TANZANITE Phase 2 Retinal vein occlusion (RVO) trial

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RVO treatment hypothesis

The hypothesis to be tested

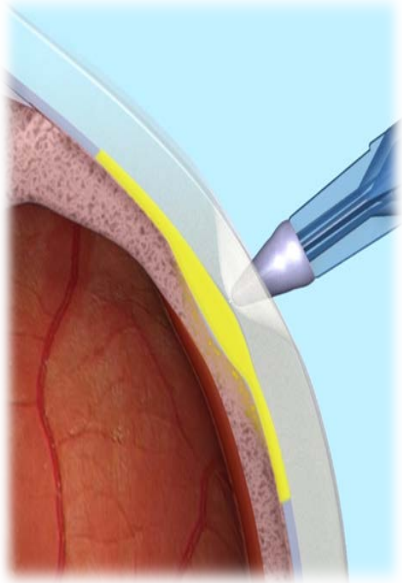
- **Combination** treatment given **every 3 months** with an **anti-VEGF** and **a corticosteroid** will provide benefit in visual acuity improvements and reductions in macular edema that are seen with monthly anti-VEGF alone, and with less frequent treatment (quarterly)

Phase 2 trial – TANZANITE design

This study was a *proof of concept trial* to look for an effect from a suprachoroidally injected drug in RVO patients: in other words,
Can suprachoroidal administration positively affect a retinal vascular disease?

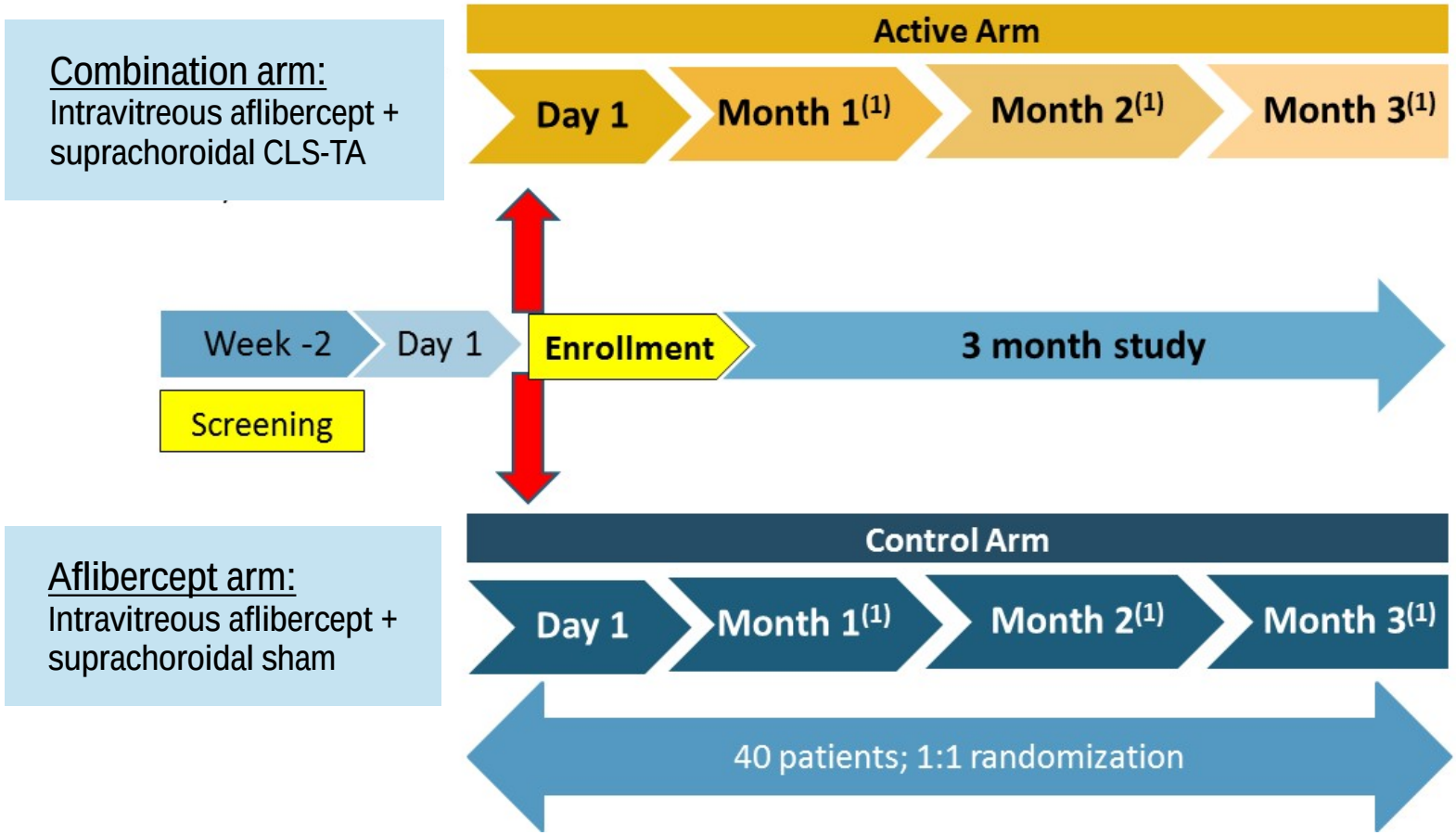
- Treatment naïve RVO subjects were randomized 1-1
  - **Combination arm**: received **intravitreous aflibercept in addition to suprachoroidal triamcinolone (CLS-TA)**
  - **Aflibercept arm**: received **intravitreous aflibercept alone**

- All subjects were followed for 3 months after treatment at baseline; only additional treatments were intravitreal aflibercept injections



Phase 2 trial in treatment naïve RVO patients

Intravitreous aflibercept + suprachoroidal CLS-TA versus intravitreous aflibercept



(1) Determination for treatments with intravitreous aflibercept at Months 1, 2, and 3 using quantifiable criteria involving the presence of macular edema and decreases in best corrected visual acuity (Loss of 10 letters BCVA, or OCT>340 um)

Disposition

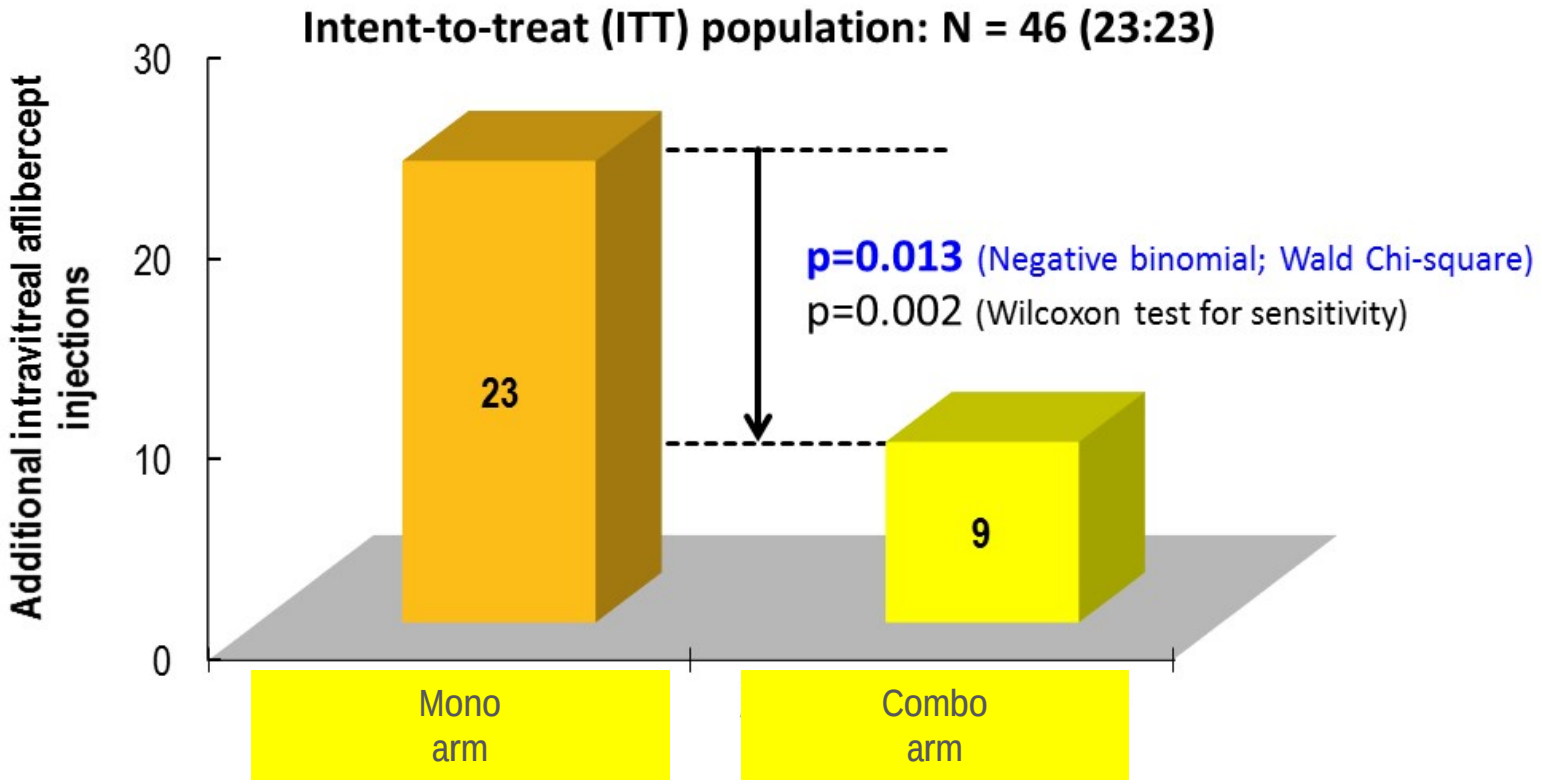
Patients randomized 46 (23:23)

TOTAL NUMBER OF SUBJECTS	Aflibercept arm N=23	Combination arm 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**

Demographics

	Aflibercept arm N=23	Combination arm 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)

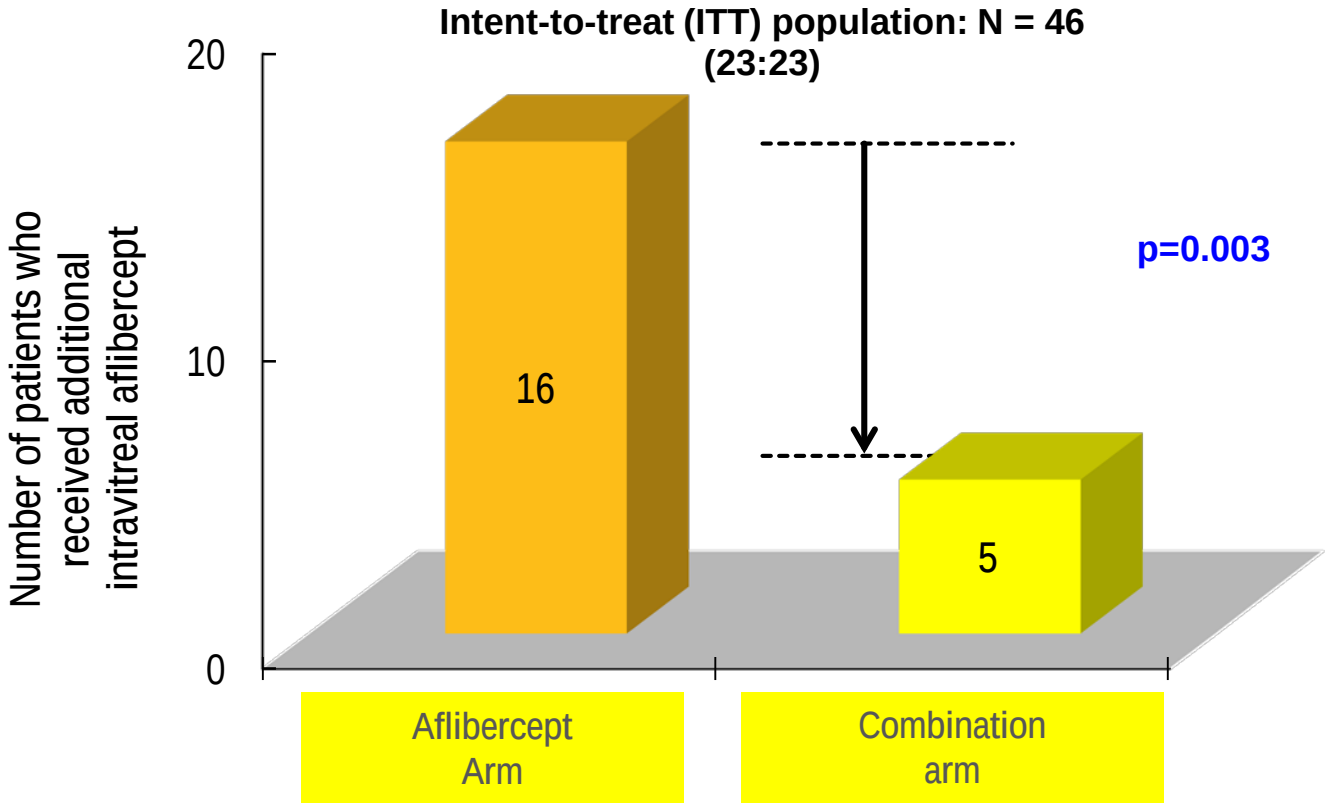
Primary endpoint – number of additional intravitreous aflibercept injections required



There were 14 fewer injections in the Combination arm compared to the Aflibercept arm, or a **61% reduction** in the requirement for additional aflibercept

Number of subjects who received PRN aflibercept

Post-hoc analysis

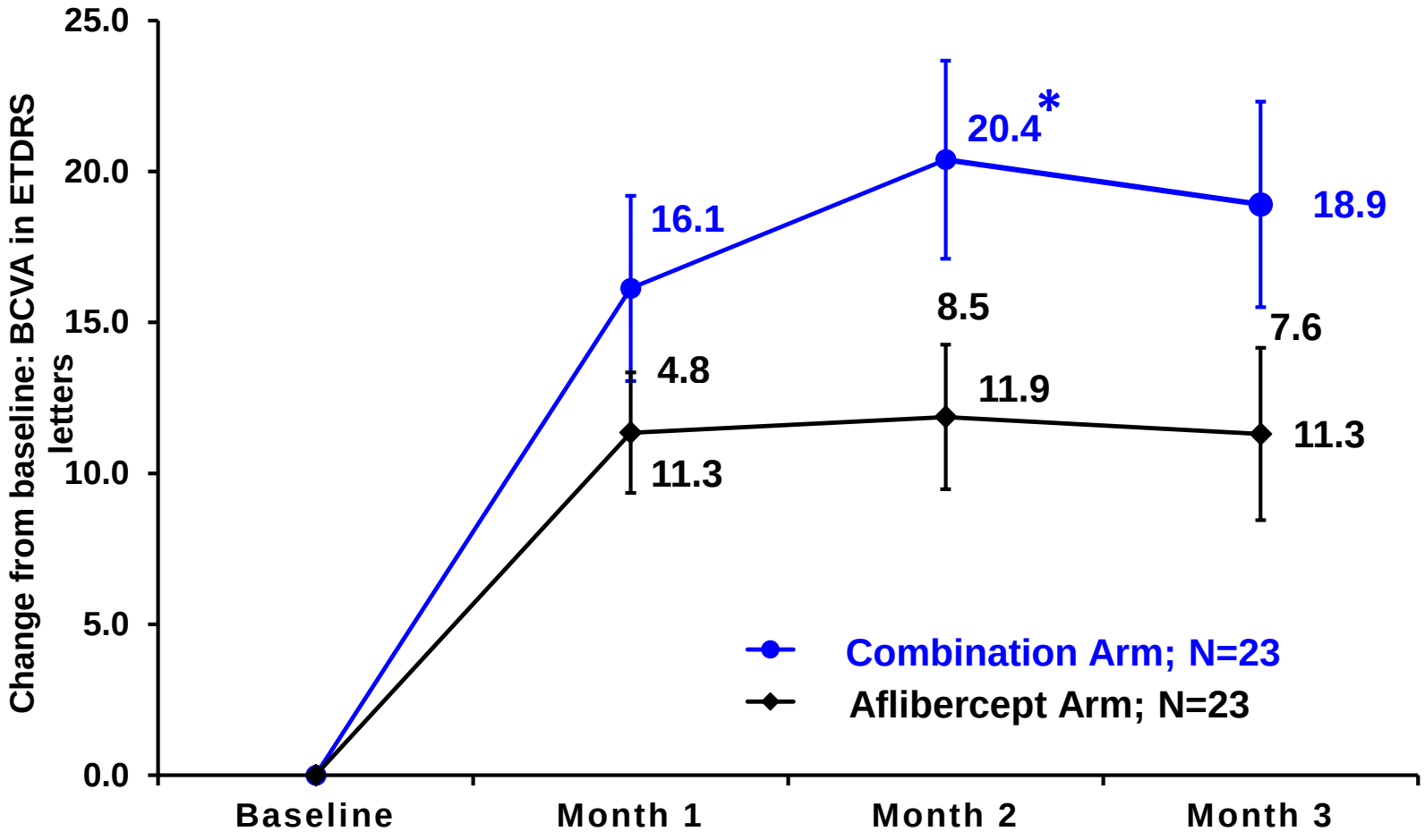


Seventy-eight (78%) percent (18/23) of patients in the combination arm in this trial did not require additional aflibercept treatments during the three-month trial compared to 30% (7/23) in the control, aflibercept arm (p=0.003)

What was learned

- **Potential for significantly fewer treatments in a majority of the subjects** in the combination arm (aflibercept +CLS-TA) in this study over a three month time-period compared to the subjects who initially received aflibercept only

Change in BCVA



Baseline: 49 ETDRS letters read in each arm

Note: Bars are standard error of the mean; * only month 2 showed p<0.05

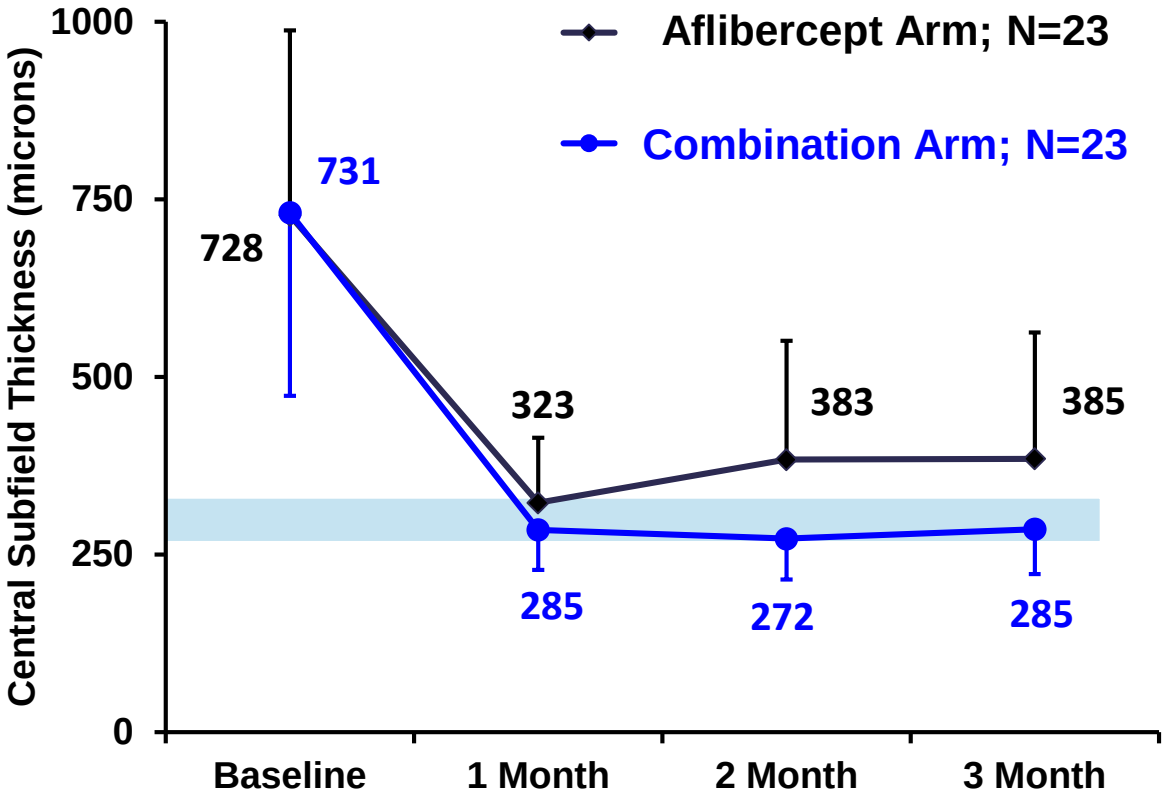
Percent of subjects gaining ≥ 15 letters

	Aflibercept arm	Combination arm
MONTH 1	N=23	N=23
NUMBER (%) WHO GAINED ≥ 15 LETTERS	09 (39.1)	12 (52.2)
MONTH 2		
NUMBER (%) WHO GAINED ≥ 15 LETTERS	09 (39.1)	14 (60.9)
MONTH 3		
NUMBER (%) WHO GAINED ≥ 15 LETTERS	10 (43.5)	12 (52.2)

What was learned in terms of functional outcomes

- Potential for **improved visual outcome in the combination arm** compared to the monotherapy aflibercept arm ***at Month 1***
- **Improved visual acuity in the combination arm** seen at *Month 1* appears to be maintained over the 3 months **of the study with significantly fewer additional injections.**
- **These findings were also maintained when CRVO and BRVO patients were examined separately.**

Retinal thickness data by SD-OCT (Heidelberg)

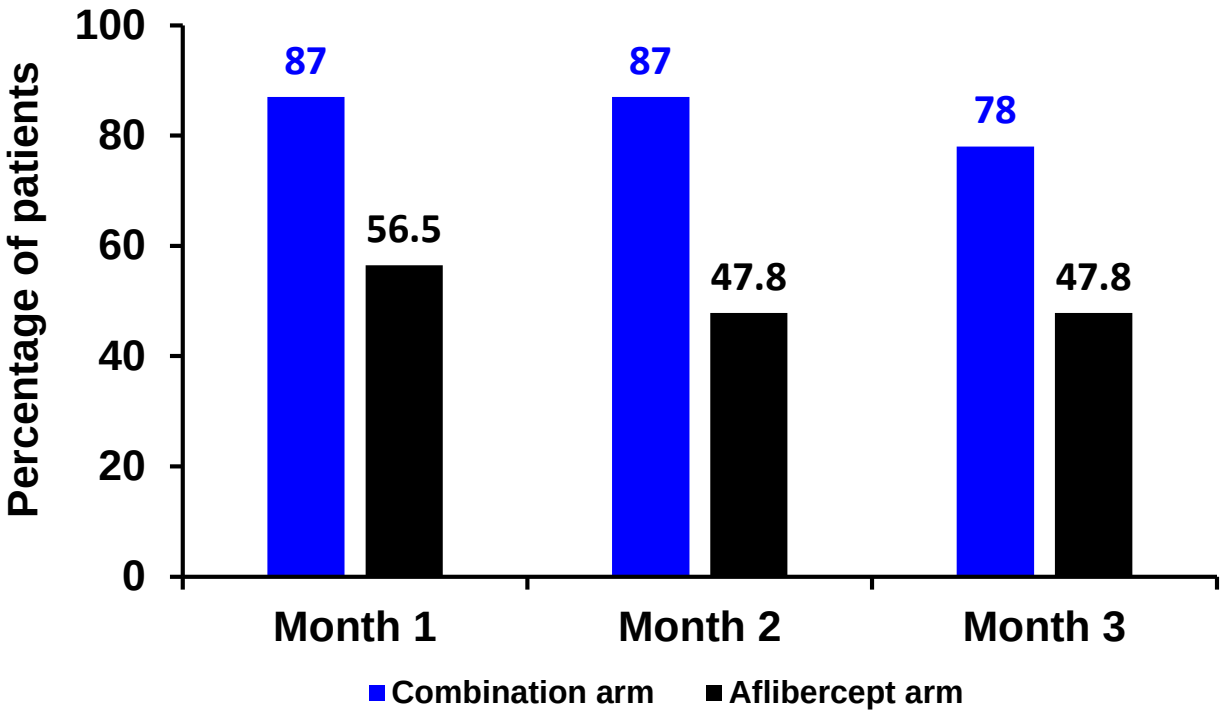


Baseline

728 µm and 731 µm in the Aflibercept and Combination arms respectively

Note: Bars are one-sided standard deviations

Percentages of subjects with resolution* of macular edema



*defined as having CST <310 microns on a Heidelberg Spectralis

(only OCT in this study required by the protocol)

What was learned for the combination in anatomical outcomes

- **Potential for improved anatomical outcome observed in the combination arm** compared to the monotherapy arm at Month 1
- **Improved outcome from month 1** was maintained over the 3 months of the study with significantly fewer additional injections
- **These findings were also maintained when CRVO and BRVO patients were examined separately.**

Ocular AEs – details

System Organ Class Preferred term	Aflibercept arm N=23; n (%)	Combination arm N=23; n (%)	Total N=46; n (%)
Cataract	0	1 (4.3)	1 (2.2)
Anterior chamber inflammation	0	1 (20)	1 (5)
Conjunctival hemorrhage	1 (4.3)	2 (8.7)	3 (6.5)
Conjunctival hyperemia	1 (4.3)	0	1 (2.2)
Corneal edema	0	1 (4.3)	1 (2.2)
Foreign body sensation in eyes	0	1 (4.3)	1 (2.2)
Eye pain	1 (4.3)	8 (34.8)	19 (19.6)
Lacrimation increased	0	1 (4.3)	1 (2.2)
Macular fibrosis	1 (4.3)	0	1 (2.2)
Ocular discomfort	2 (8.7)	0	2 (4.3)
Ocular hypertension	0	2 (8.7)	1 (5)
Optic disc vascular disorder	1 (4.3)	0	1 (2.2)
Optic nerve disorder	0	1 (4.3)	1 (2.2)
Punctate keratitis	0	1 (4.3)	1 (2.2)
Retinal degeneration	1 (4.3)	0	1 (2.2)
Retinal hemorrhage	0	1 (4.3)	1 (2.2)
Vision blurred	1 (4.3)	0	1 (2.2)
Visual acuity reduced	2 (8.7)	0	2 (4.3)
Vitreous detachment	0	1 (4.3)	1 (2.2)
Vitreous floaters	0	1 (4.3)	1 (2.2)
Intraocular pressure increased	0	2 (8.7)	2 (4.3)

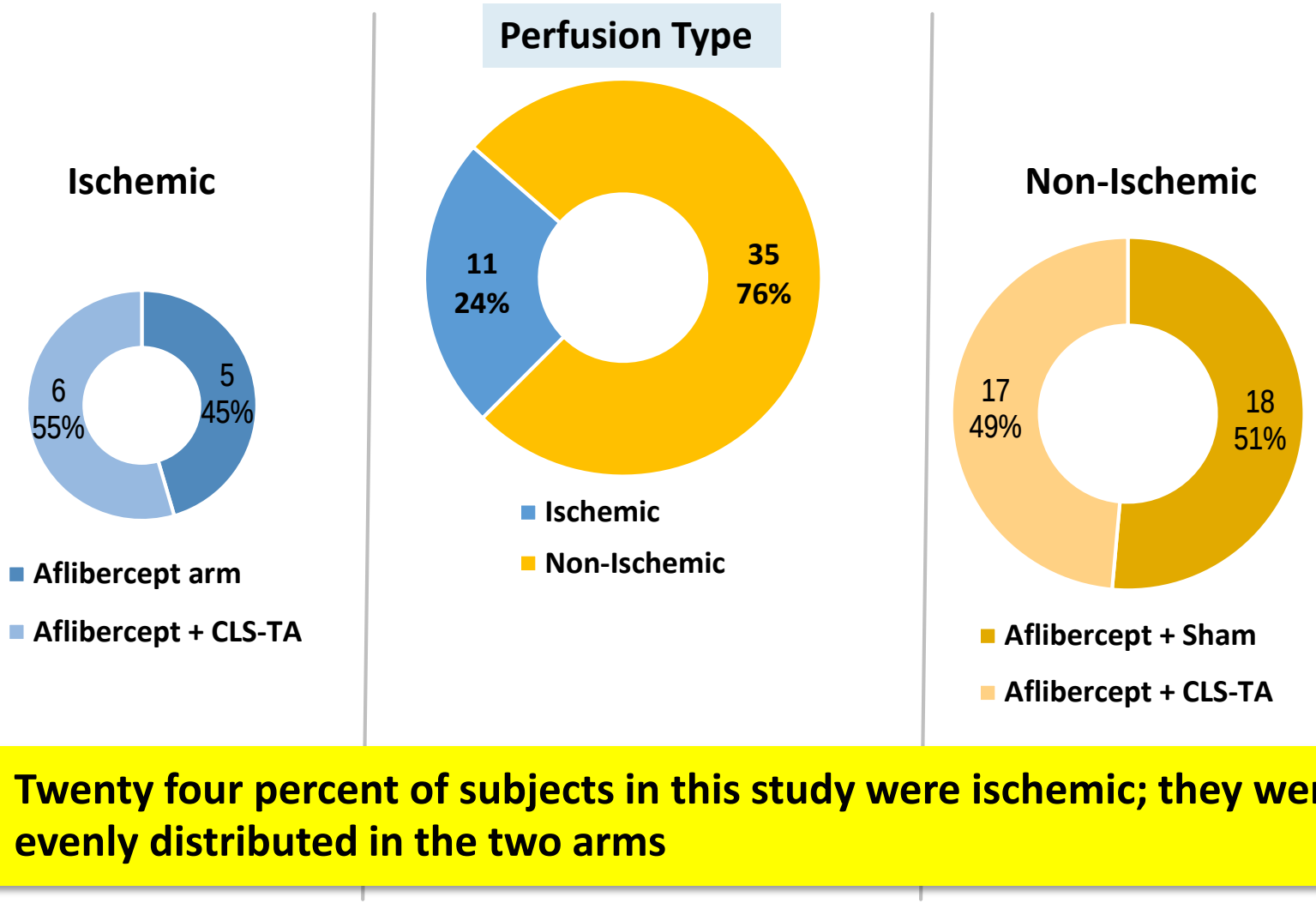
Sub-analysis: Perfusion status

Perfusion status at baseline

Randomized: 46 (23:23)

TOTAL NUMBER OF SUBJECTS	Aflibercept Arm N=23 (%)	Combination Arm N=23 (%)	TOTAL
PERFUSION TYPE			
ISCHEMIC	**5(21.7)**	**6 (26.1)**	**11 (23.9)**
NON-ISCHEMIC	**18 (78.3)**	**17 (73.9)**	**35 (76.1)**

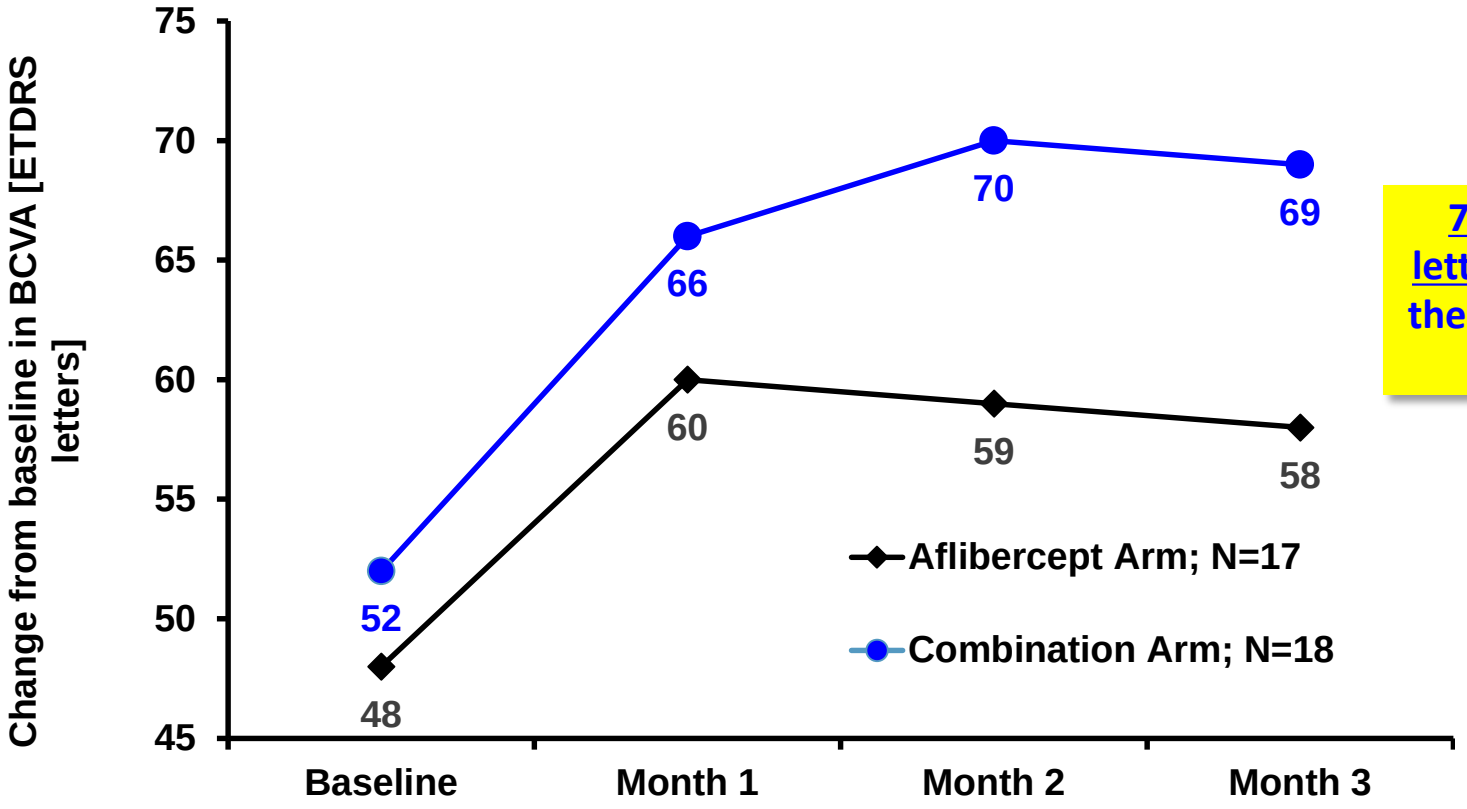
Patient numbers: Ischemic vs Non-Ischemic



Twenty four percent of subjects in this study were ischemic; they were evenly distributed in the two arms

Changes from baseline in BCVA for non-ischemic subjects

Slight imbalance in mean BCVA at baseline in non-ischemic subjects with 52 letters read in the combination arm versus 48 letters read in the aflibercept alone arm

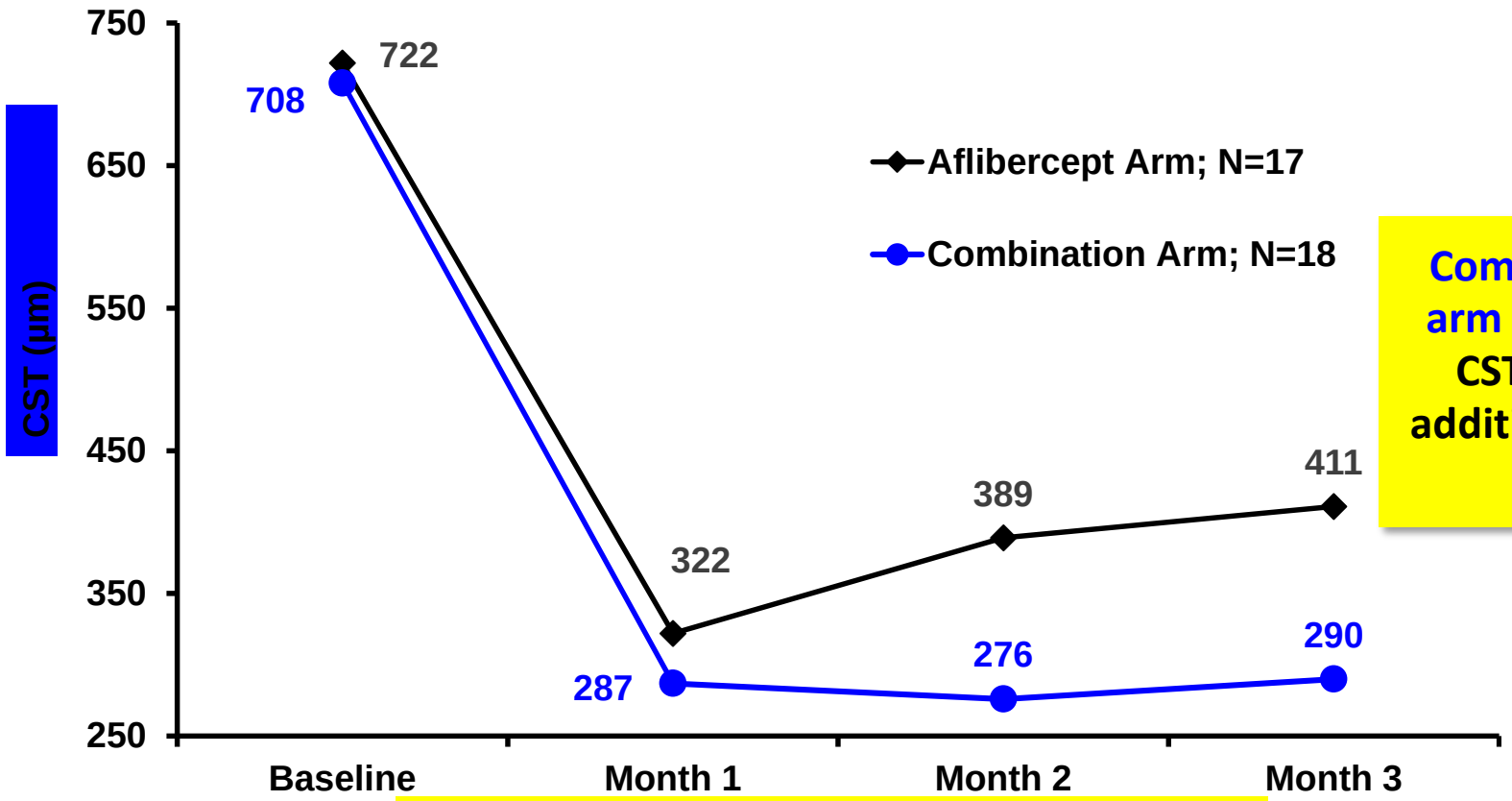


7 additional letters gained in the combination arm

Combination arm: 17 letter gain from baseline at Month 3
Aflibercept arm: 10 letter gain from baseline at Month 3

Changes from baseline in CST for non-ischemic subjects

Mean CST at baseline in subjects was similar: 708 µm in the combination arm versus 722 µm in the aflibercept alone arm

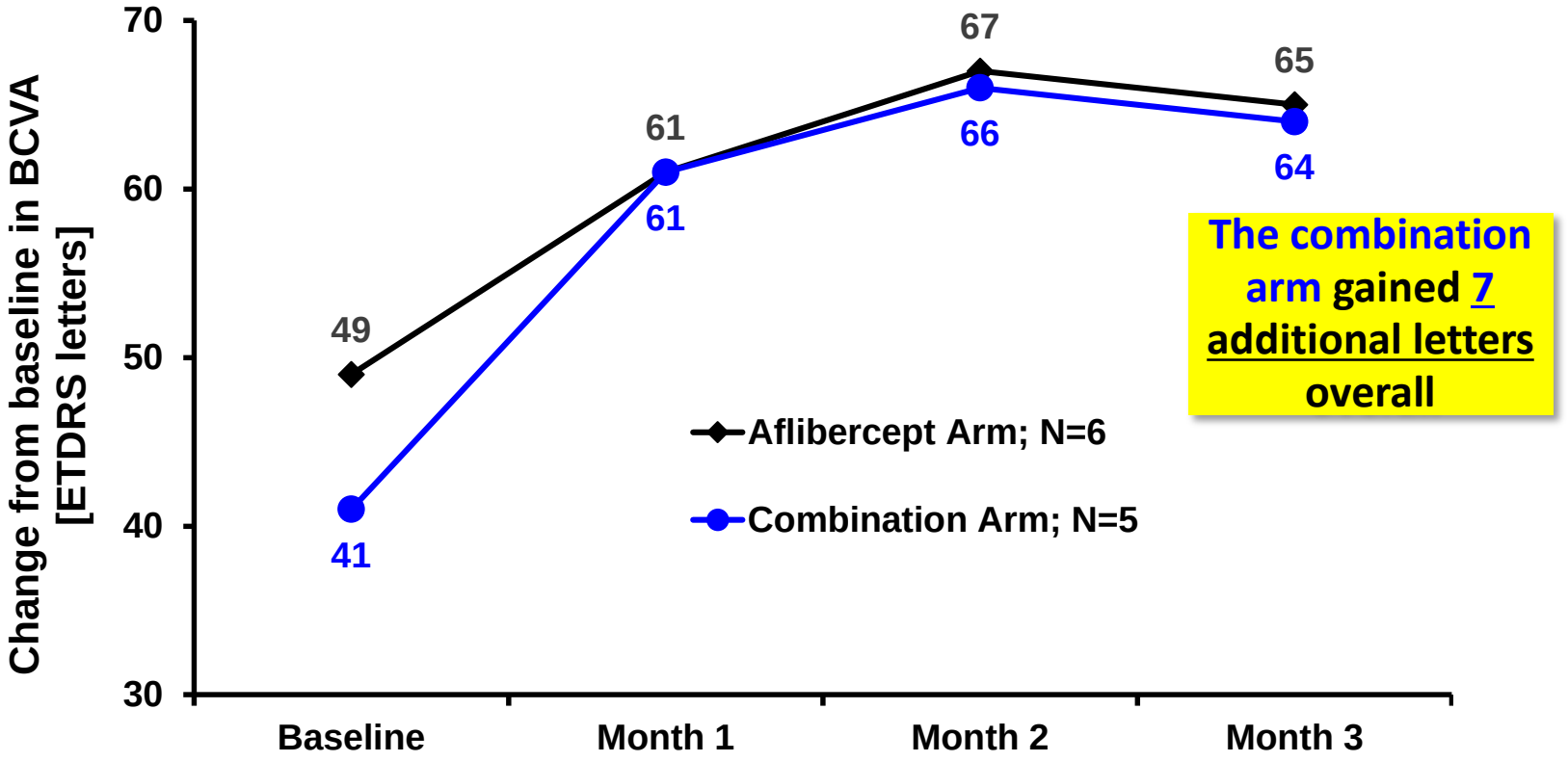


Combination arm reduced CST by an additional 107 µm

Combination arm: 418 µm reduction
Aflibercept arm: 311 µm reduction

Changes from baseline in BCVA for ischemic subjects

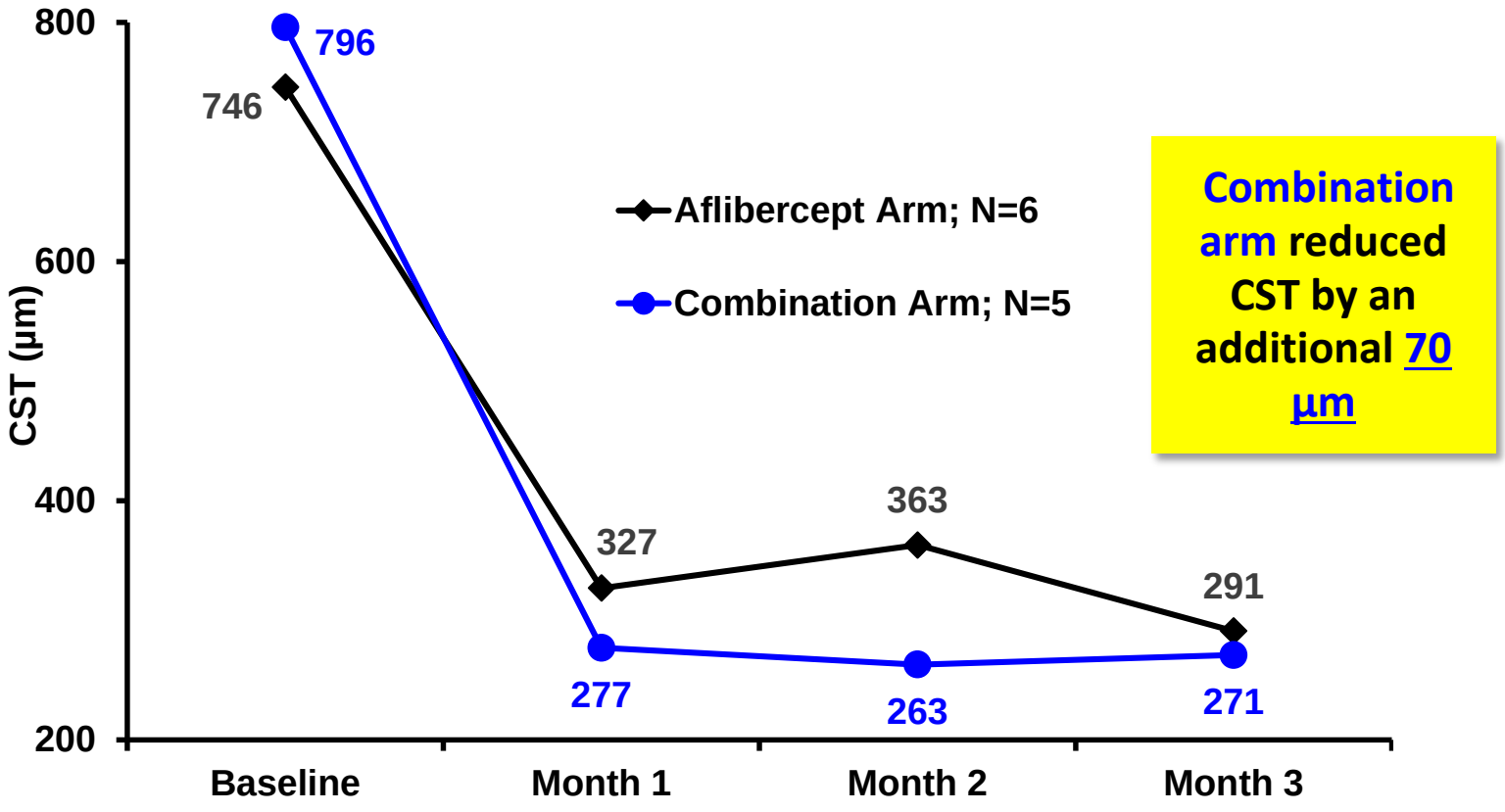
There was an imbalance in mean BCVA at baseline in ischemic subjects with 41 letters read in the **combination arm versus 49 letters** read in the **aflibercept arm**



Combination arm: 23 letter gain from baseline at Month 3
Aflibercept arm: 16 letter gain from baseline at Month 3

CST changes from baseline for ischemic subjects

There was an imbalance in mean CST at baseline in subjects with CRVO; 796 µm in the combination arm versus 746 µm in the aflibercept alone arm



Combination arm reduced CST by an additional 70 µm

Combination arm: 525 µm reduction
Aflibercept arm: 455 µm reduction

Ischemic and non-ischemic take home

- While the sample size is small, the trends are clear…

- **Regardless of perfusion status, combination therapy appears to be better**

Phase 3 trial: SAPPHIRE design

Phase 3 RVO program

- **RVO phase 3 trials** are 6 months for efficacy and an additional 6 months follow-up for safety

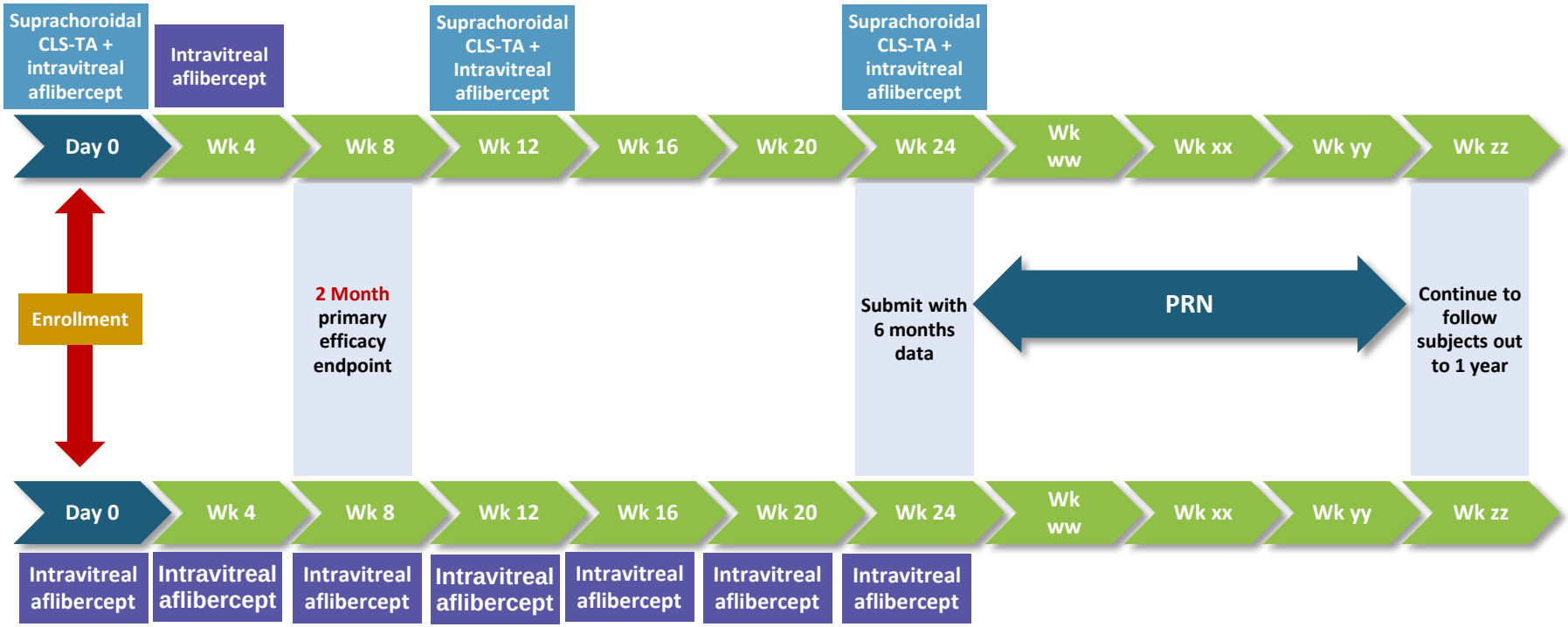
- **<u>For this combination therapy</u>**
  - **Maximal efficacy in the phase 2 study was seen as early as Month 2**
  - The phase 3 study was designed to highlight this potential advantage for the combination therapy

SAPPHIRE, Phase 3, trial design

- **The SAPPHIRE study incorporates this potential advantage:**
  - **The primary endpoint of change in BCVA is at Month 2 (the earliest point where maximum BCVA was obtained)**
  - **The second stage** is from **Month 2 through Month 6** to see if the benefit is maintained with quarterly treatment
  - **The third stage** is from **Month 5 through Month 12** when therapy is given on **a *PRN* basis**
  - **There are two phase 3 studies: each with 460 patients with approximately equal numbers with BRVO and CRVO**

Design for Phase 3 Clinical Trials

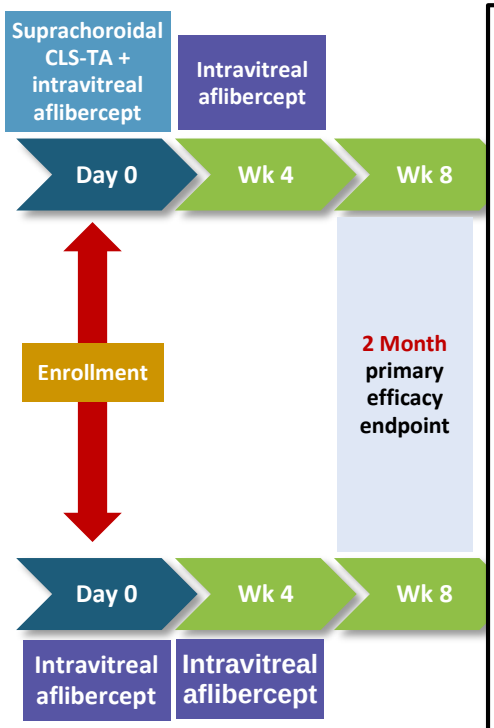
Combination arm: suprachoroidal CLS-TA + Intravitreal aflibercept; Q12Wk



Control arm: Intravitreal aflibercept; Q4Wk

Protocol discussion – Stage 1

Combination arm: suprachoroidal CLS-TA + Intravitreal aflibercept; Q12Wk



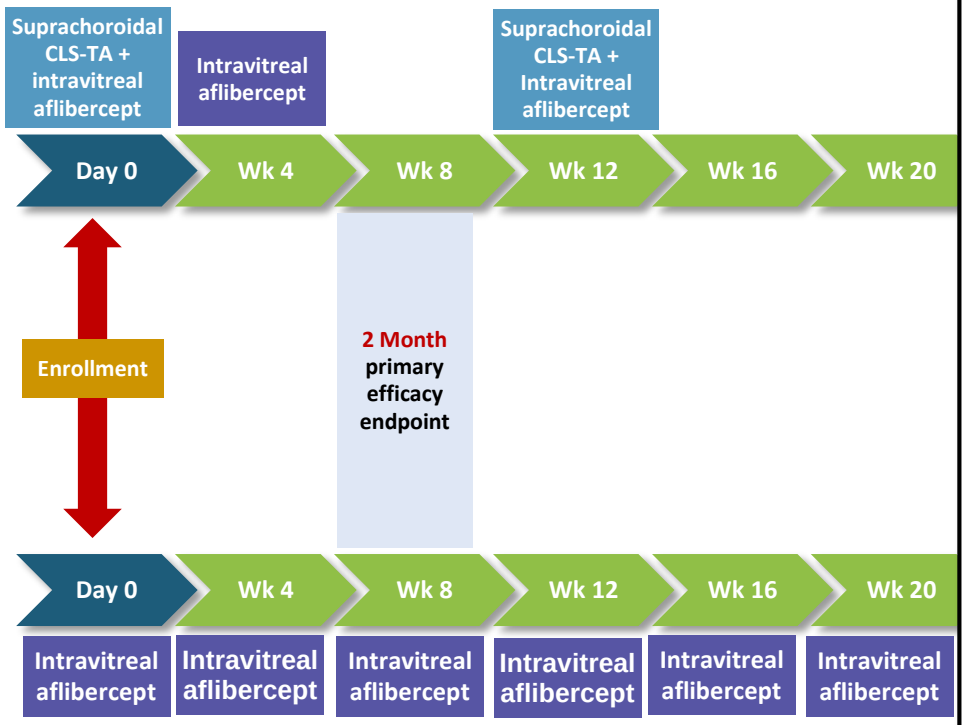
Conceptually there are three portions to the phase 3 design

Stage 1: Through Month2 [Week 8]
Does CLS-TA given in combination with intravitreal aflibercept contribute to an earlier beneficial outcome in RVO patients?

Control arm: Intravitreal aflibercept; Q4Wk

Protocol discussion – Stage 2

Combination arm: suprachoroidal CLS-TA + Intravitreal aflibercept; Q12Wk



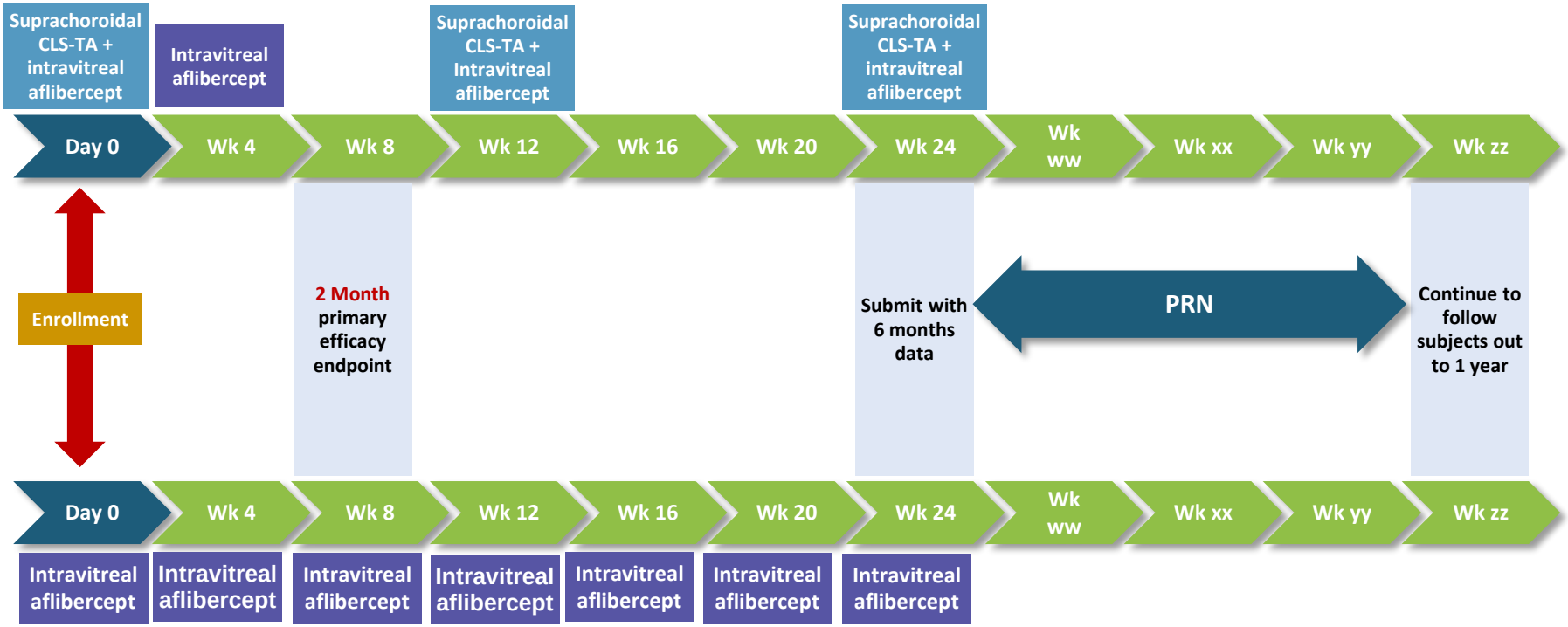
Control arm: Intravitreal aflibercept; Q4Wk

Stage 2: Week 8 through Week 24

Are the outcomes seen through Month 2 *maintained through Month 6* using a quarterly combination dosing regimen?

Protocol discussion – Stage 3

Combination arm: suprachoroidal CLS-TA + Intravitreal aflibercept; Q12Wk



Control arm: Intravitreal aflibercept; Q4Wk

<u>Stage 3</u>: Month 6 through the end of the study

How long does treatment last following dosing at Month 6?

Thank You