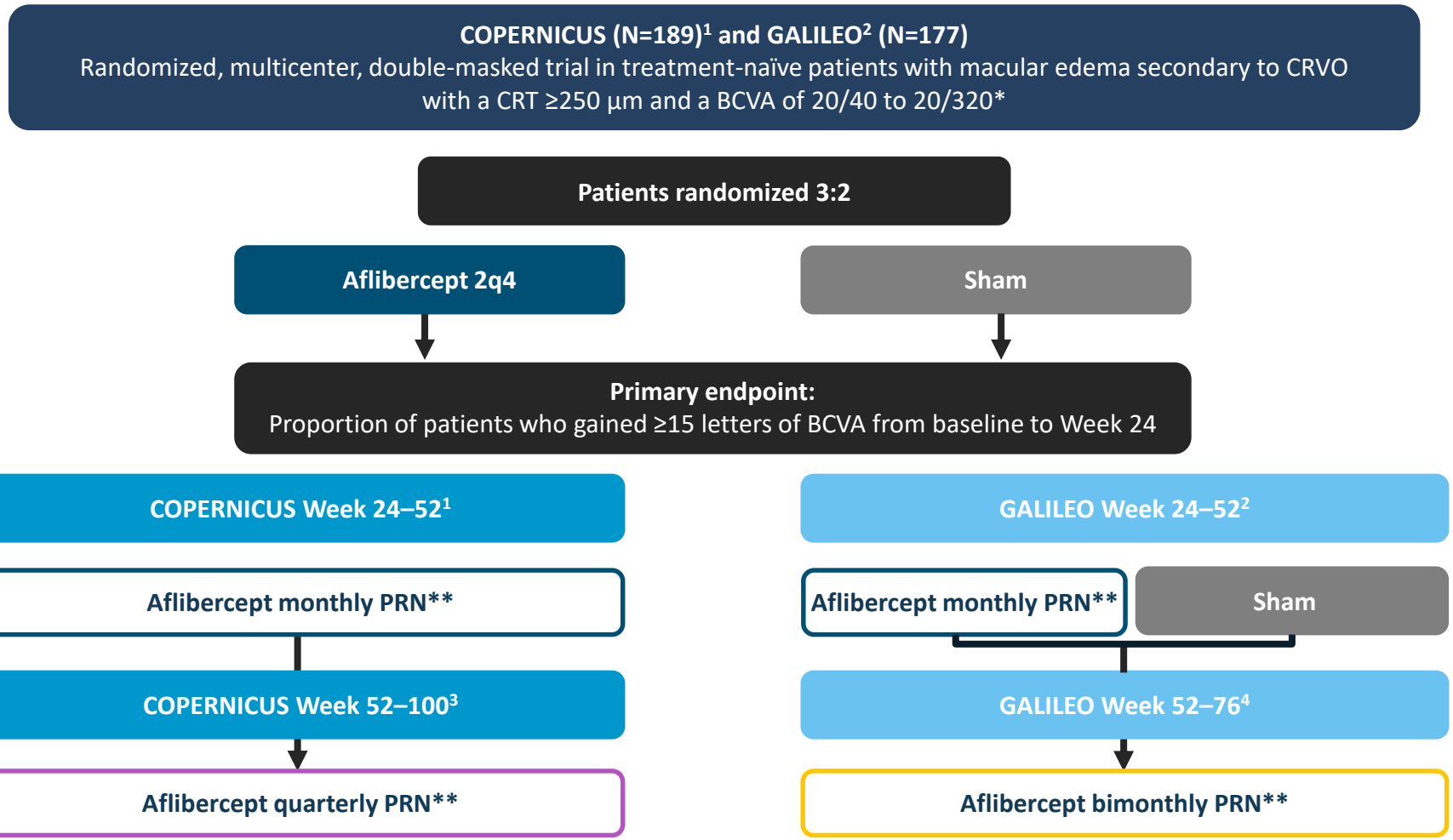
Aflibercept Main Studies in macular edema secondary to Retinal Vein Occlusion (RVO)

COPERNICUS and GALILEO

COPERNICUS and GALILEO: Study design

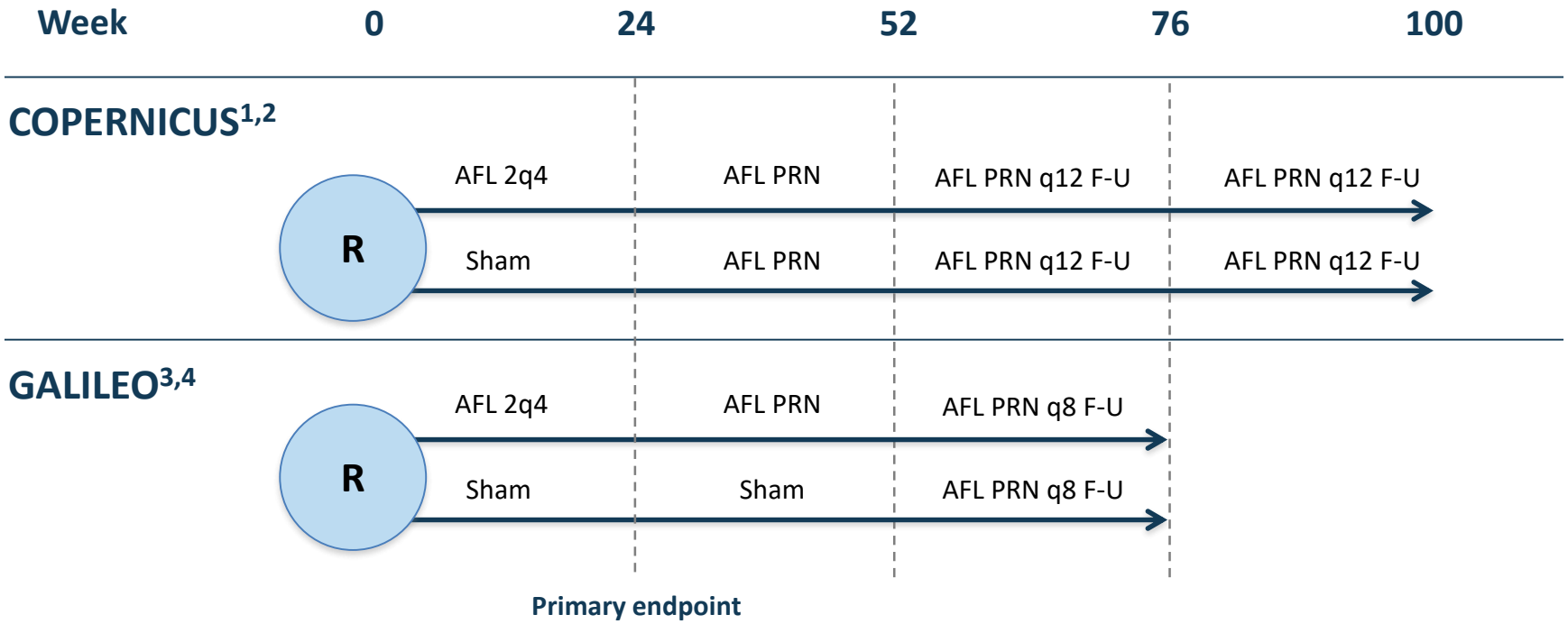


*Snellen equivalent; 73 to 24 ETDRS letters. **Patients could receive injections of intravitreal aflibercept up to monthly if re-treatment criteria were met. 2q4, 2 mg every 4 weeks; BCVA, best corrected visual acuity; CRT, central retinal thickness; CRVO, central retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, pro re nata (as needed).

1. Boyer D, et al. *Ophthalmology*. 2012;119(5):1024–32. 2. Holz FG, et al. *Br J Ophthalmol*. 2013;97(3):278–84. 3. Heier JS, et al. *Ophthalmology*. 2014;121(7):1414–20. 4. Ogura Y, et al. *Am J Ophthalmol*. 2014;158(5):1032–8.

COPERNICUS and GALILEO

COPERNICUS and GALILEO: Study schedule



GALILEO retreatment criteria[4]: increase of >50 µm in CRT from lowest previous measurement; new/persistent cystic retinal changes or subretinal fluid or persistent diffuse edema ≥250 µm in central subfield; loss of ≥5 letters from best previous measurement with any increase in CRT; increase of ≥5 letters between current and most recent visit with no retinal edema in the central subfield.

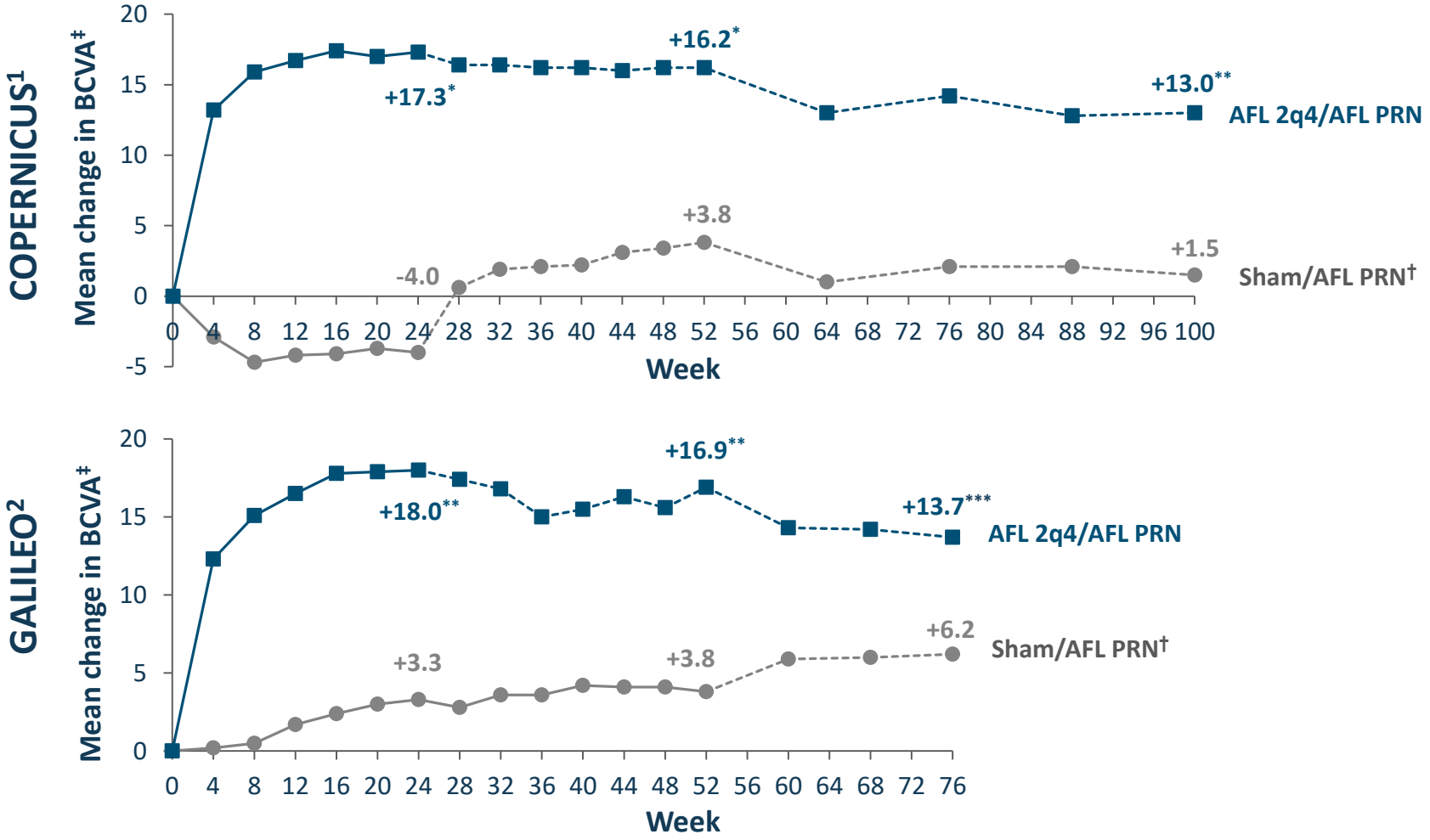
COPERNICUS retreatment criteria[1]: increase of >50 µm in CRT; new/persistent cystic retinal changes or subretinal fluid or persistent diffuse edema ≥250 µm in central subfield; decrease of ≥5 letters between current and most recent visit.

AFL, aflibercept; CRT, central retinal thickness; F-U, follow-up; PRN, *pro re nata* (as needed); q8, every 8 weeks; q12, every 12 weeks; R, randomization.

1. Boyer D, et al. *Ophthalmology.* 2012;119(5):1024–32. 2. Holz FG, et al. *Br J Ophthalmol.* 2013;97(3):278–84. 3. Heier JS, et al. *Ophthalmology.* 2014;121(7):1414–20. 4. Ogura Y, et al. *Am J Ophthalmol.* 2014;158(5):1032–8.

COPERNICUS and GALILEO: Mean change in BCVA was greater with aflibercept at all time points

COPERNICUS and GALILEO



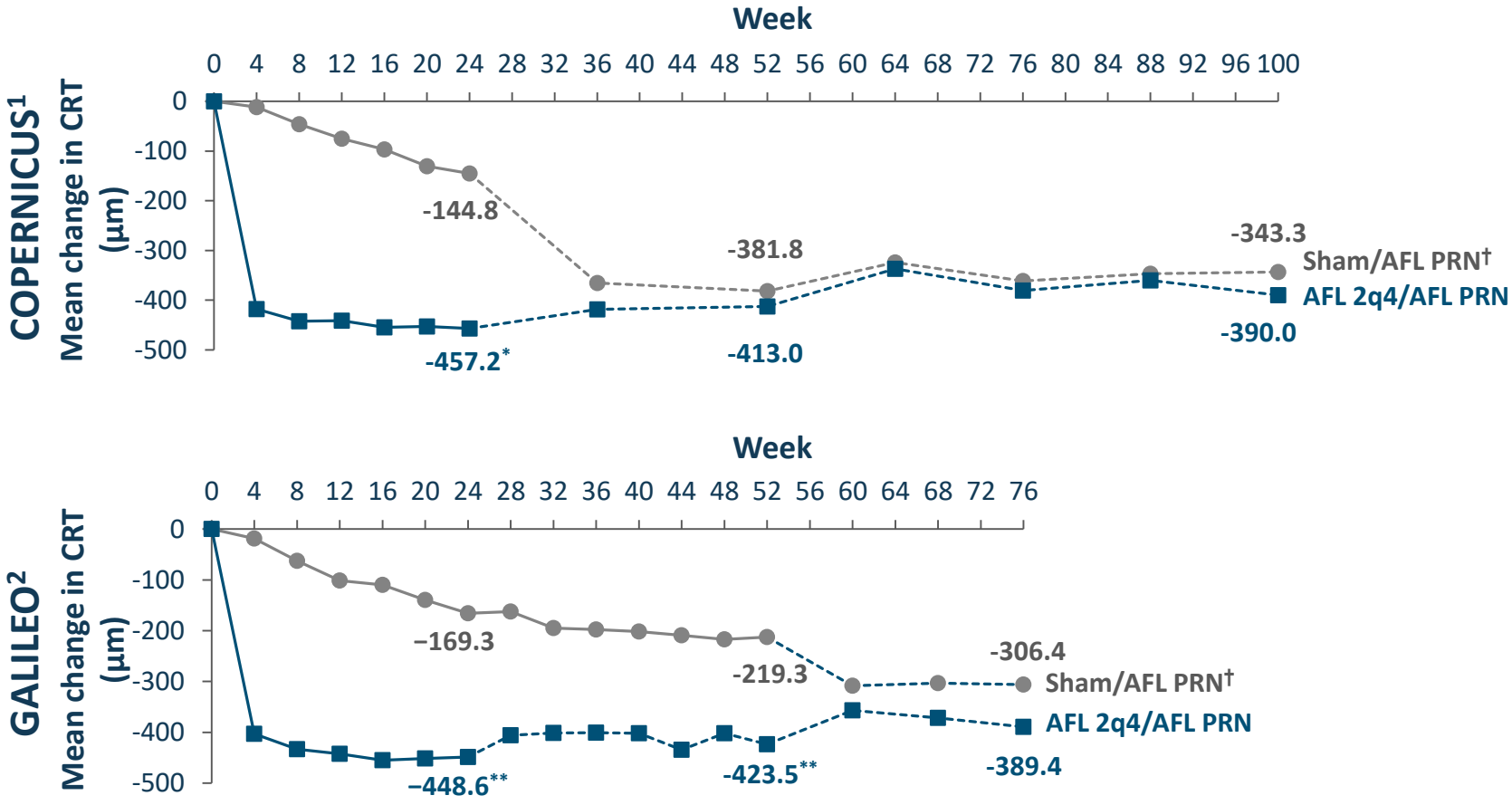
*p<0.001 vs. sham. **p<0.0001 vs. sham. ***p<0.1 vs. sham. ‡ETDRS letters. †AFL treatment became available at 24 weeks in COPERNICUS, and at 48 weeks in GALILEO.

2q4, 2 mg every 4 weeks; AFL, aflibercept; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, *pro re nata* (as needed).

1. Heier JS, et al. *Ophthalmology.* 2014;121(7):1414–20. 2. Ogura Y, et al. *Am J Ophthalmol.* 2014;158(5):1032–8.

COPERNICUS and GALILEO: Aflibercept-treated patients demonstrated improved reductions in CRT

COPERNICUS and GALILEO



*p<0.001 vs. sham. **p<0.0001 vs. sham. †AFL treatment became available at 24 weeks in COPERNICUS, and at 48 weeks in GALILEO.

2q4, 2 mg every 4 weeks; AFL, aflibercept; CRT, central retinal thickness; PRN, pro re nata (as needed).

1. Heier JS, et al. *Ophthalmology*. 2014;121(7):1414–20. 2. Ogura Y, et al. *Am J Ophthalmol*. 2014;158(5):1032–8.

COPERNICUS and GALILEO

COPERNICUS and GALILEO: Overall efficacy

	Week 24				Week 52				Week 100		Week 76	
	COPERNICUS[1]		GALILEO[2]		COPERNICUS[1]		GALILEO[2]		COPERNICUS[1]		GALILEO[2]	
	Sham	AFL 2q4	Sham	AFL 2q4	Sham/ AFL PRN	AFL 2q4/ AFL PRN	Sham	AFL 2q4	Sham/ AFL PRN	AFL 2q4/ AFL PRN	Sham/ AFL PRN	AFL 2q4/ AFL PRN
Patients who gained ≥15 ETDRS letters (%)	12.3	56.1*	22.1	60.2**	30.1	55.3*	32.4	60.2**	23.3	49.1*	29.4	57.3*
Mean change in BCVA (ETDRS letters)	–4.0	17.3*	3.3	18.0*	3.8	16.2*	3.8	16.9*	1.5	13.0**	6.2	13.7†
Mean change in CRT (µm)	–144.8	–457.2*	–169.3	–448.6**	–381.8	–413.0	–219.3	–423.5**	–343.3	–390.0	–306.4	–389.4

*p<0.001 vs. sham. **p<0.0001 vs. sham. †p<0.1 vs. sham.

2q4, 2 mg every 4 weeks; AFL, aflibercept; BCVA, best corrected visual acuity; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, *pro re nata* (as needed).

1. Heier JS, et al. *Ophthalmology.* 2014;121(7):1414–20. 2. Ogura Y, et al. *Am J Ophthalmol.* 2014;158(5):1032–8.

COPERNICUS and GALILEO: Integrated analysis, study eye SAEs through Week 52

COPERNICUS and GALILEO

Study eye SAEs, n (%)	Baseline–Week 52*		
	Sham (n=68)	Sham/AFL PRN (n=74)	AFL 2q4/AFL PRN (n=218)
Patients with ≥1 ocular SAE	**16 (7.3)**	**12 (16.2)**	**6 (8.8)**
Cataract	1 (0.5)	1 (1.4)	0
Corneal abrasion	1 (0.5)	0	0
Cystoid macular edema	1 (0.5)	0	0
Endophthalmitis	1 (0.5)	0	0
Glaucoma	0	3 (4.1)	2 (2.9)
Iris neovascularization	1 (0.5)	2 (2.7)	0
Macular fibrosis	1 (0.5)	0	0
Macular ischemia	1 (0.5)	0	0
Macular edema	4 (1.8)	0	2 (2.9)
Retinal artery occlusion	1 (0.5)	0	0
Retinal hemorrhage	0	2 (2.7)	0
Retinal tear	0	2 (2.7)	0
Retinal vein occlusion	2 (0.9)	1 (1.4)	0
Visual acuity reduced	1 (0.5)	1 (1.4)	1 (1.5)
Vitreous detachment	1 (0.5)	0	0
Vitreous hemorrhage	2 (0.9)	5 (6.8)	1 (1.5)

2q4, 2 mg every 4 weeks; AFL, aflibercept; PRN, *pro re nata* (as needed).

Pielen A, et al. *Clin Ophthalmol.* 2017;11:1533–40.

COPERNICUS and GALILEO: No increased risk of APTC-ATEs was seen with aflibercept*

COPERNICUS and GALILEO

APTC-ATEs, n (%)	Sham (n=68)	Sham/AFL PRN (n=74)	AFL 2q4/AFL PRN (n=218)
Patients with any APTC-ATE	**0**	**1 (1.4)**	**1 (0.5)**
Non-fatal myocardial infarction	0	0	1 (0.5)
Non-fatal stroke	0	0	0
Vascular death	0	1 (1.4)	0

*Integrated analysis.

2q4, 2 mg every 4 weeks; AFL, aflibercept; APTC-ATE, Antiplatelet Trialists' Collaboration arterial thromboembolic event; PRN, *pro re nata* (as needed).

Pielen A, et al. *Clin Ophthalmol.* 2017;11:1533–40.

COPERNICUS and GALILEO: Summary

- GALILEO and COPERNICUS demonstrated that aflibercept solution for intravitreal injection results in substantial improvement of visual acuity[1,2]
- The studies demonstrated that aflibercept solution for intravitreal injection, after the initial monthly dosing phase, maintained efficacy beyond 52 weeks, even with extended treatment intervals[1,2]
- Intravitreal aflibercept was generally well tolerated[1,2]
- Most common ocular AEs reported were typical of those associated with intravitreal injections and the underlying disease[1,2]

1.Brown DM, et al. *Am J Ophthalmol*. 2013;155(3):429-437 2.Holz FG, et al. *Br J Ophthalmol*. 2013;97(3):278-284.

VIBRANT: Study design

VIBRANT

VIBRANT (N=183)
24-week, Phase 3, active-controlled, double-masked, randomized trial in patients aged ≥18 years with foveal center-involved macular edema secondary to BRVO or HRVO with a BCVA of 20/40 to 20/320*

Patients randomized 1:1

Aflibercept 2q4

Laser

Primary endpoint:
Proportion of patients who gained ≥15 letters in BCVA from baseline to Week 24

Secondary endpoint:
Change from baseline in BCVA, CRT, and NEI VFQ -25 total scores at Week 52

*Snellen equivalent; 73 to 24 ETDRS letters.
2q4, 2 mg every 4 weeks; BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; HRVO, hemiretinal vein occlusion; NEI VFQ-25, National Eye Institute 25-Item Visual Function Questionnaire.

1. Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44. 2. https://clinicaltrials.gov/ct2/show/NCT01521559.

VIBRANT

VIBRANT: Defining ischemia in BRVO clinical trials

- Retinal capillary nonperfusion is a measure of ischemia:
  - Historically measured in disc diameters (horizontal optic disc diameter)
  - Recently measured in disc areas (absolute optic disc size)
- Ischemic RVOs have been defined differently in different studies:
  - >5 disc diameters of retinal capillary nonperfusion (e.g. BVOS)[1]
  - ≥10 disc areas of retinal capillary nonperfusion (e.g. VIBRANT)[2]

10 disc areas of retinal capillary nonperfusion represents approximately 50% of ischemia (i.e. 50% of the macula/central retina)[3] in CRVO and is the threshold for increased risk of neovascular events

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion.

1. Branch Vein Occlusion Study Group. *Arch Ophthalmol*. 1986;104(1):34–41. 2. Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44.
3. Magargal LE, et al. *Ophthalmic Surg*. 1986;17(4):240–6.

VIBRANT

VIBRANT: Aflibercept is effective and well tolerated in BRVO

- The first Phase III trial to:[1]
  - Compare an anti-VEGF agent with the prior standard of care (macular grid laser photocoagulation therapy) in BRVO
  - Prove the efficacy of an anti-angiogenic agent in BRVO patients with retinal capillary nonperfusion

Key outcomes in patients receiving aflibercept

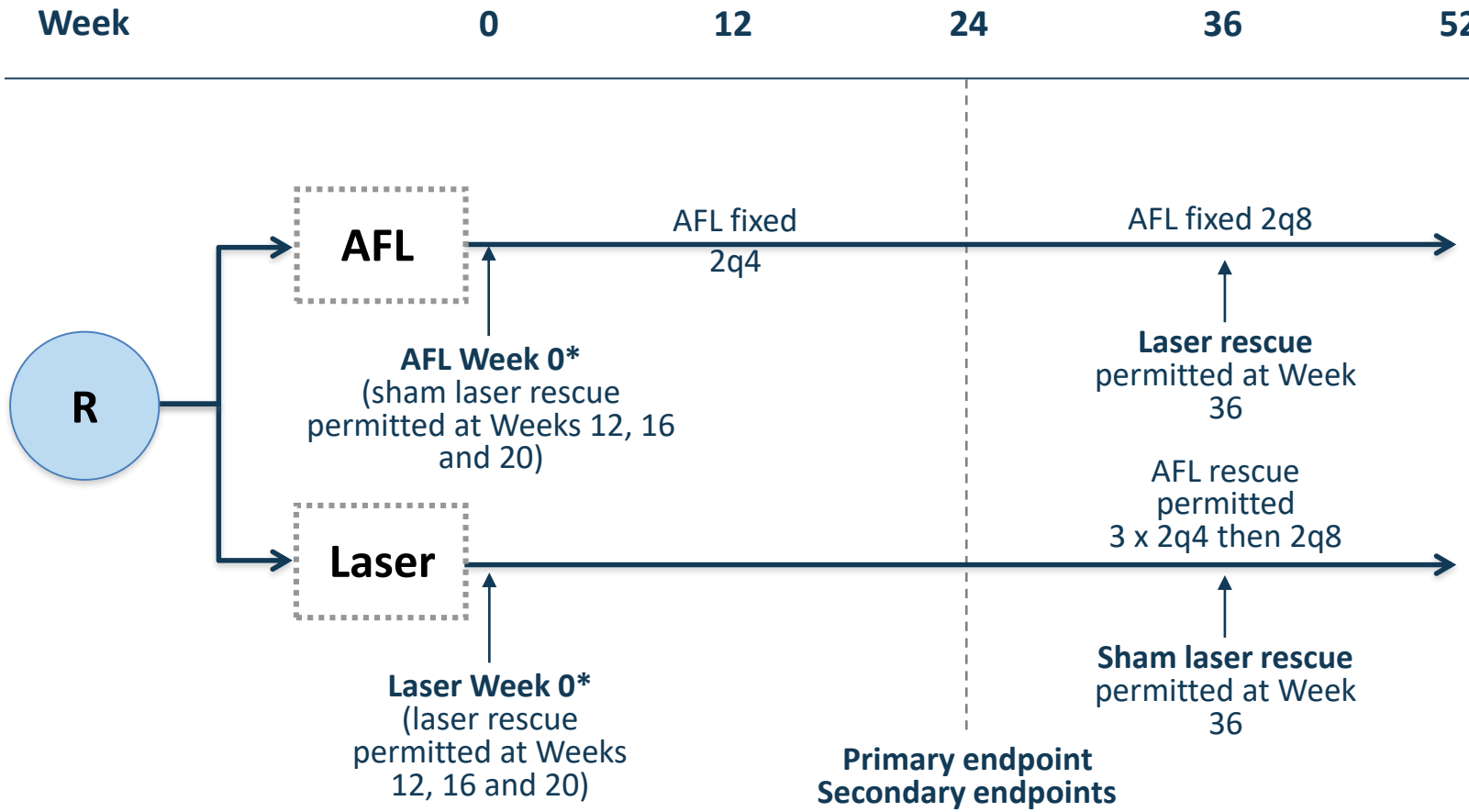
- Eyes received aflibercept 2q4 through Week 24 and 2q8 through Week 52[2]
- Early, significantly greater gains in BCVA versus laser[1]
- BCVA benefits maintained to Week 52[2]
- Well tolerated, consistent with other indications[3–5]

2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; VEGF, vascular endothelial growth factor.

1. Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44; 2. Clark WL, et al. *Ophthalmology*. 2016;123(2):330–6; 3. Heier JS, et al. *Ophthalmology*. 2014;121(7):1414–20; 4. Ogura Y, et al. *Am J Ophthalmol*. 2014;158(5):1032–8; 5. Schmidt-Erfurth U, et al. *Ophthalmology*. 2014;121(1):193–201.

VIBRANT

VIBRANT: Treatment schedule, including rescue



*Rescue laser ≥12 weeks apart from the last laser treatment
2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; AFL, aflibercept; BRVO, branch retinal vein occlusion.

1. Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44. 2. Clark WL, et al. *Ophthalmology*. 2016;123(2):330–6. 3. Data on File. Regeneron Pharmaceuticals Inc. Clinical trial Report VGFTe-RVO-1027 (Week 52). 2014.

VIBRANT

VIBRANT: Criteria-driven assessment for rescue treatment

- Eyes in both treatment groups were evaluated for rescue treatment using the following criteria:[1]
  - >50 µm increase in CRT compared with the lowest previous measurement
  - New or persistent cystic retinal changes, subretinal fluid, or persistent diffuse edema in the central OCT subfield
  - Loss of ≥5 letters compared with the best previous measurement because of BRVO in conjunction with any increase in CRT
- The aflibercept group became eligible for rescue grid laser photocoagulation at 36 weeks
- All eyes were eligible to receive scatter laser photocoagulation at any time during the trial if they developed clinically significant ocular neovascularization

BRVO, branch retinal vein occlusion; CRT, central retinal thickness; OCT, optical coherence tomography.

Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44.

VIBRANT: Baseline demographics and disease characteristics were balanced between treatment arms

VIBRANT

	Laser (n=90)†	AFL (n=91)
Mean age, years (SD)	63.9 (11.4)	67.0 (10.4)
Women, n (%)	36 (40.0)	47 (51.6)
Race [white], n (%)	62 (68.9)	70 (76.9)
BCVA		
Mean, letters (SD)	57.7 (11.3)	58.6 (11.4)
>20/200 (35–73 letters), n (%)	83 (92.2)	85 (93.4)
≤20/200 (24–34 letters), n (%)	7 (7.8)	6 (6.6)
Retinal perfusion status, n (%)		
Perfused*	62 (68.9)	55 (60.4)
Nonperfused**	16 (17.8)	20 (22.0)
Cannot grade	10 (11.1)	16 (17.6)
Missing	2 (2.2)	0
Mean CRT, µm (SD)	553.5 (188.1)	558.9 (185.9)
Time since BRVO diagnosis		
Mean, days (SD)	43.1 (38.8)	42.4 (43.4)
<3 months, n (%)	72 (80.0)	75 (82.4)
≥3 months, n (%)	11 (12.2)	7 (7.7)
Missing	7 (7.8)	9 (9.9)

Full analysis set. *<10 disc areas of retinal capillary nonperfusion. **≥10 disc areas of retinal capillary nonperfusion. †BCVA data not available for 2/92 randomized patients.
AFL, aflibercept; BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CRT, central retinal thickness; SD, standard deviation.

Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44.

VIBRANT: Fewer patients given aflibercept vs laser photocoagulation required rescue treatment

VIBRANT

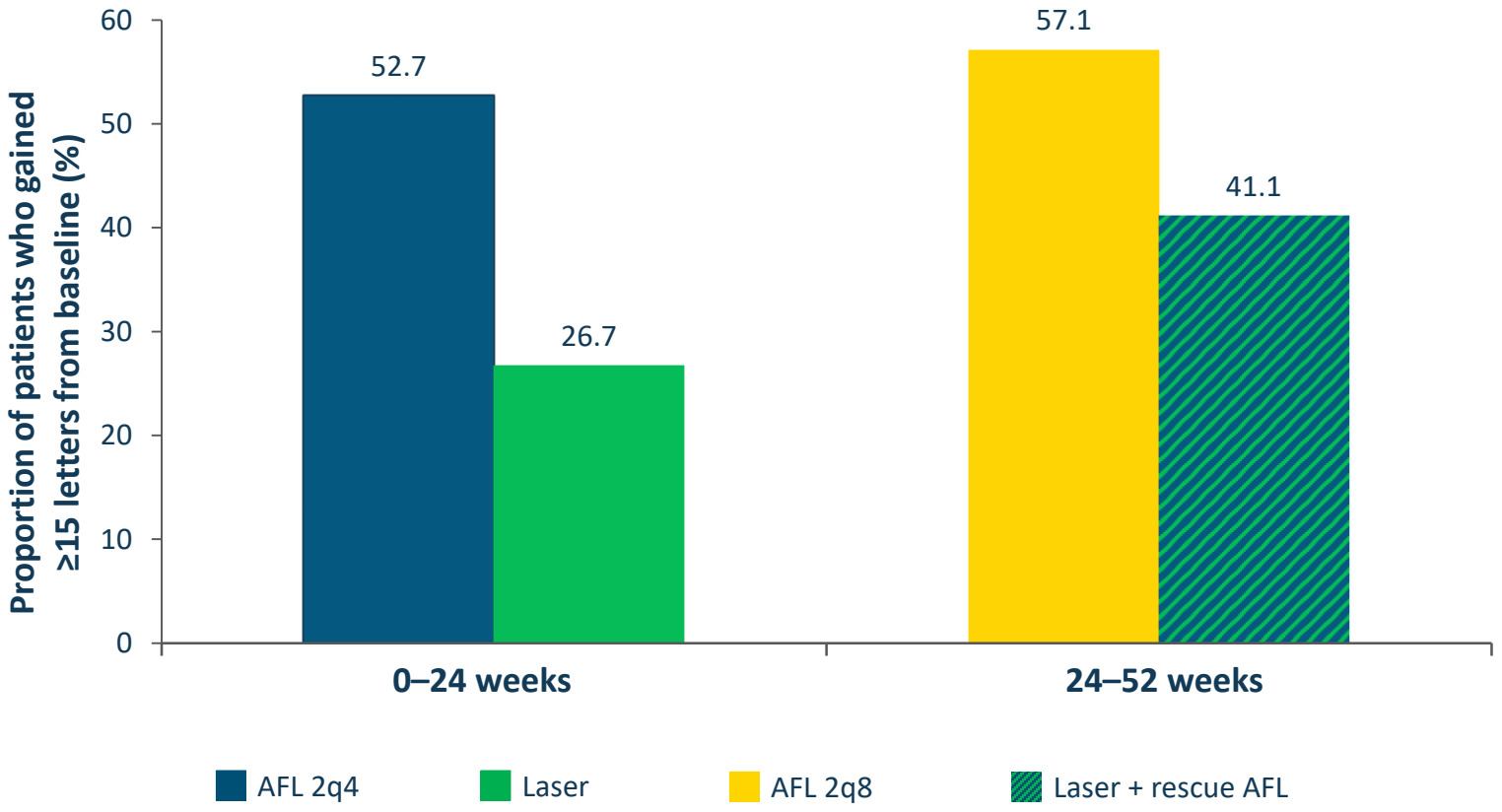
	Baseline–Week 24	Week 24–52	Baseline–Week 52
AFL arm (n=85)*			
Mean number of AFL injections received in the AFL arm	5.7		9.0
Patients receiving rescue laser in the AFL arm, n (%)		9 (10.6)	
Laser arm (n=83)*			
Mean number of laser treatments received	1.7		
Mean number of rescue AFL injections received**		4.4	
Patients receiving rescue AFL injections in the laser arm, n (%)		67 (80.7)	

*Number of eyes completing Week 24. **Eyes in the laser group that required rescue could receive 2 mg AFL every 8 weeks after three initial monthly doses.
AFL, aflibercept.

1. Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44. 2. Clark WL, et al. *Ophthalmology*. 2016;123(2):330–6.

VIBRANT: Significantly more eyes gained ≥15 ETDRS letters with aflibercept vs laser therapy

VIBRANT



Full analysis set. Missing data imputed using the last observation carried forward method. *p=0.0003 versus laser; **p<0.03 versus laser.
2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; AFL, aflibercept; ETDRS, Early Treatment Diabetic Retinopathy Study.
1. Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44. 2. Clark WL, et al. *Ophthalmology*. 2016;123(2):330–6.

VIBRANT: More patients gained vision and fewer lost vision with aflibercept vs laser at Week 24

VIBRANT

Full analysis set. Missing data imputed using the last observation carried forward method. *p<0.05 versus laser. **BCVA data not available for 2/92 randomized patients.

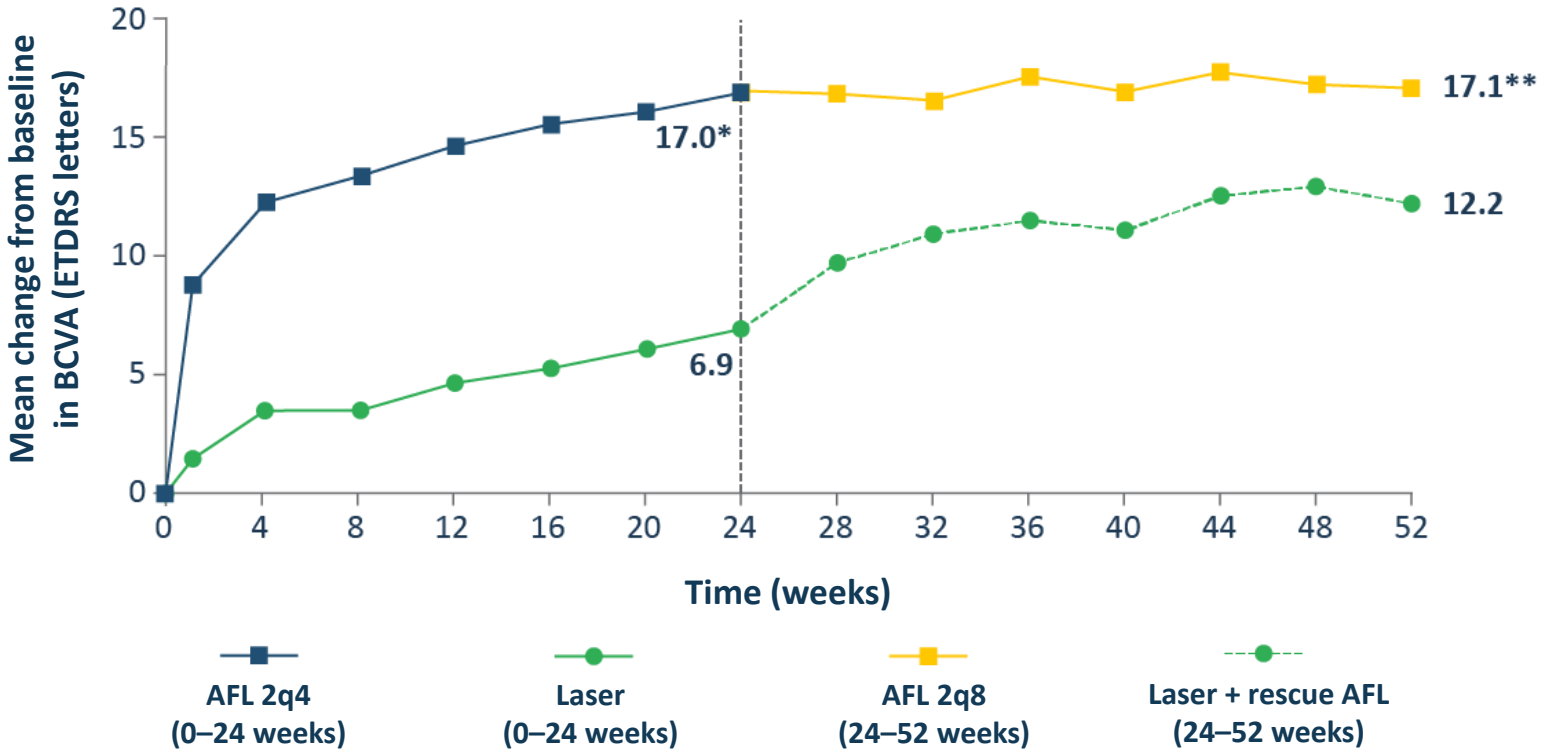
AFL, aflibercept; BCVA, best corrected visual acuity.

Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44.

VIBRANT: Gains in BCVA were rapid and sustained to Week 52 in eyes treated with aflibercept

VIBRANT

- After 12 weeks, 55% of patients had gained ≥3 lines[1]



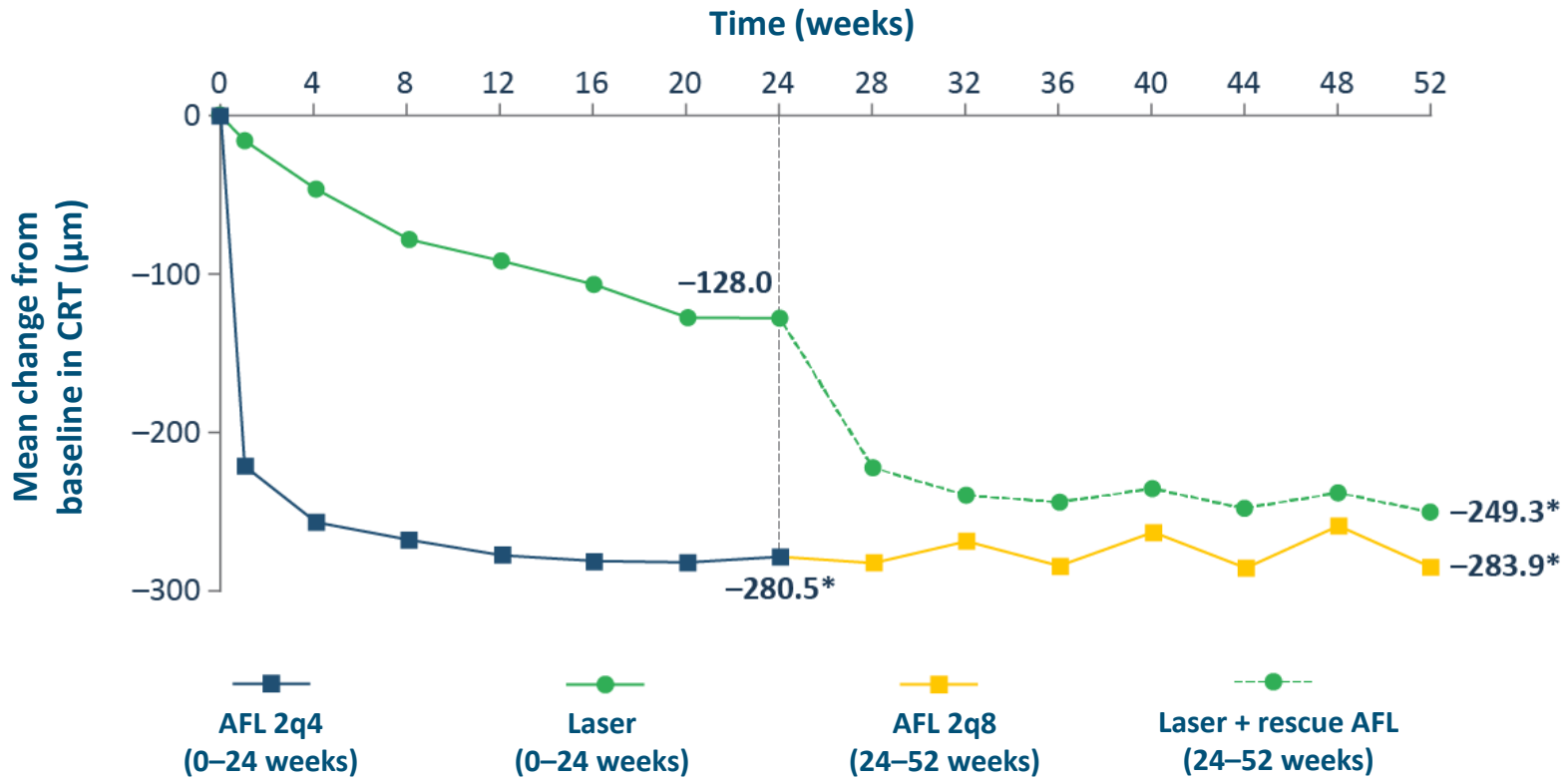
Full analysis set. Missing data imputed using the last observation carried forward method. *p<0.0001; **p<0.004 versus laser.
2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; AFL, aflibercept; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

1. Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44. 2. Clark WL, et al. *Ophthalmology*. 2016;123(2):330–6.

VIBRANT: CRT reductions were rapid and sustained over 52 weeks in eyes treated with aflibercept

VIBRANT

- Although CRT was similar after rescue, this was not reflected in BCVA gains

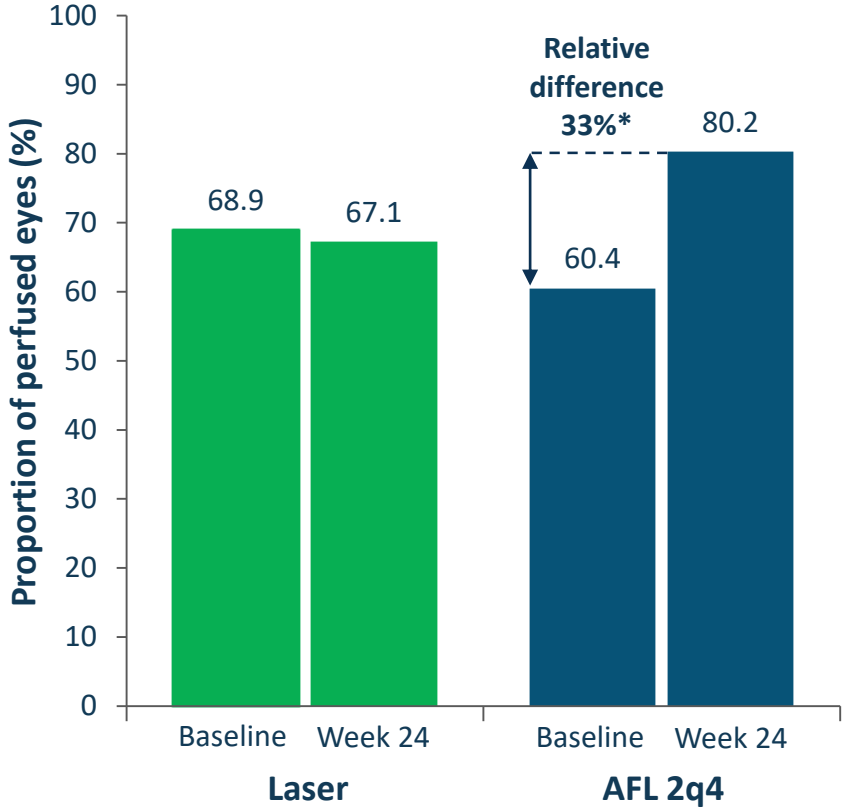


Full analysis set. Missing data imputed using the last observation carried forward method. *p<0.0001; **p<0.004 versus laser.
2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; AFL, aflibercept; BCVA, best corrected visual acuity; CRT, central retinal thickness.

1. Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44. 2. Clark WL, et al. *Ophthalmology*. 2016;123(2):330–6.

VIBRANT: Aflibercept increased the proportion of eyes with retinal capillary perfusion

VIBRANT



- At Week 24, in the arm treated with aflibercept there was a relative increase in the proportion of perfused eyes of 33% from baseline
- At Week 52, after rescue treatment in the laser arm, the perfusion status was effectively identical in the two arms
  - These findings suggest an important effect of aflibercept on the underlying disease mechanism

*p<0.05 aflibercept versus laser.

2q4, 2 mg every 4 weeks; AFL, aflibercept.

1. Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44. 2. Clark WL, et al. *Ophthalmology*. 2016;123(2):330–6.

VIBRANT: Incidence of adverse events from baseline to Weeks 24 and 52 was similar for aflibercept vs laser

VIBRANT

	Week 24[1]		Week 52[2,3]	
	Laser (n=92)	AFL (n=91)	Laser + rescue AFL (n=92)	AFL (n=91)
Ocular AEs, n (%)	25 (27.2)	34 (37.4)	44 (47.8)	45 (49.5)
Ocular SAEs, n (%)	0	1 (1.1)	0	1 (1.1)
Nonocular AEs, n (%)	46 (50.0)	43 (47.3)	63 (68.5)	61 (67.0)
Nonocular SAEs, n (%)	9 (9.8)	8 (8.8)	10 (10.9)	13 (14.3)
APTC-defined ATEs,* n (%)	1 (1.1)	0	2 (2.2)	0
Death, n (%)	1 (1.1)	0	1 (1.1)	0

Safety analysis set. *APTC-defined ATEs include non-fatal stroke, non-fatal MI, and vascular death, as adjudicated by a masked committee.
AE, adverse event; AFL, aflibercept; APTC, Antiplatelet Trialists' Collaboration; ATE, arterial thromboembolic events; SAE, serious adverse event.

1. Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44. 2. Clark WL, et al. *Ophthalmology*. 2016;123(2):330–6. 3. Data on File. Regeneron Pharmaceuticals Inc. *BRVO Year 1 Final Clinical Study Report VGFTe-RVO-1027*.

VIBRANT: Conclusions I

VIBRANT

- The first Phase III trial to compare an anti-VEGF agent with the prior standard of care (macular grid laser photocoagulation therapy) in BRVO
- A significantly higher proportion of patients taking aflibercept gained ≥15 ETDRS letters from baseline at Week 24 (primary endpoint) and at Week 52, compared with patients receiving laser therapy
  - At Week 24, fewer patients receiving aflibercept lost vision
- VIBRANT demonstrated that aflibercept is effective and well tolerated in the treatment of macular edema secondary to BRVO
  - Fewer patients in the aflibercept arm required rescue treatment
- The results of VIBRANT highlight the importance of early rather than delayed treatment in patients with BRVO
  - Although CRT in the rescue arm decreased to a level similar to the early treatment arm, BCVA did not rebound to the same level after delayed treatment

BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor.

1. Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44. 2. Clark WL, et al. *Ophthalmology*. 2016;123(2):330–6.

VIBRANT: Conclusions II

VIBRANT

- Increases in mean BCVA from baseline to Week 24 and Week 52 (secondary endpoint) were significantly greater in the aflibercept arm vs the laser arm
  - There was an early, rapid improvement in mean BCVA
  - Mean CRT reductions from baseline to Week 24 and Week 52 were significantly greater
  - At 24 weeks, patients with nonperfused BRVO treated with aflibercept achieved a 19 ETDRS letter mean change from baseline BCVA
  - Improvements in BCVA from baseline were maintained to Week 52 with a reduced dosing frequency of 2 mg every 8 weeks
- Aflibercept reduced the proportion of nonperfused eyes, and the proportion of perfused eyes increased during treatment
  - VIBRANT is the only Phase III BRVO trial to demonstrate efficacy in both perfused and nonperfused patients
- Vision-related quality of life for patients in the aflibercept arm was sustained, and marginally increased, over the 52-week trial

BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor.

1. Campochiaro PA, et al. *Ophthalmology*. 2015;122(3):538–44. 2. Clark WL, et al. *Ophthalmology*. 2016;123(2):330–6.

LEAVO: Objectives and rationale

LEAVO

- The primary objective of the LEAVO study was to determine whether intravitreal aflibercept or bevacizumab results in a non-inferior mean change in vision at Week 100 compared with ranibizumab for eyes with CRVO-related macular edema
- At the time the trial was designed, aflibercept and bevacizumab were not licensed for the treatment of CRVO
  - The clinical effectiveness of aflibercept and ranibizumab were assessed based on non-inferiority in BCVA compared with ranibizumab (the standard of care), which was the only anti-VEGF treatment for CRVO licensed in the UK at the time of study initiation

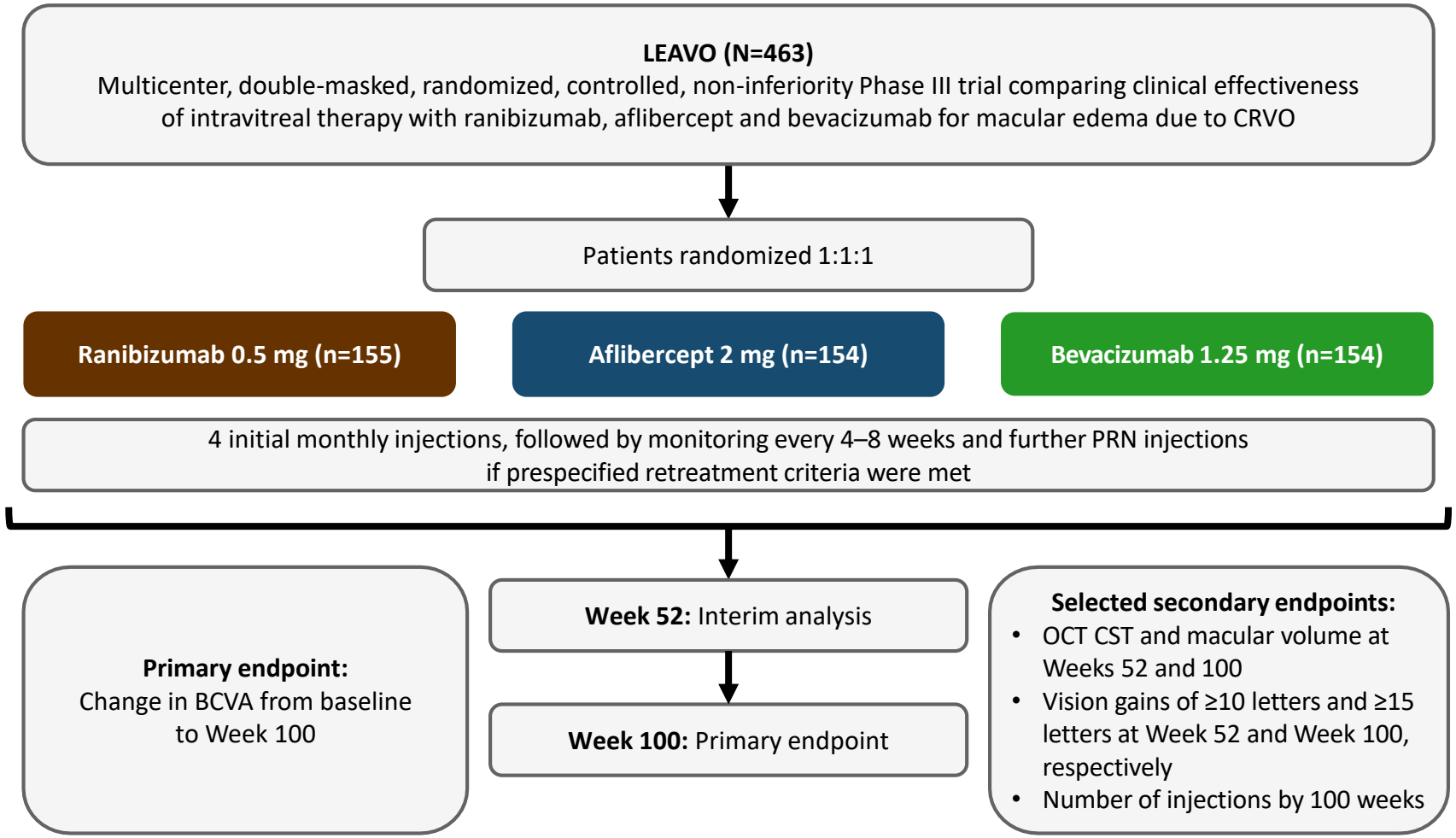
Predefined criteria to assess non-inferiority	
Primary outcome	Mean change in BCVA from baseline to Week 100
Statistic	Adjusted difference of the means
Non-inferiority margin	–5 letters

BCVA, best corrected visual acuity; CRVO, central retinal vein occlusion; VEGF, vascular endothelial growth factor.

Hykin P *et al. JAMA Ophthalmol.* 2019.

LEAVO

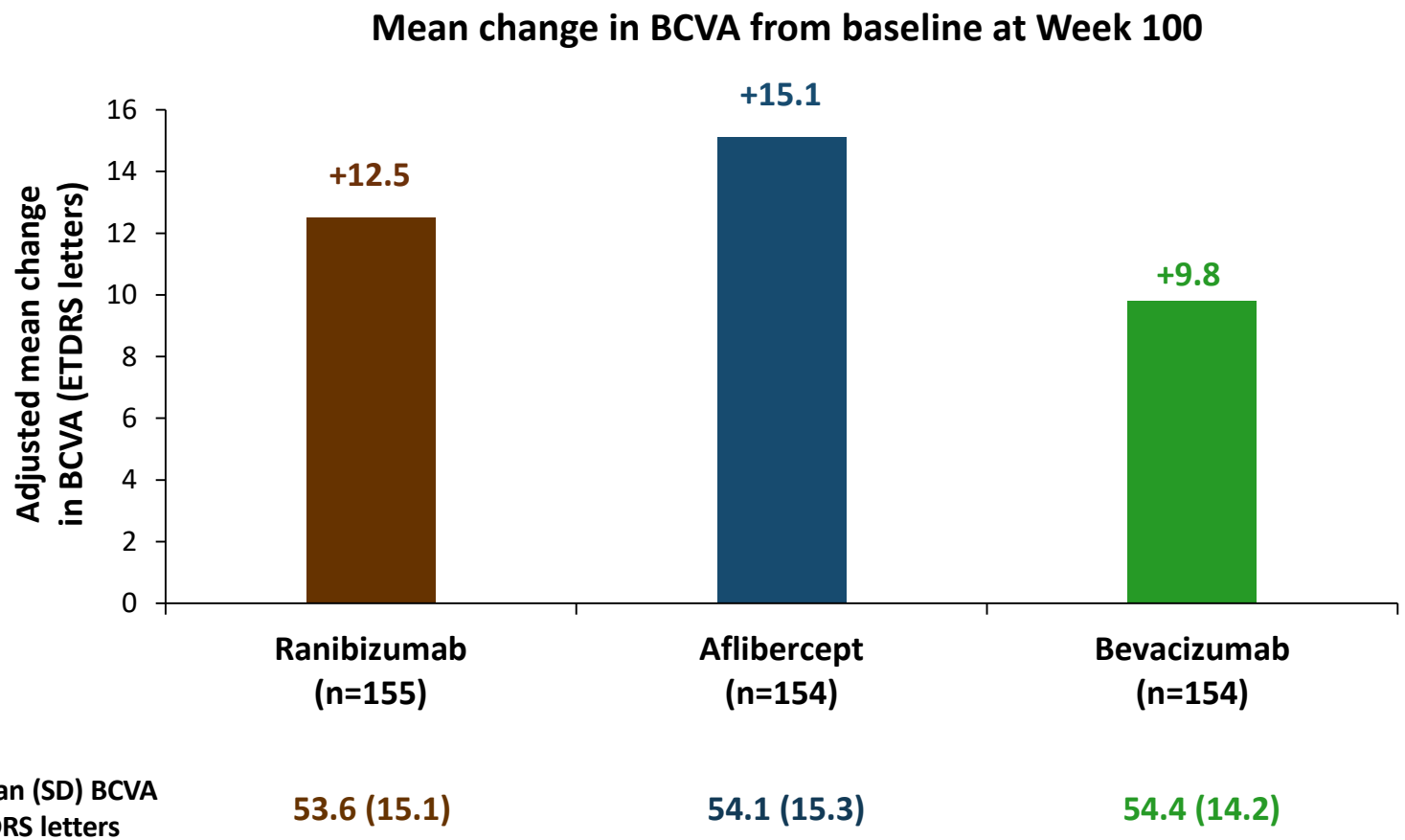
LEAVO: Study design



BCVA, best corrected visual acuity; CRVO, central retinal vein occlusion; CST, central subfield thickness; PRN, *pro re nata* (as needed).
Hykin P *et al. JAMA Ophthalmol.* 2019.

LEAVO: Change in BCVA from baseline at Week 100 (**primary endpoint**)

LEAVO

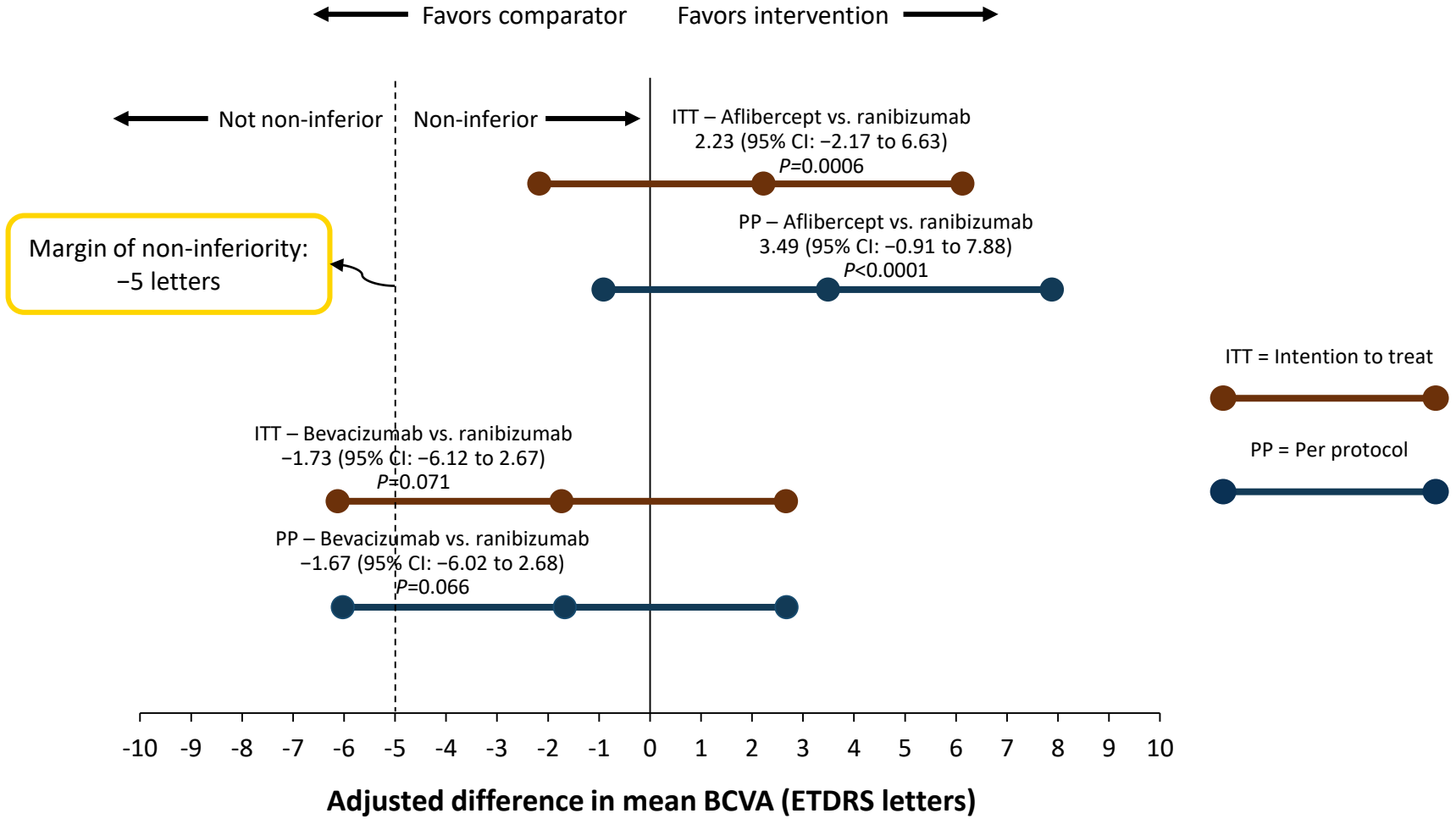


CVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SS, standard deviation.

Hykin P *et al. JAMA Ophthalmol.* 2019.

LEAVO

LEAVO: Non-inferiority of visual outcomes (**primary endpoint**)

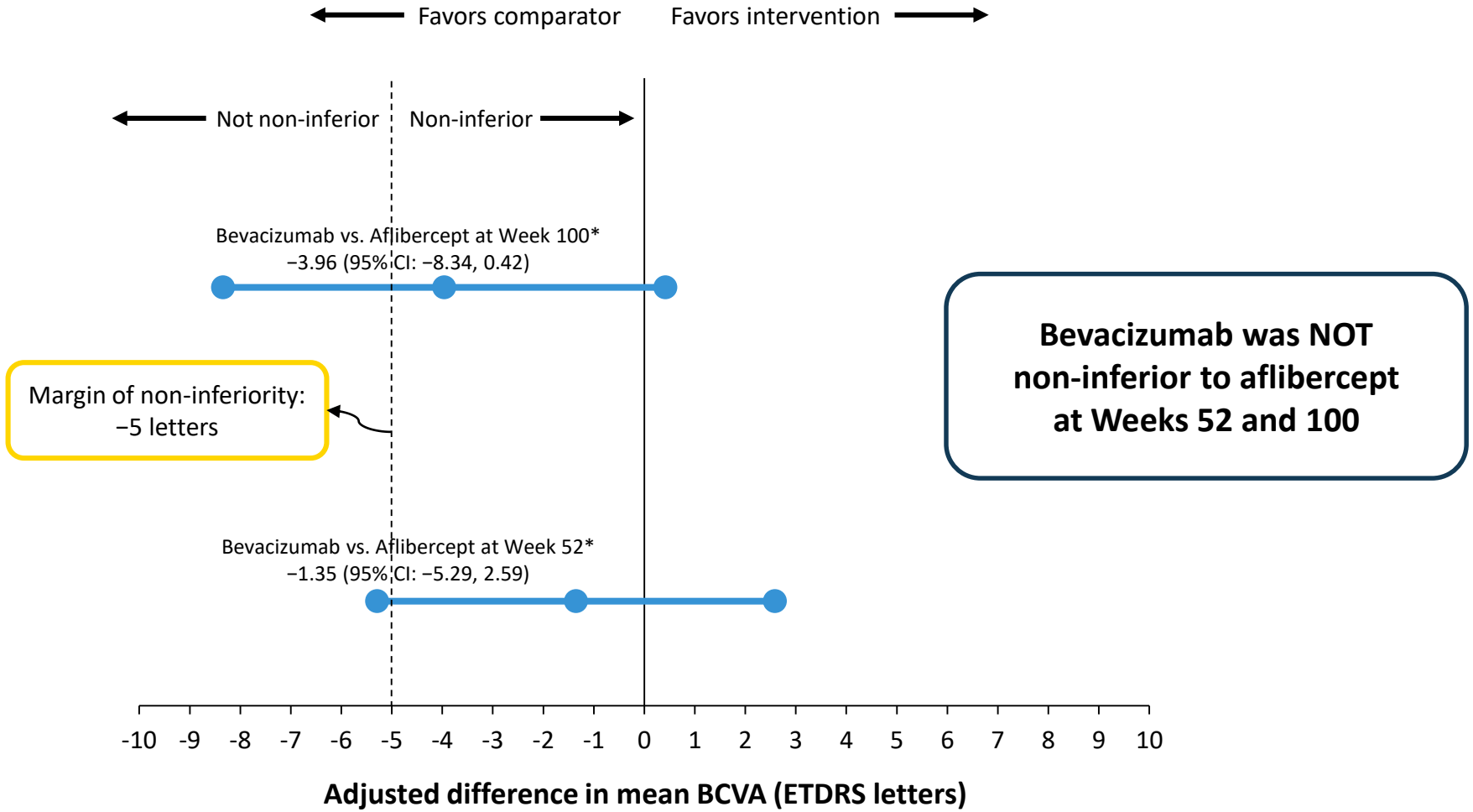


BCVA, best corrected visual acuity; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study.

Hykin P *et al. JAMA Ophthalmol.* 2019. doi: 10.1001/jamaophthalmol.2019.3305.

Hykin P *et al. JAMA Ophthalmol.* 2019. doi: 10.1001/jamaophthalmol.2019.3305– Supplement 2.

LEAVO: Non-inferiority of visual outcomes (**post hoc analysis**)



Bevacizumab was NOT non-inferior to aflibercept at Weeks 52 and 100

*This analysis was conducted in the ITT population.
BCVA, best corrected visual acuity; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intention to treat.

Hykin P *et al. JAMA Ophthalmol.* 2019. doi: 10.1001/jamaophthalmol.2019.3305.

LEAVO: Non-inferiority (adjusted difference – **primary endpoint**)

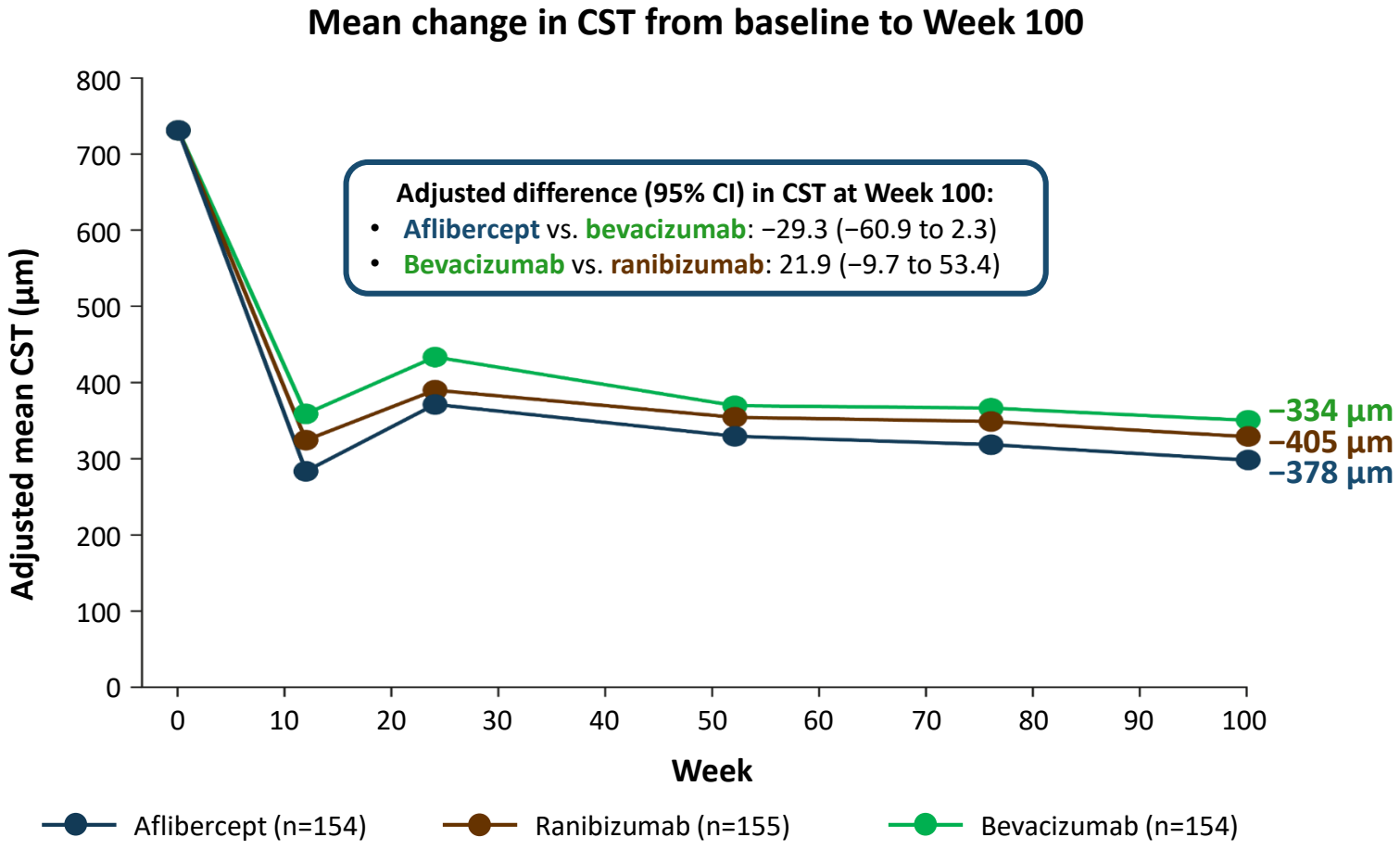
Intergroup comparisons	Week 52	Week 100 (primary endpoint)
Aflibercept vs. ranibizumab	Non-inferior	Non-inferior
Bevacizumab vs. aflibercept*	**Not non-inferior**	**Not non-inferior**
Bevacizumab vs. ranibizumab	Non-inferior	**Not non-inferior**

*Please note that this intergroup comparison was a post hoc analysis.

Hykin P *et al. JAMA Ophthalmol.* 2019. doi: 10.1001/jamaophthalmol.2019.3305.

LEAVO: Anatomic outcomes from baseline through Week 100 (**secondary endpoint**)

LEAVO



CI, confidence interval; CST, central subfield thickness.

Hykin P *et al. JAMA Ophthalmol.* 2019. doi: 10.1001/jamaophthalmol.2019.3305

LEAVO

LEAVO: Safety outcomes

	Ranibizumab (n=155)	Aflibercept (n=154)	Bevacizumab (n=154)
Infectious endophthalmitis, n (%)	0 (0)	0 (0)	1 (0.6)
Traumatic cataract, n (%)	0 (0)	0 (0)	0 (0)
Retinal tear, n (%)	1 (0.6)	0 (0)	0 (0)
Retinal detachment, n (%)	0 (0)	1 (0.6)	2 (1.3)
Conversion to ischemic CRVO, n (%)	8 (5.2)	10 (6.5)	7 (4.5)
Anterior segment neovascularization, n (%)	5 (3.2)	5 (3.2)	3 (1.9)
Retinal neovascularization, n (%)	1 (0.6)	4 (2.6)	1 (0.6)
Vitreous hemorrhage, n (%)	0 (0)	2 (1.3)	4 (2.6)
IOP elevation, n (%)	13 (8.4)	9 (5.8)	5 (3.2)
Systemic APTC events			
Cardiovascular – vascular deaths	2 (1.3)	2 (1.3)	1 (0.6)
Cardiovascular – non fatal MI	0 (0)	0 (0)	2 (1.3)
Cardiovascular – non fatal stroke	2 (1.3)	4 (2.6)	0 (0)

Both comparator and intervention event rates were low

APTC, Anti-Platelet Trialists' Collaboration; CRVO, central retinal vein occlusion; IOP, intraocular pressure; MI, myocardial infarction.

Hykin P *et al. JAMA Ophthalmol.* 2019. doi: 10.1001/jamaophthalmol.2019.3305– Supplement 2.

Summary and conclusions

LEAVO

For the management of macular edema due to CRVO:

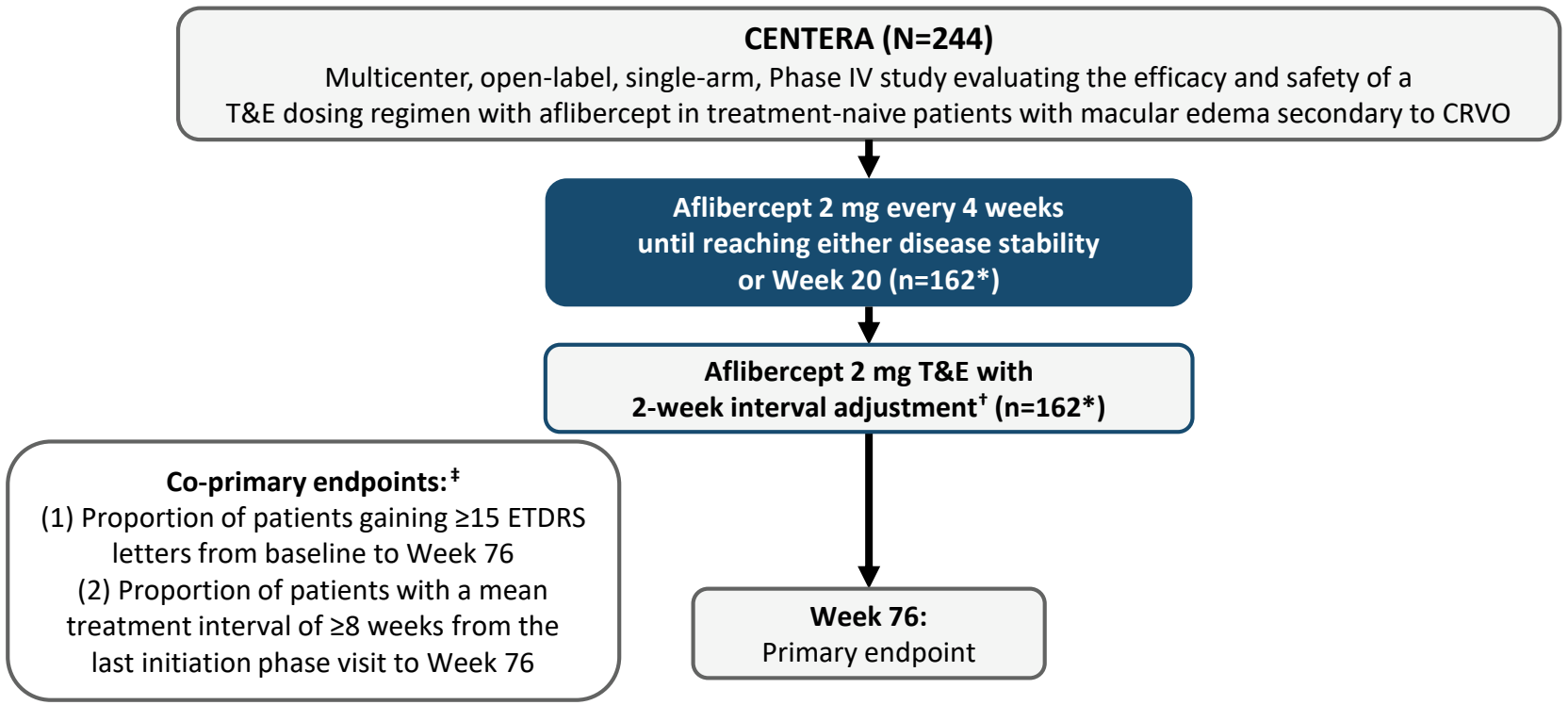
- Ranibizumab, aflibercept, and bevacizumab provided substantial and sustained improvement in VA throughout the study
  - Bevacizumab was NOT non-inferior to ranibizumab at Week 100
  - Aflibercept was non-inferior to ranibizumab but not superior
  - Bevacizumab was NOT non-inferior to aflibercept at Weeks 52 and 100
  - During the second year, a follow-up regimen of 4- to 8-weekly visits and retreatment criteria based on VA and OCT changes might be more appropriate compared with follow-up every 3months to maintain VA gains achieved in Year 1
- Significantly fewer injections were required with aflibercept than with ranibizumab or bevacizumab at both Weeks 52 and 100
- No new safety concerns were identified
- In the UK, for routine treatment of macular edema due to CRVO, these clinical data:
  - Support both EMA-licensed medications, aflibercept and ranibizumab, for use in this indication
  - Suggest that bevacizumab may or may not be worse than ranibizumab
  - Suggest that bevacizumab is not non-inferior to aflibercept

CRVO, central retinal vein occlusion; EMA, European Medicines Agency; OCT, optical coherence tomography; VA, visual acuity.

Hykin P *et al. JAMA Ophthalmol.* 2019. doi: 10.1001/jamaophthalmol.2019.3305.

CENTERA was designed to assess the efficacy and safety of aflibercept T&E in patients with macular edema secondary to CRVO

CENTERA



*2 patients had no post-baseline BCVA assessments available and were not included in the full analysis set. †According to functional and anatomic criteria, with mandatory visits at Weeks 24, 53, and 76. ‡These endpoints were met if significantly ≥40% of patients gained ≥15 ETDRS letters and significantly ≥50% of patients had a mean treatment interval of ≥8 weeks.
BCVA, best corrected visual acuity; CRVO, central retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; T&E, treat-and-extend.

Korobelnik J-F *et al*. *Am J Ophthalmol* 2021; Online ahead of print (DOI: 10.1016/j.ajo.2021.01.027).

CENTERA

Adjustment of treatment intervals was guided by specified criteria

2-week extension

Stable condition

- No new cysts

and

- BCVA within a ±5 letter ‘stability corridor’*

and

- CRT within a ±20% ‘stability corridor’†

Maintenance of interval

Condition improving

- No new cysts

and

- Improvement in at least 1 disease activity criteria (BCVA or CRT) and improvement or stability in the other

2-week shortening

Deteriorating condition

- New cysts

and/or

- Deterioration of BCVA and/or CRT

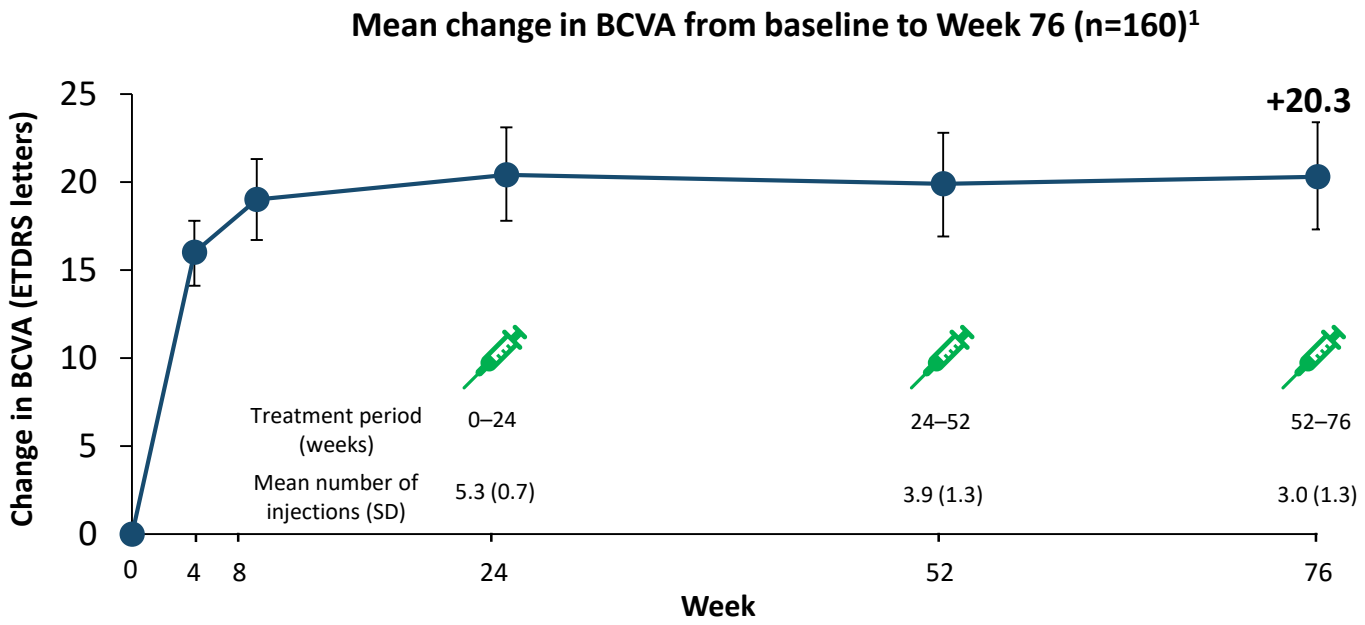
The minimum treatment interval was every 4 weeks

*Defined as no more than 5 letters gained since the last or second to last visit and no more than 5 letters lost from best previous BCVA at any visit. †Defined as no more than a 20% reduction in retinal thickness since the last or second to last visit and no more than a 20% increase in retinal thickness from best previous CRT at any visit. BCVA, best corrected visual acuity; CRT, central retinal thickness.

Korobelnik J-F *et al*. *Am J Ophthalmol* 2021

Rapid and clinically meaningful improvements in BCVA were achieved and maintained to Week 76 with aflibercept

CENTERA



The mean vision gains observed in CENTERA are among the highest reported in clinical trials in CRVO[1–4]

Full analysis set; last observation carried forward. Error bars are 95% CI.

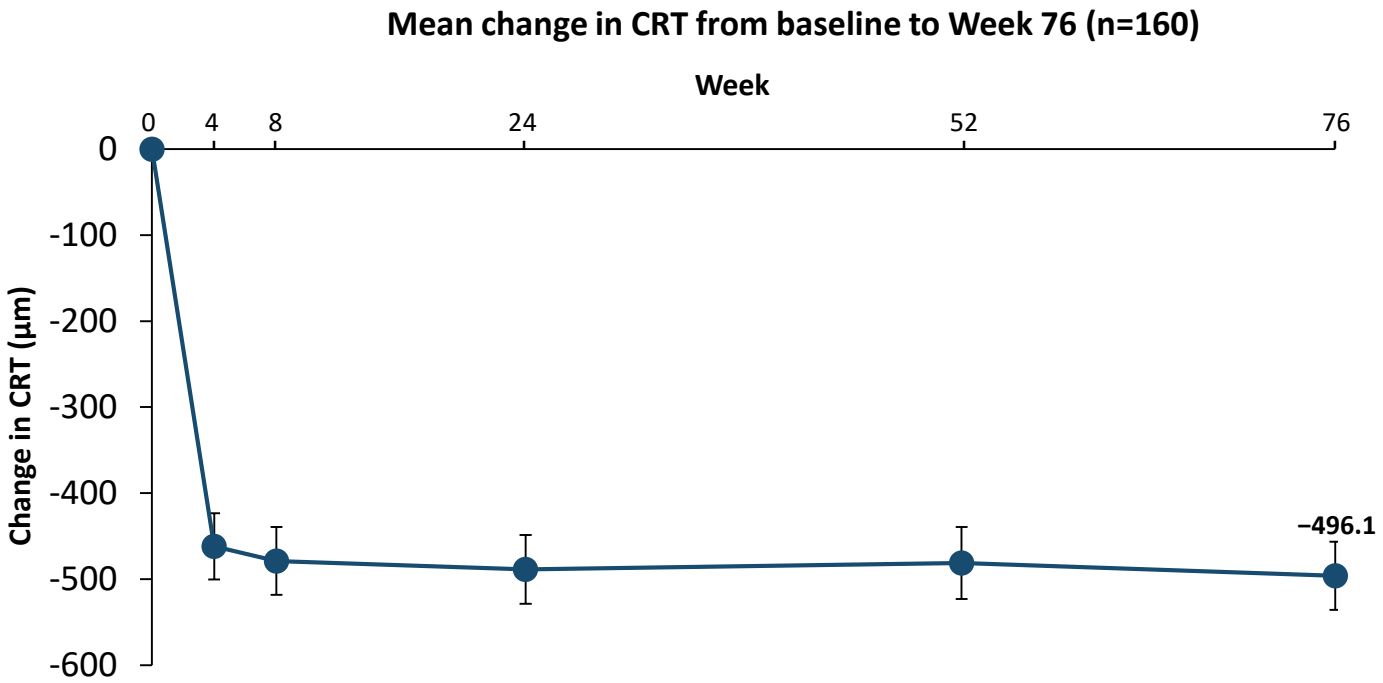
BCVA, best corrected visual acuity; CI, confidence interval; CRVO, central retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation.

1. Korobelnik J-F *et al*. *Am J Ophthalmol* 2021; Online ahead of print (DOI: 10.1016/j.ajo.2021.01.027). 2. Heier JS *et al*. *Ophthalmology* 2014; 121 (7): 1414–1420.e1. 3. Ogura Y *et al*. *Am J Ophthalmol* 2014; 158 (5): 1032–1038.

4. Hykin P *et al*. *JAMA Ophthalmol* 2019; 137 (11): 1256–1264.

Rapid and clinically meaningful improvements in CRT were also achieved and maintained to Week 76 with aflibercept

CENTERA



Full analysis set; last observation carried forward. Error bars are 95% CI.

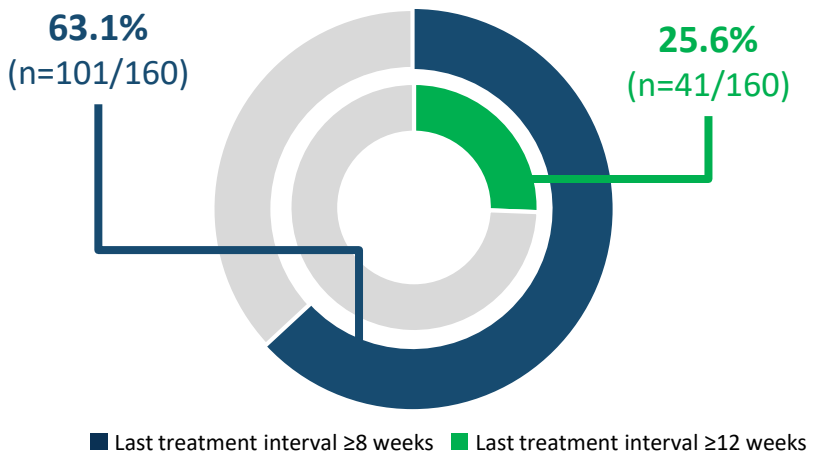
CI, confidence interval; CRT, central retinal thickness.

Korobelnik J-F *et al*. *Am J Ophthalmol* 2021

Around two-thirds of patients had a last treatment interval of ≥8 weeks

CENTERA

Proportion of patients with a last treatment interval of ≥8 weeks or ≥12 weeks



63.1% of patients had a last treatment interval of ≥8 weeks, and 25.6% of patients had a last treatment interval of ≥12 weeks

Treatment exposure outcomes*	Aflibercept (n=160)
Proportion of patients with a mean treatment interval of ≥8 weeks during the T&E phase, %†	45
Mean (SD) treatment interval over the 76-week study, weeks‡	7.6 (1.9)
Proportion of patients with a next planned treatment interval of ≥8 weeks, %	67.5
Proportion of patients with a next planned treatment interval of ≥12 weeks, %	36.9
Mean (SD) last treatment interval, weeks‡	9.3 (3.5)
Mean (SD) next planned treatment interval, weeks‡	9.7 (3.8)
Mean (SD) number of injections from baseline to Week 24, n	5.3 (0.7)
Mean (SD) number of injections from Week 24 to Week 52, n	3.9 (1.3)
Mean (SD) number of injections from Week 52 to Week 76, n	3.0 (1.3)

*Post hoc analyses. †95% CI: 37.1–53.1; *P*=0.8822 (tested against a 50% threshold). ‡Study completers in the full analysis set (n=150). CI, confidence interval; SD, standard deviation; T&E, treat-and-extend.

Korobelnik J-F *et al*. *Am J Ophthalmol* 2021

AEs were consistent with the known safety profile of aflibercept

CENTERA

AE, n (%)	Aflibercept (n=162)
Any TEAE	131 (80.9)
Any ocular TEAE	98 (60.5)
Any ocular TEAE in the study eye	90 (55.6)*
Any non-ocular TEAE	106 (65.4)
Any TEAE related to study drug	6 (3.7)
Any serious TEAE†	32 (19.8)
Serious TEAE related to study drug	2 (1.2)
Endophthalmitis	0
Iridocyclitis	1 (0.6)
Intraocular inflammation	1 (0.6)
Retinal artery occlusion	1 (0.6)
Discontinuation of treatment due to TEAEs	2 (1.2)
Any APTC event	1 (0.6)
Any deaths	4 (2.5)‡

Safety analysis set. *The most common ocular TEAEs in the study eye were reduced VA (14.8%), increased intraocular pressure (12.3%), conjunctival hemorrhage (9.3%), and retinal ischemia (9.3%). †Any serious AEs were reported in 22.8% of patients (n=37). ‡Pulmonary embolism, atrial flutter, and lower respiratory tract infection (n=1); B-cell lymphoma (n=1); intestinal perforation (n=1); and pneumonia (n=1); 2 deaths were treatment-emergent and none were assessed as being related to treatment. AE, adverse event; APTC, Antiplatelet Trialists' Collaboration; TEAE, treatment-emergent adverse event; VA, visual acuity.

Korobelnik J-F *et al*. *Am J Ophthalmol* 2021; Online ahead of print (DOI: 10.1016/j.ajo.2021.01.027). Korobelnik J-F *et al*. *Am J Ophthalmol* 2021; Online ahead of print (DOI: 10.1016/j.ajo.2021.01.027) – Supplemental Table 2.

Summary and conclusions

CENTERA

- CENTERA was one of the first large studies evaluating a T&E regimen in patients with macular edema secondary to CRVO, and demonstrated the efficacy and safety of T&E with aflibercept in this patient population[1]
  - With a mean vision gain at Week 76 of +20.3 letters from baseline, the functional outcomes achieved in CENTERA represent some of the highest VA gains reported in any clinical trial of patients with CRVO[1–4]
- Patients achieved and maintained clinically meaningful vision gains from baseline to Week 76, with 65.6% of patients gaining ≥15 letters[1]
  - The proportion of patients with BCVA of ≥70 letters increased from 13.8% at baseline to 66.9% at Week 76
  - Rapid anatomic improvements were also maintained through Week 76, with a mean decrease in CRT from baseline of 496.1 µm
  - These improvements were achieved with a decrease in treatment burden over the course of the study
- A last treatment interval of ≥8 weeks was achieved by 63.1% of patients, and 25.6% of patients had last treatment interval of ≥12 weeks[1]

BCVA, best corrected visual acuity; CRT, central retinal thickness; CRVO, central retinal vein occlusion; T&E, treat-and-extend; VA, visual acuity.

1. Korobelnik J-F *et al*. *Am J Ophthalmol* 2021; Online ahead of print (DOI: 10.1016/j.ajo.2021.01.027). 2. Heier JS *et al*. *Ophthalmology* 2014; 121 (7): 1414–1420.e1. 3. Ogura Y *et al*. *Am J Ophthalmol* 2014; 158 (5): 1032–1038. 4. Hykin P *et al*. *JAMA Ophthalmol* 2019; 137 (11): 1256–1264.