

Anti- VEGFs Main Clinical Studies in Wet Age-Related Macular Degeneration (wAMD)



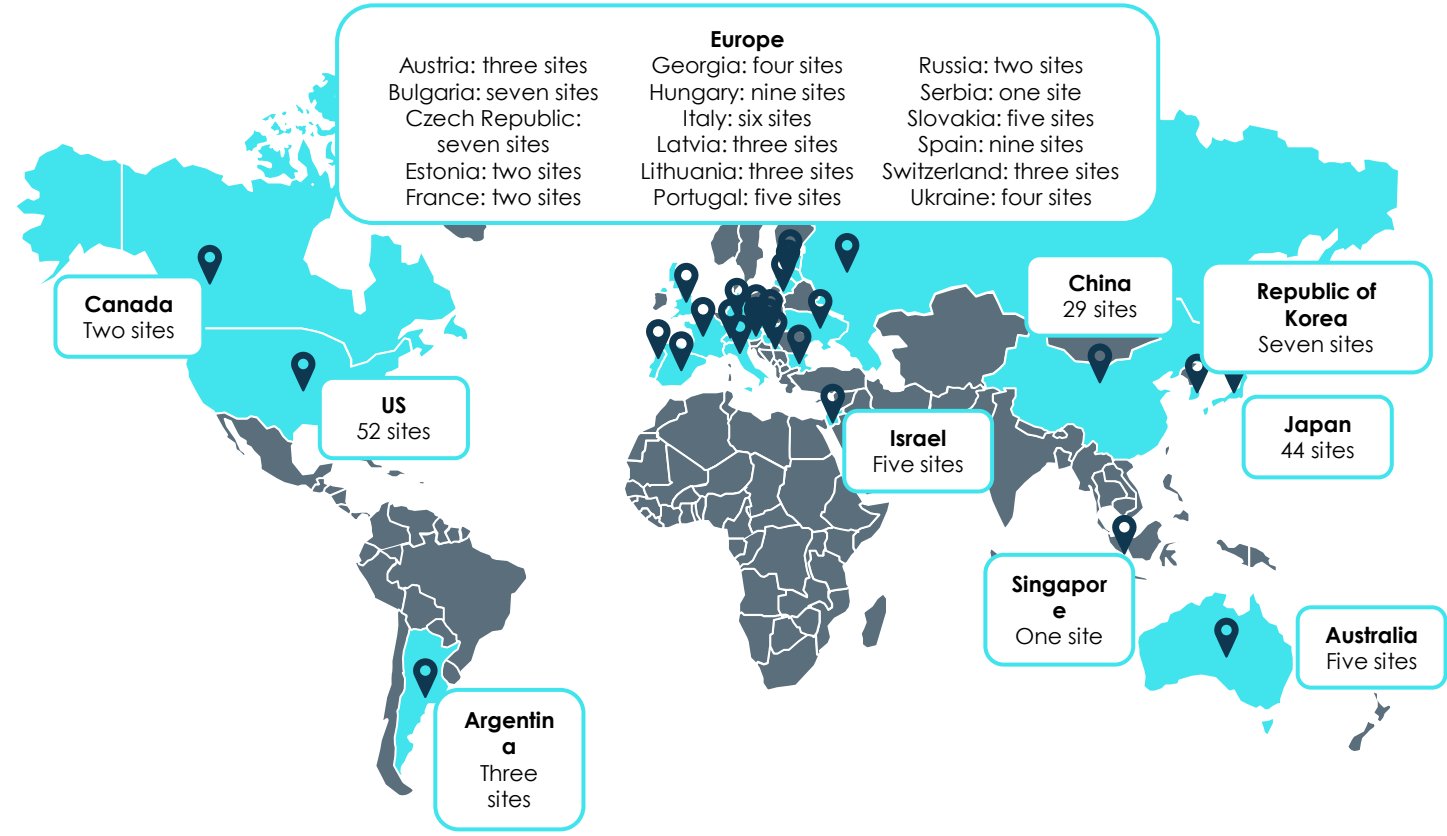
**Aflibercept 8mg:
Phase III PULSAR (nAMD)**

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PULSAR study sites

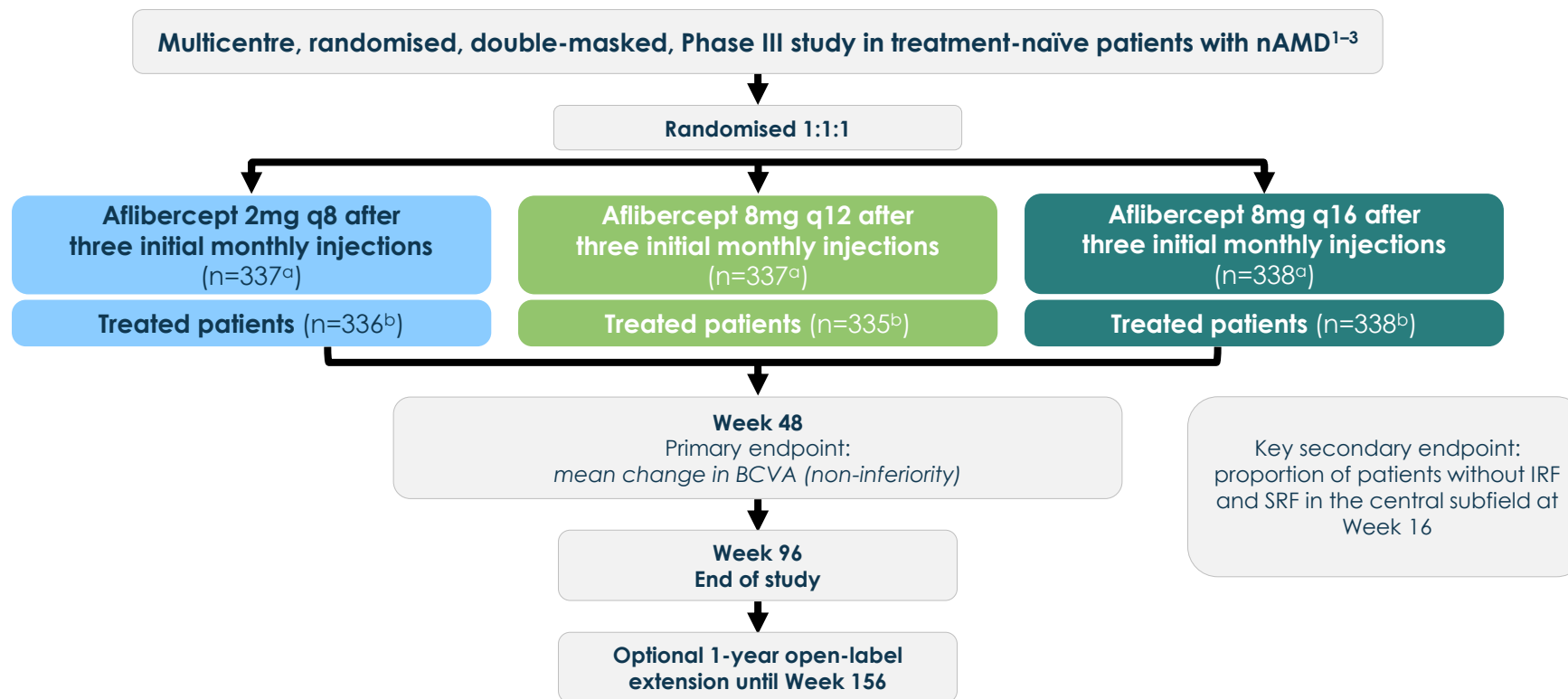
nAMD





PULSAR trial design

nAMD



1. Korobelnik J-F. AAO 2023. 3–6 November 2023. San Francisco, US. 2. Spitzer M. ARVO 2023. 23–27 April 2023. New Orleans, US. 3. ClinicalTrials.gov. Identifier: NCT04423718. Accessed: January 2024.

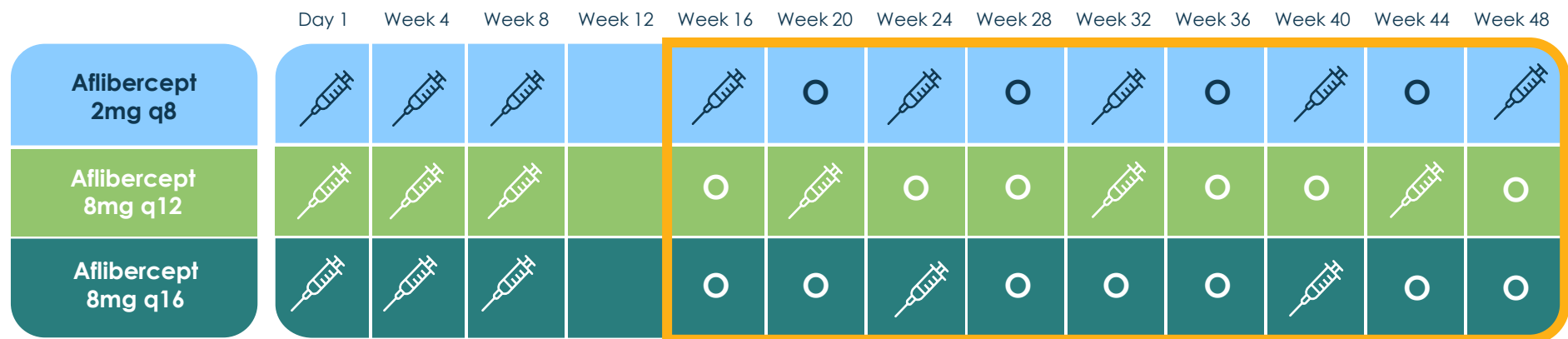


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Dosing schedule in Year 1

nAMD



 Active injection

 Sham injection

All patients were **randomly** assigned from the outset

Three initial monthly doses for **all treatment groups**

Patients were treated according to their assigned treatment interval and dose:

- 2mg every 8 weeks
- 8mg every 12 weeks
- 8mg every 16 weeks

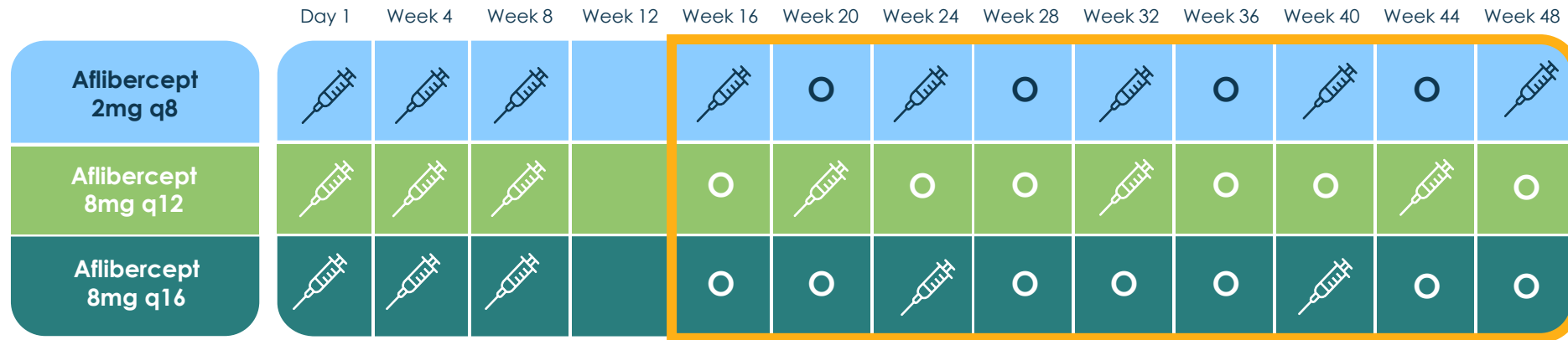
Korobelnik J-F. AAO 2023. 3–6 November 2023. San Francisco, US.
 This figure does not represent all dosing options once a treatment interval has been shortened.



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Dosing schedule in Year 1

nAMD



Active injection

Sham injection

All patients were **randomly** assigned from the outset

Three initial monthly doses for **all treatment groups**

From Week 16 onwards, patient visits were every 4 weeks, where they either received an:

Active injection **or a**

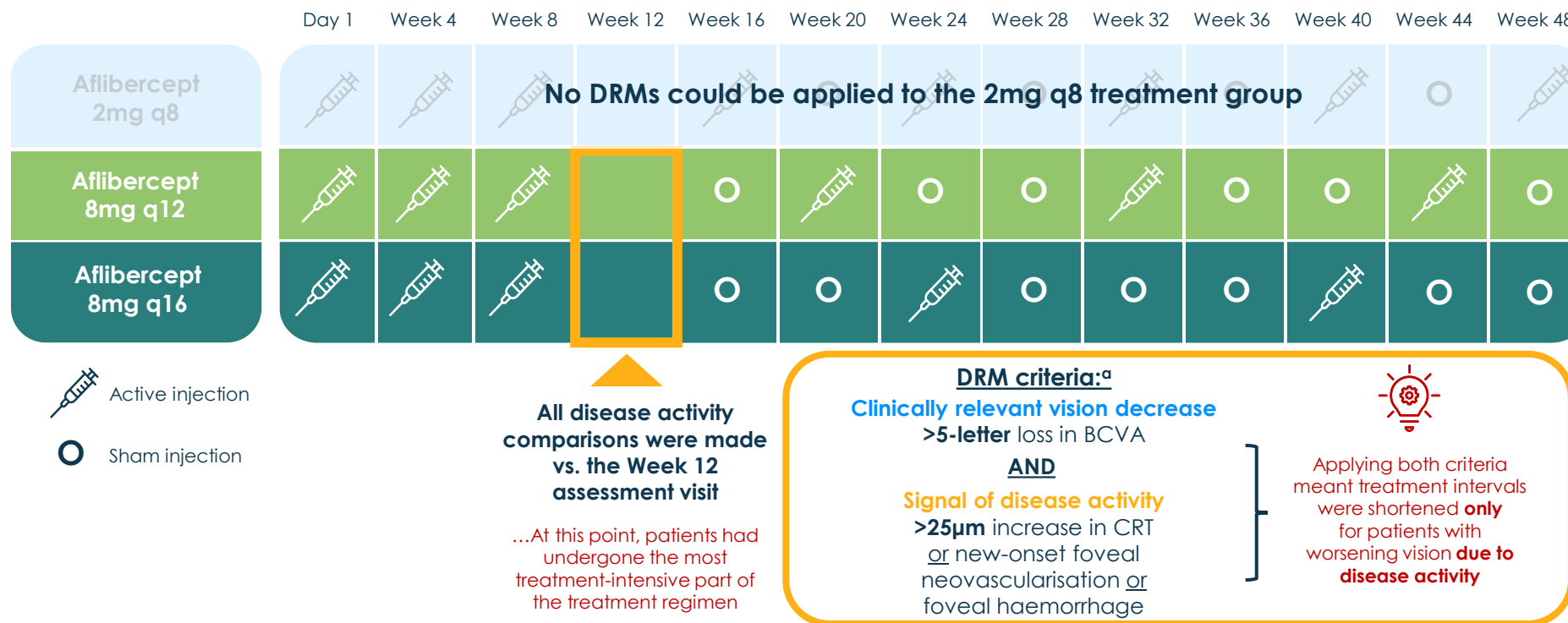
Sham injection

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Dose regimen modification (DRM) criteria for the aflibercept 8mg groups in Year 1

nAMD



This figure does not represent all dosing options once a treatment interval has been shortened. ^aPatients who met the DRM criteria had treatment intervals shortened to q8 at Week 16 and Week 20 or by 4-week increments from Week 24. The minimum assigned treatment interval was q8. No interval extension was allowed in the first year.

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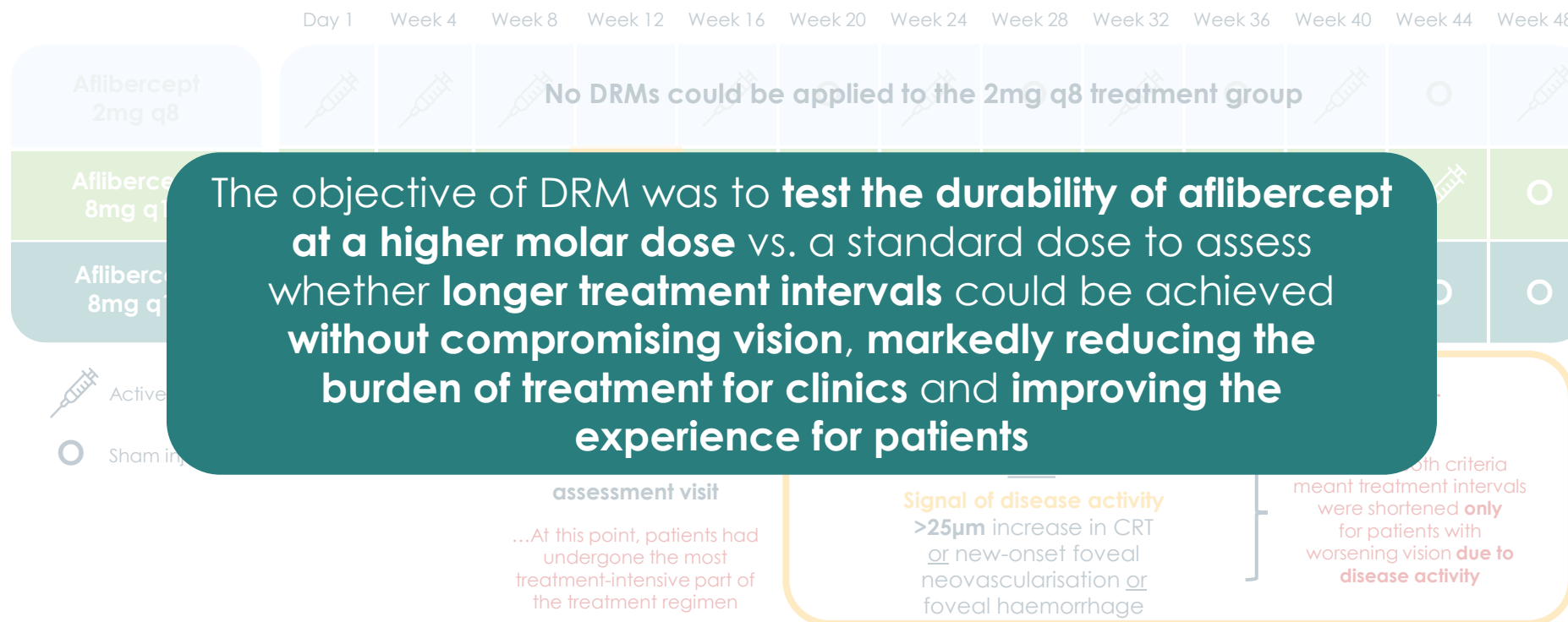


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DRM criteria for the aflibercept 8mg groups in Year 1

nAMD



This figure does not represent all dosing options once a treatment interval has been shortened. ^aPatients who met the DRM criteria had treatment intervals shortened to q8 at Week 16 and Week 20 or by 4-week increments from Week 24. The minimum assigned treatment interval was q8. No interval extension was allowed in the first year.

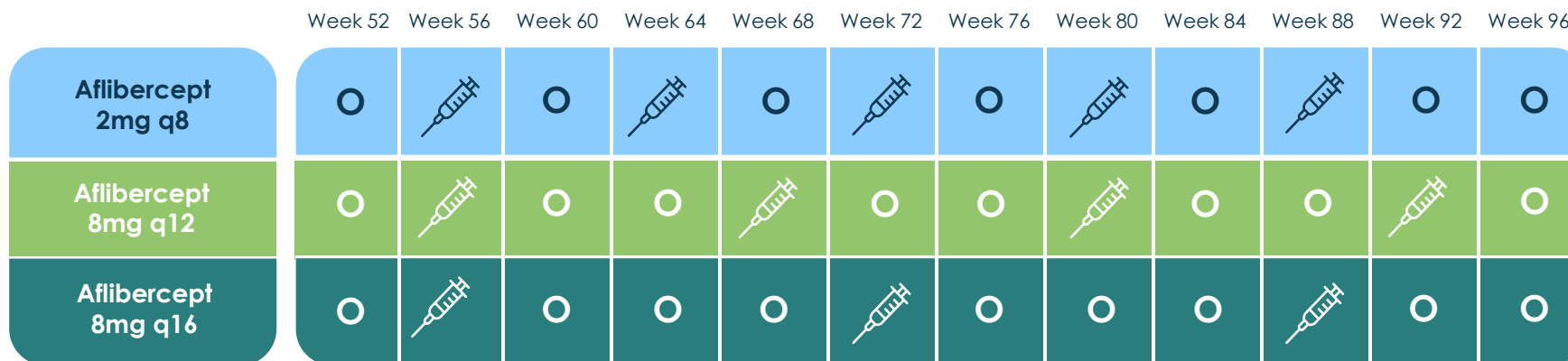
Korobelnik J-F. AAO 2023. 3-6 November 2023. San Francisco, US.



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Dosing schedule in Year 2

nAMD



📄 Active injection
○ Sham injection

Patients were treated according to their assigned treatment interval and dose:

- 2mg every 8 weeks
- 8mg every 12 weeks
- 8mg every 16 weeks

This figure does not represent all dosing options once a treatment interval has been shortened or extended.
Korobelnik J-F. AAO 2023. 3–6 November 2023. San Francisco, US.



Dosing schedule in Year 2

nAMD



	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96
Aflibercept 2mg q8	○		○		○		○		○		○	○
Aflibercept 8mg q12	○		○	○		○	○		○	○		○
Aflibercept 8mg q16	○		○	○	○		○	○	○		○	○

Active injection

○ Sham injection

Patient visits were every 4 weeks, where they either received an:

Active injection
OR a
 Sham injection

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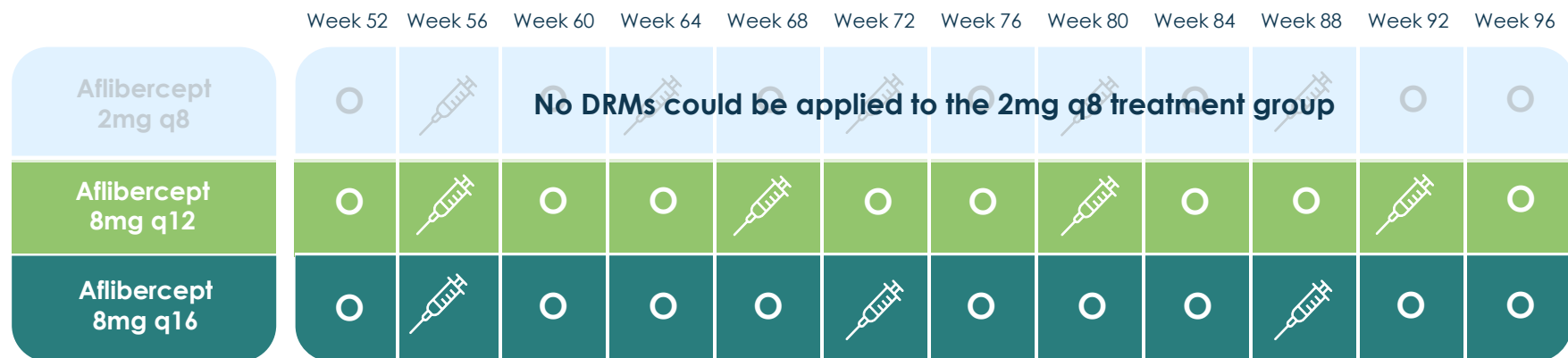




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DRM criteria for the aflibercept 8mg groups in Year 2

nAMD



-  Active injection
-  Sham injection

In Year 2, **patients could be extended by 4-week increments** if they met the following criteria:^a

<p><5-letter loss in BCVA (from Week 12) AND No fluid at the central subfield on OCT AND No new-onset foveal neovascularisation <u>or</u> foveal haemorrhage</p>	 <p>Applying both criteria meant treatment intervals were extended only for patients who were stable</p>	<p>The maximum assigned treatment interval was q24</p>
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^aPatients could still have their interval shortened using the same criteria as in Year 1. This figure does not represent all dosing options once a treatment interval has been shortened or extended.

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Key eligibility criteria

nAMD



Inclusion criteria

- Men or women ≥ 50 years of age with treatment-naïve nAMD
- Active subfoveal CNV, with a total area $>50\%$ of the total lesion area in the study eye
- Presence of IRF and/or SRF in the central subfield on OCT
- BCVA of 78–24 letters (Snellen equivalent of 20/32–20/320) with decreased vision due to nAMD

Exclusion criteria

- DR, DME or any retinal vascular disease other than nAMD in either eye
- RPE tears or rips, scarring, fibrosis, or atrophy involving the central subfield in the study eye
- Total lesion size >12 disc areas (30.5mm^2 , including blood, scars and neovascularisation) as assessed by FA in the study eye
- Uncontrolled glaucoma (IOP $>25\text{mmHg}$ despite antiglaucoma medication) in the study eye
- Extra-/periocular infection or inflammation in either eye at screening/randomisation
- Uncontrolled blood pressure (SBP $>160\text{mmHg}$ or DBP $>95\text{mmHg}$)

Patient disposition

nAMD



	Aflibercept 2mg q8	Aflibercept 8mg q12	Aflibercept 8mg q16	Total
Patients randomised, n¹	337	337	338	1012
Patients treated, %²	99.7	99.7	100	99.8
Patients completing Week 48, n (%)^{1, a}	309 (91.7)	316 (94.0)	312 (92.3)	937 (92.7)
Patients completing Week 96, n (%)^{1, a}	286 (84.9)	291 (86.4)	292 (86.4)	869 (85.9)
Patients discontinued before Week 48, %²	7.4	5.1	7.1	6.5
Reasons for discontinuation before Week 48, %²				
Withdrawal by patient	1.8	1.5	3.8	2.4
AE	1.5	0.6	1.2	1.1
COVID-19-related	0.6	0.6	0.6	0.6
Physician decision	0.3	0.6	0.6	0.5
Death	1.5	0.9	0.3	0.9
Other ^b	1.8	0.9	0.6	1.1

Adapted from Korobelnik J-F, 2023 and Spitzer M, 2023.

^aThe proportions of patients who completed Week 48 and Week 96 do not add up to 100% because of missing information from the study sites.¹

^bIncludes patients who were lost to follow-up, lost to lack of efficacy and lost to protocol deviation; categories were combined to maintain masking of individual patients.²

Baseline demographics^a

nAMD



	Aflibercept 2mg q8 (n=336)	Aflibercept 8mg q12 (n=335)	Aflibercept 8mg q16 (n=338)	Total (n=1009)
Mean (SD) age, years¹	74.2 (8.8)	74.7 (7.9)	74.5 (8.5)	74.5 (8.4)
Female, %¹	56.0	54.3	53.3	54.5
Race, %^{1,2}				
Asian	24.7	22.1	22.8	23.2
Black or African American	1.2	1.5	0.3	1.0
White	74.1	76.4	76.9	75.8
Not reported	1.2	1.5	0.3	1.0
Hispanic or Latino, %^{1,2}	3.6	2.1	2.7	2.8
Hypertension, %²	60.7	66.3	64.8	63.9

Adapted from Korobelnik J-F, 2023 and Spitzer M, 2023.

^aData represent FAS.^{1,2}

1. Korobelnik J-F. AAO 2023. 3–6 November 2023. San Francisco, US. 2. Spitzer M. ARVO 2023. 23–27 April 2023. New Orleans, US.

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Baseline characteristics of the study eye^a

nAMD



	Aflibercept 2mg q8 (n=336)	Aflibercept 8mg q12 (n=335)	Aflibercept 8mg q16 (n=338)	Total (n=1009)
Mean (SD) BCVA, ETDRS letters^{1,2}	58.9 (14.0)	59.9 (13.4)	60.0 (12.4)	59.6 (13.3)
Snellen equivalent	20/63	20/63	20/63	20/63
73–78 ETDRS letters, %	14.6	12.5	14.2	13.8
≤73 ETDRS letters, %	85.4	87.5	85.8	86.2
Mean (SD) CST, μm¹	367 (134)	370 (124)	371 (133)	369 (130)
Mean (SD) total lesion area, mm² ¹	6.9 (5.4)	6.4 (5.1)	6.9 (5.7)	6.7 (5.4)
Lesion type, %¹				
Occult	58.3	60.3	55.9	58.2
Predominantly classic	21.1	21.2	19.8	20.7
Minimally classic	18.5	17.0	20.4	18.6

Adapted from Korobelnik J-F, 2023 and Spitzer M, 2023.

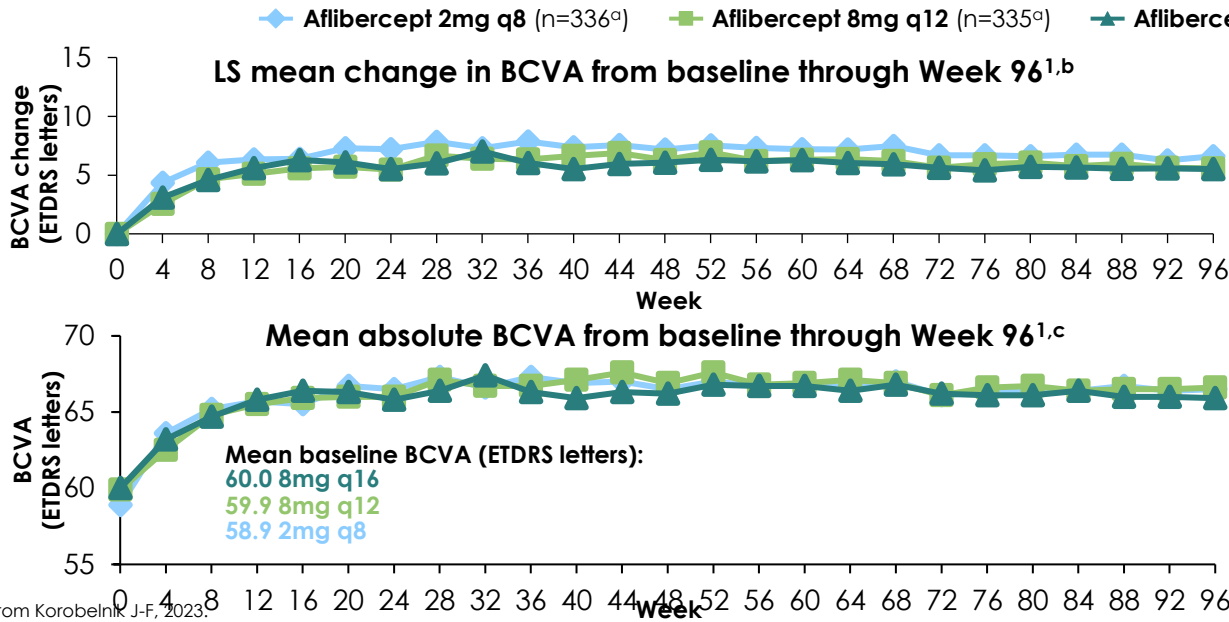
^aData represent FAS.^{1,2}

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LS mean change in BCVA and mean absolute BCVA through Week 96



Adapted from Korobelnik J-F, 2023.

	Week 48 ¹	Week 96 ¹
2q8	+7.0	+6.6
8q12	+6.1	+5.6
8q16	+5.9	+5.5

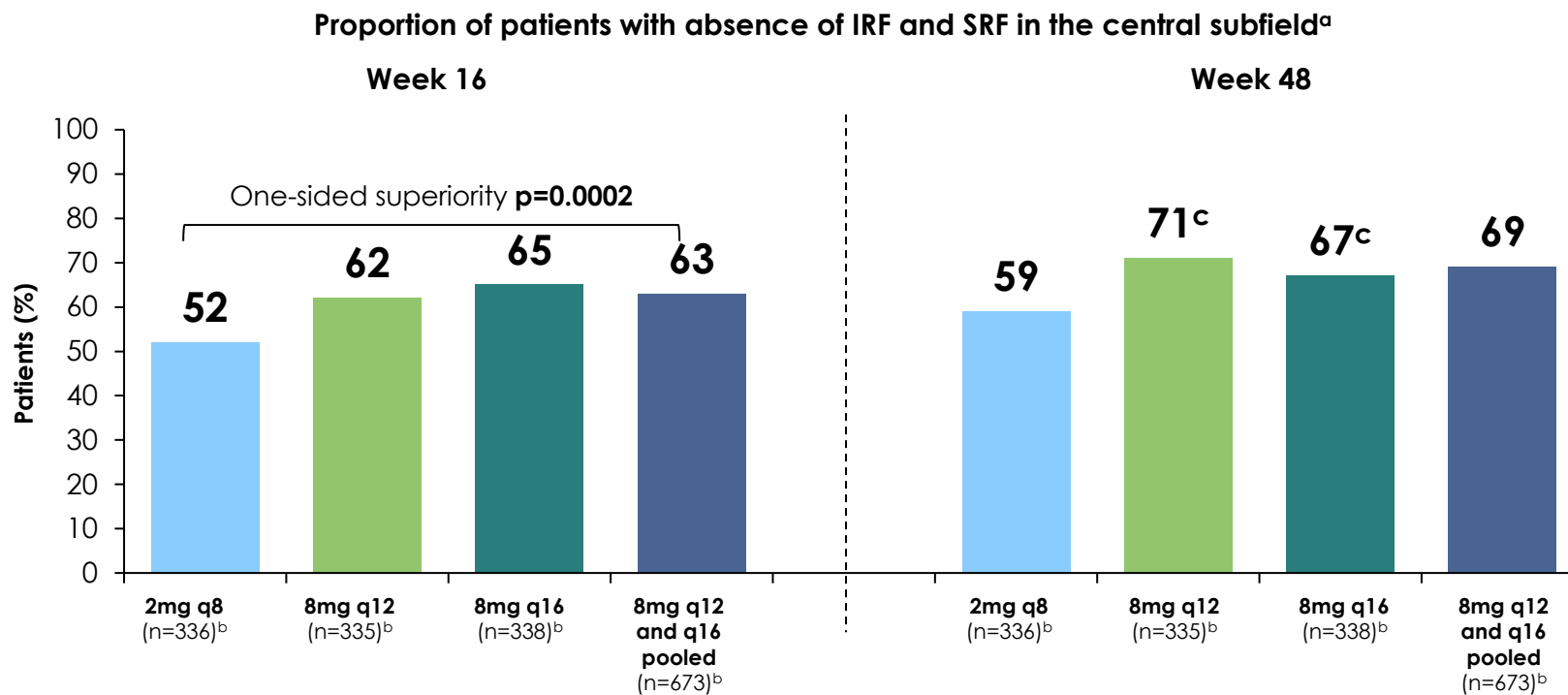
	Week 48 ¹	Week 96 ¹
2q8	66.5	66.5
8q12	66.9	66.6
8q16	66.3	65.9

	Week 48 ^{1,2}			Week 96 ¹		
	Mean number of injections up to Week 48	LS mean change in BCVA from baseline, ETDRS letters	Difference in LS means vs. 2mg q8 (95% CI; p value)	Mean number of injections up to Week 96	LS mean change in BCVA from baseline, ETDRS letters	Difference in LS means vs. 2mg q8 (95% CI; p value ^d)
Aflibercept 2mg q8	6.9	+7.0	-	12.8	+6.6	-
Aflibercept 8mg q12	6.1	+6.1	-0.97 (-2.87, 0.92; p=0.0009)	9.7	+5.6	-1.01 (-2.82, 0.80; p=0.0006)
Aflibercept 8mg q16	5.2	+5.9	-1.14 (-2.97, 0.69; p=0.0011)	8.2	+5.5	-1.08 (-2.87, 0.71; p=0.0007)



Proportion of patients without fluid in the central subfield at Week 16 (key secondary endpoint) and Week 48

nAMD



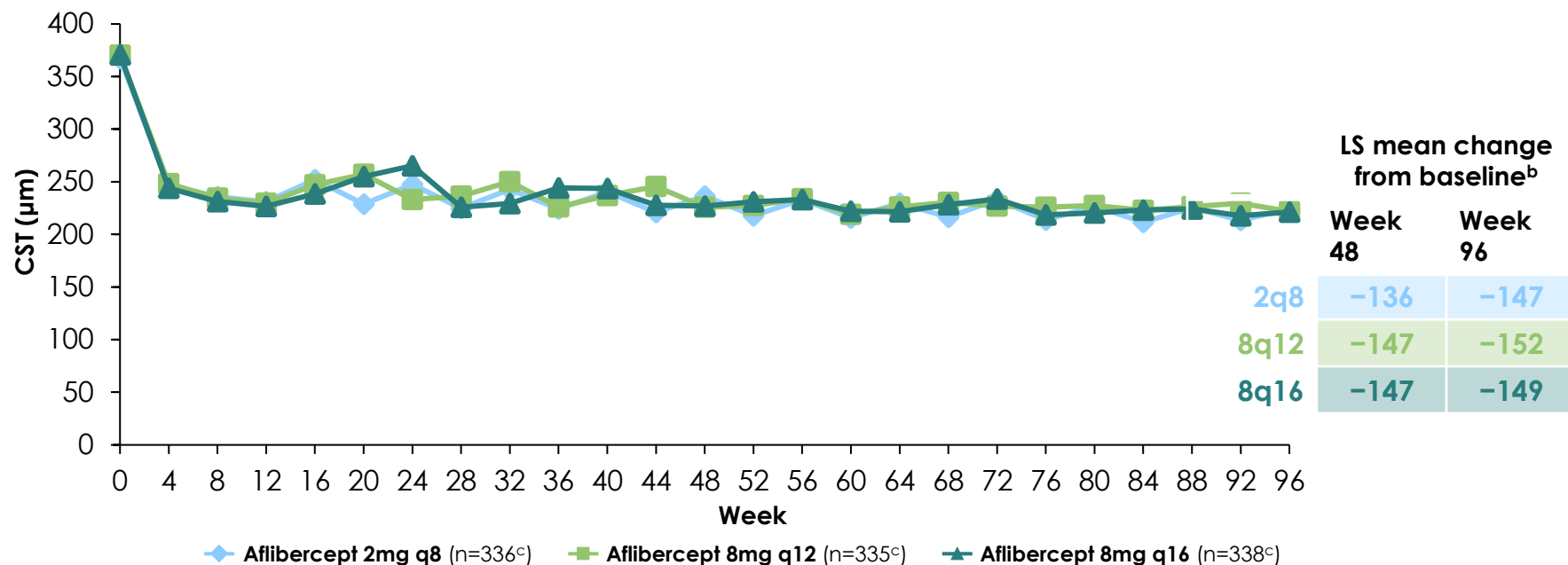
^aLOCF (censoring data after ICE); data represent FAS; groups sizes at baseline. ^bPrespecified endpoint, p value: one-sided Cochran–Mantel–Haenszel; weighting scheme adjusted by geographical region and baseline BCVA (<60 vs. ≥60). ^cp values vs. aflibercept 2mg at Week 48 are nominal, not prespecified and cannot be used to make a formal statistical conclusion (8q12: p=0.0015; 8q16: p=0.0458).

Absolute CST up to Week 96

nAMD



Absolute CST from baseline up to Week 96^a



^aObserved values (censoring data after ICE); data represent FAS. ^bLS mean values (censoring data after ICE). LS means were generated using MRMM, with baseline CST measurement as a covariate; treatment group (aflibercept 2q8, 8q12, 8q16), visit and stratification variables (geographic region [Japan vs. rest of the world] and baseline BCVA [<60 vs. ≥ 60]) as fixed factors; and interaction terms for 'baseline' and 'visit' and for 'treatment' and 'visit'. ^cGroup sizes at baseline.

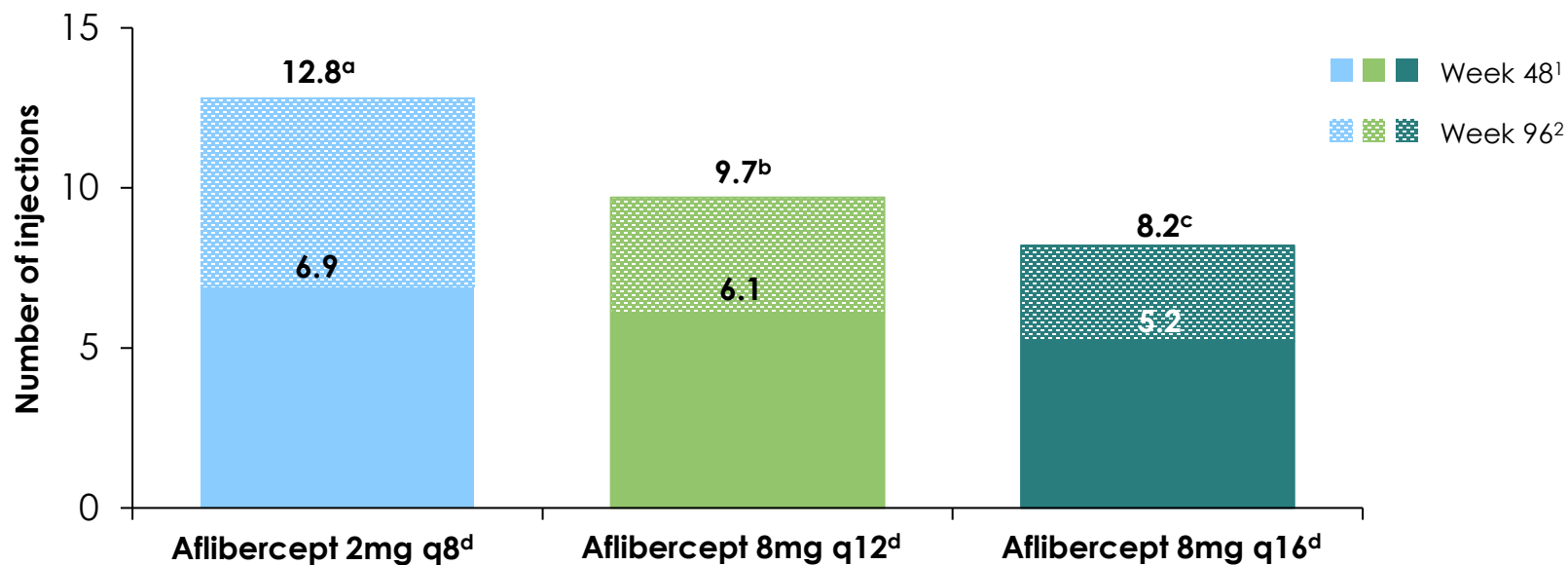


Mean number of injections up to Week 48 and Week 96

nAMD



Mean number of injections administered up to Week 48 and Week 96

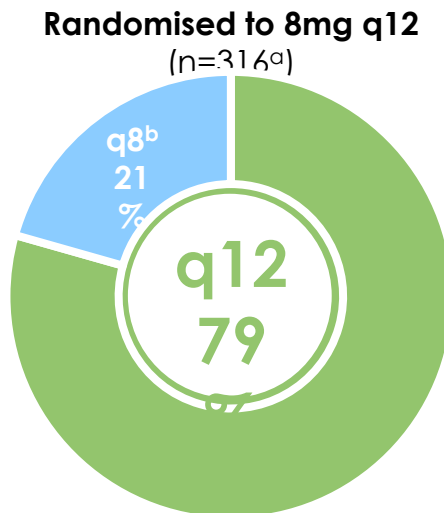


^a 5.9 injections given on average in Year 2 (calculated). ^b 3.6 injections given on average in Year 2 (calculated). ^c 3.0 injections given on average in Year 2 (calculated).
^d Number of patients completing Week 48 of treatment: 2q8 (n=309), 8q12 (n=316), 8q16 (n=312); number of patients completing Week 96 of treatment: 2q8 (n=286), 8q12 (n=291), 8q16 (n=292).^{1,2}

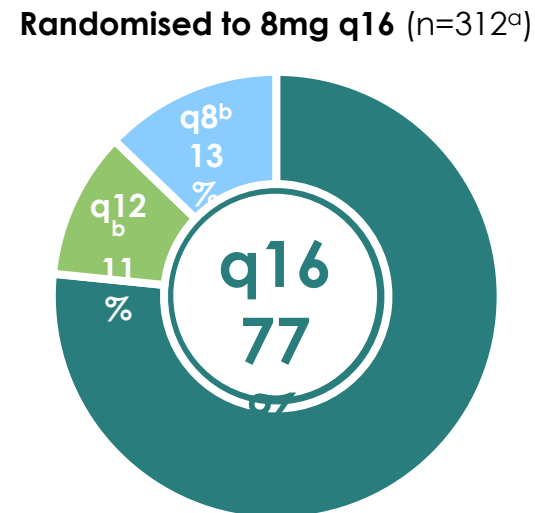


Proportion of patients maintaining q12 and q16 treatment intervals up to Week 48 with aflibercept 8mg

nAMD



79% of patients randomised to aflibercept 8mg q12 were maintained on a **q12** dosing regimen up to Week 48



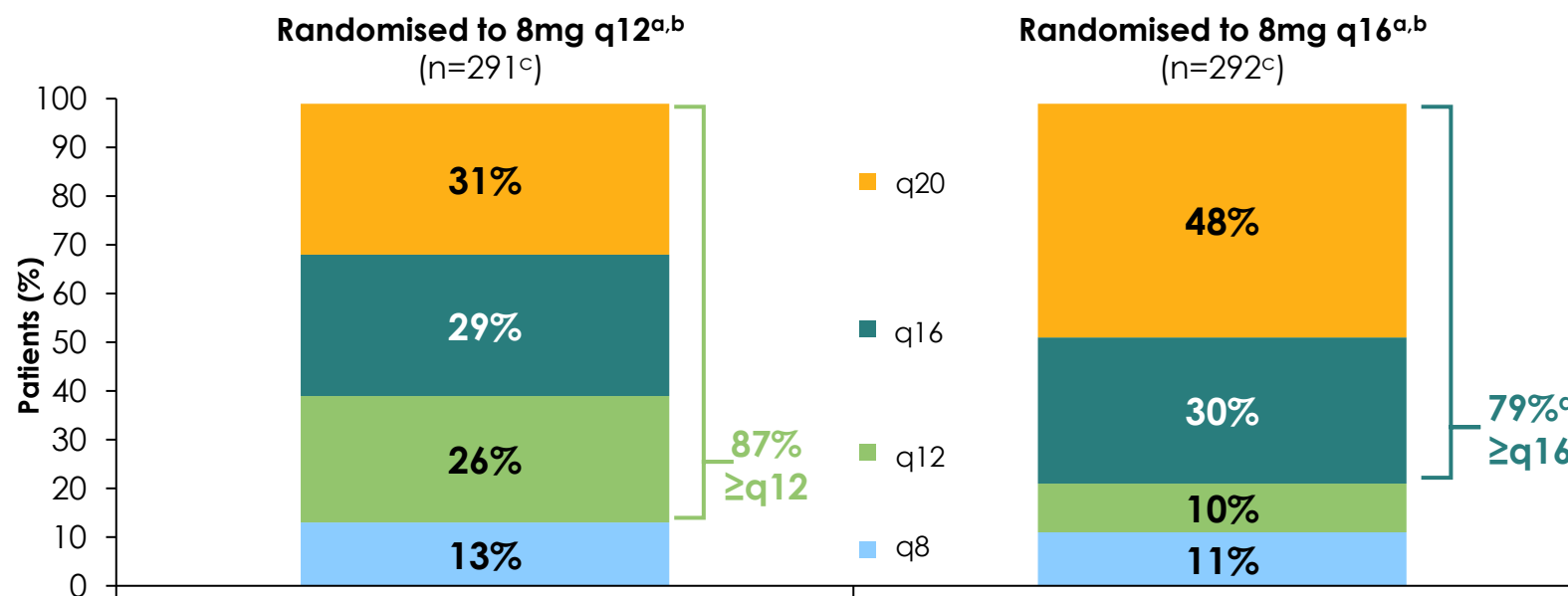
77% of patients randomised to aflibercept 8mg q16 were maintained on a **q16** dosing regimen up to Week 48

Adapted from Spitzer M, 2023.

^a Values may not add up to 100% because of rounding. ^aNumber of patients completing Week 48 of treatment. ^bPatient treatment intervals shortened based on disease activity assessments up to Week 48.

Last completed treatment intervals at Week 96

nAMD



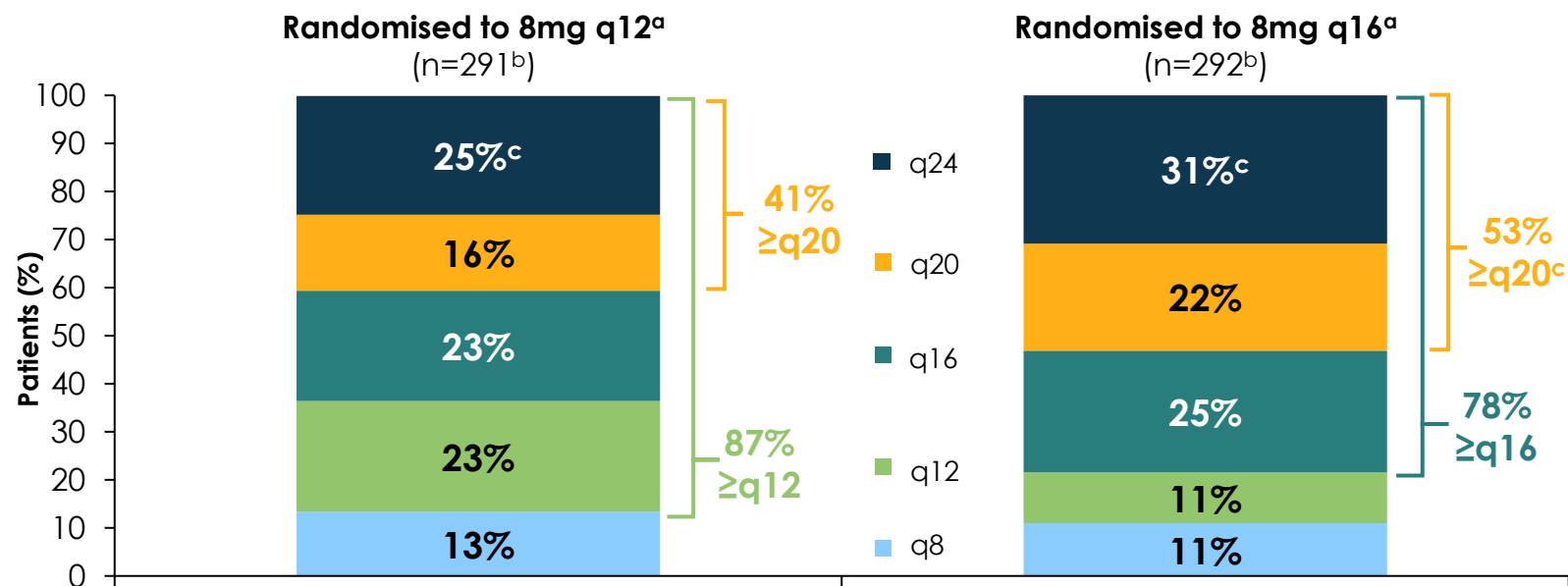
Adapted from Korobelnik J-F, 2023.

^aTreatment intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 AND no fluid at the central subfield on OCT AND no new-onset foveal neovascularisation or foveal haemorrhage. ^bValues may not add up to 100% because of rounding. ^cPatients completing Week 96 of treatment. ^dRounded value.

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Last assigned treatment intervals at Week 96

nAMD



Adapted from Korobelnik J-F, 2023.

^aTreatment intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 AND no fluid at the central subfield on OCT AND no new-onset foveal neovascularisation or foveal haemorrhage. ^bPatients completing Week 96 of treatment. ^cPatients were assigned to q24 treatment intervals if they continued to meet extension criteria but did not have enough time to complete the previous interval within the 96-week study period.

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Aflibercept 8mg treatment interval adjustment up to Week 96^a

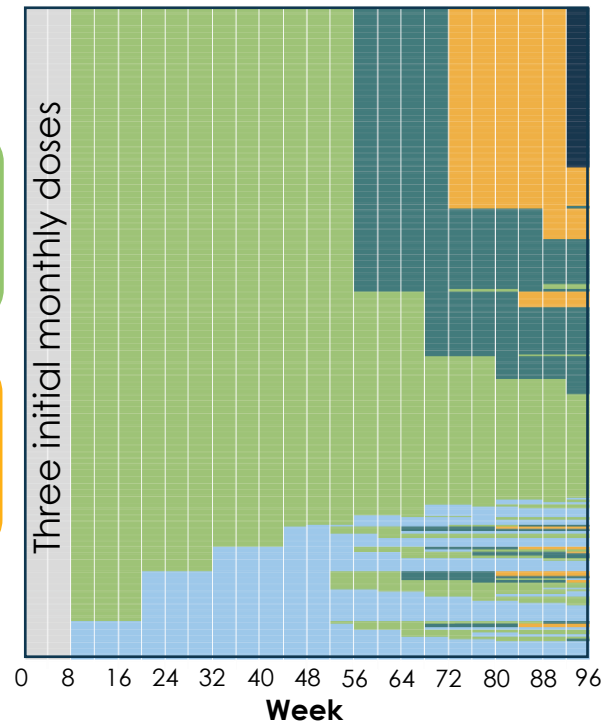
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Randomised to aflibercept 8mg q12 (n=291^b)

75%
maintained
treatment
interval \geq q12^c

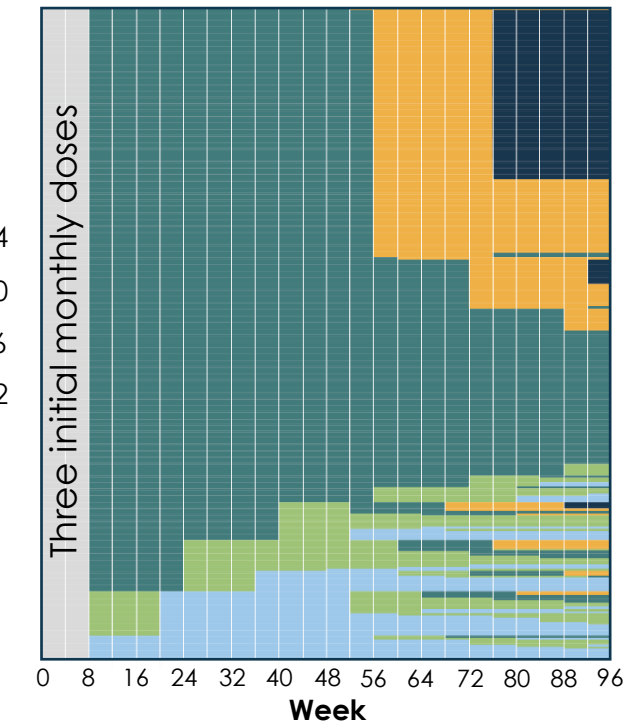
41%
last assigned
treatment
interval \geq q20^c



Randomised to aflibercept 8mg q16 (n=292^b)

70%
maintained
treatment
interval \geq q16^c

53%
last assigned
treatment
interval \geq q20^c



^aSAF. ^bNumber of patients completing Week 96 of treatment. ^cData at Week 96.



Most frequent ocular AEs through Week 48^a

nAMD



	Aflibercept 2mg q8 (n=336)	Aflibercept 8mg q12 (n=335)	Aflibercept 8mg q16 (n=338)	Aflibercept 8mg pooled (n=673)
Any ocular TEAE, %	38.7	38.5	37.6	38.0
Any ocular TEAE ≥3% in any group, %				
Cataract	3.0	3.6	3.6	3.6
IOP increased	2.1	3.3	2.7	3.0
Retinal haemorrhage	4.2	3.3	3.0	3.1
SRF	3.3	3.0	1.5	2.2
VA reduced	6.0	3.6	5.3	4.5
Vitreous floaters	3.3	1.2	3.6	2.4

Adapted from US Clinical Study 2023.

^aSAF; groups sizes at baseline.

Most frequent ocular AEs through Week 48^a

nAMD



	Aflibercept 2mg q8 (n=336)	Aflibercept 8mg q12 (n=335)	Aflibercept 8mg q16 (n=338)	Aflibercept 8mg pooled (n=673)
Any serious ocular TEAE, %				
Angle closure glaucoma	0.3	0	0.3	0.1
Retinal detachment	0	0.9	0.3	0.6
Retinal haemorrhage	0.3	0.3	0.3	0.3
Cataract	One case ^b			
Choroidal detachment	One case ^b			
Vitreous haemorrhage	One case ^b			
Skin laceration	One case ^b			
IOP	Two cases ^b			

Adapted from Korobelnik J-F, 2023.

^aSAF; groups sizes at baseline. ^bData presented in this way to avoid unintentional patient unmasking.

Most frequent ocular AEs through Week 96^a

nAMD



	Aflibercept 2mg q8 (n=336)	Aflibercept 8mg q12 (n=335)	Aflibercept 8mg q16 (n=338)	Aflibercept 8mg pooled (n=673)
Patients with ≥ 1 TEAE, n (%)	181 (53.9)	171 (51.0)	174 (51.5)	345 (51.3)

Adapted from Korobelnik J-F, 2023.

Ocular TEAEs occurring in $\geq 5\%$ of patients in any treatment group were cataract, retinal hemorrhage, reduced visual acuity and vitreous floaters

^aData represent SAF; groups sizes at baseline.



IOI through Week 96^a

nAMD



	Aflibercept 2mg q8 (n=336)	Aflibercept 8mg q12 (n=335)	Aflibercept 8mg q16 (n=338)	Aflibercept 8mg pooled (n=673)
Patients with IOI^b, n (%)	7 (2.1)	6 (1.8)	3 (0.9)	9 (1.3)

Adapted from Korobelnik J-F, 2023.

No cases of endophthalmitis, ischemic optic neuropathy, occlusive retinitis, or retinal vasculitis were observed

^aData represent SAF; groups sizes at baseline. ^bReported IOI terms: anterior chamber cell, chorioretinitis, iridocyclitis, iritis, uveitis, vitreal cells and vitritis.





IOP through Week 48^a

nAMD



	Aflibercept 2mg q8 (n=336)	Aflibercept 8mg q12 (n=335)	Aflibercept 8mg q16 (n=338)	Aflibercept 8mg pooled (n=673)
Patients with IOP \geq35mmHg prior to or after injection, %	0.3	0.9	0.3	0.6

Adapted from Spitzer M, 2023.

Pre-injection IOP values were similar to baseline values at all time points through Week 48

^aSAF; groups sizes at baseline.



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Non-ocular events through Week 48^a

nAMD



	Aflibercept 2mg q8 (n=336)	Aflibercept 8mg q12 (n=335)	Aflibercept 8mg q16 (n=338)	Aflibercept 8mg pooled (n=673)
Any non-ocular TEAE, %	53.0	52.2	53.8	53.0
Any non-ocular TEAE ≥3% in any group, %				
COVID-19	3.3	3.0	6.2	4.6
Hypertension	2.4	4.2	3.8	4.0
UTI	2.7	2.1	3.0	2.5
Nasopharyngitis	4.5	3.6	4.1	3.9
Back pain	4.5	3.6	3.8	3.7
Any serious non-ocular TEAE, %	13.7	10.1	9.5	9.8
Any serious non-ocular TEAE ≥1% in any group, %				
UTI	1.2	0.3	0	0.1
Antiplatelet Trialists' Collaboration (APTC) events	1.5	0.3	0.3	0.3
Hypertension	3.6	4.8	4.7	4.8
Deaths	1.5	0.9	0.3	0.6

^aAP, groups sizes at baseline.



Non-ocular events through Week 96^a

nAMD



	Aflibercept 2mg q8 (n=336)	Aflibercept 8mg q12 (n=335)	Aflibercept 8mg q16 (n=338)	Aflibercept 8mg pooled (n=673)
APTC events, %	3.3	1.5	2.1	1.8
Hypertension, %	8.0	8.1	8.3	8.2
Non-ocular serious TEAEs, %	19.6	21.8	18.9	20.4
Deaths, %	3.6	3.0	2.1	2.5

Adapted from Korobelnik J-F, 2023.

^aData represent FAS; groups sizes at baseline.

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