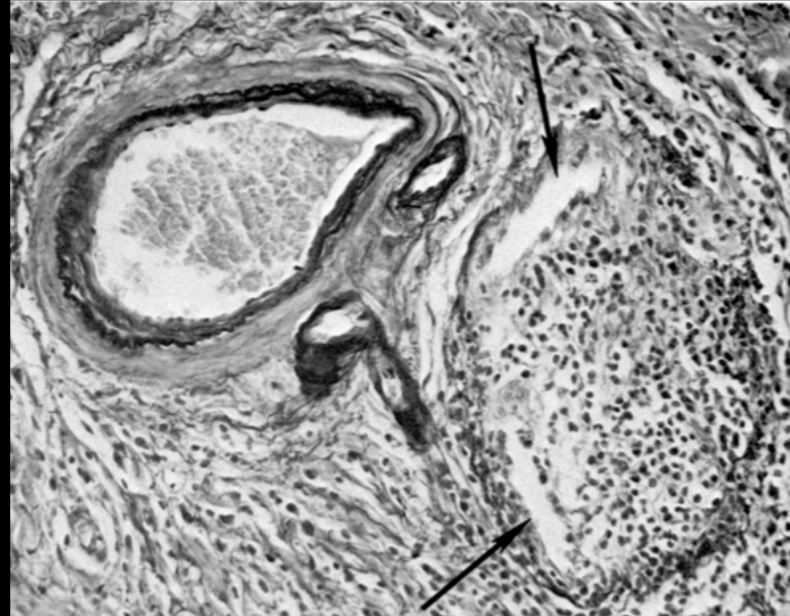
This study was reported in part at the 116th Annual Meeting of the American Ophthalmological Society, Kamuela, Hawaii, May 13, 1980.

Supported in part by Research Grant 1 RO1 EY 03088 (Dr. Green) from the National Eye Institute, DPHS.
Reprint requests: W. Richard Green, MD, Eye Pathology Laboratory, Johns Hopkins Hospital, 600 N Wolfe Street, Baltimore, MD 21205.

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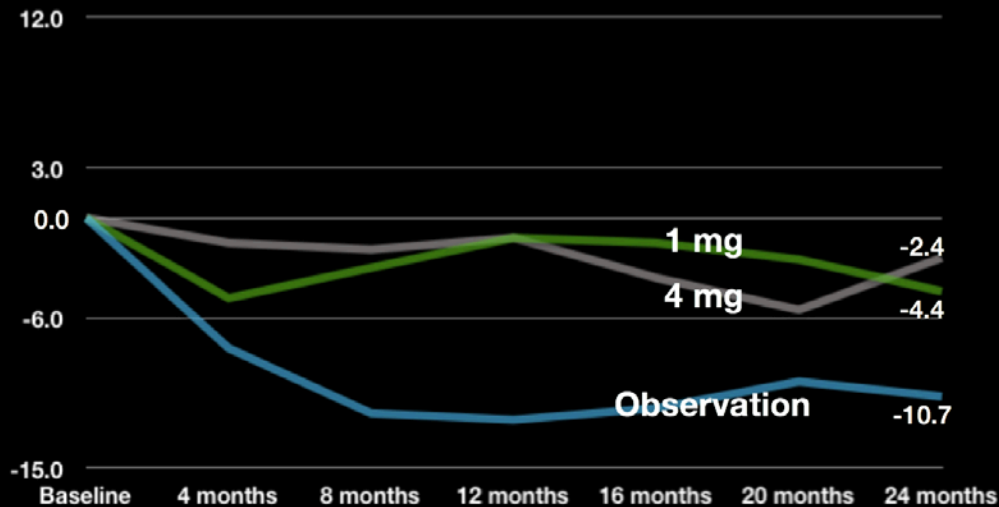
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SCORE CRVO

Mean Letters Gain/Lost from Baseline



A Randomized Trial Comparing the Efficacy and Safety of Intravitreal Triamcinolone With Standard Care to Treat Vision Loss Associated With Macular Edema Secondary to Branch Retinal Vein Occlusion

The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study Report 4

Objective: To compare the efficacy and safety of 1 mg and 4 mg of intravitreal triamcinolone with standard care in the treatment of macular edema secondary to branch retinal vein occlusion (BRVO).

Design: Randomized, controlled, clinical trial of an interventional study.

Setting: Tertiary care centers, 1994 and 1995 at a tertiary care center in the United States.

Participants: Patients with macular edema secondary to BRVO.

Interventions: Intravitreal triamcinolone (1 mg or 4 mg) or standard care.

Measurements and Main Results: At 24 months, the mean change in visual acuity was significantly greater in the 1 mg triamcinolone group than in the standard care group.

Conclusions: There was no difference identified in the mean change in visual acuity between the 1 mg and 4 mg groups. The mean change in visual acuity was significantly greater in the 1 mg triamcinolone group than in the standard care group.

Application to Clinical Practice: Intravitreal triamcinolone (1 mg) is a safe and effective treatment for macular edema secondary to BRVO.

Keywords: triamcinolone, macular edema, branch retinal vein occlusion, visual acuity.

Introduction: Branch retinal vein occlusion (BRVO) is a common cause of macular edema and vision loss. The standard of care for BRVO is observation.

Conclusion: Intravitreal triamcinolone (1 mg) is a safe and effective treatment for macular edema secondary to BRVO.

A Randomized Trial Comparing the Efficacy and Safety of Intravitreal Triamcinolone With Observation to Treat Vision Loss Associated With Macular Edema Secondary to Central Retinal Vein Occlusion

The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study Report 5

Objective: To compare the efficacy and safety of 1 mg and 4 mg of intravitreal triamcinolone with observation in the treatment of macular edema secondary to central retinal vein occlusion (CRVO).

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Setting: Tertiary care centers, 1994 and 1995 at a tertiary care center in the United States.

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Application to Clinical Practice: Intravitreal triamcinolone (1 mg) is a safe and effective treatment for macular edema secondary to CRVO.

Keywords: triamcinolone, macular edema, central retinal vein occlusion, visual acuity.

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Conclusion: Intravitreal triamcinolone (1 mg) is a safe and effective treatment for macular edema secondary to CRVO.

CLINICAL TRIALS
A Randomized Trial Comparing the Efficacy and Safety of Intravitreal Triamcinolone With Standard Care to Treat Vision Loss Associated With Macular Edema Secondary to Branch Retinal Vein Occlusion

The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study Report 4
 Drs. Li-Hsiang Su, Ronald Chang*

Objective: To compare the efficacy and safety of 1 mg and 4 mg of intravitreal triamcinolone with standard care in the treatment of vision loss associated with macular edema secondary to branch retinal vein occlusion (BRVO).

Methods: Retrospective analysis of a randomized trial of 400 patients.

Results: Vision improvement, 10% and 14% of patients, respectively, was observed in the triamcinolone 1 mg and 4 mg groups, respectively, compared with 2% in the standard care group.

Conclusion: There was no difference identified in the efficacy of 1 mg and 4 mg of intravitreal triamcinolone with standard care in the treatment of vision loss associated with macular edema secondary to BRVO.

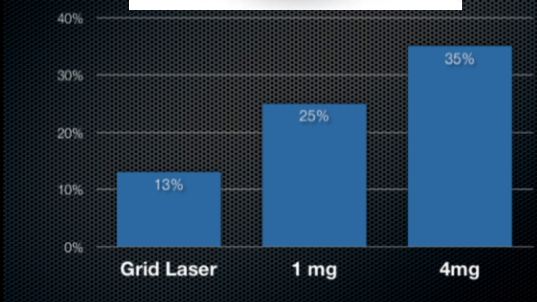
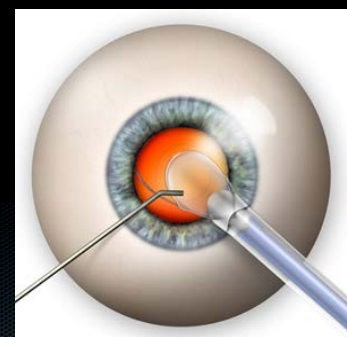
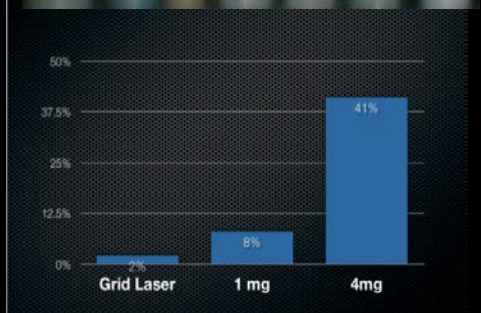
Application to Clinical Practice: Grid laser photocoagulation is the standard of care for BRVO. Intravitreal triamcinolone may be used as an adjunct to grid laser photocoagulation in the treatment of vision loss associated with macular edema secondary to BRVO.

Key Words: triamcinolone, branch retinal vein occlusion, macular edema, vision loss

Retinal vein occlusion (RVO) is a common cause of vision loss. The standard of care for RVO is grid laser photocoagulation. However, grid laser photocoagulation is not always effective in the treatment of vision loss associated with macular edema secondary to RVO. Intravitreal triamcinolone may be used as an adjunct to grid laser photocoagulation in the treatment of vision loss associated with macular edema secondary to RVO.

For editorial comment see page 1233

Introduction
 Retinal vein occlusion (RVO) is a common cause of vision loss. The standard of care for RVO is grid laser photocoagulation. However, grid laser photocoagulation is not always effective in the treatment of vision loss associated with macular edema secondary to RVO. Intravitreal triamcinolone may be used as an adjunct to grid laser photocoagulation in the treatment of vision loss associated with macular edema secondary to RVO.



CLINICAL TRIALS
A Randomized Trial Comparing the Efficacy and Safety of Intravitreal Triamcinolone With Observation to Treat Vision Loss Associated With Macular Edema Secondary to Central Retinal Vein Occlusion

The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study Report 5
 Drs. Li-Hsiang Su, Ronald Chang*

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Conclusion: There was no difference identified in the efficacy of 1 mg and 4 mg of intravitreal triamcinolone with observation in the treatment of vision loss associated with macular edema secondary to CRVO.

Key Words: triamcinolone, central retinal vein occlusion, macular edema, vision loss

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CLINICAL TRIALS
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The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study Report 6
 Drs. Li-Hsiang Su, Ronald Chang*

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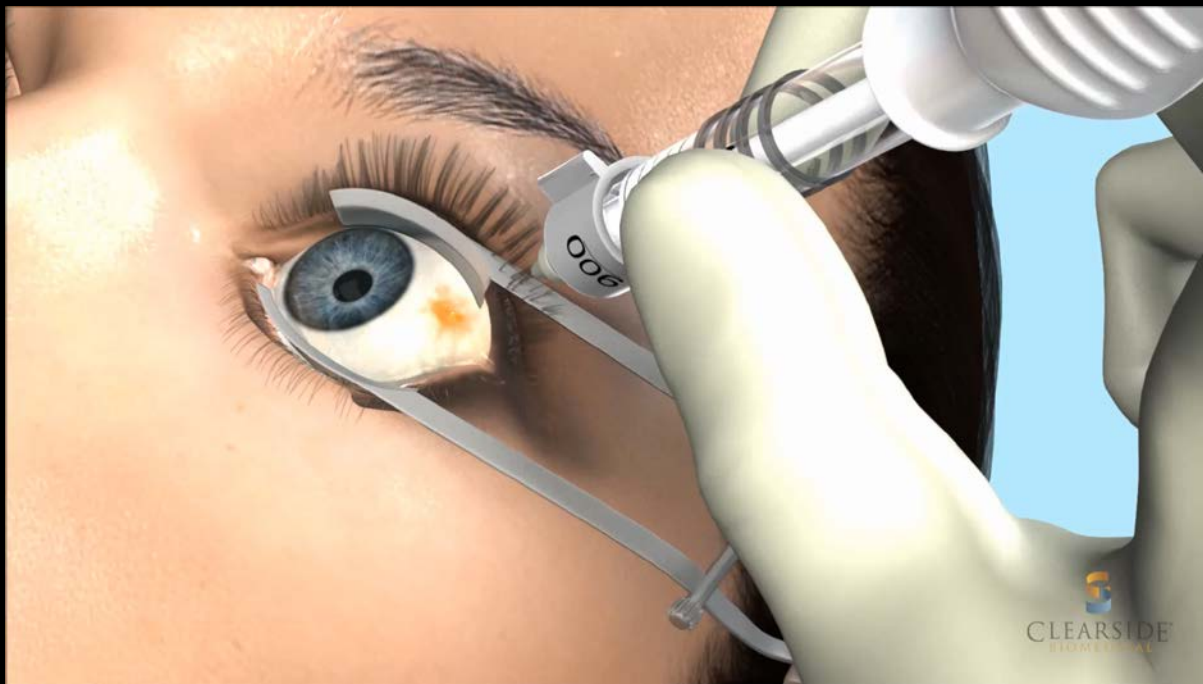
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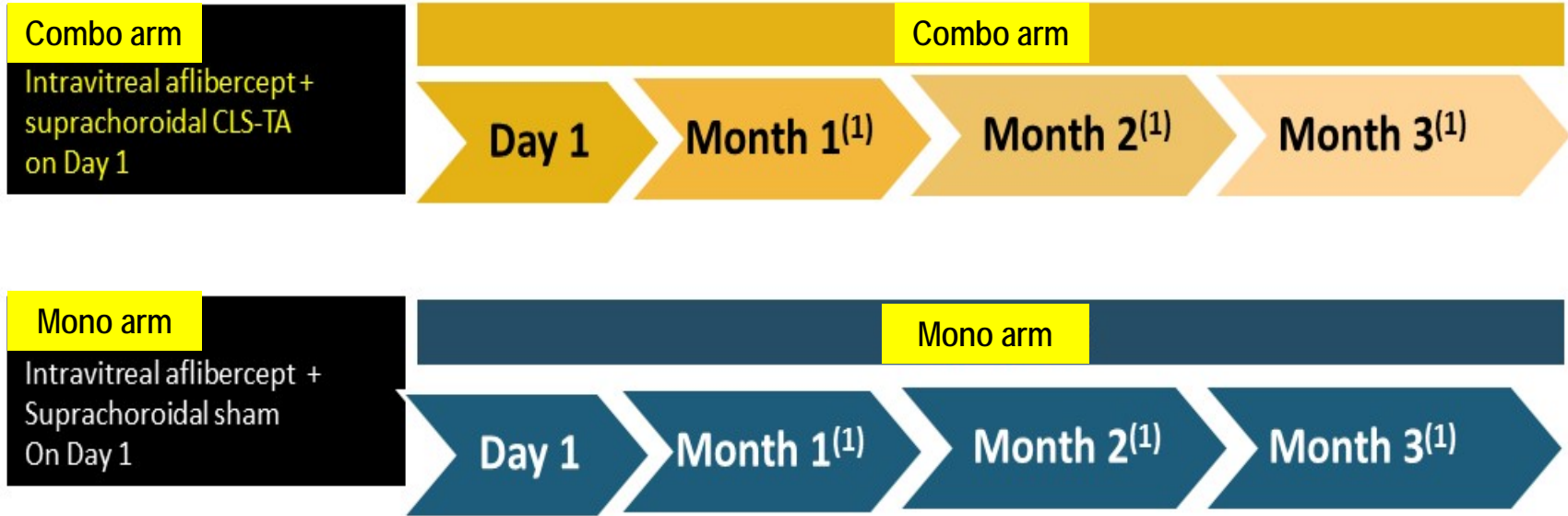


Proprietary Suprachoroidal injector 30 G needle 900 μ m
Animal models show drug compartmentalization

High amounts in the choroid and retina
Lower amounts in the anterior portions

CLS-1003-201:

Combo Intravitreal aflibercept + Suprachoroidal CLS-TA versus Mono Intravitreal aflibercept alone



Patients in each arm get one loading dose of aflibercept; the combo arm patients receive suprachoroidal CLS-TA as well.

Dosing during the course of the study is then on a PRN basis

CLS1003-201: Demographics

Protocol Design: Target 40 (1:1) subjects - Actually: 46 (23:23)

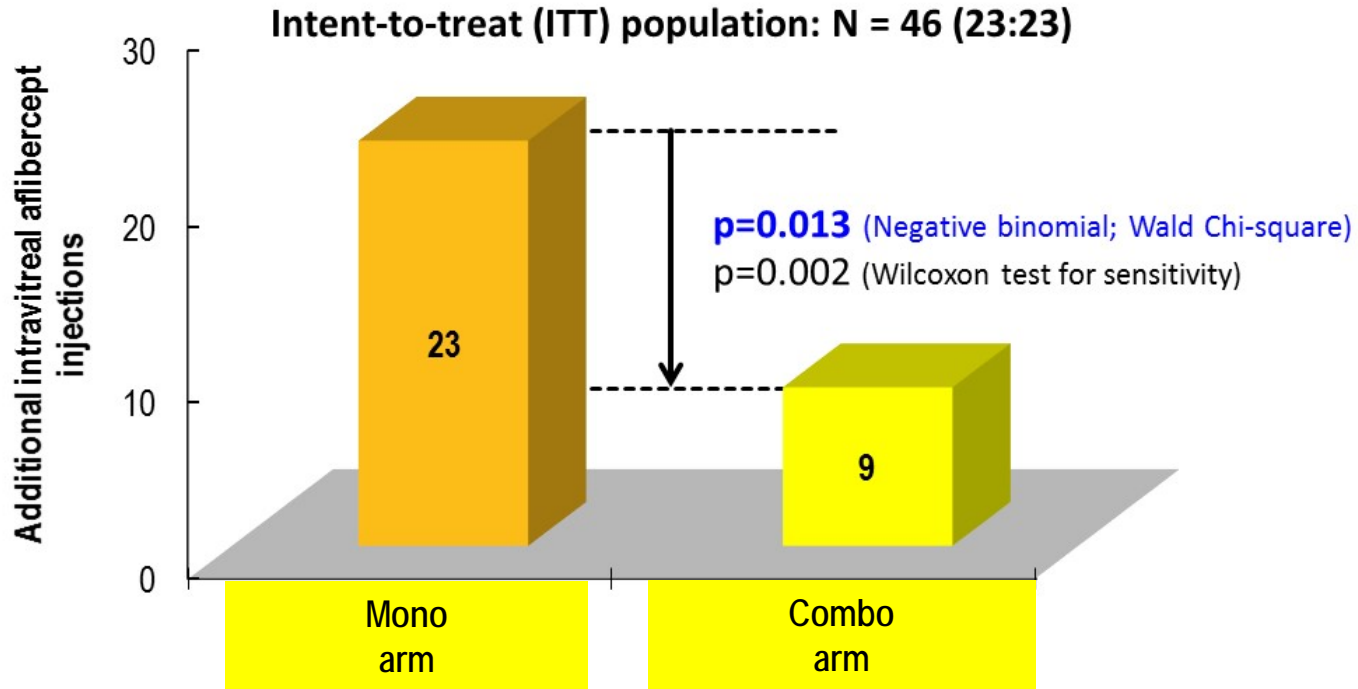
	<u>Mono</u> IVT aflibercept Alone N=23	<u>Combo</u> IVT aflibercept + Suprachoroidal CLS-TA N=23	TOTAL N=46
AGE (YEAR)			
MEAN	65.8	66.9	66.3
MEDIAN	70.0	67.0	68.0
MIN, MAX	37, 91	41, 80	37, 91
SEX n (%)			
MALE	10 (43.5)	13 (56.5)	23 (50.0)
FEMALE	13 (56.5)	10 (43.5)	23 (50.0)
RACE n (%)			
AMERICAN INDIAN OR ALASKA NATIVE	1 (4.3)	0	1 (2.2)
BLACK OR AFRICAN AMERICAN	4 (17.4)	3 (13.0)	7 (15.2)
WHITE	18 (78.3)	20 (87.0)	38 (82.6)

CLS1003-201: Disposition

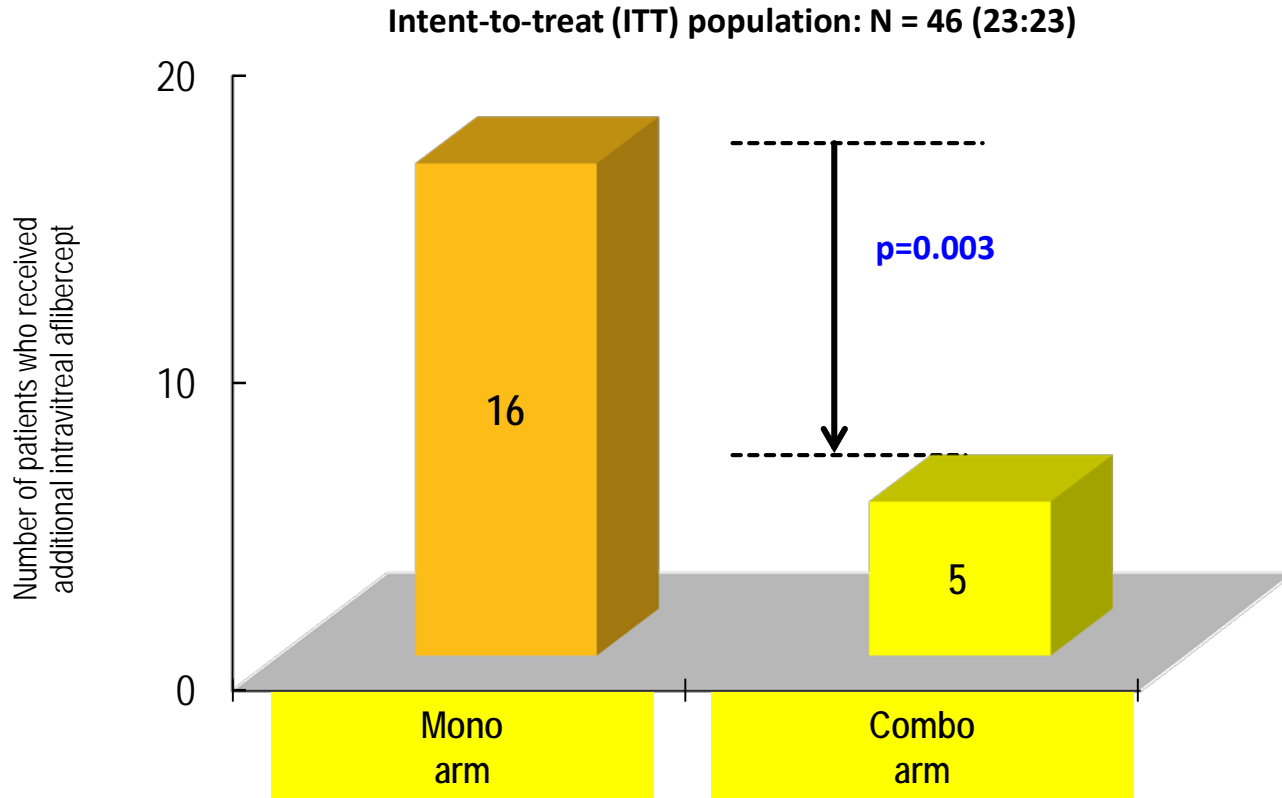
Protocol Design: Target 40 (20:20) subjects - Actually: 46 (23:23)

	<u>Mono</u> IVT aflibercept alone	<u>Combo</u> IVT aflibercept + suprachoroidal CLS-TA	TOTAL
TOTAL NUMBER OF SUBJECTS	N=23	N=23	
RANDOMIZED	23	23	46
COMPLETED	23	23	46
DISCONTINUED	0	0	0
SAFETY	23	23	46
INTENT-TO-TREAT	23	23	46

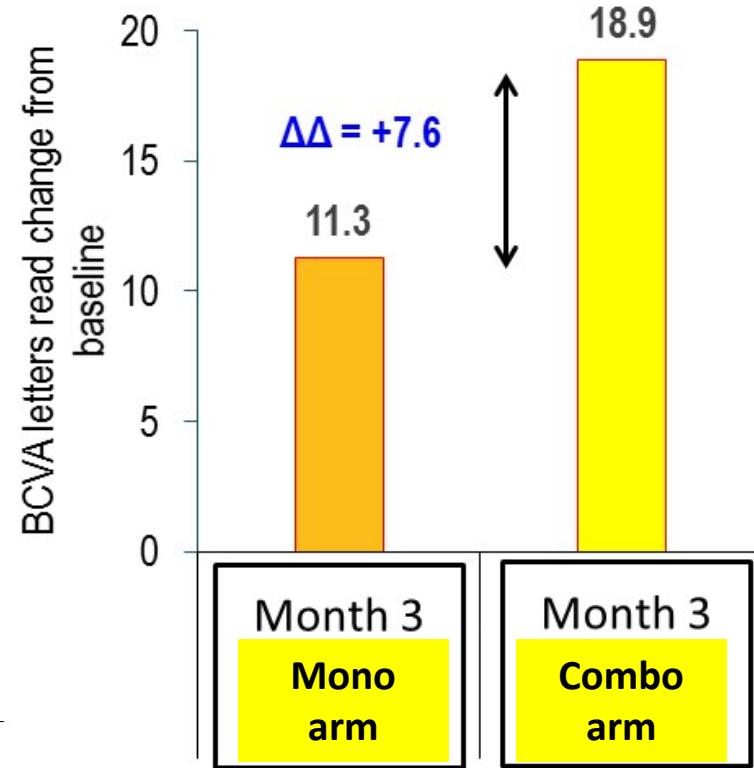
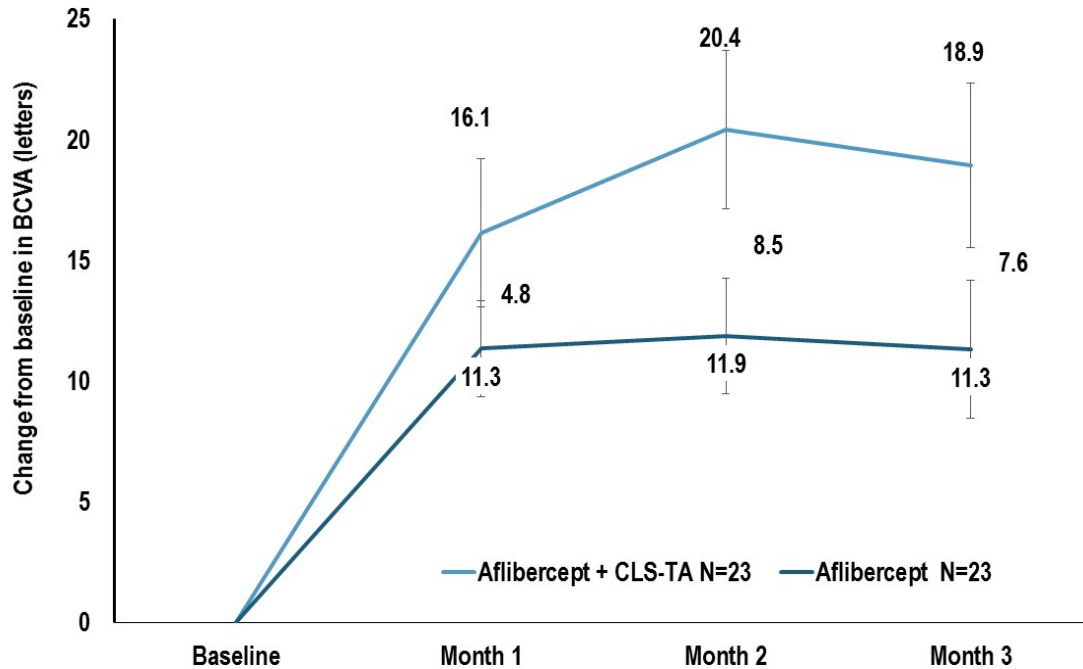
Primary Endpoint -# of PRN Intravitreal Aflibercept Injections



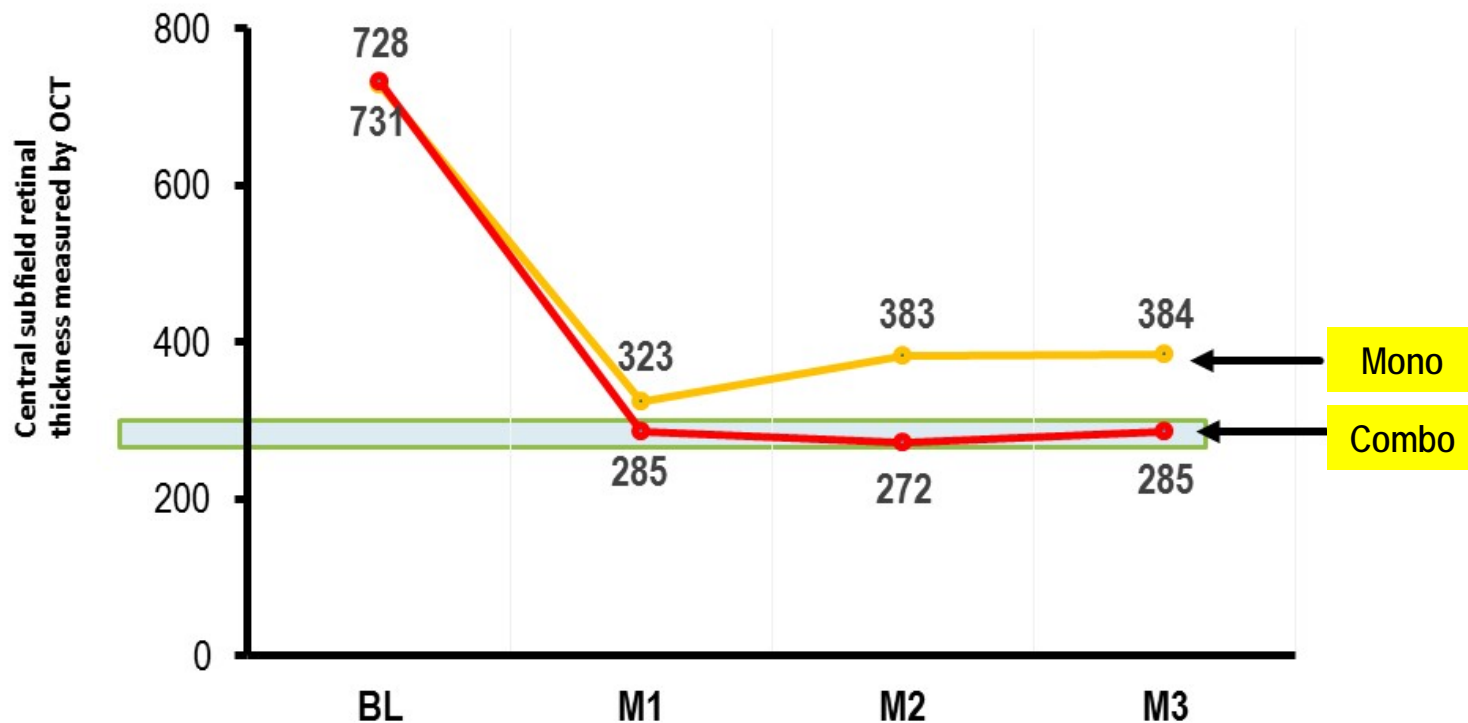
of Subjects Who Required PRN Aflibercept



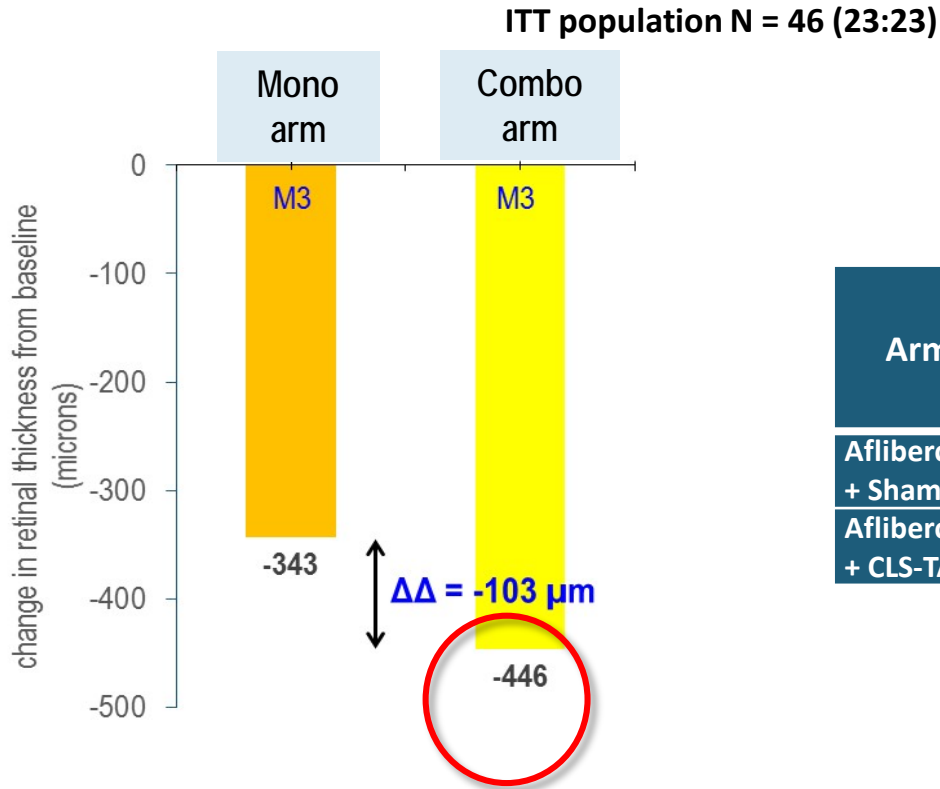
Secondary Endpoint – BCVA



Mean Central Subfield Thickness – ITT (n=23 per arm)



Secondary Endpoint – Reduction in CST From Baseline



Arm	Average for change from baseline in the Central subfield thickness (microns)			
	Month 1	Month 2	Month 3	
Aflibercept + Sham	-405	-344	-343	103
Aflibercept + CLS-TA	-446	-459	-446	
	41	115		

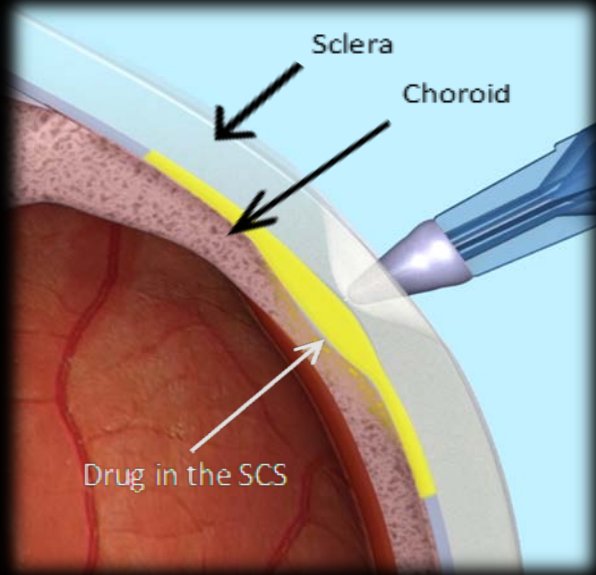
Complete list of ocular adverse events

Parameter	Mono arm (n=23) (IVT aflibercept + SC sham)	Combo arm (n=23) (IVT aflibercept + SC CLS-TA)
Number of subjects with at least 1 AE	10	12
Intraocular Pressure Increase	0	2
Allergic conjunctivitis	1	0
Corneal edema	0	1
Eye Pain	1	8
Foreign body sensation	0	1
Lacrimation increased	0	1
Macular fibrosis	1	0
Ocular discomfort	2	0
Ocular hypertension	0	2
Optic disc vascular disorder	1	0
Punctate keratitis	0	1
Retinal degeneration	1	0
Retinal exudates	1	1
Retinal haemorrhage	0	1
Vision blurred	1	0
Visual acuity reduced	2	0
Vitreous detachment	0	1
Vitreous floaters	0	1
Conjunctival haemorrhage	1	2

Summary of findings from the phase 2 trial

- *Suprachoroidal injection of CLS-TA given as a combination with intravitreal aflibercept* significantly reduced the requirement for additional aflibercept treatments compared to *intravitreal aflibercept monotherapy in this 3-month PRN study*
 - Subjects given combo CLS-TA suprachoroidal injection along with intravitreal aflibercept showed additional improvements in BCVA compared to subjects receiving aflibercept monotherapy

Conclusions



Suprachoroidal **CLS-TA** with aflibercept significantly reduced additional aflibercept requirement over 3 months

IOP rise and cataract formation potentially mitigated by the suprachoroidal approach

Improved anatomy/vision with combination therapy implies that early intervention with a steroid *along with the anti-VEGF* may improve results in treatment naïve RVO