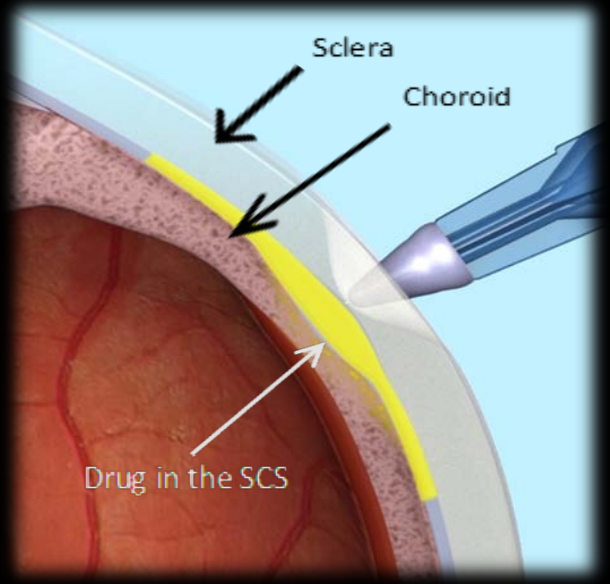
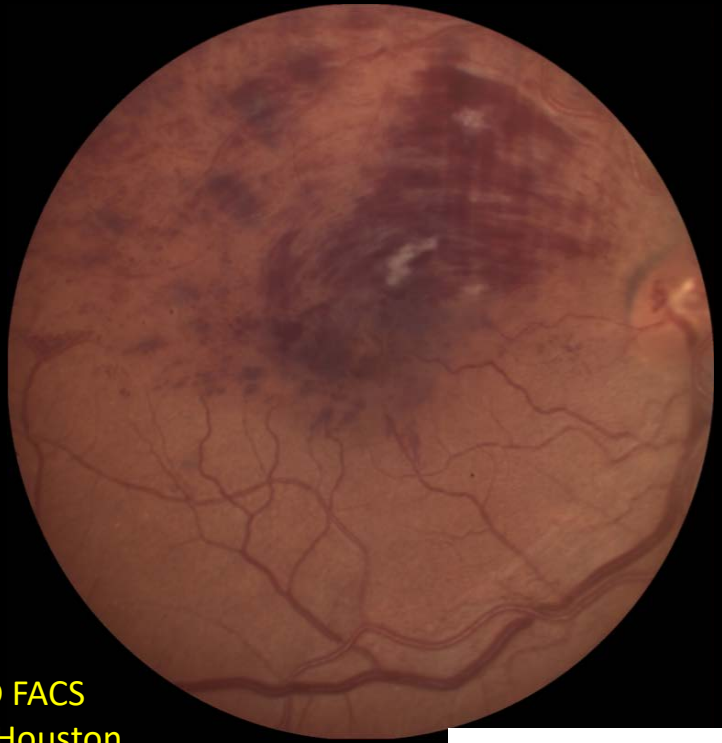
Suprachoroidal Triamcinolone Acetonide with Intravitreal Aflibercept For Retinal Vein Occlusion: Phase 2 Results – TANZANITE study





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- Research Grant Funding:

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

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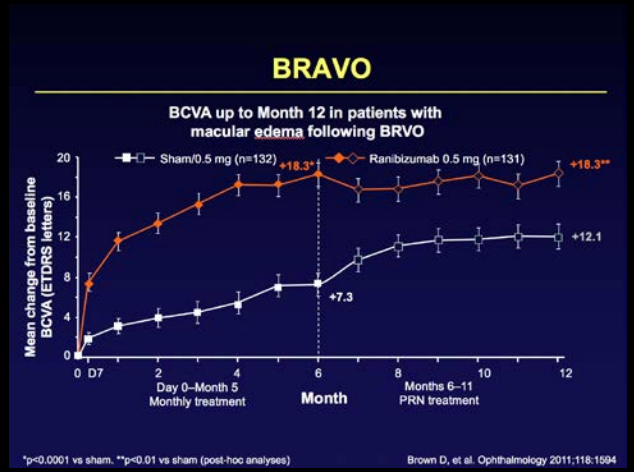
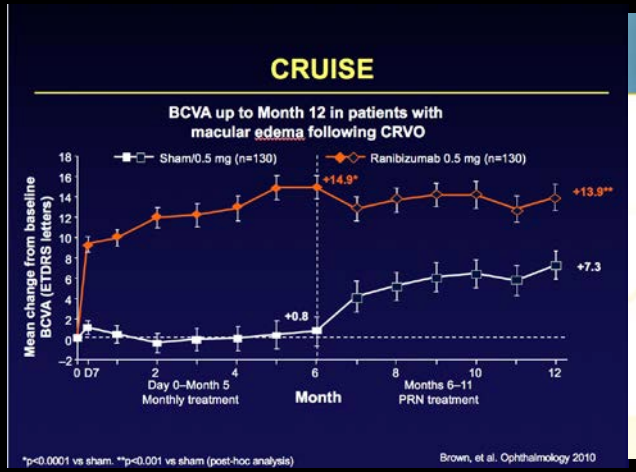
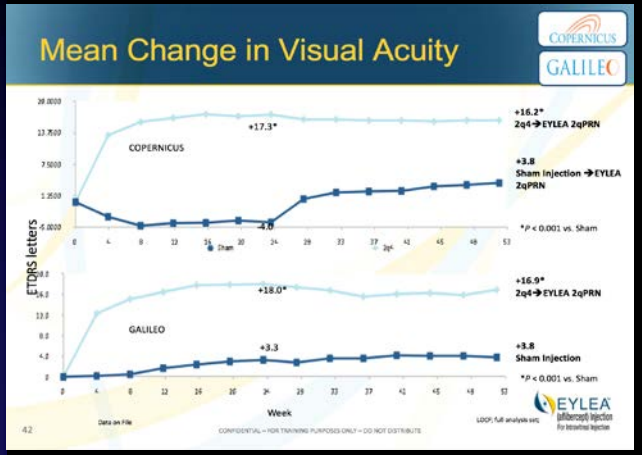
DMB had Full Control of Presentation

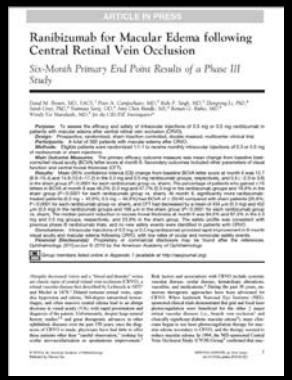
Anti-VEGF Improves VA in RVO



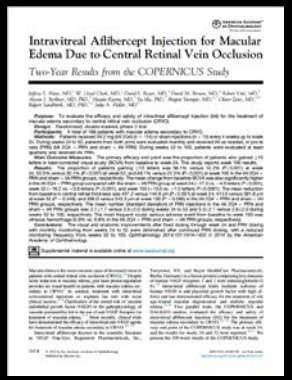




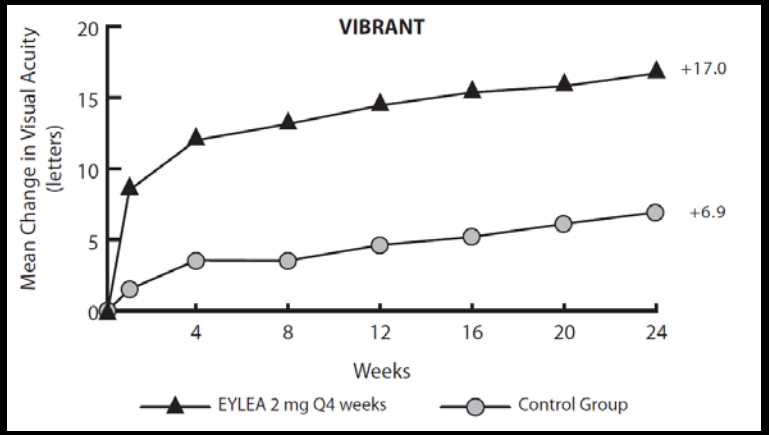

Sustained Benefits from Ranibizumab for Macular Edema Following Branch Retinal Vein Occlusion: 12-Month Outcomes of a Phase III Study


Ranibizumab for Macular Edema following Central Retinal Vein Occlusion

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


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

Two-Year Results from the COPERNICUS Study



Retinal Vein Occlusion

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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 a 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 reviewed 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 drusen of the optic nerve head. Associated systemic diseases included: hypertension, 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 (24.6%). Cystoid 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 Michel[1] in 1878. Various histopathologic features have been described in the central retinal vein(CRV) after thrombosis, including: thrombus or recanalized thrombus[2–10]; endothelial cell proliferation[3,9–11]; obliterative endophlebitis[4,6,12]; phlebitis[12]; intimal proliferation[5,13]; and phlebosclerosis.[3,8] 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.[13]

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 Grift, Verhoeff-van Gieson, Prussian blue, and phosphotungstic acid-hematoxylin. Flat preparation of portions of the retina of those eyes was made by the trypsin digestion technique.

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

This study was reported in part at the 116th Annual Meeting of the American Ophthalmological Society, Kamuela, Hawaii, May 23, 1980.

Supported in part by Research Grant 1 RO1 EY 01604 01-04) from the National Eye Institute, USPHS.

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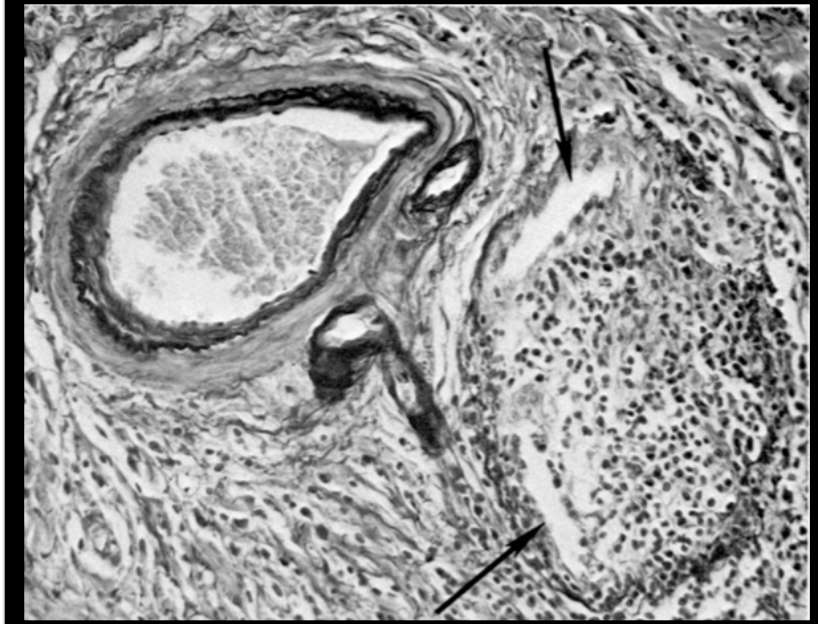
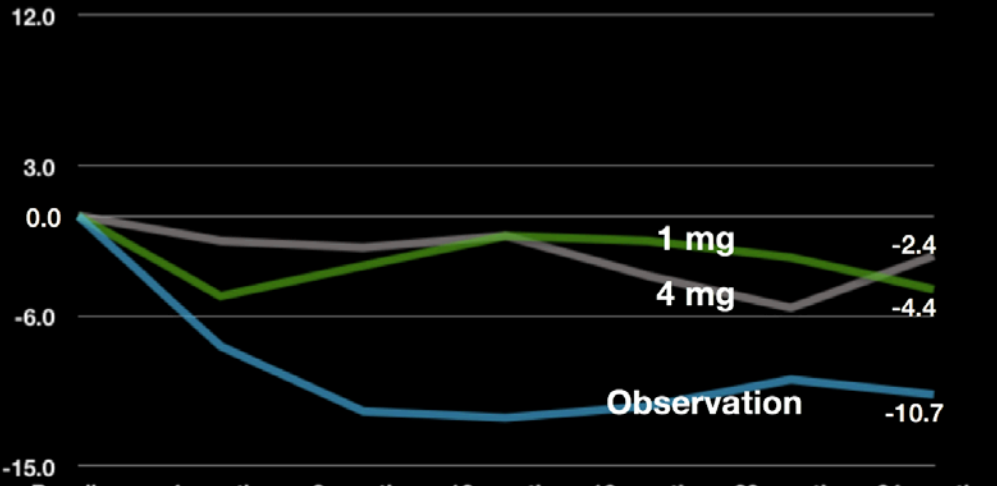


Green W, et al. Retina 1981;1:27

SCORE CRVO

Mean Letters Gain/Lost from Baseline



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 6

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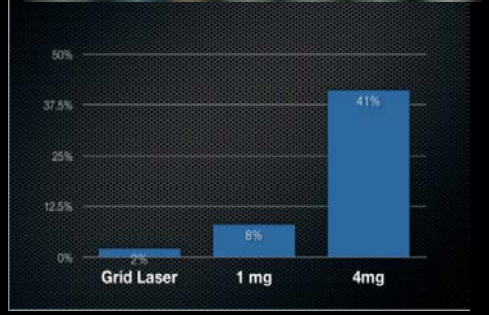

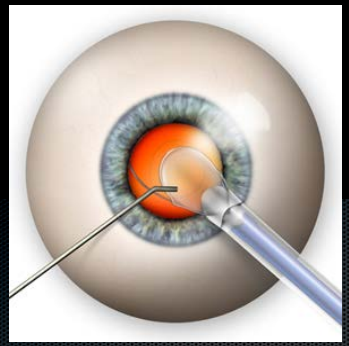

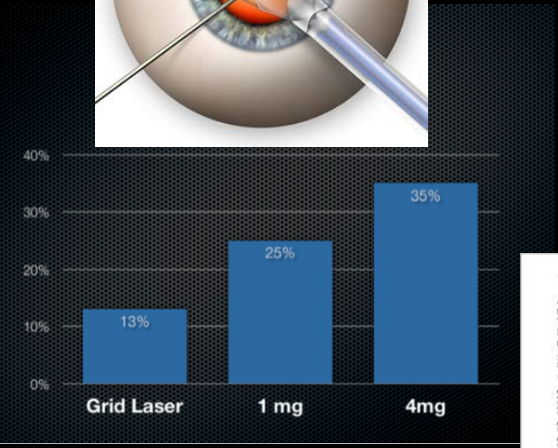

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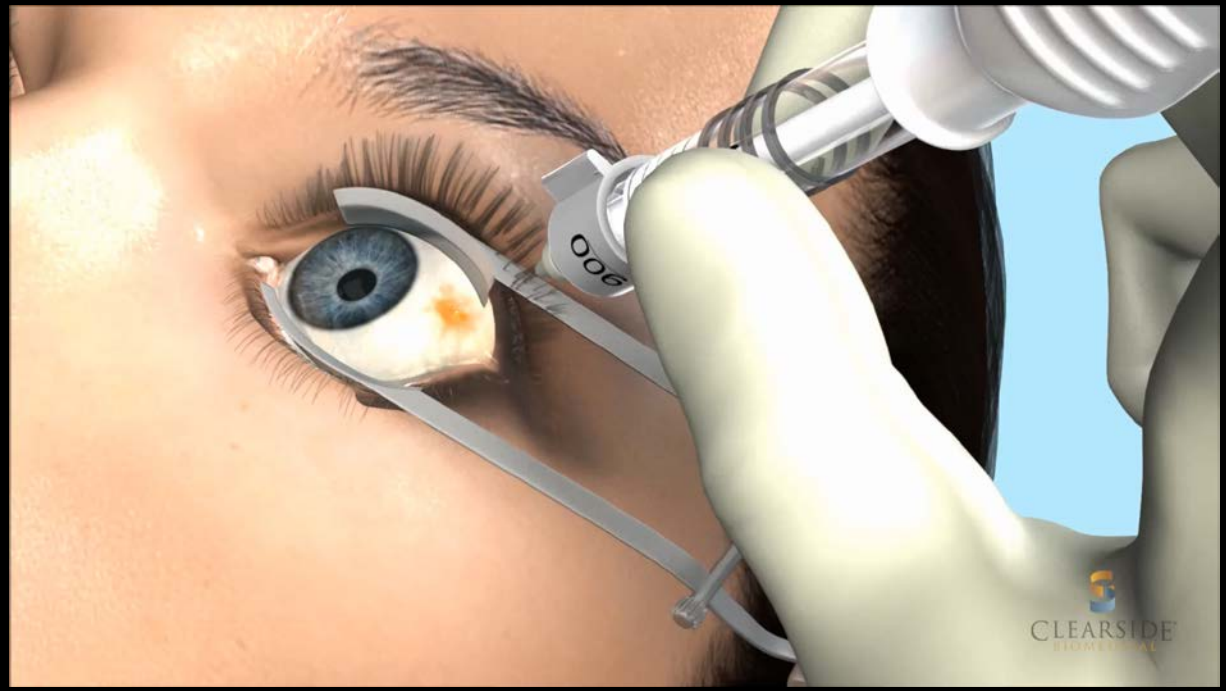
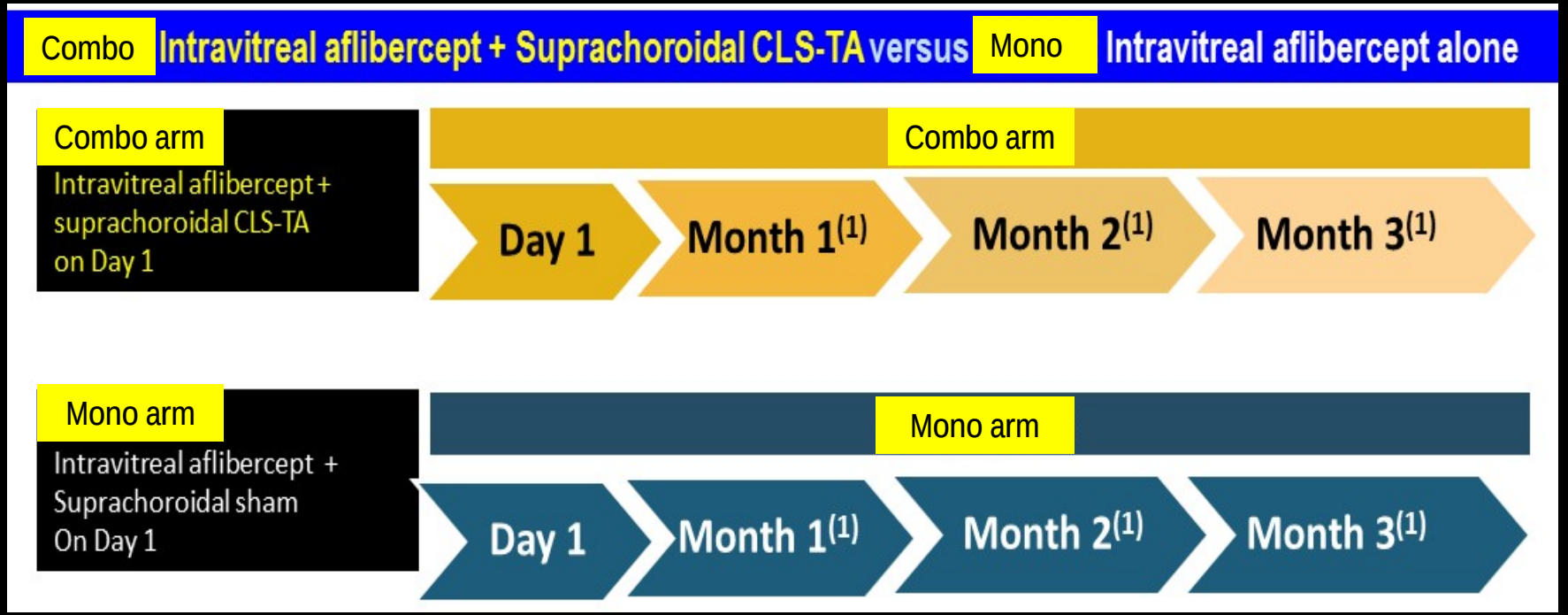


Proprietary Suprachoroidal injector <u>30 G needle 900</u> µm
Animal models show drug compartmentalization

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

CLS-1003-201:



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)

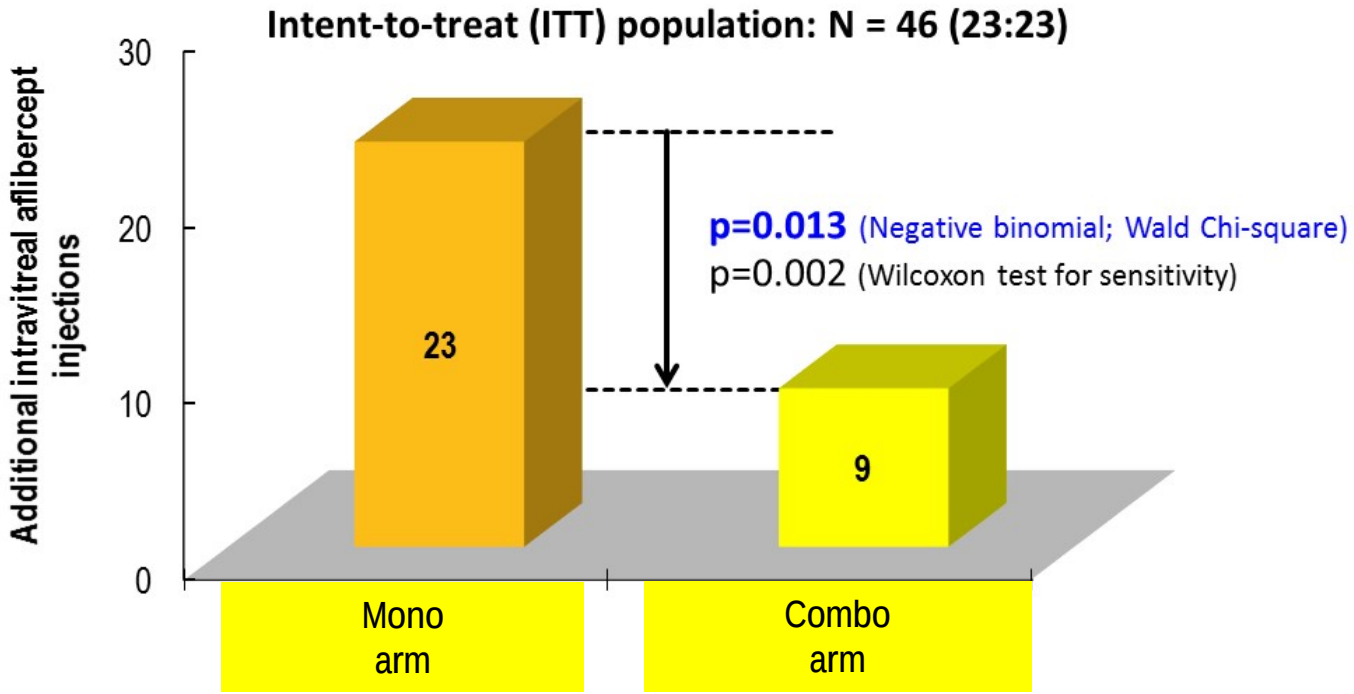
	Mono IVT aflibercept Alone N=23	Combo IVT aflibercept + Suprachoroidal CLS-TA N=23	TOTAL N=46
AGE (YEAR)			
MEAN	65.8	66.9	66.3
MEDIAN	70.0	67.0	68.0
MIN, MAX	37, 91	41, 80	37, 91
SEX n (%)			
MALE	10 (43.5)	13 (56.5)	23 (50.0)
FEMALE	13 (56.5)	10 (43.5)	23 (50.0)
RACE n (%)			
AMERICAN INDIAN OR ALASKA 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

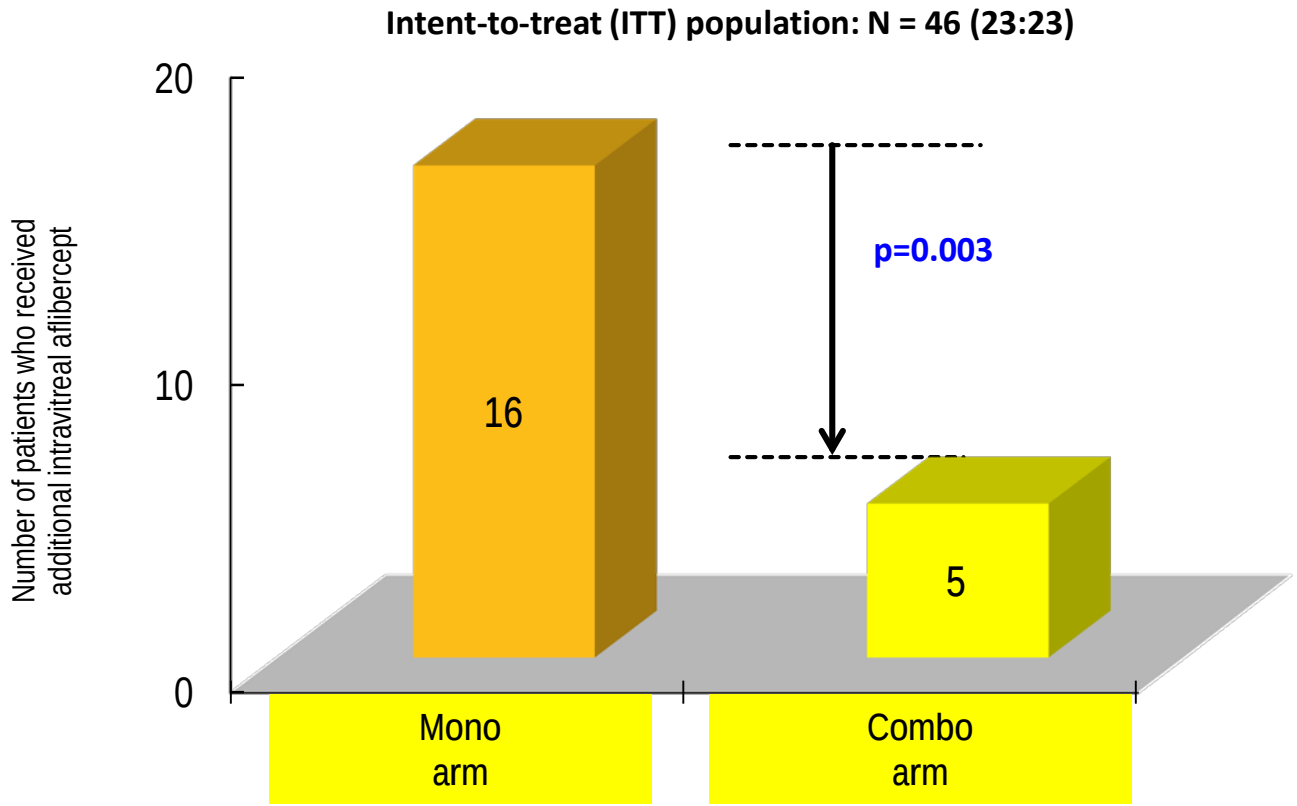
Protocol Design: Target 40 (20:20) subjects - Actually: 46 (23:23)

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

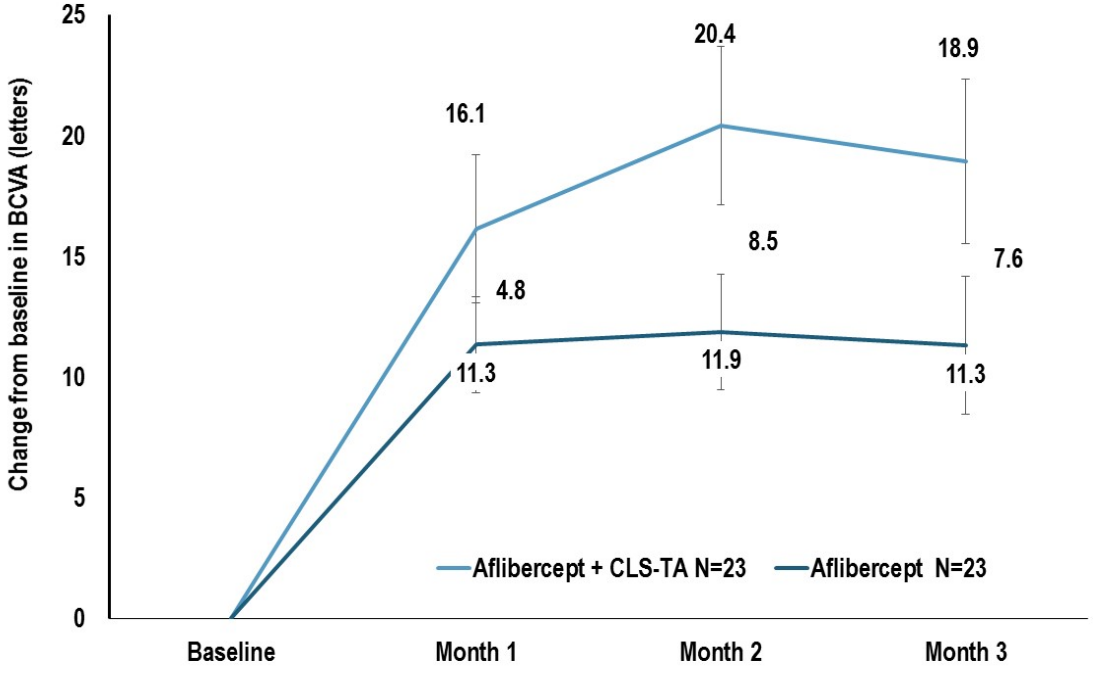
Primary Endpoint -# of PRN Intravitreal Aflibercept Injections

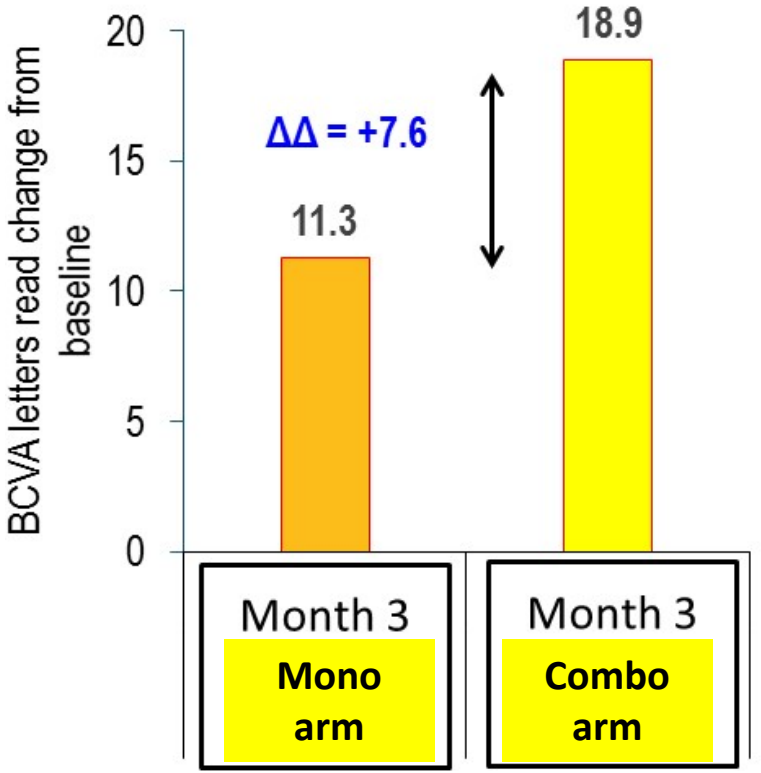


of Subjects Who Required PRN Aflibercept

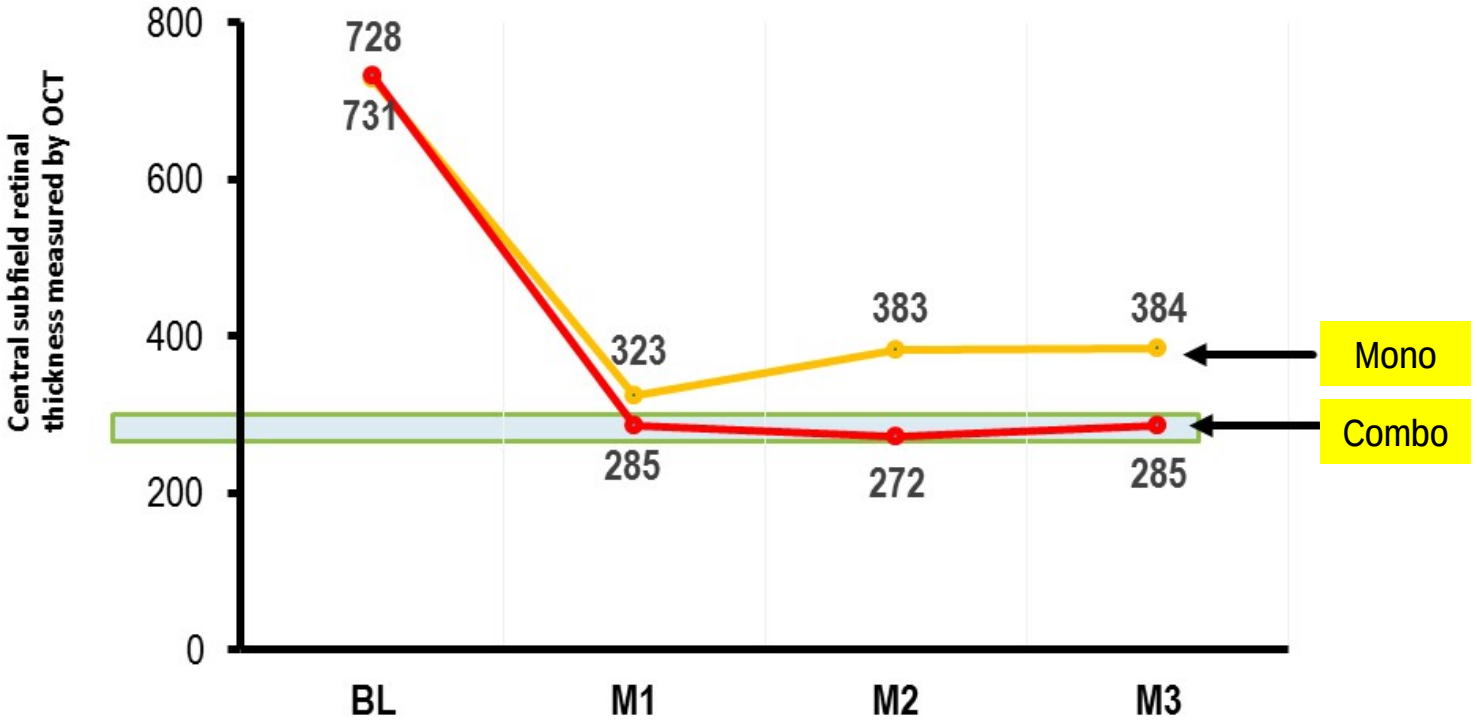


Secondary Endpoint – BCVA



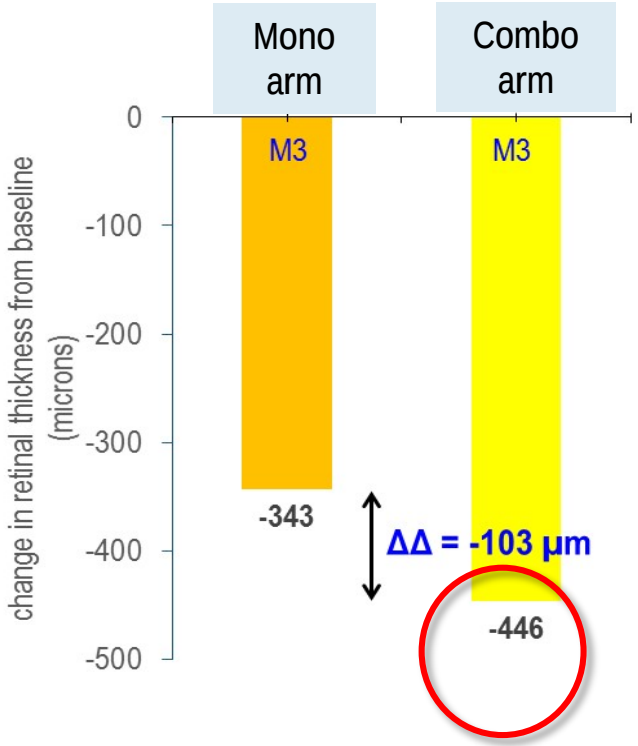


Mean Central Subfield Thickness – ITT (n=23 per arm)



Secondary Endpoint – Reduction in CST From Baseline

ITT population N = 46 (23:23)



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

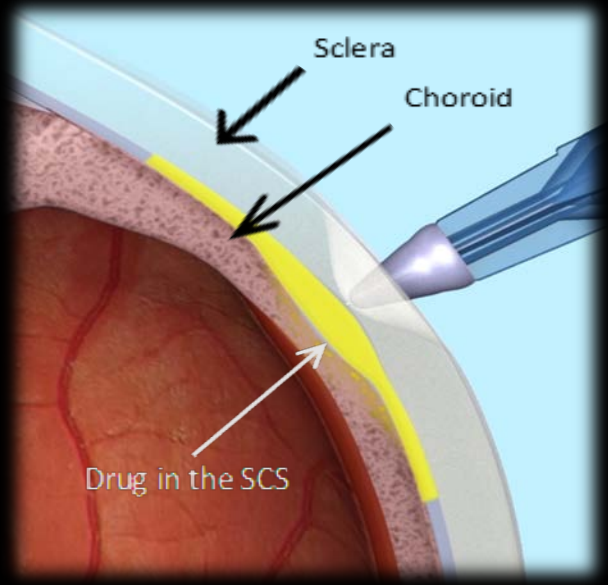
Complete list of ocular adverse events

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