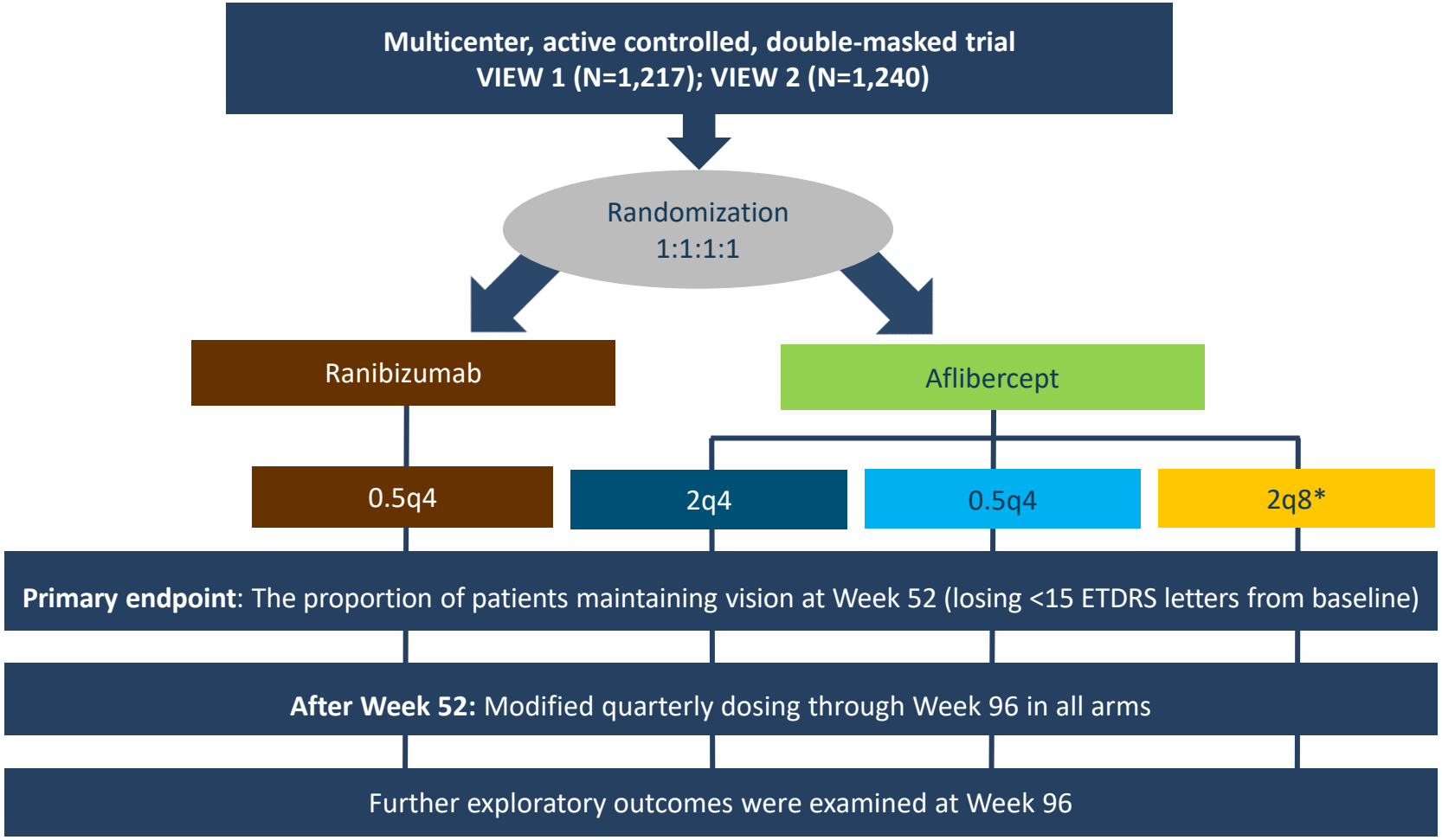
Aflibercept Main Studies in Wet Age-Related Macular Degeneration (wAMD)

VIEW 1 and 2: Study design[1,2]

VIEW



*Following 3 initial monthly doses; 2q8 is the licensed dose of EYLEA.
0.5q4, 0.5 mg every 4 weeks; 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; ETDRS, Early Treatment Diabetic Retinopathy Study.
1. Heier JS *et al. Ophthalmology* 2012; 119 (12): 2537–2548. 2. Schmidt-Erfurth U *et al. Ophthalmology* 2014; 121 (1): 193–201.

Retreatment criteria for ‘modified quarterly dosing’

VIEW

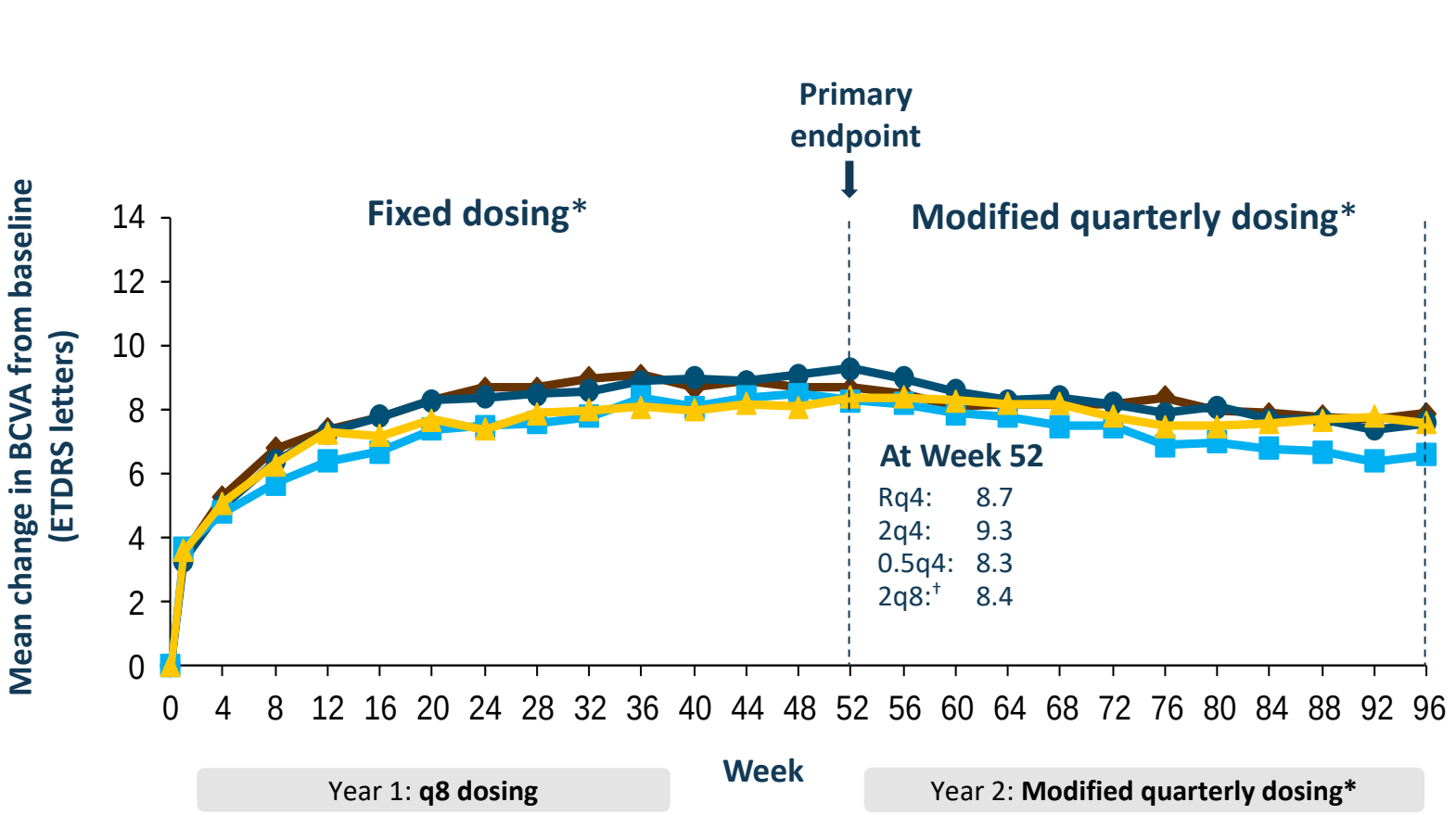
- Proactive component
  - 12 weeks since previous injection
- Reactive component
  - New or persistent fluid on OCT
  - Increase in CRT of ≥100 µm compared with the lowest previous value
  - Loss of ≥5 ETDRS letters from the best previous score in conjunction with recurrent fluid on OCT
  - New-onset classic neovascularization
  - New or persistent leak on fluorescein angiography
  - New macular hemorrhage

CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography.

Schmidt-Erfurth U *et al*. *Ophthalmology* 2014; 121 (1): 193–201.

Results: Mean change in BCVA from baseline to Week 96

VIEW



Rq4-Ranibizumab 0.5mg every 4weeks n=595
2q4-Aflibercept 2mg every 4 weeks n=613
0.5q4-Aflibercept 0.5mg every 4 weeks n=597
2q8†-Aflibercept 2mg every 8 weeks n=607

At Week 96
Rq4: 7.9
2q4: 7.6
0.5q4: 6.6
2q8:† 7.6

Year 1: **q8 dosing**

Mean number of aflibercept injections in Year 1: **7.5**[3]

Year 2: **Modified quarterly dosing***

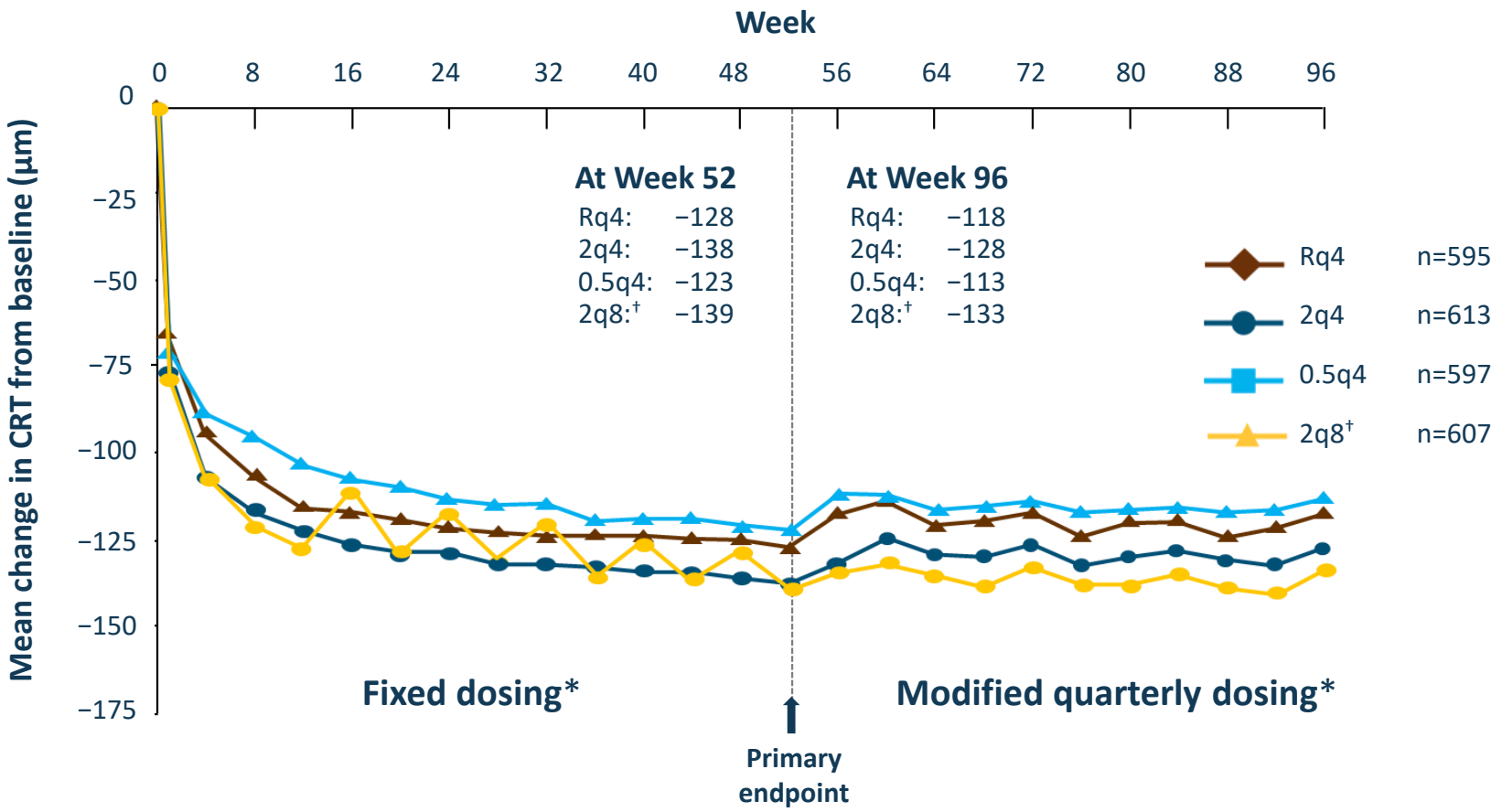
Mean number of aflibercept injections in Year 2: **4.2**[2]

48% of patients who received **aflibercept q8** in Year 1 maintained VA gains in Year 2 while only receiving the mandated **quarterly injections** (n=247/511)†,[1]

*Full analysis set. Integrated analysis. †Following 3 initial monthly doses.
BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Rq4, ranibizumab 0.5 mg every 4 weeks.
1. Richard G *et al. Ophthalmology* 2015; 122 (12): 2497–2503. 2. Schmidt-Erfurth U *et al. Ophthalmology* 2014; 121 (1): 193–201. 3. Heier JS *et al. Ophthalmology* 2012; 119 (12): 2537–2548

Results: Mean change in CRT from baseline to Week 96

VIEW



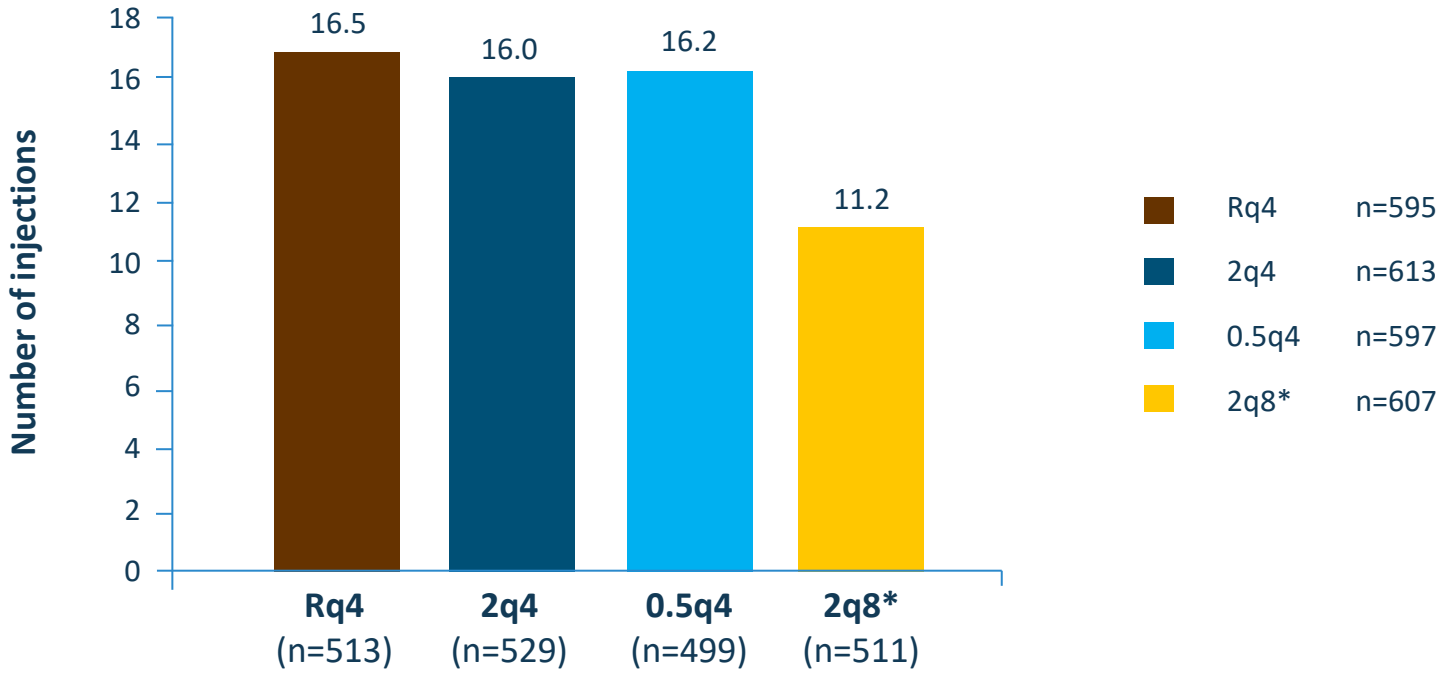
VIEW 1: OCTs mandatory at baseline, Weeks 4, 12, 24, 36, and all visits Weeks 52–96; VIEW 2: OCTs mandatory at all visits. *Full analysis set. †Following 3 initial monthly doses.

0.5q4, aflibercept 0.5 mg every 4 weeks; 2q4, aflibercept 2 mg every 4 weeks; 2q8, aflibercept 2 mg every 8 weeks; CRT, central retinal thickness; OCT, optical coherence tomography; Rq4, ranibizumab 0.5 mg every 4 weeks.

Schmidt-Erfurth U *et al*. *Ophthalmology* 2014; 121 (1): 193–201.

Results: Mean number of injections to Week 96

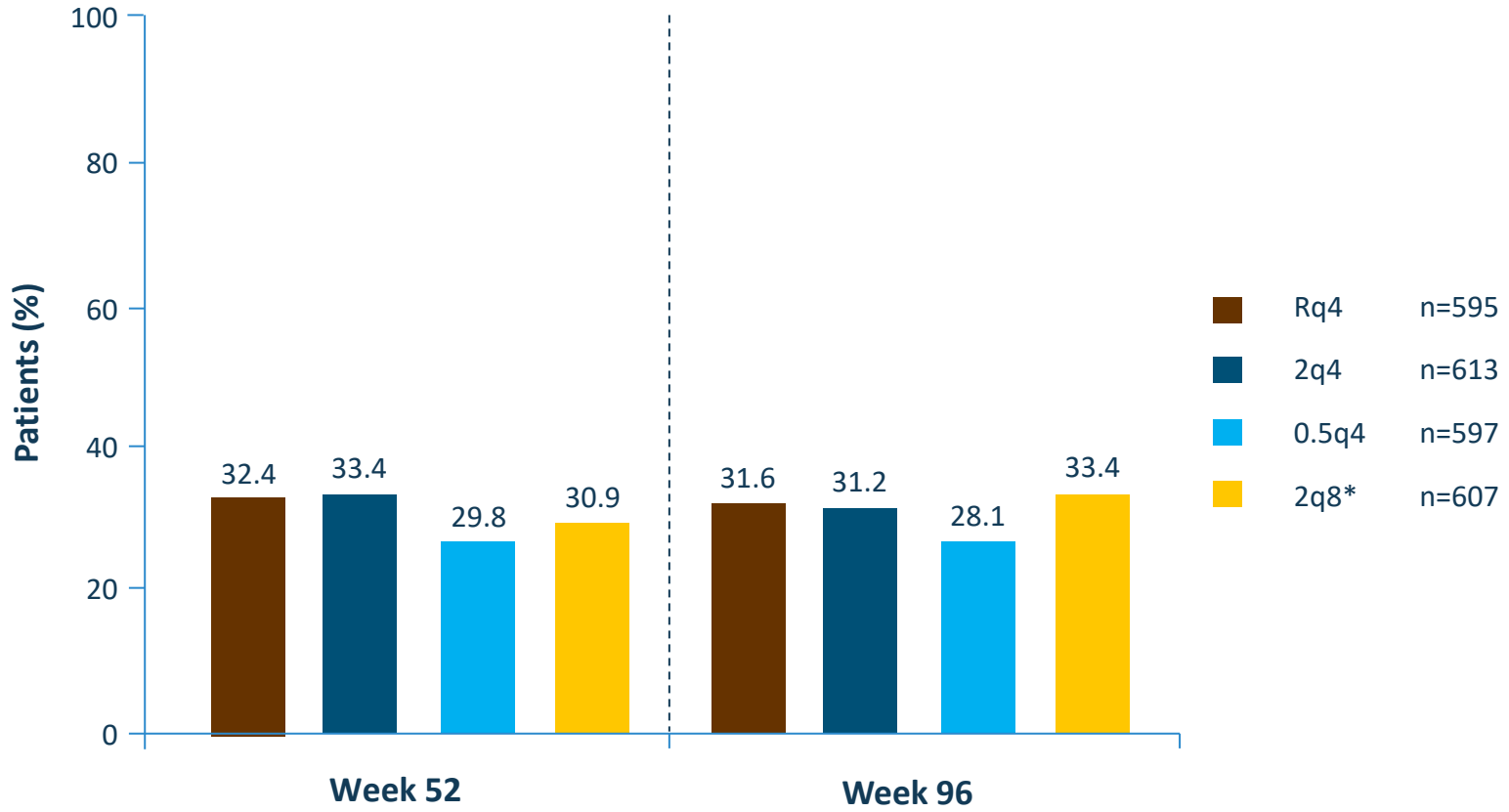
VIEW



*Following 3 initial monthly doses.
0.5q4, aflibercept 0.5 mg every 4 weeks; 2q4, aflibercept 2 mg every 4 weeks; 2q8, aflibercept 2 mg every 8 weeks; Rq4, ranibizumab 0.5 mg every 4 weeks.
Schmidt-Erfurth U *et al*. *Ophthalmology* 2014; 121 (1): 193–201.

Results: Percentage of patients who gained ≥15 letters from baseline

VIEW



Per protocol set. *Following 3 initial monthly doses.
0.5q4, aflibercept 0.5 mg every 4 weeks; 2q4, aflibercept 2 mg every 4 weeks; 2q8, aflibercept 2 mg every 8 weeks; Rq4, ranibizumab 0.5 mg every 4 weeks.
Schmidt-Erfurth U *et al*. *Ophthalmology* 2014; 121 (1): 193–201.

Study eye SAEs through Week 96

VIEW

AEs over 96 weeks

	Ranibizumab 0.5q4	Aflibercept 2q4	Aflibercept 0.5q4	Aflibercept 2q8*	All aflibercept
Patients, n (safety analysis set)	**595**	**613**	**601**	**610**	**1,824**
No. of patients with ≥1 AE, n (%)	26 (4.4)	22 (3.6)	19 (3.2)	24 (3.9)	65 (3.6)
Cataract	1 (0.2)	4 (0.7)	3 (0.5)	4 (0.7)	11 (0.6)
Endophthalmitis	5 (0.8)	4 (0.7)	1 (0.2)	0	5 (0.3)
Intraocular pressure increased	1 (0.2)	0	1 (0.2)	2 (0.3)	3 (0.2)
Macular degeneration	0	0	0	2 (0.3)	2 (0.1)
Macular hole	0	0	2 (0.3)	0	2 (0.1)
Posterior capsule opacification	2 (0.3)	0	0	0	0
Retinal detachment	3 (0.5)	1 (0.2)	2 (0.3)	0	3 (0.2)
Retinal hemorrhage	4 (0.7)	3 (0.5)	5 (0.8)	5 (0.8)	13 (0.7)
RPE tear	1 (0.2)	0	1 (0.2)	3 (0.5)	4 (0.2)
VA reduced	5 (0.8)	4 (0.7)	3 (0.5)	7 (1.1)	14 (0.8)

SAEs occurring in ≥2 patients per study group.*Following 3 initial monthly doses.
0.5q4, 0.5 mg every 4 weeks; 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; AE, adverse event; RPE, retinal pigment epithelium; SAE, serious adverse event; VA, visual acuity.
Schmidt-Erfurth U *et al. Ophthalmology* 2014; 121 (1): 193–201.

VIEW studies: Results summary

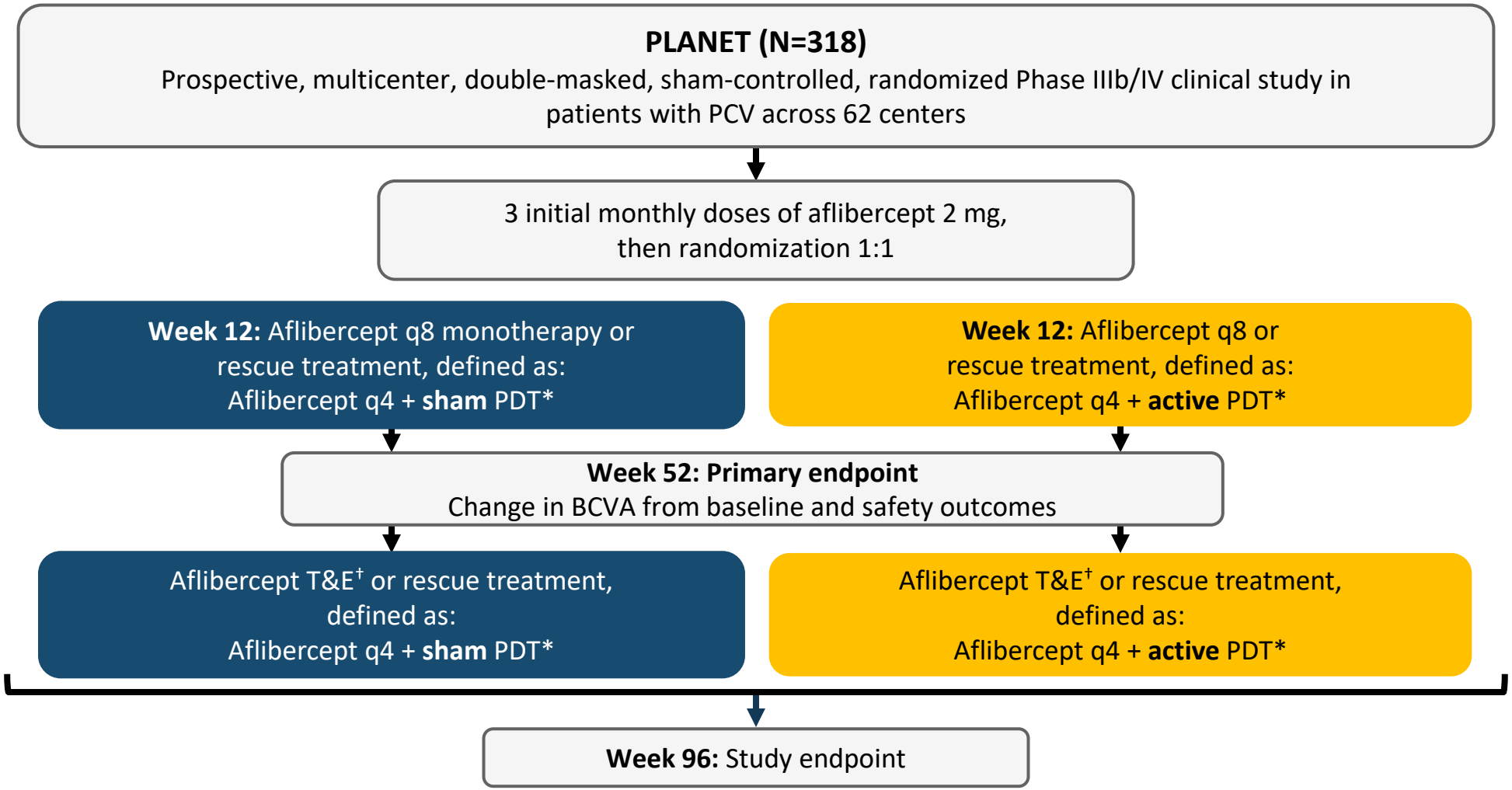
VIEW

- All aflibercept groups met non-inferiority and clinical equivalence in comparison with ranibizumab for the primary endpoint (proportion of patients maintaining vision at Week 52)[1,2]
- Aflibercept 2q8* demonstrated similar efficacy and safety to ranibizumab 0.5q4[1]
- Visual and anatomic improvements observed at Week 52 were largely maintained through Week 96 with modified quarterly dosing[2]
  - 48% of patients in the aflibercept 2q8* arm were maintained on quarterly dosing[3]
- During Weeks 52–96, fewer patients in the aflibercept 2q8* group received ≥6 injections compared with ranibizumab[2]
- At Week 96, similar proportions of patients in all study arms had BCVA ≥20/40[4]
  - In the aflibercept 2q8* arm, 33.8% of patients had BCVA ≥20/40 at Week 96[4]
- No unexpected safety signals were seen with intravitreal aflibercept injection[1,2]
  - Incidences of AEs were similar across all treatment groups[1,2]

*Following 3 initial monthly doses.
0.5q4, 0.5 mg every 4 weeks; 2q8, 2 mg every 8 weeks; AE, adverse event; BCVA, best corrected visual acuity.
1. Heier JS *et al. Ophthalmology* 2012; 119 (12): 2537–2548. 2. Schmidt-Erfurth U *et al. Ophthalmology* 2014; 121 (1): 193–201. 3. Richard G *et al. Ophthalmology* 2015; 122 (12): 2497–2503. 4. Schmidt-Erfurth U *et al. Ophthalmology* 2014; 121 (1): 193–201 – supplementary table 3.

PLANET was a prospective sham-controlled study assessing the efficacy of aflibercept monotherapy compared with aflibercept plus active PDT for the treatment of patients with PCV

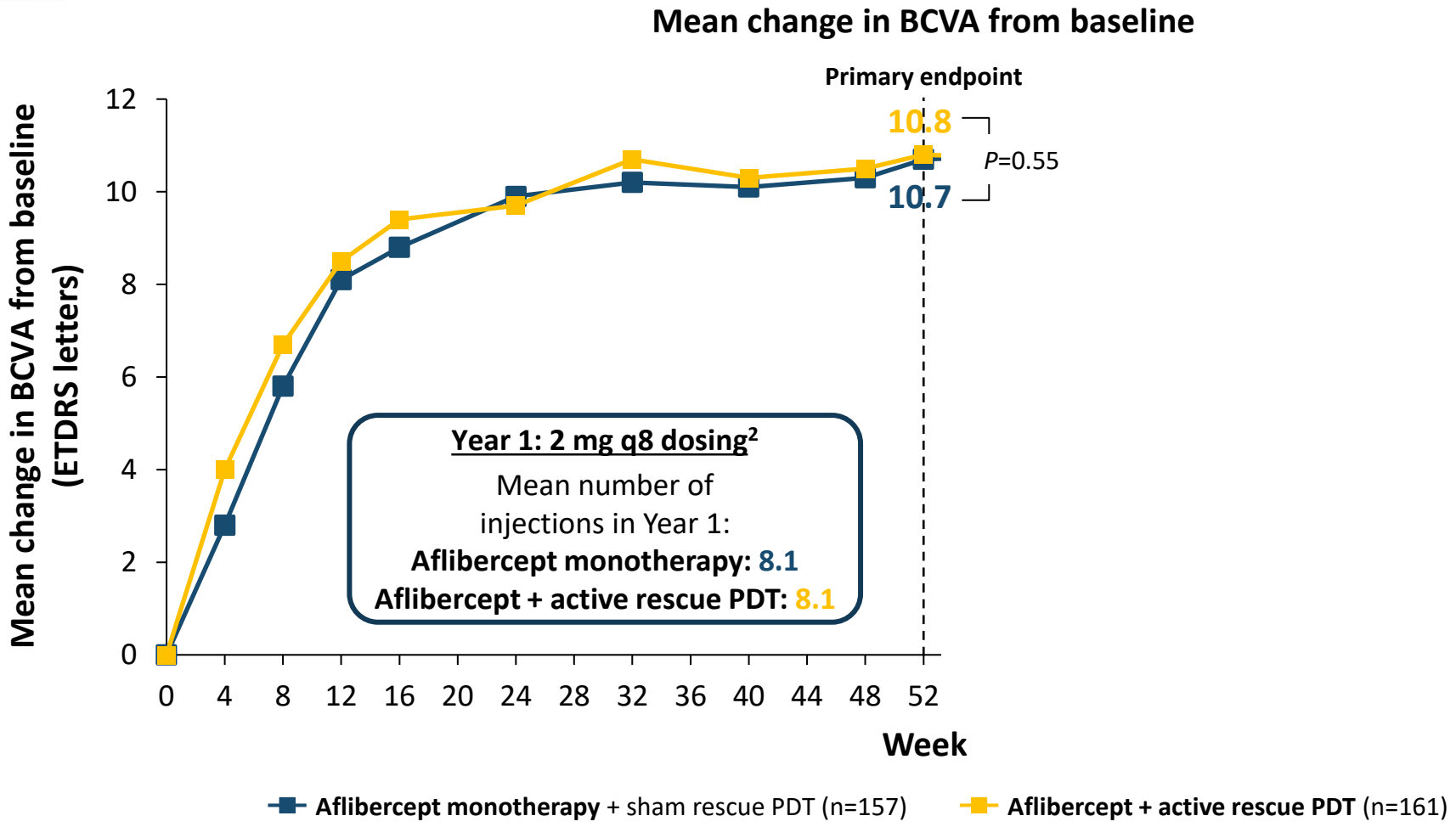
PLANET



*Determined by the rescue treatment criteria. †T&E was not protocol mandated and was performed at the discretion of the investigator.
BCVA, best corrected visual acuity; PCV, polypoidal choroidal vasculopathy; PDT, photodynamic therapy; q4, every 4 weeks; q8, every 8 weeks, after 3 initial monthly doses; T&E, treat-and-extend.
Lee WK *et al*. *JAMA Ophthalmol* 2018; 136 (7): 786–793. Wong TY *et al*. *Am J Ophthalmol* 2019; 204: 80–89.

Aflibercept monotherapy resulted in vision gains of >10 letters from baseline at Week 52

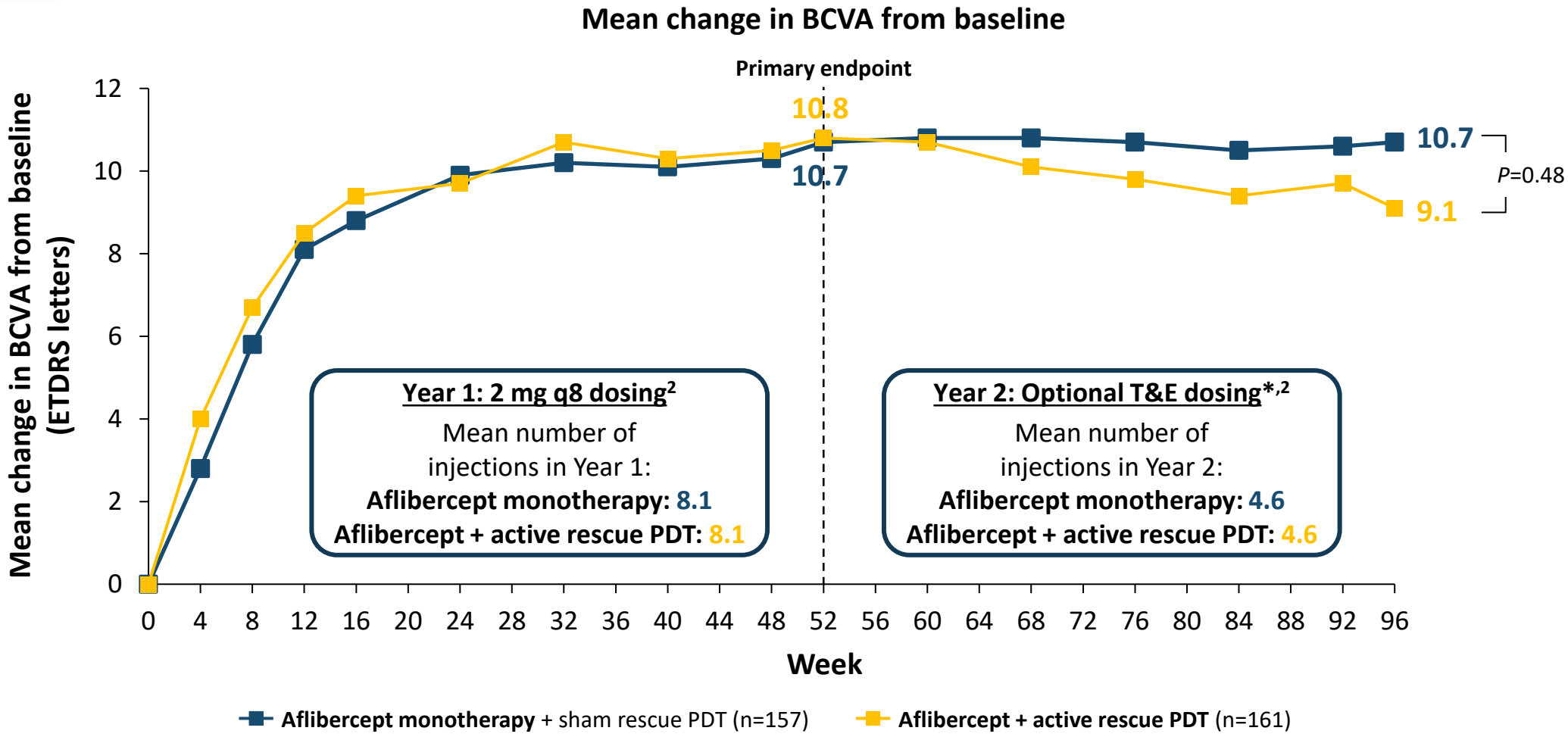
PLANET



Full analysis set; last observation carried forward.
BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PDT, photodynamic therapy; q8, every 8 weeks, after 3 initial monthly doses.
1. Lee WK *et al*. *JAMA Ophthalmol* 2018; 136 (7): 786–793. 2. Wong TY *et al*. *Am J Ophthalmol* 2019; 204: 80–89.

Aflibercept monotherapy for the treatment of PCV demonstrated meaningful VA gains that were maintained to Week 96

PLANET



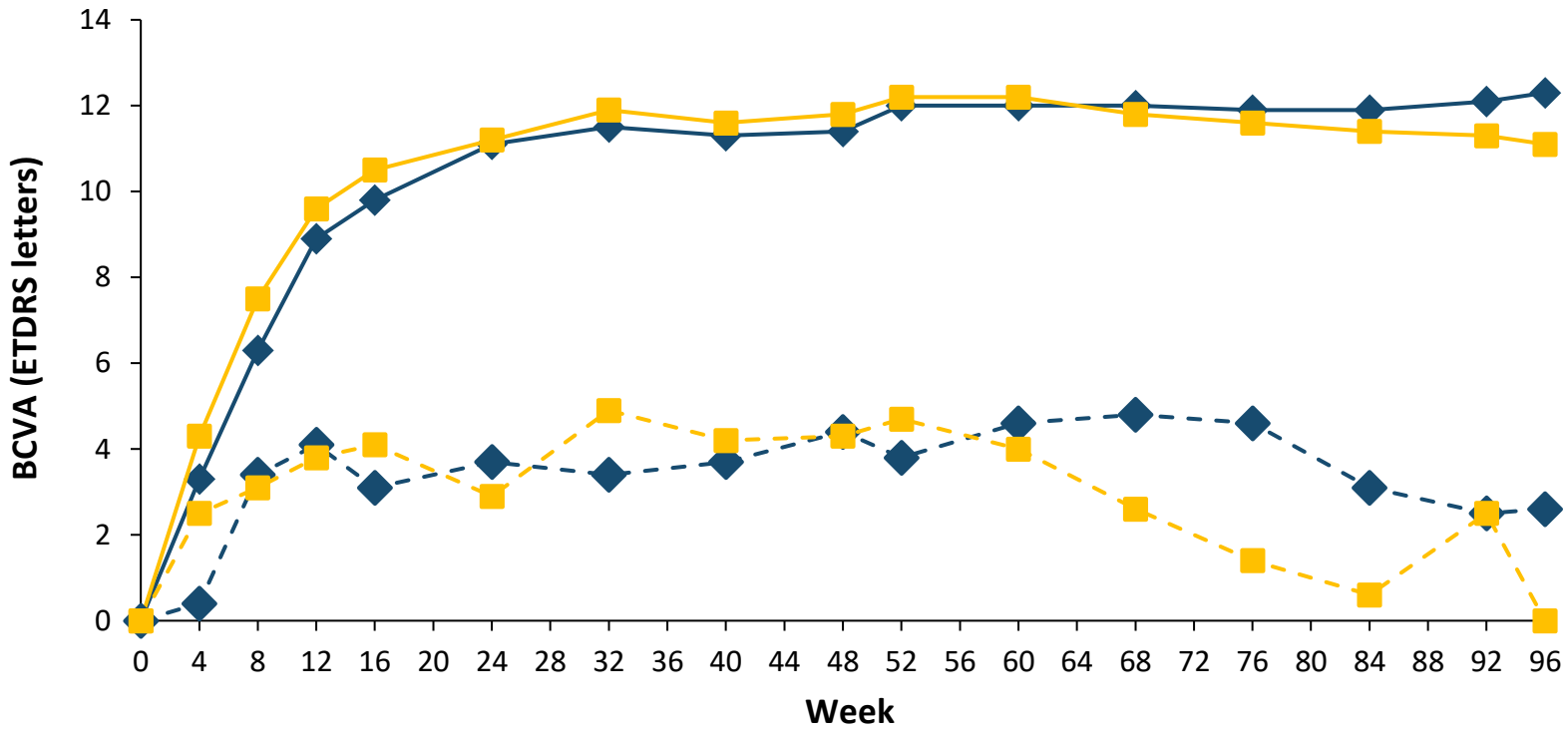
Full analysis set; last observation carried forward. *In Year 2, patients were eligible to receive optional T&E; T&E was not protocol mandated and was performed at the discretion of the investigator.
BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PCV, polypoidal choroidal vasculopathy; PDT, photodynamic therapy;
q8, every 8 weeks, after 3 initial monthly doses; T&E, treat-and-extend; VA, visual acuity.

1. Lee WK *et al*. *JAMA Ophthalmol* 2018; 136 (7): 786–793. 2. Wong TY *et al*. *Am J Ophthalmol* 2019; 204: 80–89.

Active PDT was not associated with additional vision gains vs. sham in patients meeting rescue criteria

PLANET

Mean change in BCVA from baseline to Week 96



Patients who did not require rescue PDT:

	Change in BCVA (ETDRS letters)	Complete polyp regression rate at Week 96 (%)
No rescue: Aflibercept monotherapy + sham rescue PDT (n=132)	12.3	33.1
No rescue: Aflibercept + active rescue PDT (n=132)	11.1	29.1

Patients who required rescue PDT:

	Change in BCVA (ETDRS letters)	Complete polyp regression rate at Week 96 (%)
Rescue: Aflibercept monotherapy + sham rescue PDT (n=25)	2.6	25.0
Rescue: Aflibercept + active rescue PDT (n=29)	0.0	26.1

P=0.40

No rescue: Aflibercept monotherapy + sham rescue PDT (n=132)

No rescue: Aflibercept + active rescue PDT (n=132)

Rescue: Aflibercept monotherapy + sham rescue PDT (n=25)

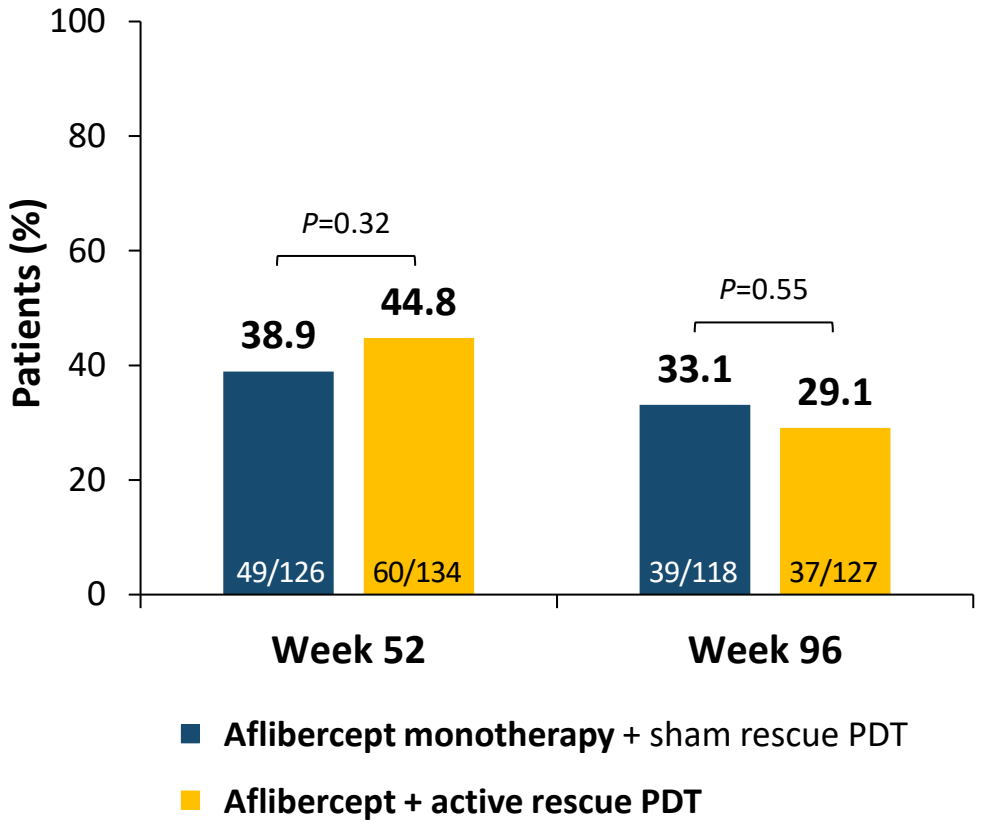
Rescue: Aflibercept + active rescue PDT (n=29)

Full analysis set; last observation carried forward.
BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PDT, photodynamic therapy.
Wong TY *et al*. *Am J Ophthalmol* 2019; 204: 80–89.

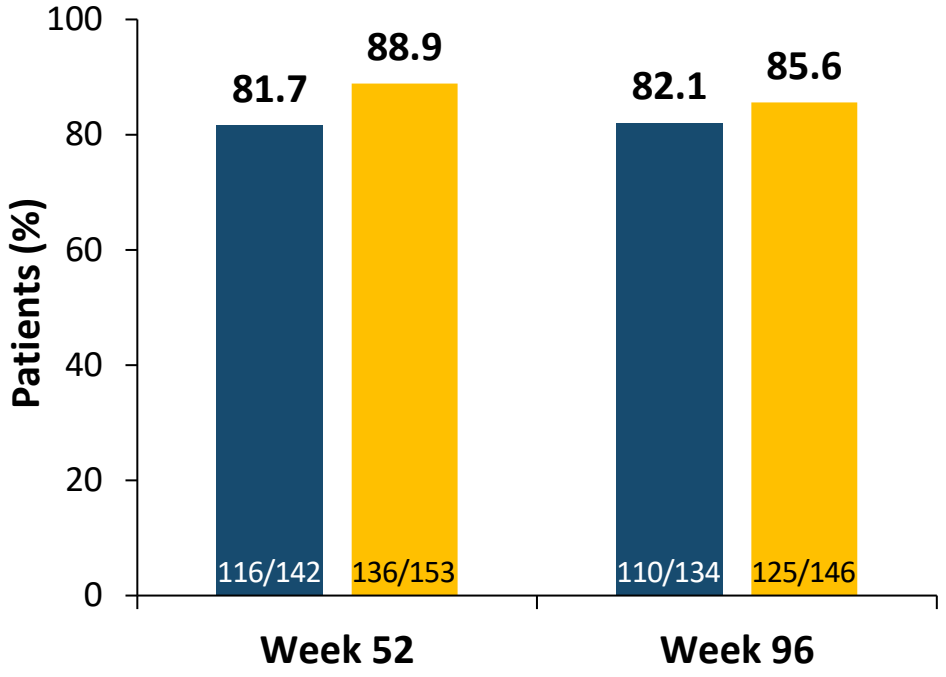
In both treatment arms, >80% of patients showed no evidence of active polyps at Weeks 52 or 96

PLANET

Proportion of patients with complete polyp regression*,[1,2]



Proportion of patients with no evidence of active polyps[1,2]



Note: No evidence of active polyps was defined as eyes without polyps on ICGA (complete polyp regression) or with polyps on ICGA but no new or persistent fluid on OCT[2]

Secondary endpoints. *Observed cases; full analysis set.
ICGA, indocyanine green angiography; OCT, optical coherence tomography; PDT, photodynamic therapy.
1. Lee WK *et al*. *JAMA Ophthalmol* 2018; 136 (7): 786–793. 2. Wong TY *et al*. *Am J Ophthalmol* 2019; 204: 80–89.

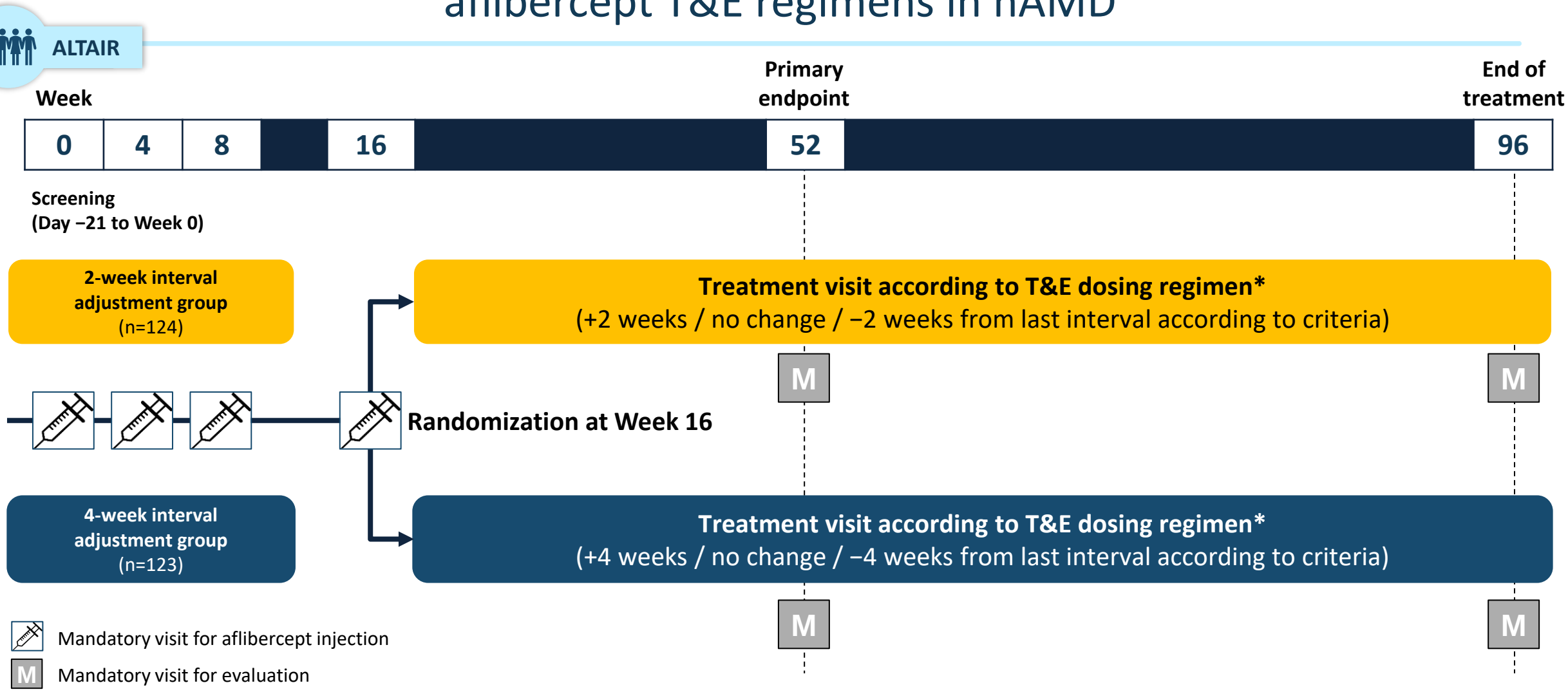
PLANET study: Results summary

PLANET

- IVT-AFL monotherapy for the treatment of PCV resulted in an improvement in BCVA of 10.7 ETDRS letters over 96 weeks
  - In patients not requiring rescue treatment, IVT-AFL monotherapy resulted in BCVA changes between +11.1 and +12.3 letters in the 2 groups
  - In patients requiring rescue treatment, BCVA changes of +2.6 letters and 0.0 letters were observed with IVT-AFL monotherapy and IVT-AFL combined with PDT, respectively
- At Week 96, more than 80% of patients in the IVT-AFL monotherapy and IVT-AFL plus PDT groups had no evidence of active polyps on ICGA
- 83% of patients did not require rescue treatment over 96 weeks
  - The addition of PDT to IVT-AFL did not show any additional functional or anatomic benefits
- During the second year, the optional T&E regimen resulted in a meaningful reduction of the number of visits and total treatments
- The safety profile of IVT-AFL was consistent with the previously reported literature

1. Lee WK *et al*. *JAMA Ophthalmol* 2018; 136 (7): 786–793. 2. Wong TY *et al*. *Am J Ophthalmol* 2019; 204: 80–89

ALTAIR was designed to assess the efficacy of two different aflibercept T&E regimens in nAMD



*The minimum treatment interval was 8 weeks and the maximum treatment interval was 16 weeks; the decision to adjust the treatment interval was based on the T&E regimen criteria, assessed by OCT. If a patient in the 4-week adjustment group had a previous interval shortened by 4 weeks, any subsequent extension or shortening of the interval was done in 2-week increments.

nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; T&E, treat-and-extend.

Ohji M *et al*. *Adv Ther* 2020; 37 (3): 1173–1187.

Adjustment of T&E treatment intervals was guided by specific criteria

ALTAIR

Extension of interval

- No fluid*

AND

- No loss of ≥5 ETDRS letters†
- No increase in CRT of ≥100 µm‡
- No new neovascularization
- No new macular hemorrhage

Maintenance of interval

- Residual fluid with decreased fluid volume*

AND

- No loss of ≥5 ETDRS letters†
- No increase in CRT of ≥100 µm‡
- No new neovascularization
- No new macular hemorrhage

Shortening of interval

- New fluid*

OR

- Persistent fluid with unchanged or increased fluid volume*

OR any of the following:

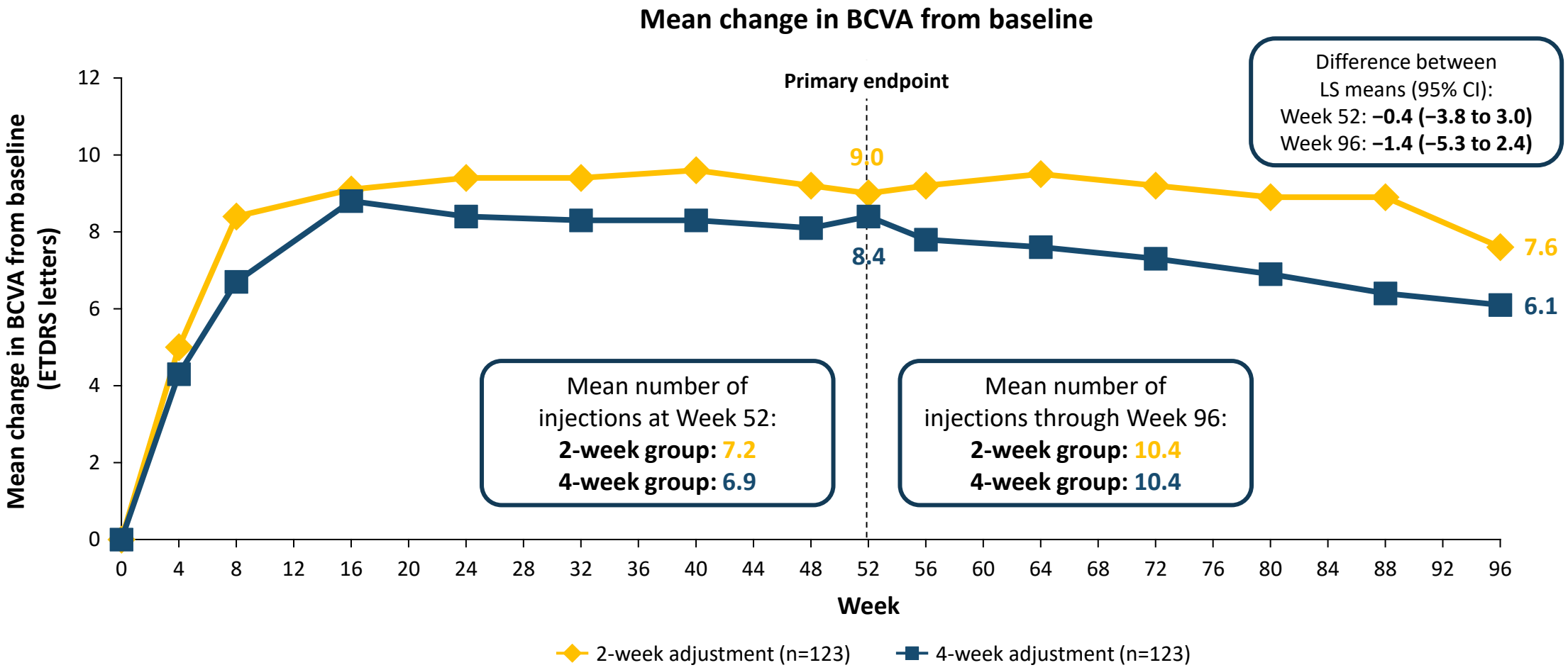
- Loss of ≥5 ETDRS letters†
- Increase in CRT of ≥100 µm‡
- New neovascularization
- New macular hemorrhage

Minimum treatment interval: 8 weeks
Maximum treatment interval: 16 weeks

*As assessed by OCT. †From the last treatment visit, in conjunction with recurrent fluid on OCT. ‡At the central 1 mm compared with the lowest previous value by OCT.
CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography; T&E, treat-and-extend.
Ohji M *et al*. *Adv Ther* 2020; 37 (3): 1173–1187.

Vision gains achieved in Year 1 were maintained to Week 96 with fewer than 4 injections in Year 2 in both treatment groups

ALTAIR

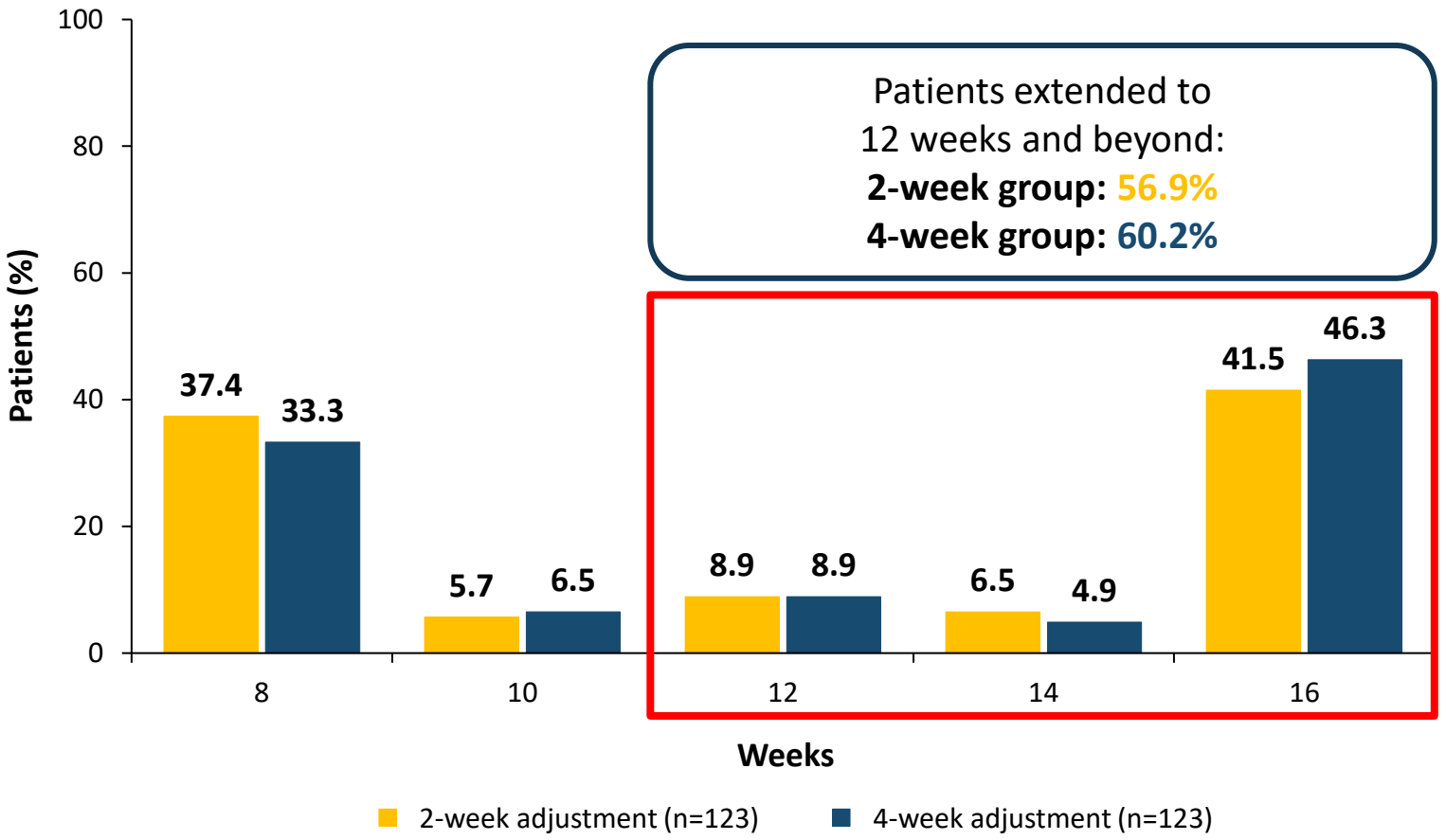


Full analysis set; last observation carried forward.
BCVA, best corrected visual acuity; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; LS, least squares.
Ohji M *et al*. *Adv Ther* 2020; 37 (3): 1173–1187.

By Week 96, 56.9%–60.2% of patients were maintained at injection intervals of 12 weeks and beyond

ALTAIR

Last injection interval at the final visit up to Week 96*



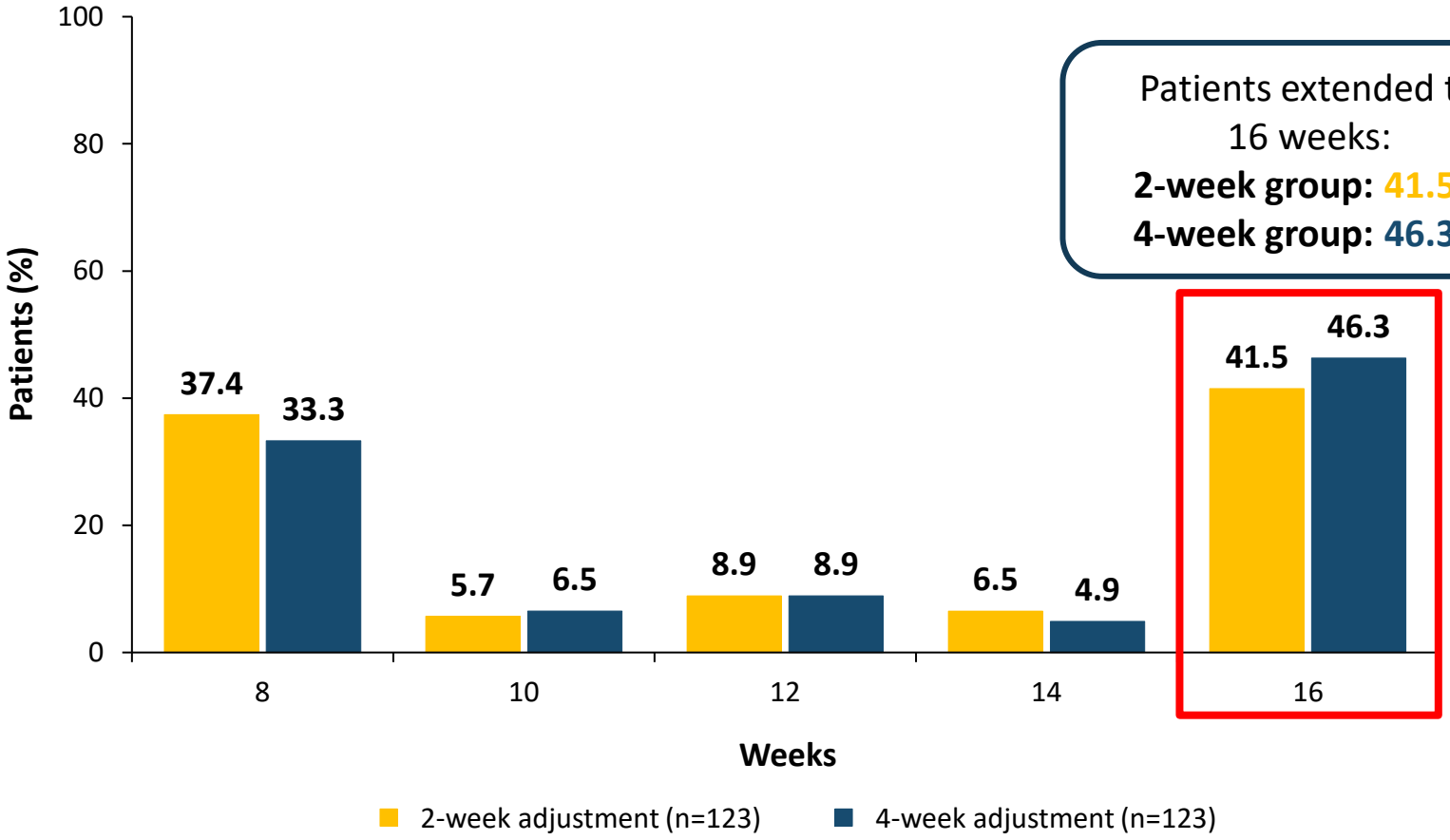
Mean last injection interval ± SD:
2-week group: 12.2 ± 3.6 weeks
4-week group: 12.5 ± 3.6 weeks

Full analysis set. *The minimum treatment interval was 8 weeks and the maximum treatment interval was 16 weeks; the decision to adjust the treatment interval was based on the T&E regimen criteria, assessed by OCT.
OCT, optical coherence tomography; SD, standard deviation; T&E, treat-and-extend.
Ohji M *et al*. *Adv Ther* 2020; 37 (3): 1173–1187.

By Week 96, 41.5%–46.3% of patients were maintained at the maximum treatment interval of 16 weeks

ALTAIR

Last injection interval at the final visit up to Week 96*



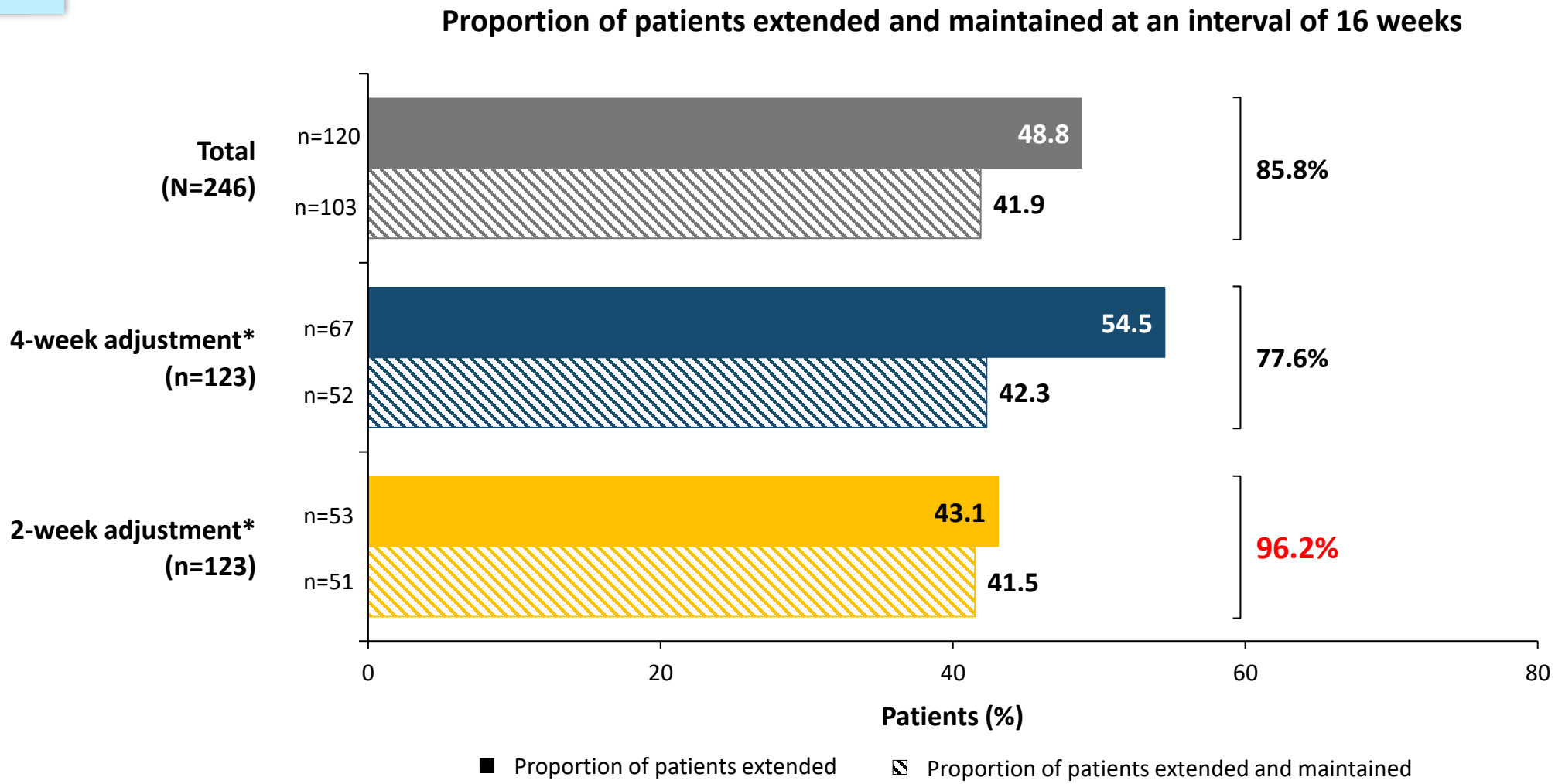
Patients extended to 16 weeks:
2-week group: 41.5%
4-week group: 46.3%

Mean last injection interval ± SD:
2-week group: 12.2 ± 3.6 weeks
4-week group: 12.5 ± 3.6 weeks

Full analysis set. *The minimum treatment interval was 8 weeks and the maximum treatment interval was 16 weeks; the decision to adjust the treatment interval was based on the T&E regimen criteria, assessed by OCT.
OCT, optical coherence tomography; SD, standard deviation; T&E, treat-and-extend.
Ohji M *et al*. *Adv Ther* 2020; 37 (3): 1173–1187.

Between 77.6% and 96.3% of patients who reached the maximum possible treatment interval of 16 weeks were maintained at this interval to Week 96

ALTAIR



Full analysis set. *The minimum treatment interval was 8 weeks and the maximum treatment interval was 16 weeks; the decision to adjust the treatment interval was based on the T&E regimen criteria, assessed by OCT.
OCT, optical coherence tomography; T&E, treat-and-extend.
Ohji M *et al*. *Adv Ther* 2020; 37 (3): 1173–1187.

ALTAIR study: Results summary

ALTAIR

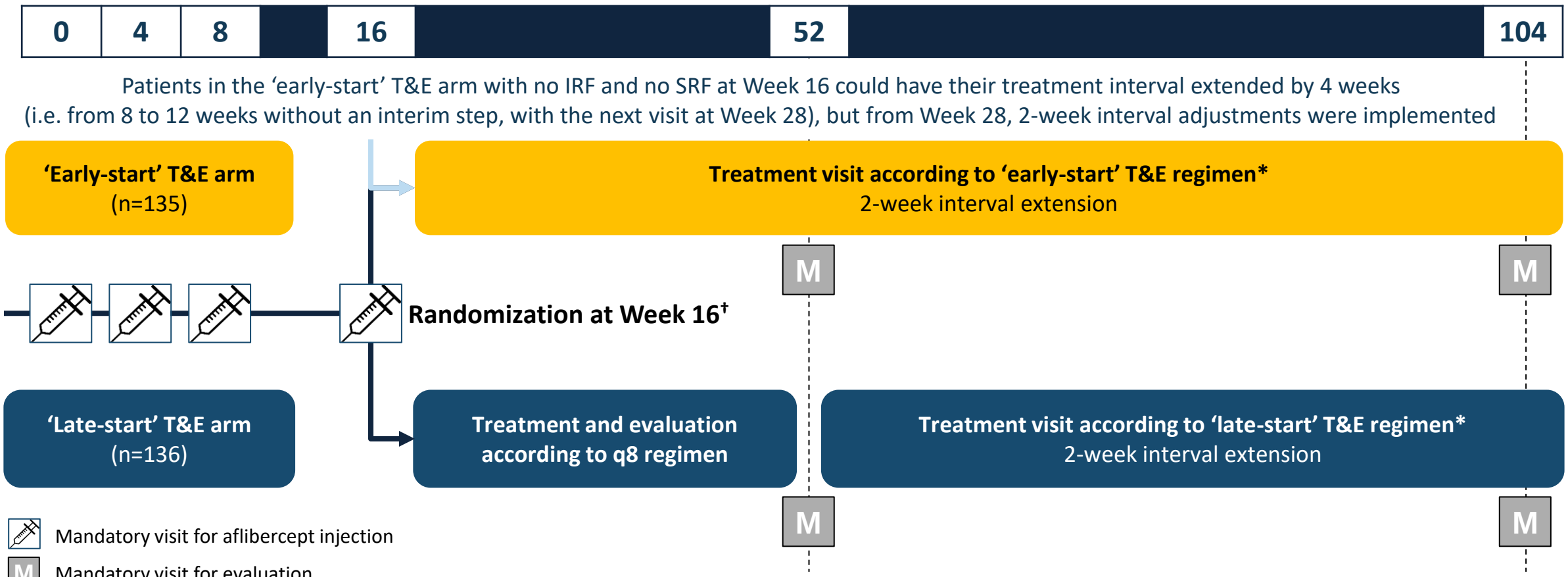
- Patients gained a mean of 9.0 and 8.4 letters at the Week 52 primary endpoint in the 2-week and 4-week adjustment groups, respectively, with a mean of around 7 injections
- VA gains were maintained to Week 96 in both treatment groups with continued aflibercept T&E, with around half the number of injections in the second year
- CRT reductions of −130.5 µm and −125.3 µm were achieved in the 2-week and 4-week adjustment groups, respectively, at Week 96
- 57% of patients had a ‘next intended’ injection interval of 12 weeks or beyond at the last visit up to Week 52
- By Week 96, approximately 57–60% of patients had a last injection interval of 12 weeks or beyond and more than 40% of patients had a last injection interval of 16 weeks
- AEs were consistent with the known safety profile of aflibercept in nAMD

AE, adverse event; CRT, central retinal thickness; nAMD, neovascular age-related macular degeneration; T&E, treat-and-extend; VA, visual acuity.

Ohji M *et al*. *Adv Ther* 2020; 37 (3): 1173–1187

ARIES was designed to assess the efficacy of ‘early’ vs. ‘late’ initiation of T&E with aflibercept in nAMD over 2 years

ARIES



*The maximum treatment interval was 16 weeks; the decision to adjust the treatment interval was based on the T&E regimen criteria, assessed by SD-OCT.
†Patients were stratified based on change in BCVA from baseline to Week 16 (gain of <8 letters or ≥8 letters).
BCVA, best corrected visual acuity; IRF, intraretinal fluid; nAMD, neovascular age-related macular degeneration; SD-OCT, spectral domain optical coherence tomography; q8, every 8 weeks, after 3 initial monthly doses; SRF, subretinal fluid; T&E, treat-and-extend.
Mitchell P *et al. Retina* 2021; Sep 1;41(9):1911-1920.

Adjustment of T&E treatment intervals was guided by specified anatomic criteria*

ARIES

Extend

- Absence of IRF

and

- Absence of new neovascularization or hemorrhage

and

- SRF ≤50 µm in thickness

Shorten

- Any IRF

or

- New neovascularization or hemorrhage

or

- SRF >50 µm in thickness

Treatment intervals were adjusted in 2-week increments to a maximum treatment interval of 16 weeks. Treatment intervals could be shortened to <8 weeks.

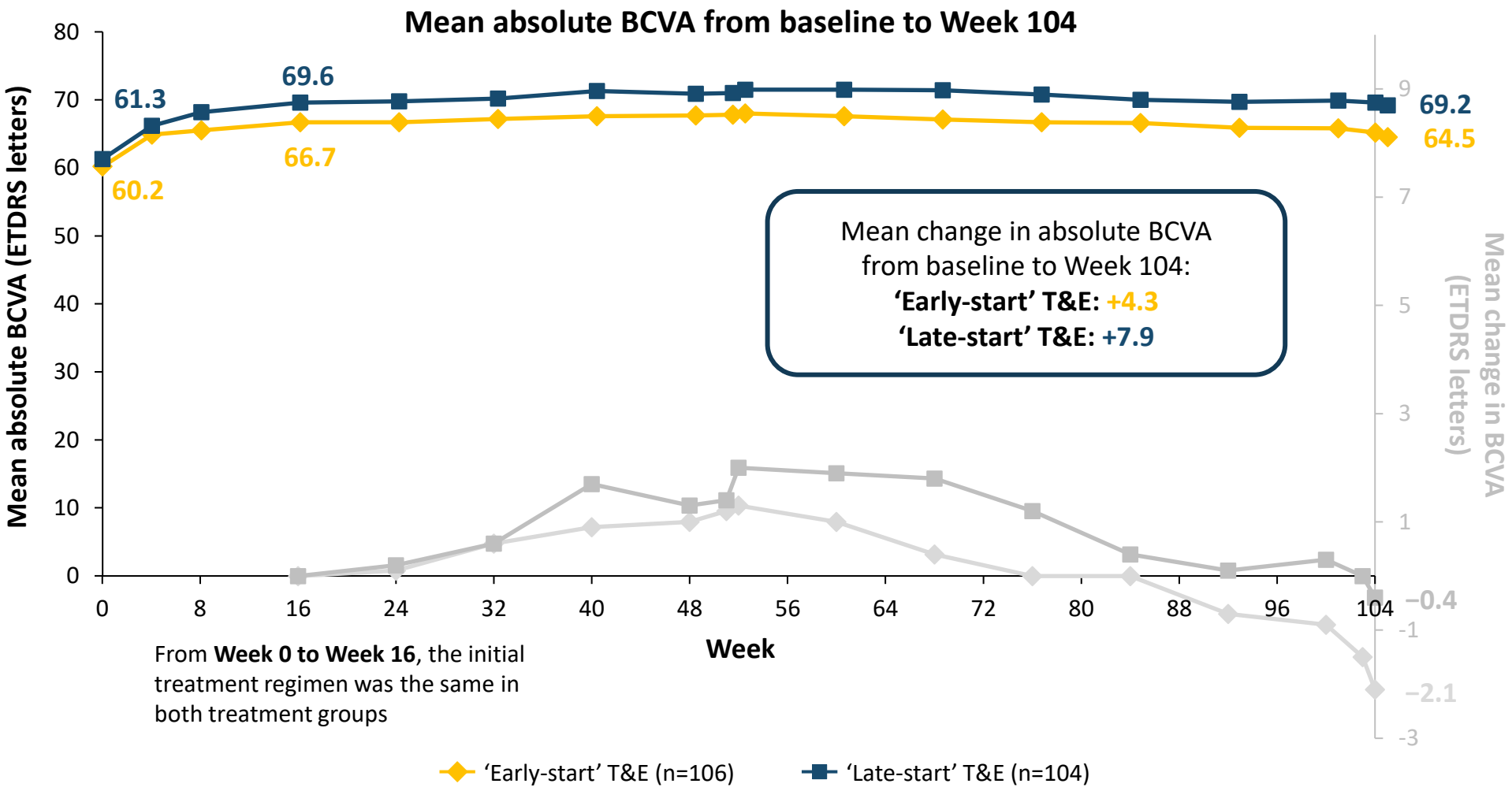
The criteria for extending the treatment interval permitted tolerance of some residual SRF ≤50 µm.

Unlike in the ALTAIR study, ARIES did not include an option for patients to be maintained on their current treatment interval in the presence of residual but decreased fluid

*Based on SD-OCT; functional criteria not assessed.
IRF, intraretinal fluid; SD-OCT, spectral domain optical coherence tomography; SRF, subretinal fluid; T&E, treat-and-extend.
Mitchell P *et al. Retina* 2021; Sep 1;41(9):1911-1920.

Vision gains were maintained to Week 104 and were similar in both treatment groups

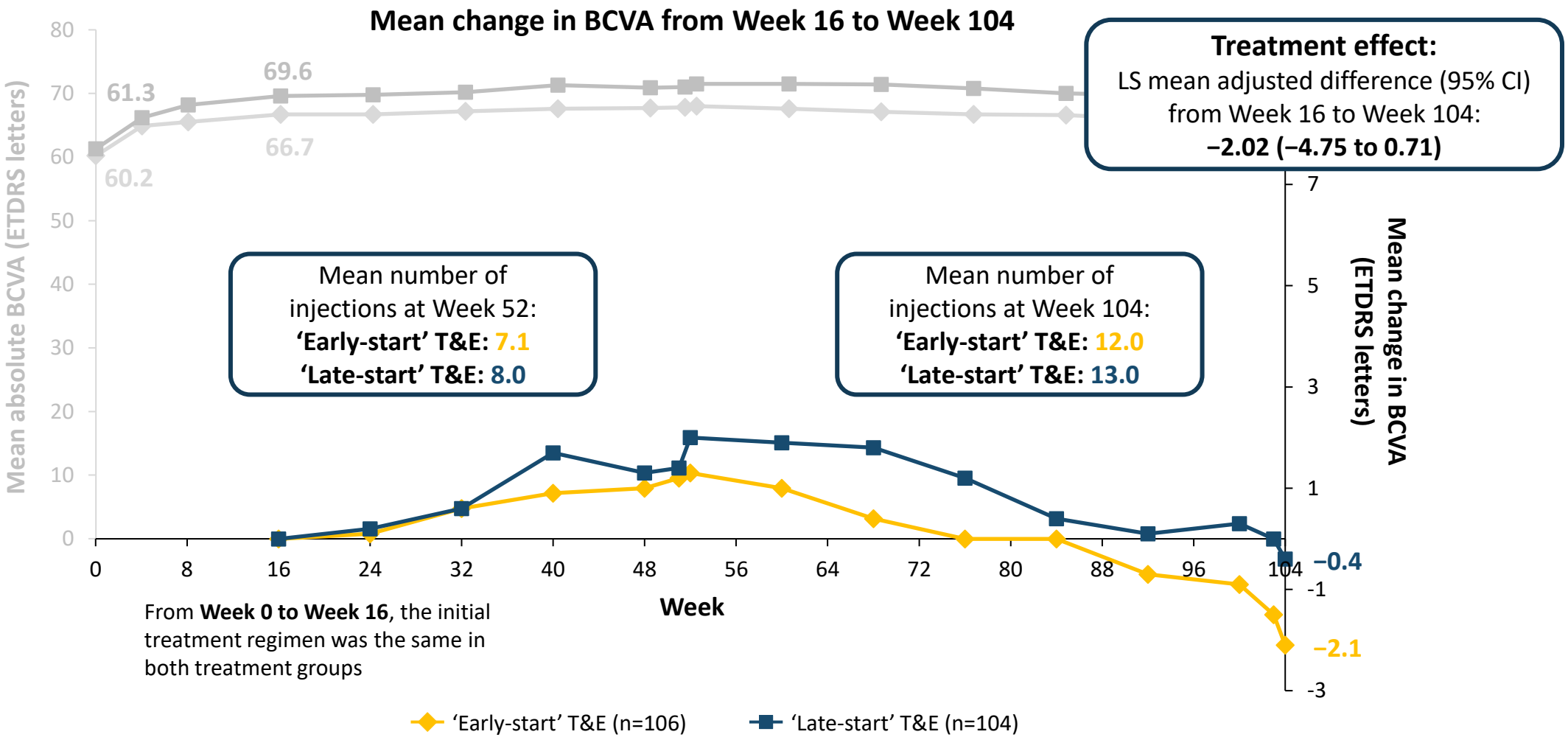
ARIES



Per-protocol set; last observation carried forward. The per-protocol set included all randomized patients who had completed all scheduled treatment visits from baseline through Week 104.
BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; T&E, treat-and-extend.
Mitchell P *et al. Retina* 2021; Sep 1;41(9):1911-1920.

‘Early-start’ T&E was non-inferior, with one fewer injection to ‘late-start’ T&E at the Week 104 final analysis

ARIES

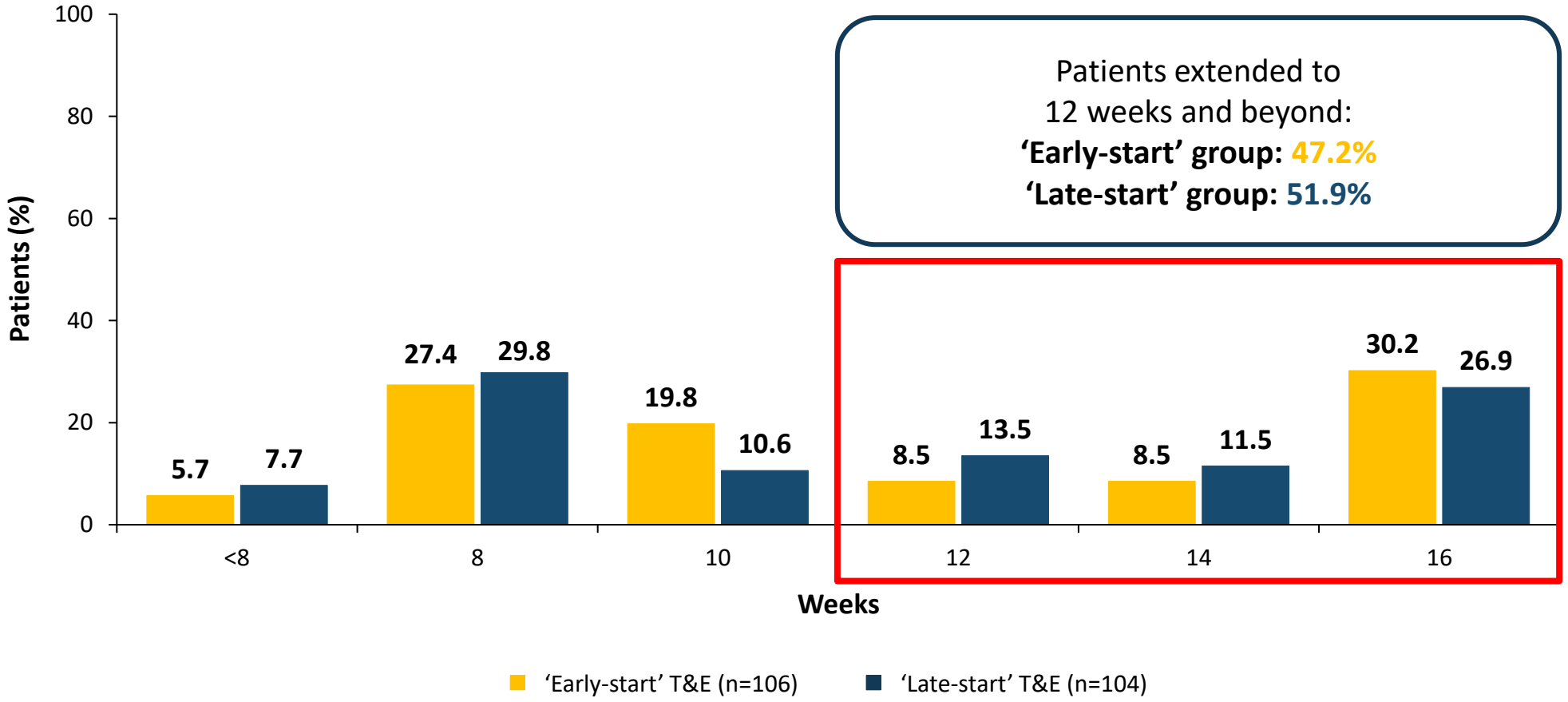


Per-protocol set. The per-protocol set included all randomized patients who had completed all scheduled treatment visits from baseline through Week 104.
BCVA, best corrected visual acuity; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; LS, least squares; T&E, treat-and-extend.
Mitchell P *et al. Retina* 2021; Sep 1;41(9):1911-1920.

By Week 104, approximately 50% of patients across both groups were maintained at intervals of 12 weeks and beyond

ARIES

Last injection interval at the final visit up to Week 104*

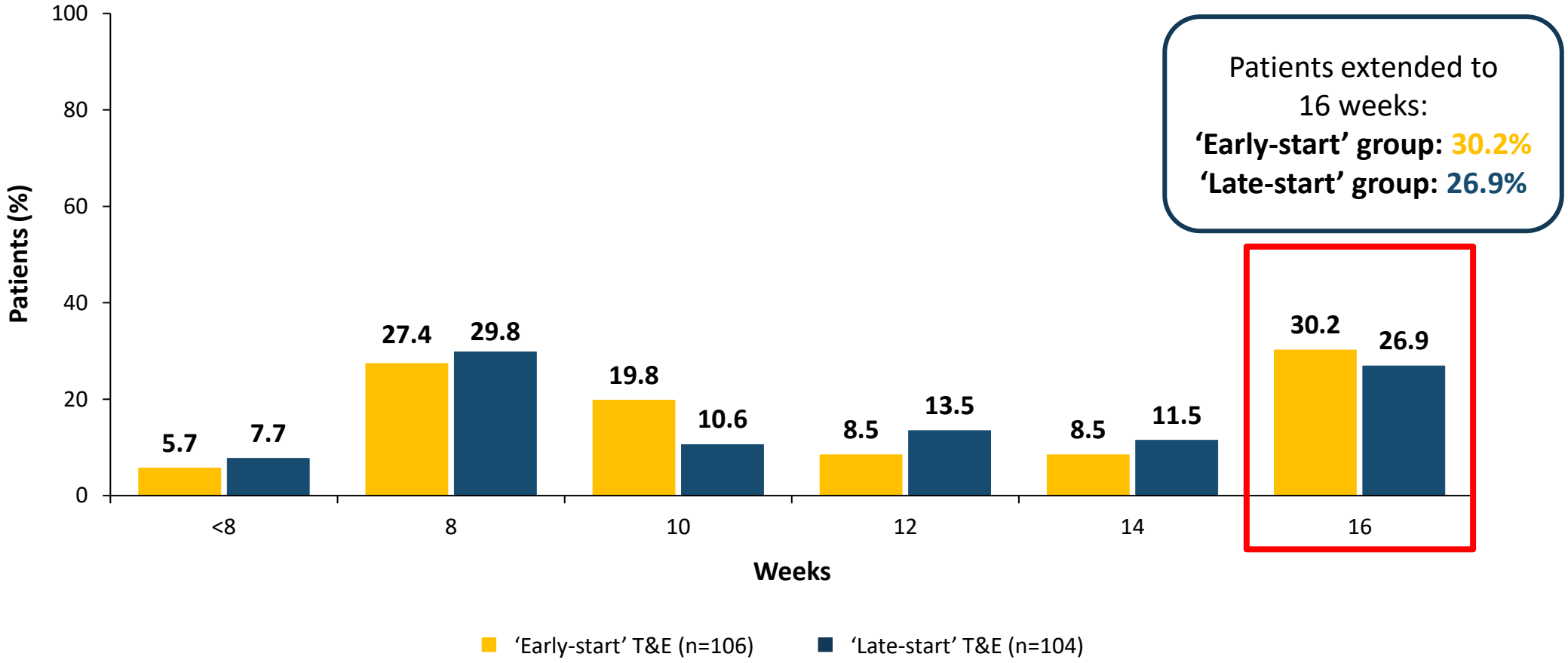


Per-protocol set; last observation carried forward. The per-protocol set included all randomized patients who had completed all scheduled treatment visits from baseline through Week 104.
*The maximum treatment interval was 16 weeks; the decision to adjust the treatment interval was based on the T&E regimen criteria, assessed by OCT.
OCT, optical coherence tomography; T&E, treat-and-extend.
Mitchell P *et al. Retina* 2021; Sep 1;41(9):1911-1920.

By Week 104, approximately 30% of patients in both groups had achieved the maximum interval of 16 weeks

ARIES

Last injection interval at the final visit up to Week 104*



Per-protocol set; last observation carried forward. The per-protocol set included all randomized patients who had completed all scheduled treatment visits from baseline through Week 104.
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ARIES study: Results summary

ARIES

- ARIES demonstrated that a proactive T&E regimen with aflibercept initiated immediately after three loading doses (‘early-start’ T&E) was non-inferior to fixed q8 dosing in Year 1 (‘late-start’ T&E) for mean change in BCVA from Week 16 to Week 104
  - Outcomes were similar in both treatment arms through Week 104, with one injection difference over 2 years
  - Over 90% of patients in both treatment arms maintained vision at Week 104 compared with baseline*
  - Mis-stratification of 23 patients contributed to a slightly greater proportion of low gainers (<8-letter gain) being randomized to the ‘early-start’ T&E arm than to the ‘late-start’ T&E arm;

- By Week 104, approximately half of patients had reached a last treatment interval of ≥12 weeks, and almost one-third of patients had achieved a last treatment interval of 16 weeks this probably accounts for the slight BCVA imbalance observed at Week

Maintenance was defined as loss of <15 ETDRS letters.
BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; q8, every 8 weeks, after 3 initial monthly doses; T&E, treat-and-extend.
Mitchell P *et al*. *Retina* 2021; Sep 1;41(9):1911-1920.