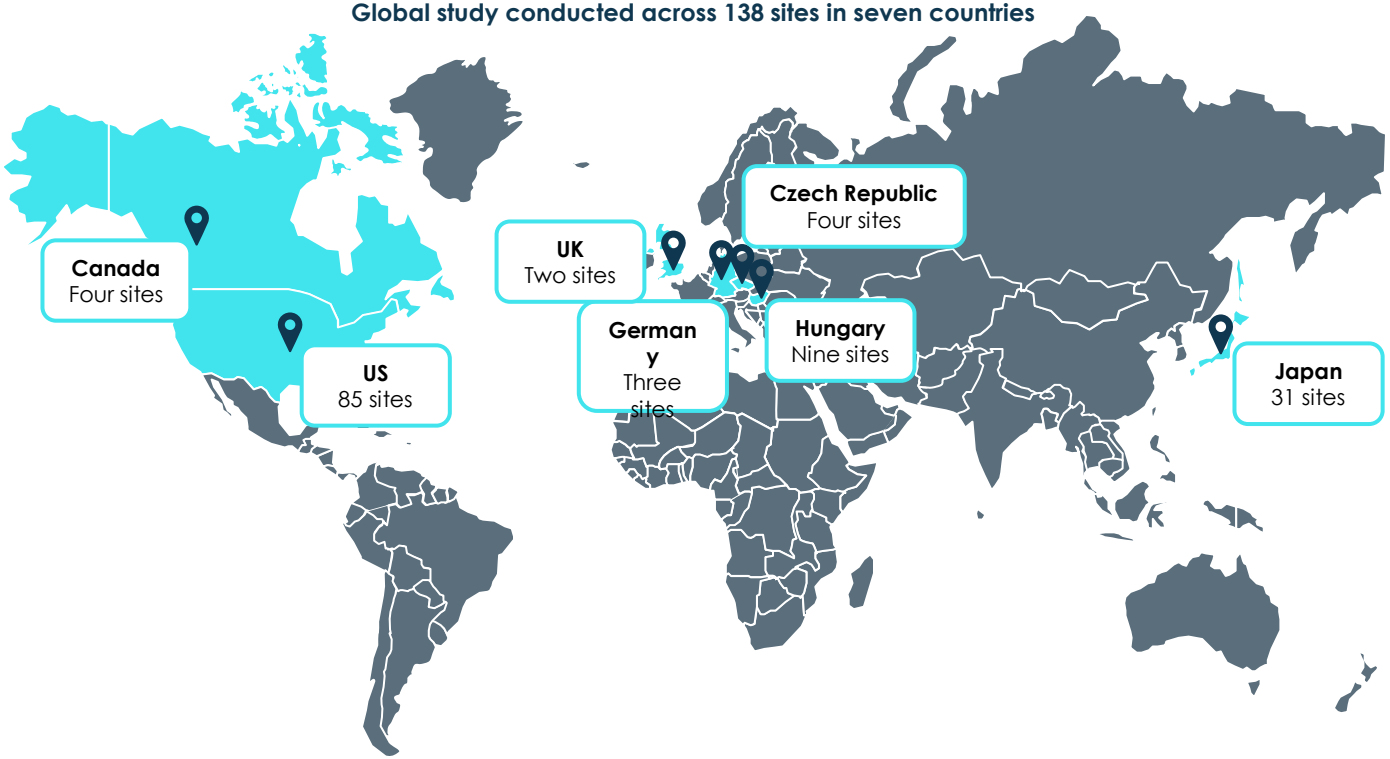
Anti- VEGFs Main Clinical Studies in Diabetic Macular Edema (DME)

Aflibercept 8mg:
Phase II/III PHOTON (DME)

PHOTON study sites

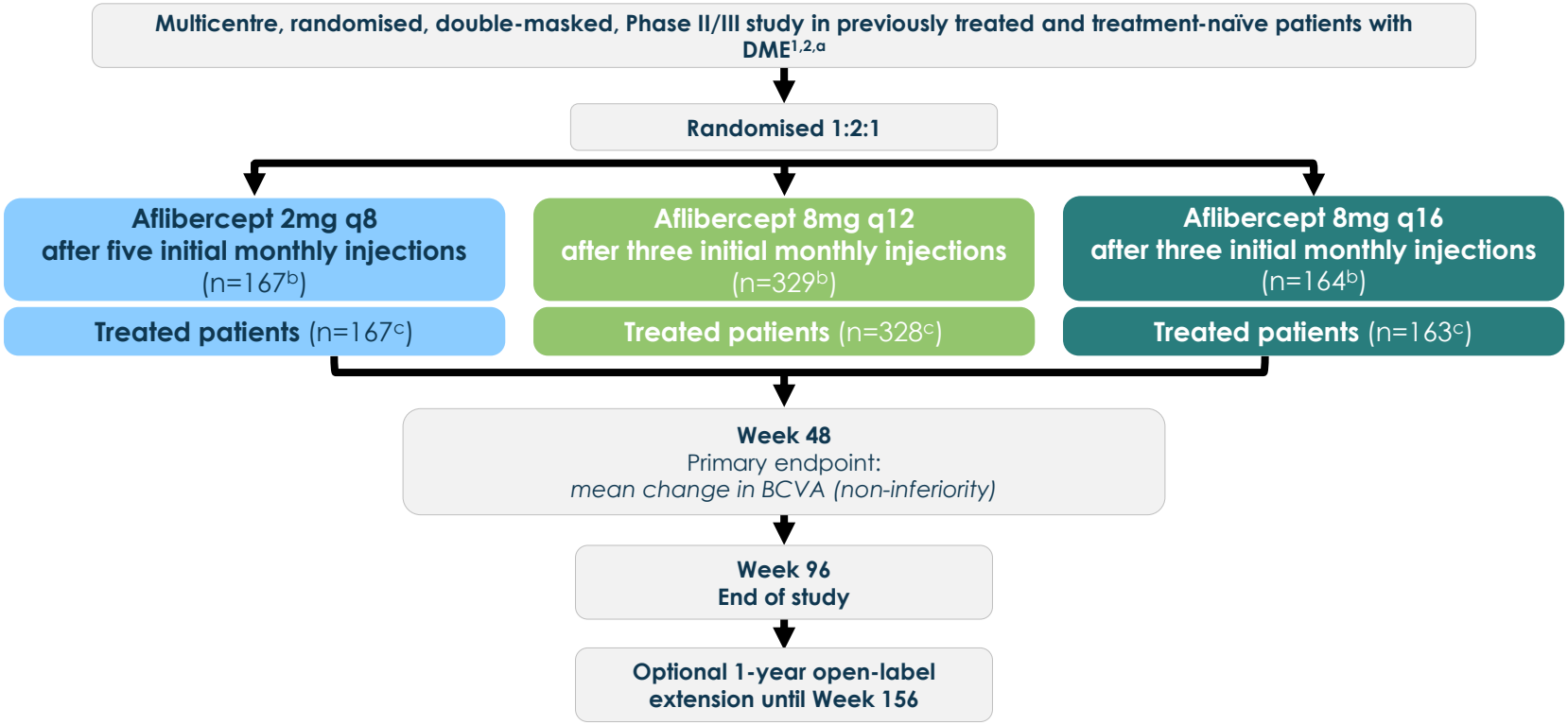
DME

Global study conducted across 138 sites in seven countries



PHOTON trial design

DME

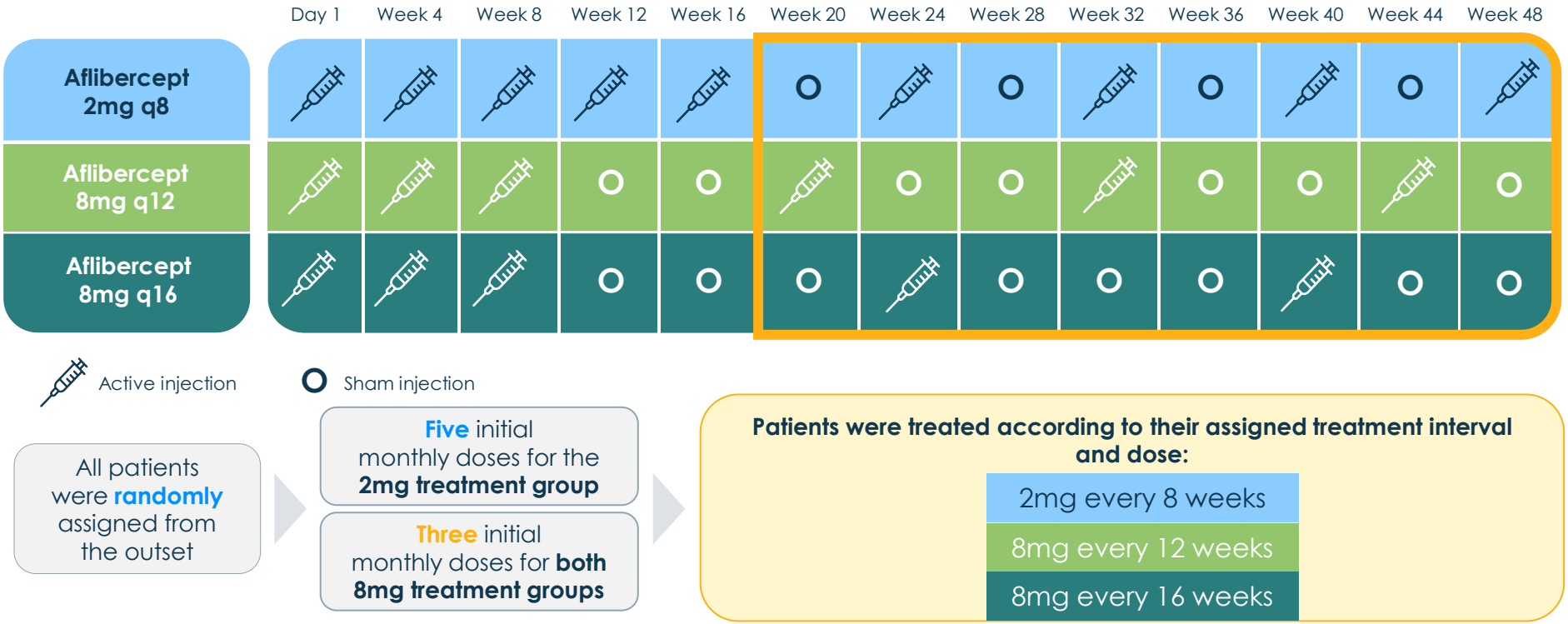


. [a]Previously treated and naïve patients aged ≥18 years with type 1 or type 2 diabetes, DME with central involvement with CRT ≥300µm in the study eye, and BCVA of 78–24 letters (Snellen equivalent of 20/32–20/320) with decreased vision due to DME.[1] [b]Randomised patients.[2] [c]FAS.[1]

1. Do DV. AAO 2023. 3–6 November 2023. San Francisco, US. **2.** Do DV. ASRS 2023. 28 July – 1 August 2023. Seattle, US.

Dosing schedule in Year 1

DME



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

Five initial monthly doses for the **2mg treatment group**

Three initial monthly doses for **both 8mg treatment groups**

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

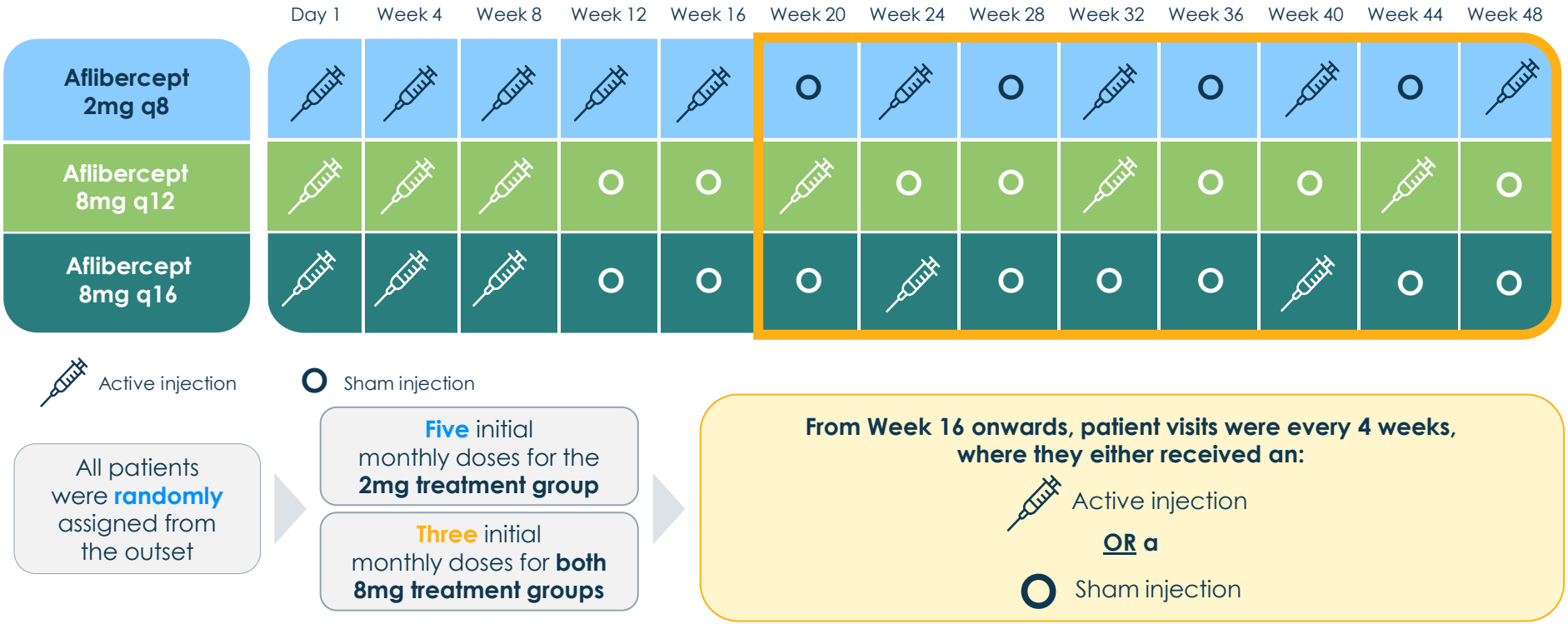
- 2mg every 8 weeks
- 8mg every 12 weeks
- 8mg every 16 weeks

This figure does not represent all dosing options once a treatment interval has been shortened. No interval extension was allowed in the first year.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

Dosing schedule in Year 1

DME

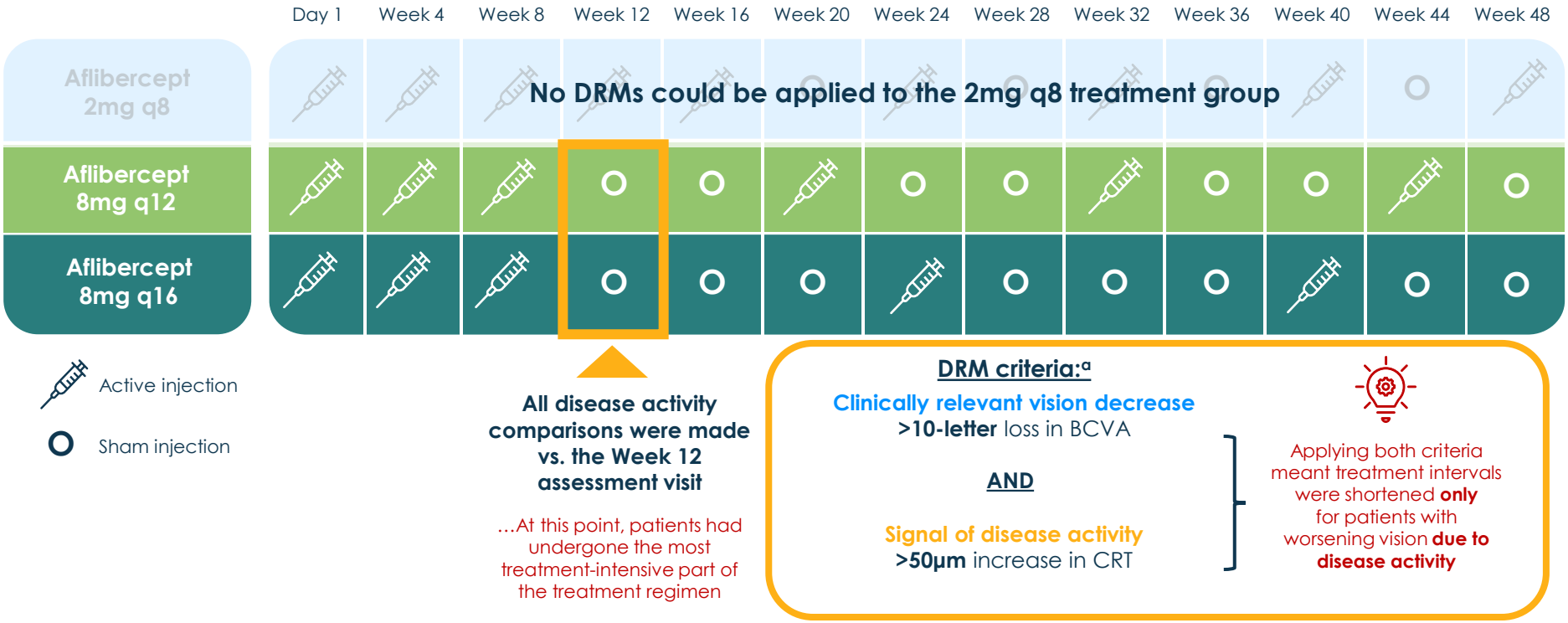


This figure does not represent all dosing options once a treatment interval has been shortened. No interval extension was allowed in the first year.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

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

DME

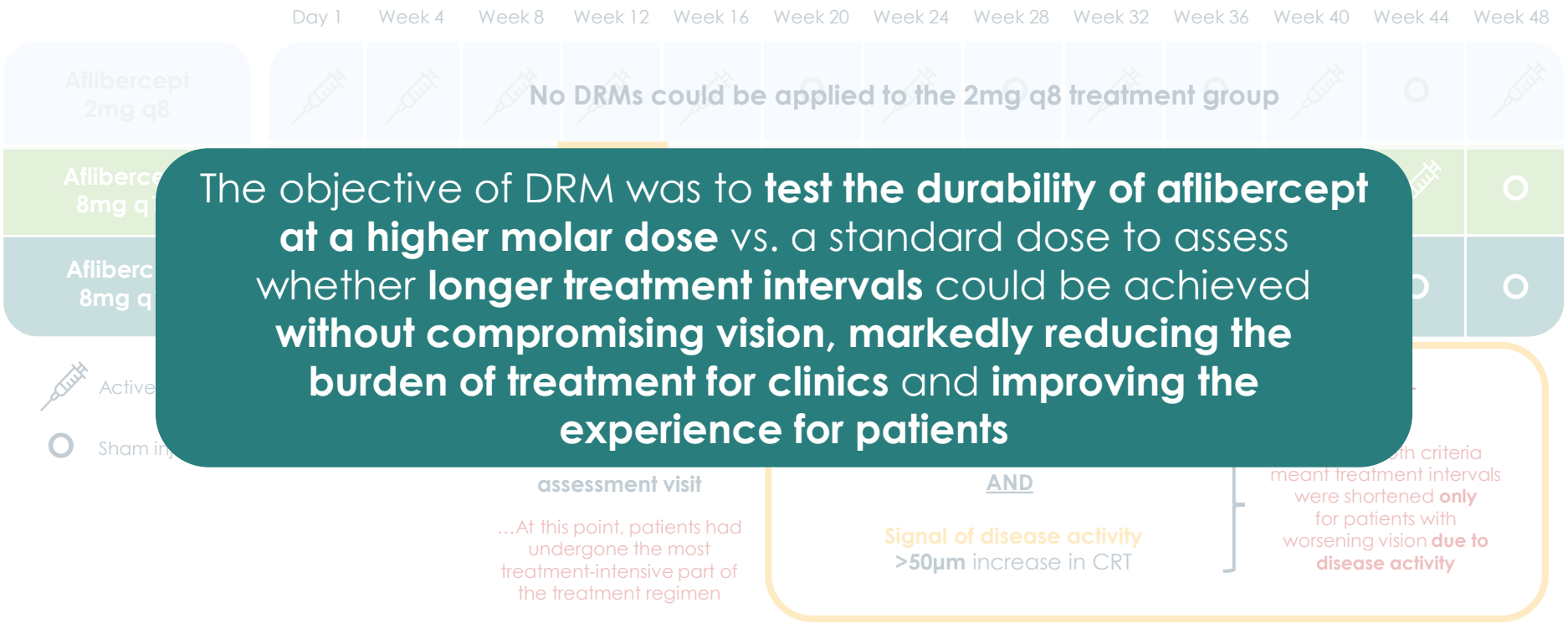


This figure does not represent all dosing options once a treatment interval has been shortened. [a]Patients who met the DRM criteria had treatment intervals shortened to q8 at Week 16 and Week 20 or by 4-week increments from Week 24. The minimum assigned treatment interval was q8. No interval extension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

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

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

DME



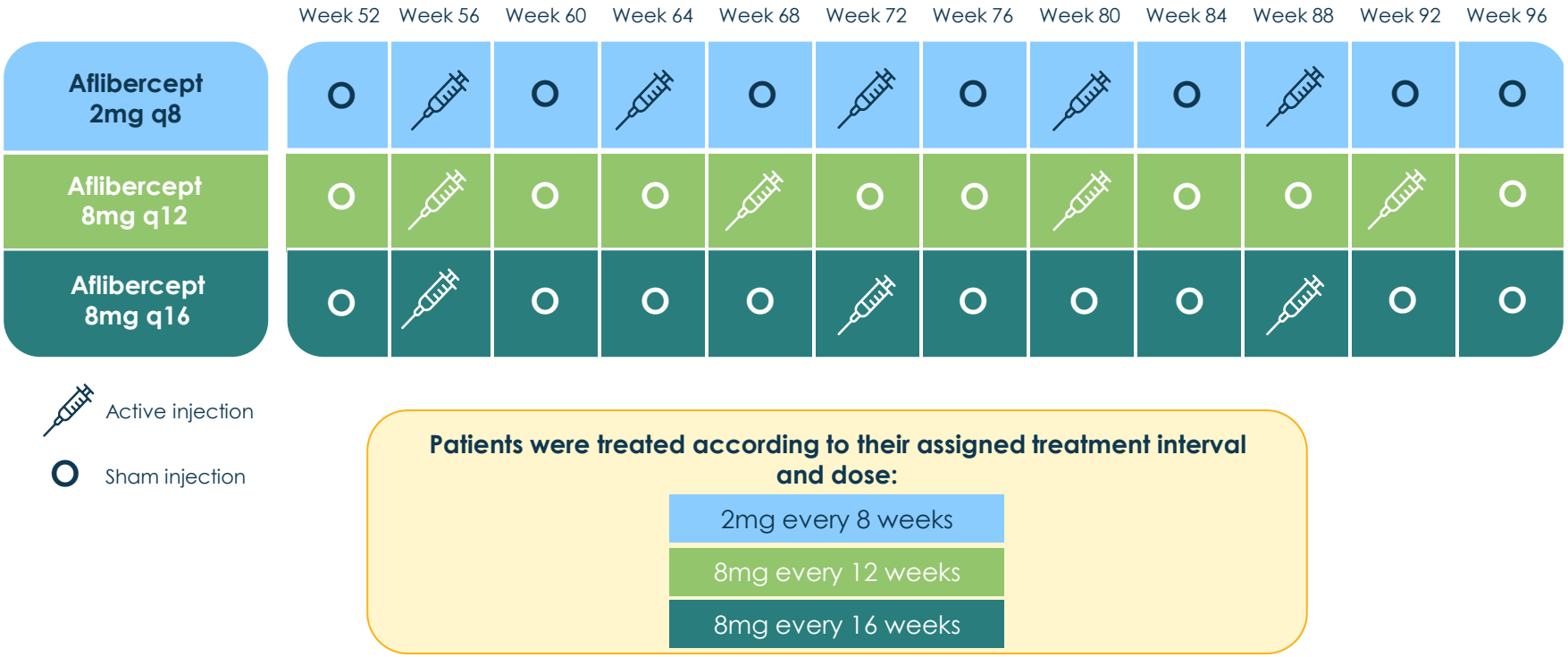
The objective of DRM was to **test the durability of aflibercept at a higher molar dose** vs. a standard dose to assess whether **longer treatment intervals** could be achieved **without compromising vision, markedly reducing the burden of treatment for clinics** and **improving the experience for patients**

. This figure does not represent all dosing options once a treatment interval has been shortened. [a]Patients 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.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

Dosing schedule in Year 2

DME



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

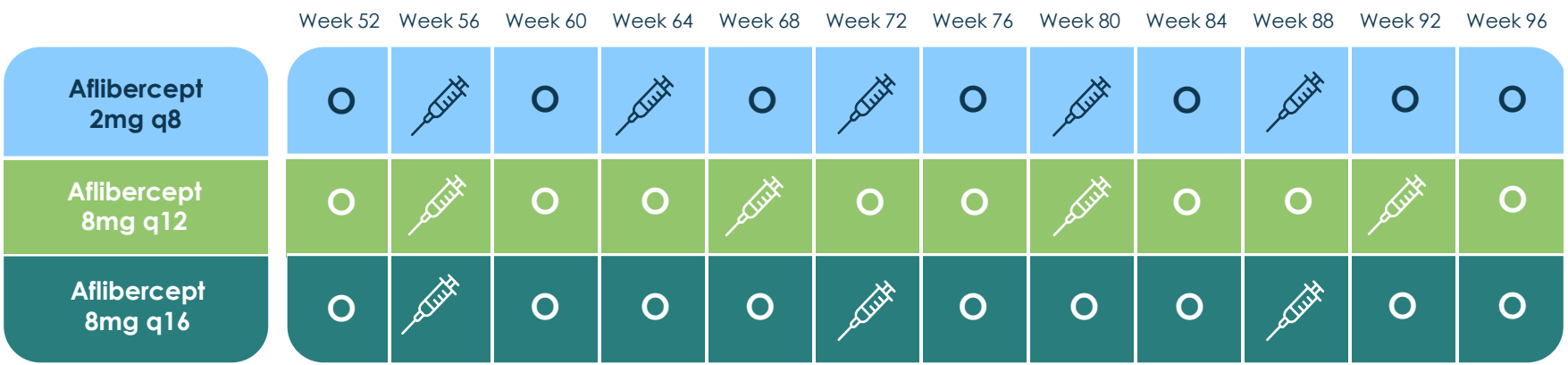
- 2mg every 8 weeks
- 8mg every 12 weeks
- 8mg every 16 weeks

This figure does not represent all dosing options once a treatment interval has been shortened or extended.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

Dosing schedule in Year 2

DME



Active injection

Sham injection

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

Active injection

OR a

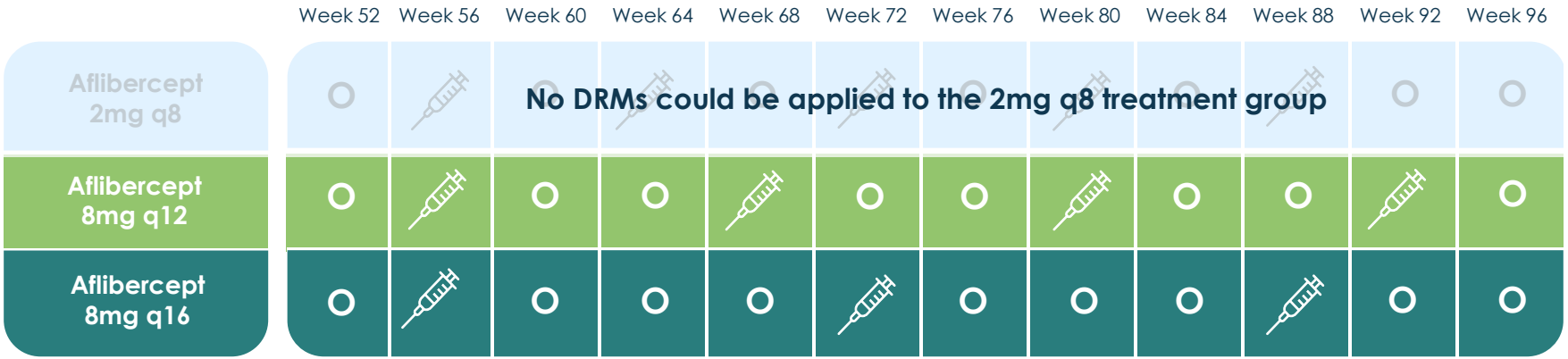
Sham injection

. This figure does not represent all dosing options once a treatment interval has been shortened or extended.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

DRM criteria for the aflibercept 8mg groups in Year 2

DME



Active injection

Sham injection

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

<5-letter loss in BCVA (from Week 12)

AND

CRT **<300µm** on SD-OCT
(or **<320µm** on SPECTRALIS® SD-OCT)

Applying both criteria meant treatment intervals were extended only for patients who were **stable**

The maximum assigned treatment interval was q24

[a]Patients 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.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

Key eligibility criteria

DME

Inclusion criteria

- Adults (≥18 years of age) with type 1 or type 2 diabetes
- DME with central involvement with CRT ≥300µm (or ≥320µm on SPECTRALIS®) in the study eye as determined by the reading centre
- BCVA of 78–24 letters (Snellen equivalent of 20/32–20/320) with decreased vision due to DME

Exclusion criteria

- Active PDR in the study eye
- PRP or laser photocoagulation in the study eye within 12 weeks of screening visit
- IVT anti-VEGF treatment in the study eye within 12 weeks of screening visit
- Intraocular or periocular steroids in the study eye within 16 weeks of the screening visit

Patient disposition at Week 96[a]

DME

	Aflibercept 2mg q8	Aflibercept 8mg q12	Aflibercept 8mg q16	Total
Patients treated, n	167	328	163	658
Patients completing Week 48, %	94.0	91.2	95.1	92.9
Patients completing Week 96, %	83.2	77.8	84.8	80.9
Patients discontinued before Week 96, %	16.8	22.2	15.2	19.1
Reasons for discontinuation through Week 96, %				
Withdrawal by patient	5.4	5.2	4.9	5.2
AE	0.6	2.7	1.2	1.8
Lost to follow-up	3.0	5.8	4.3	4.7
Investigator decision	1.2	2.7	1.8	2.1
Non-compliance with protocol	1.2	0.3	0	0.5
Death	5.4	5.5	3.0	4.8

Adapted from Do DV, 2023.

[a]Data represent FAS/SAF.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

Baseline demographics[a]

DME

	Aflibercept 2mg q8 (n=167)	Aflibercept 8mg q12 (n=328)	Aflibercept 8mg q16 (n=163)	Total (N=658)
Mean (SD) age, years	63.0 (9.8)	62.1 (11.1)	61.9 (9.5)	62.3 (10.4)
Female, %	44.9	36.0	39.3	39.1
Race, %				
White	67.1	70.4	78.5	71.6
Black or African American	10.8	10.7	5.5	9.4
Asian	18.0	14.6	14.1	15.3
Other	2.4	3.0	0.6	2.4
Not reported	1.8	1.2	1.2	1.4
Hispanic or Latino, %	18.6	16.5	20.9	18.1
Mean (SD) duration of diabetes, years	15.9 (10.0)	15.1 (10.0)	15.7 (10.7)	15.5 (10.2)
Mean (SD) haemoglobin A1c, %	8.1 (1.5)	7.9 (1.5)	7.8 (1.5)	8.0 (1.5)
Hypertension, %	77.8	77.4	79.8	78.1
Mean (SD) BMI, kg/m²	29.9 (6.5)	30.4 (6.2)	31.0 (6.1)	30.5 (6.2)

Adapted from Do DV, 2023.

[a]Data represent FAS/SAF.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

Baseline characteristics of the study eye[a]

DME

	Aflibercept 2mg **q8** (n=167)	Aflibercept 8mg **q12** (n=328)	Aflibercept 8mg **q16** (n=163)	Total (N=658)
Mean (SD) BCVA, ETDRS letters[1]	61.5 (11.2)	63.6 (10.1)	61.4 (11.8)	62.5 (10.9)
Snellen equivalent	20/63	20/50	20/63	20/63
>73–78 ETDRS letters, %	12.0	18.0	14.1	15.5
≤73 ETDRS letters, %	88.0	82.0	85.9	84.5
Mean (SD) CRT, µm[1]	457.2 (144.0)	449.1 (127.4)	460.3 (117.8)	454.0 (129.5)
Prior treatment for DME, %[1]	44.3	43.6	43.6	43.8
DRSS categories, %[2]				
Better or equal to Level 43	62.9	60.1	65.6	62.2
Level 47 or worse	31.7	34.5	28.2	32.4
Missing/ungradable	5.4	5.5	6.1	5.6

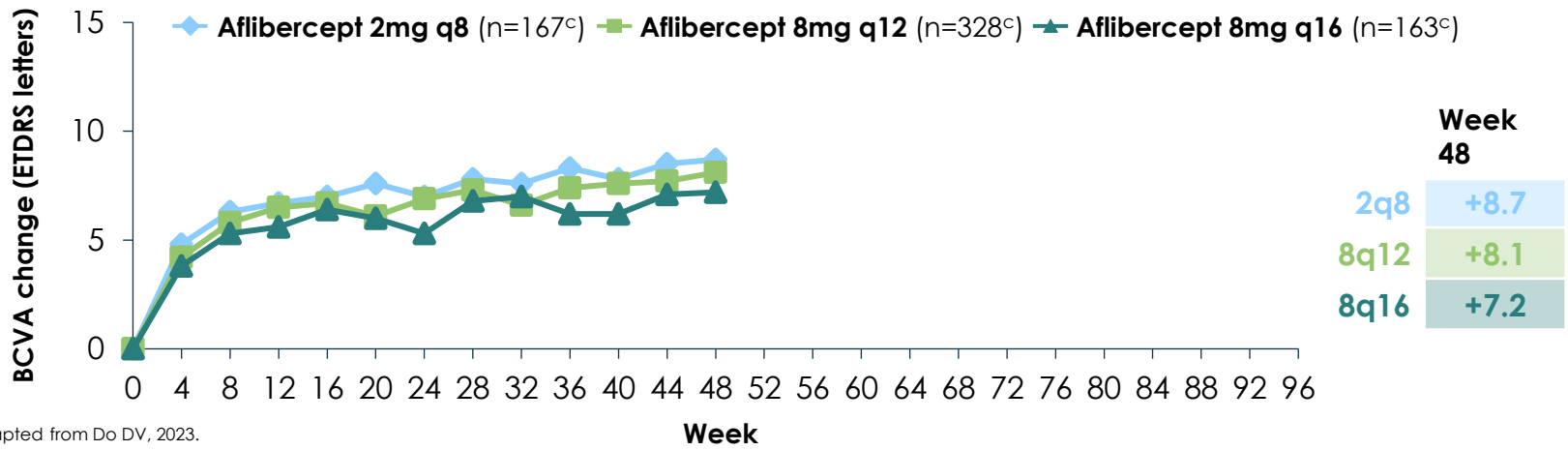
[a]Data represent FAS/SAF.[1]

1. Do DV. AAO 2023. 3–6 November 2023. San Francisco, US. **2.** Do DV. ASRS 2023. 28 July – 1 August 2023. Seattle, US.

LS mean change in BCVA up to Week 48 (primary endpoint)

DME

LS mean change in BCVA from baseline up to Week 48 (primary endpoint)[a,b]



Adapted from Do DV, 2023.

	Mean number of injections up to Week 48	LS mean change in BCVA from baseline, ETDRS letters	Difference in LS means vs. 2mg q8	Two-sided 95% CI	p-value for non-inferiority[d]
Aflibercept 2mg q8	7.9	+8.7	–	–	–
Aflibercept 8mg q12	6.0	+8.1	−0.6	−2.3, 1.1	p<0.0001
Aflibercept 8mg q16	5.0	+7.2	−1.4	−3.3, 0.4	p=0.0031

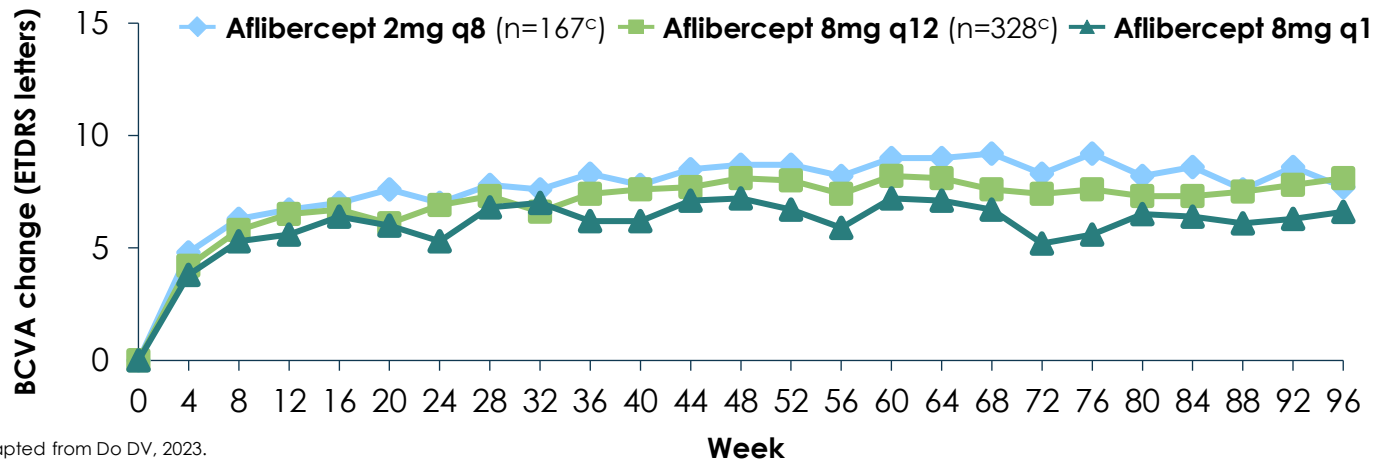
. [a]LS mean values (censoring data after ICE); data represent FAS. [b]LS mean values were generated using MMRM, with baseline BCVA as a covariate; the following as fixed factors: treatment group (aflibercept 2q8, 8q12, 8q16) and stratification variables (geographic region [Japan vs. rest of the world], baseline CRT [<400µm vs. ≥400µm], prior treatment for DME [yes vs. no]); and interaction terms for 'baseline' and 'visit' and 'treatment' and 'visit'. [c]Group sizes at baseline; patients completing Week 48: 2q8 (n=157), 8q12 (n=300), 8q16 (n=156). [d]One-sided test for non-inferiority at four-letter margin vs. 2mg q8 group.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

LS mean change in BCVA up to Week 96

DME

LS mean change in BCVA from baseline up to Week 96[a,b]



	Week 48	Week 96
2q8	+8.7	+7.7
8q12	+8.1	+8.2
8q16	+7.2	+6.6

Adapted from Do DV, 2023.

	Mean number of injections up to Week 96	LS mean change in BCVA from baseline, ETDRS letters	Difference in LS means vs. 2mg q8	Two-sided 95% CI	p-value for non-inferiority[d]
Aflibercept 2mg q8	13.8	+7.7	–	–	–
Aflibercept 8mg q12	9.5	+8.2	+0.5	−1.6, 2.5	p<0.0001
Aflibercept 8mg q16	7.8	+6.6	−1.1	−3.3, 1.1	p=0.0044

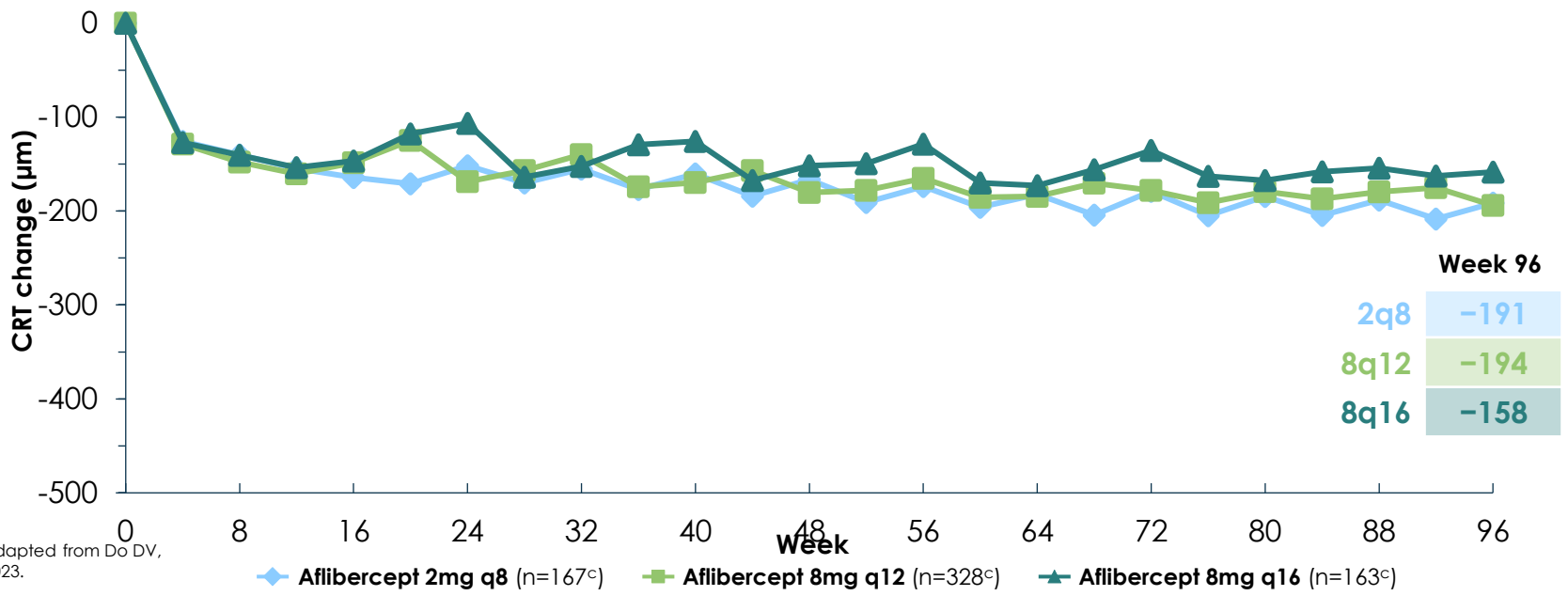
. [a]LS mean values (censoring data after ICE); data represent FAS. [b]LS mean values were generated using MMRM, with baseline BCVA as a covariate; the following as fixed factors: treatment group (aflibercept 2q8, 8q12, 8q16) and stratification variables (geographic region [Japan vs. rest of the world], baseline CRT [<400µm vs. ≥400µm], prior treatment for DME [yes vs. no]); and interaction terms for 'baseline' and 'visit' and 'treatment' and 'visit'. [c]Group sizes at baseline; patients completing Week 96: 2q8 (n=139), 8q12 (n=256), 8q16 (n=139). [d]Nominal p values; one-sided test for non-inferiority at four-letter margin vs. 2mg q8 group.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

LS mean change in CRT up to Week 96

DME

LS mean change in CRT from baseline up to Week 96[a,b]



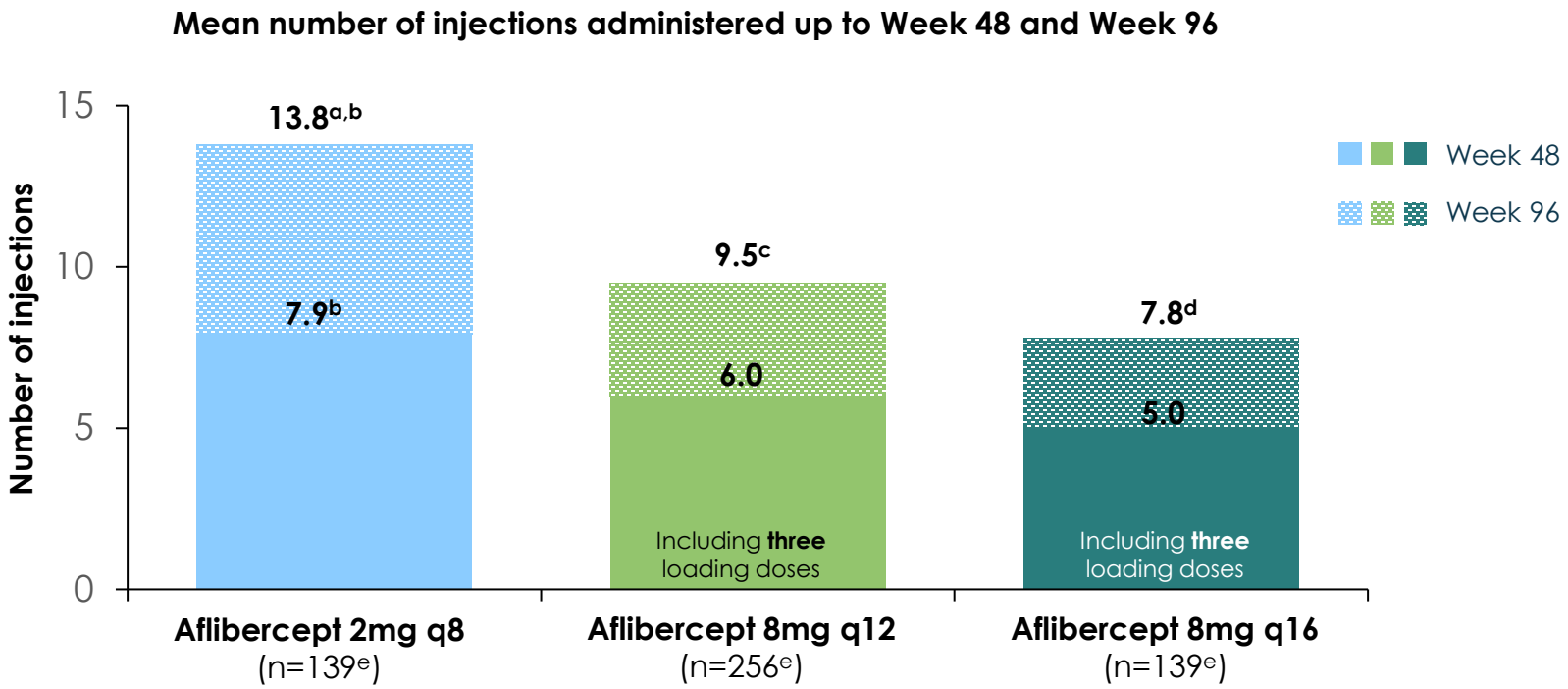
Adapted from Do DV, 2023.

. [a]LS mean values (censoring data after ICE); data represent FAS. [b]LS mean values were generated using MMRM, with baseline CRT as a covariate; the following as fixed factors: treatment group (aflibercept 2q8, 8q12, 8q16) and stratification variables (geographic region [Japan vs. rest of the world], baseline CRT [<400µm vs. ≥400µm], prior treatment for DME [yes vs. no]); and interaction terms for 'baseline' and 'visit' and 'treatment' and 'visit'. [c]Group sizes at baseline.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

Mean number of injections up to Week 48 and Week 96

DME

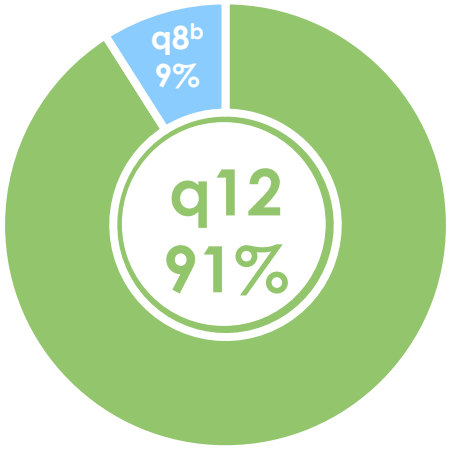


[a]5.9 injections given on average in Year 2 (calculated). [b]Includes five loading doses. [c]3.5 injections given on average in Year 2 (calculated). [d]2.8 injections given on average in Year 2 (calculated). [e]Number of patients completing Week 96 of treatment; number of patients completing Week 48 of treatment: 2q8, n=157; 8q12, n=300; 8q16, n=156.

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

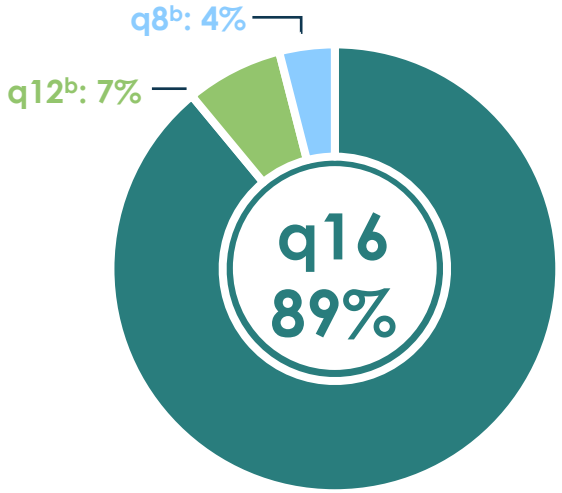
DME

Randomised to 8mg q12 (n=300[a])



91% of patients randomised to 8mg q12 were maintained on **q12** dosing up to Week 48

Randomised to 8mg q16 (n=156[a])



89% of patients randomised to 8mg q16 were maintained on **q16** dosing up to Week 48

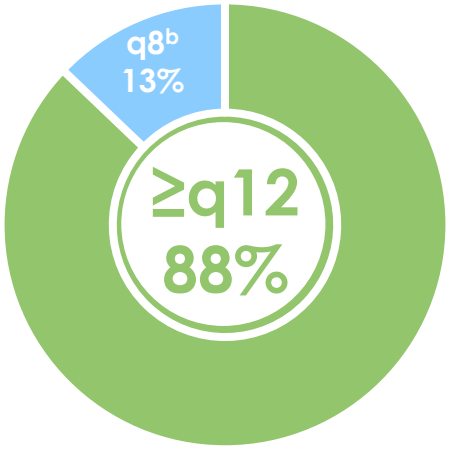
Values may not add up to 100% because of rounding. [a]Number of patients completing Week 48 of treatment. [b]Patient treatment intervals shortened based on disease activity assessments up to Week 48.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

Proportion of patients maintaining ≥q12 and ≥q16 treatment intervals up to Week 96 with aflibercept 8mg

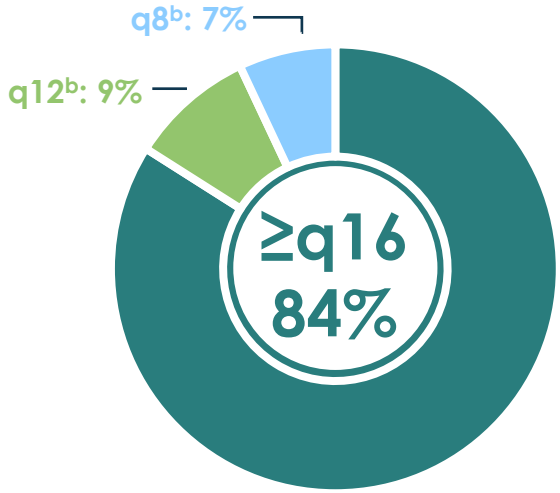
DME

Randomised to 8mg q12 (n=256[a])



88% of patients randomised to 8mg q12 were maintained on ≥q12 dosing up to Week 96

Randomised to 8mg q16 (n=139[a])



84% of patients randomised to 8mg q16 were maintained on ≥q16 dosing up to Week 96

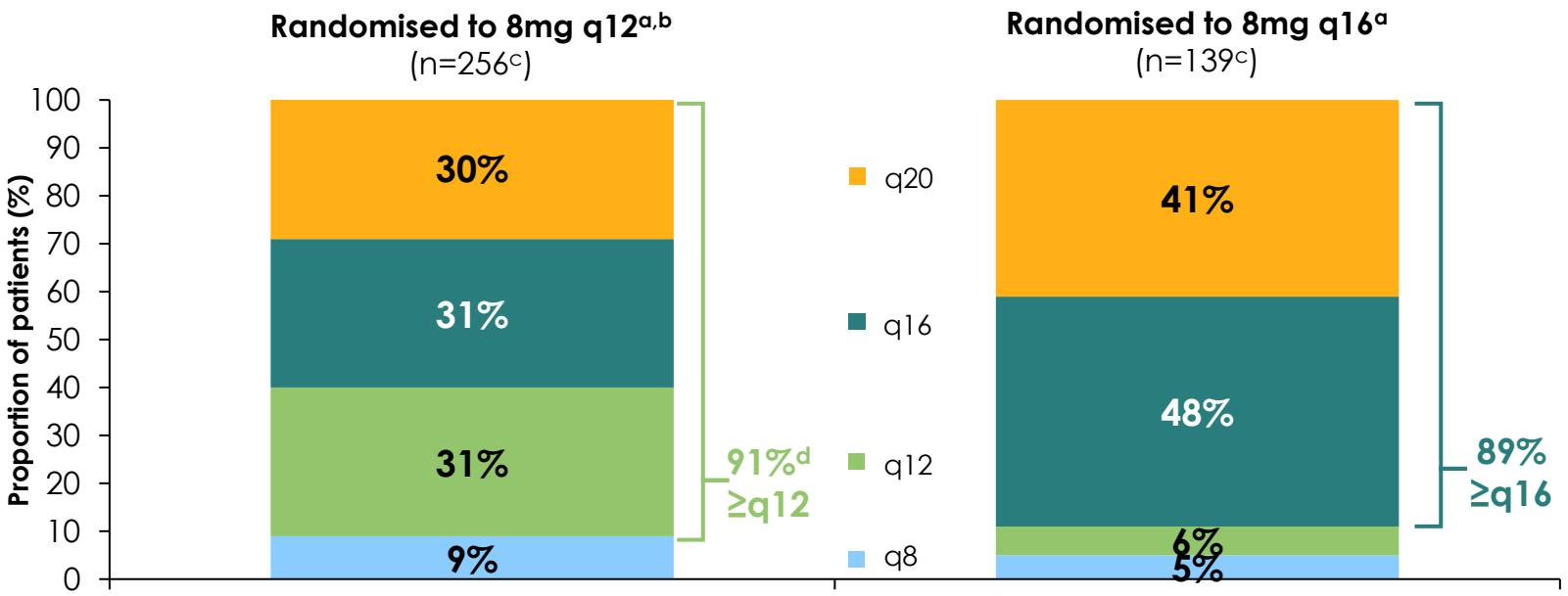
Adapted from Do DV, 2023.

. Values may not add up to 100% because of rounding. [a]Number of patients completing Week 96 of treatment. [b]Patient treatment intervals shortened based on disease activity assessments up to Week 96.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

Last completed treatment intervals at Week 96

DME



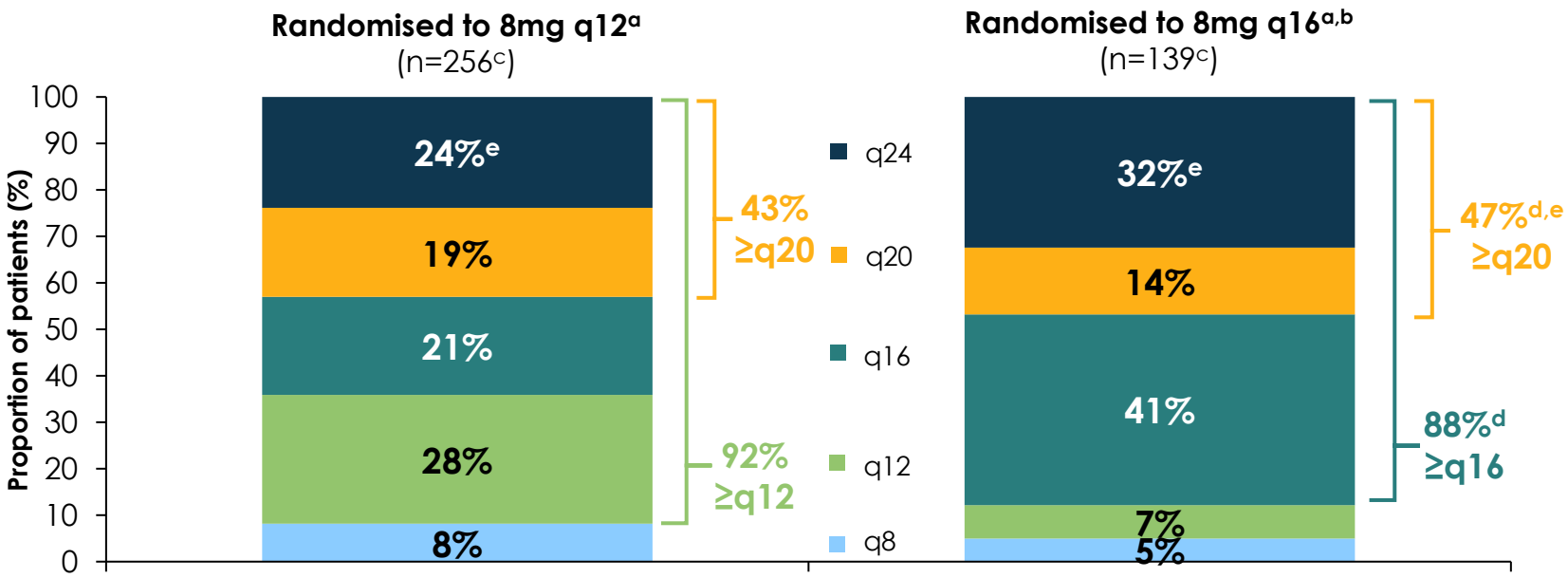
Adapted from Do DV, 2023.

[a]Treatment intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 AND CRT <300µm (or <320µm on SPECTRALIS® SD-OCT). [b]Values may not add up to 100% because of rounding. [c]Number of patients completing Week 96 of treatment. [d]Rounded value.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

Last assigned treatment intervals at Week 96

DME



Adapted from Do DV, 2023.

[a]Treatment intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 AND CRT <300µm (or <320µm on SPECTRALIS® SD-OCT). [b]Values may not add up to 100% because of rounding. [c]Number of patients completing Week 96 of treatment. [d]Rounded value. [e]Patients 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.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

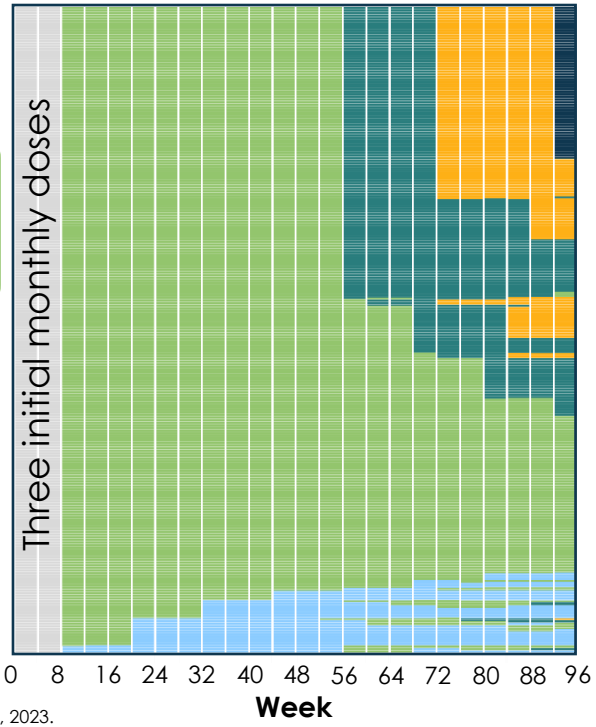
Aflibercept 8mg treatment interval adjustment up to Week 96[a]

DME

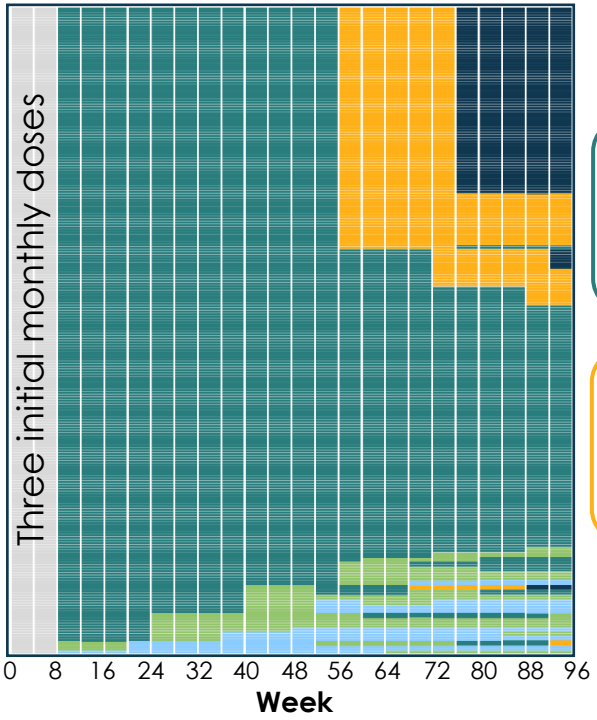
Randomised to aflibercept 8mg q12 (n=256[a])

88% maintained treatment interval **≥q12[b]**

43% last assigned treatment interval **≥q20[b]**



Randomised to aflibercept 8mg q16 (n=139[a])



84% maintained treatment interval **≥q16[b]**

47% last assigned treatment interval **≥q20[b]**

Adapted from Do D, 2023.

Do D. ARVO 2023. 23–27 April 2023. New Orleans, USA.

[a]Number of patients completing Week 96 of treatment. [b]Data at Week 96.

Most frequent ocular AEs through Week 48[a]

DME

	Aflibercept 2mg q8 (n=167)	Aflibercept 8mg q12 (n=328)	Aflibercept 8mg q16 (n=163)	Aflibercept 8mg pooled (n=491)
Patients with ≥1 AE[b], %	27.5	31.7	29.4	31.0
Cataract, %	1.2	1.5	4.9	2.6
Conjunctival haemorrhage, %	3.6	4.3	3.7	4.1
IOP increased, %	3.6	2.1	0.6	1.6
Punctate keratitis, %	0.6	1.5	3.7	2.2
Retinal haemorrhage, %	0.6	0	3.7	1.2
Vitreous floaters, %	2.4	4.9	1.8	3.9

Adapted from Do D, 2023.

[a]SAF; groups sizes at baseline. [b]Any ocular TEAE in the study eye.

Do D. ARVO 2023. 23–27 April 2023. New Orleans, US.

Ocular AEs through Week 96[a]

DME

	Aflibercept 2mg q8 (n=167)	Aflibercept 8mg q12 (n=328)	Aflibercept 8mg q16 (n=163)	Aflibercept 8mg pooled (n=491)
Patients with ≥1 AE[b], %	37.1	43.9	45.4	44.4

Adapted from Do DV, 2023.

No cases of ischemic optic neuropathy, retinal vasculitis, or occlusive retinitis were reported through Week 96

[a]SAF; groups sizes at baseline. [b]Any ocular TEAE in the study eye. Ocular AEs occurring in ≥5% of patients in any treatment group were cataract, vitreous floaters and conjunctival haemorrhage.

Do DV. AAO 2023. 3–6 November 2023. San Francisco, US.

IOI through Week 96[a]

DME

	Aflibercept 2mg q8 (n=167)	Aflibercept 8mg q12 (n=328)	Aflibercept 8mg q16 (n=163)	Aflibercept 8mg pooled (n=491)
Patients with ≥1 IOI AE[b], %	1.2	1.5	0.6	1.2

Adapted from Do DV, AAO 2023.

No cases of retinal vasculitis, occlusive retinitis or endophthalmitis were observed through Week 96[1,2]

[a]SAF; groups sizes at baseline.[1] [b]Any ocular TEAE in the study eye.[1] Reported IOI terms: anterior chamber cell; iridocyclitis; iritis; uveitis; vitreal cells; vitritis.[2]

1. Do DV. AAO 2023. 3–6 November 2023. San Francisco, US. **2.** Do DV. ASRS 2023. 28 July – 1 August 2023. Seattle, US.

IOP through Week 96[a]

DME

	Aflibercept 2mg q8 (n=167)	Aflibercept 8mg q12 (n=328)	Aflibercept 8mg q16 (n=163)	Aflibercept 8mg pooled (n=491)
Patients with IOP ≥35mmHg prior to or after injection[b], %	1.2	0.6	0	0.4

Adapted from Do DV, 2023.

Mean changes from baseline in pre-dose IOP did not exceed ±1mmHg at any time point through Week 96

[a]SAF; groups sizes at baseline. [b]IOP in the study eye.

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Non-ocular events through Week 96[a]

DME

	Aflibercept 2mg q8 (n=167)	Aflibercept 8mg q12 (n=328)	Aflibercept 8mg q16 (n=163)	Aflibercept 8mg pooled (n=491)
Antiplatelet Trialists' Collaboration (APTC) events[b], %	7.2	6.7	6.7	6.7
Hypertension events[b],%	16.2	15.5	20.9	17.3
Non-ocular SAEs[b],%	25.1	22.9	23.9	23.2
Deaths[c],%	5.4	5.5	3.1	4.7

Adapted from Do DV, 2023.

[a]SAF; groups sizes at baseline. [b]TEAEs. [c]All events.

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