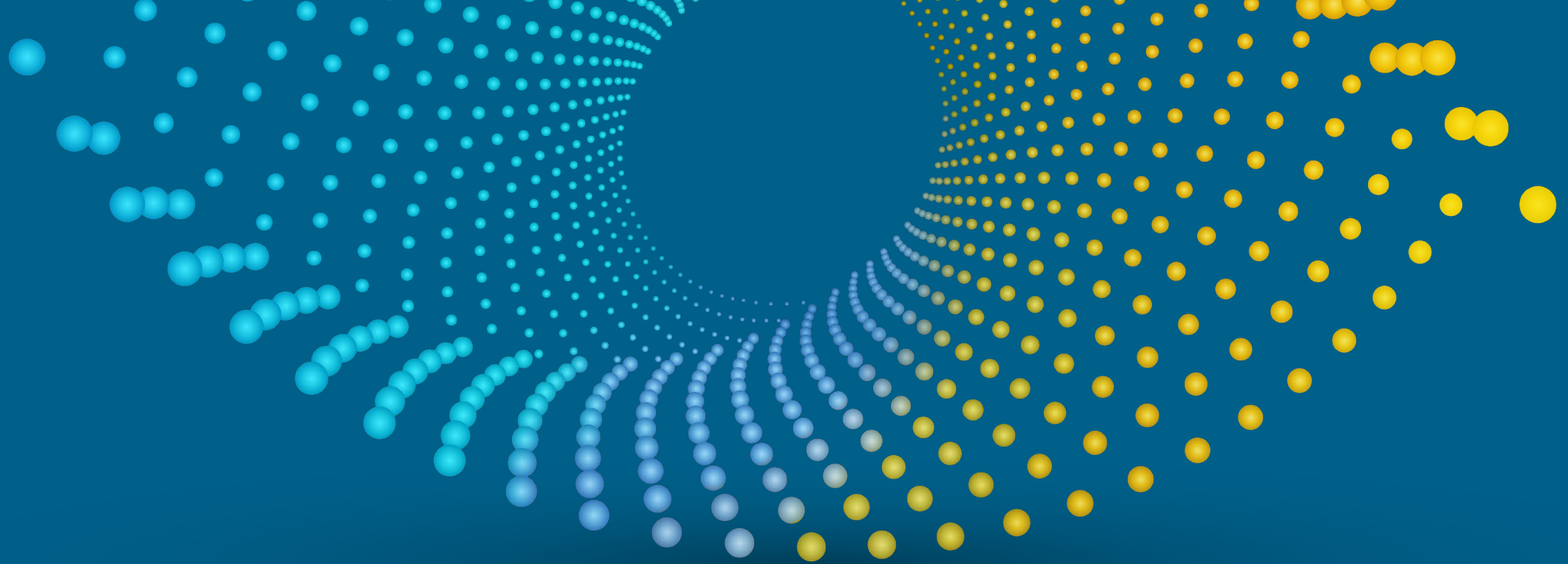

A post hoc analysis of intravitreal aflibercept–treated patients from ARIES and ALTAIR applying treatment regimen criteria from TENAYA & LUCERNE

Michael W. Stewart,[1] Amelie Pielen,[2] Annabelle A. Okada,[3] Paula Scholz,[4] Xin Zhang,[5] Tobias Machewitz,[6] Scott Fitzpatrick[7]

[1]Mayo Clinic College of Medicine and Science, Department of Ophthalmology, Mayo Clinic, Jacksonville, FL, USA; [2]Maximilians-Augenklinik, Nürnberg, Germany, and University Eye Hospital, Hannover Medical School, Hannover, Germany; [3]Kyorin University Faculty of Medicine, Tokyo, Japan; [4]Bayer Vital GmbH, Leverkusen, Germany; [5]Bayer Consumer Care AG, Basel, Switzerland; [6]Bayer AG, Berlin, Germany; [7]Bayer Consumer Care AG, ON, Canada

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1. LaTora LM et al. *Ann Intern Med.* 2022;175:1298–1304.
Part of these data have been presented previously at The Association for Research in Vision and Ophthalmology (ARVO) 2023 Annual Meeting, New Orleans, LA, USA, April 23–27, 2023.

Introduction

Study design can have a direct impact on outcomes, and cross-comparison studies, including those using constructed data, should be conducted with appropriate caveats

Improper cross-trial comparisons should be avoided; however, cross-comparison analyses may provide insights into drug properties and characteristics when direct comparison data are not available

To demonstrate how study design may impact treatment distribution and outcomes, this analysis evaluated the proportion of intravitreal aflibercept-treated patients in **ARIES and ALTAIR** that would have been assigned to fixed ≥q12 treatment intervals **using similar DAA criteria** from TENAYA & LUCERNE, and how this compared to patients' actual intervals at W52

DAA, disease activity assessment; IVT-AFL, intravitreal aflibercept; q, every *x* weeks; W, week.

ARIES and ALTAIR study designs

ARIES and **ALTAIR** were Phase 3b/4 studies in patients with nAMD randomized to receive individualized, flexible, **proactive T&E** regimens of **IVT-AFL 2 mg** following three initial monthly injections[1,2]

ARIES:[1]
At W16, patients were randomized 1:1 to an early start T&E arm (extended by 2 weeks, or an initial 4-week interval with a maximum of 16 weeks) or to a late start T&E arm (IVT-AFL 2q8 until W52 followed by T&E; not examined here due to lack of T&E in the first year).
Treatment interval extension/shortening was based on prespecified criteria reassessed continuously throughout the study at all visits. Extension based on absence of IRF, absence of new neovascularization or hemorrhage, or SRF <50 µm

ALTAIR:[2]
At W16, patients were randomized 1:1 to receive T&E with either 2- or 4-week adjustments.
Treatment interval extension/maintenance/shortening was possible based on prespecified criteria reassessed continuously throughout the study at all visits. Extension based on absence of new/persistent fluid, loss of <4 ETDRS letters from previous visit in conjunction with no recurrent fluid, no increase in CRT ≥100 µm, and no new-onset neovascularization or macular hemorrhage

1. Mitchell P et al. *Retina.* 2021;41:1911–20; **2.** Ohji M et al. *Adv Ther.* 2020;37:1173–87.
2q8, 2 mg IVT-AFL every 8 weeks; CRT, central retinal thickness; ETDRS, Early Treatment of Diabetic Retinopathy Study; IRF, intraretinal fluid; nAMD, neovascular age-related macular degeneration; SRF, subretinal fluid; T&E, treat and extend.

TENAYA & LUCERNE study designs

TENAYA & LUCERNE were Phase 3 trials in patients with nAMD evaluating noninferiority in visual outcomes of 6 mg faricimab vs 2 mg IVT-AFL[1,2]

The patients receiving faricimab received four initial monthly injections, then were **assigned different fixed treatment intervals** until W48 based on a DAA at W20 and W24:

- An increase of >50 µm in central subfield thickness (CST; compared with the average CST) or an increase of ≥75 µm in CST (compared with the lowest CST value) at either of the previous two scheduled visits
- A decrease of ≥5 best-corrected visual acuity (BCVA) letters (compared with the average BCVA) or a decrease of 10 BCVA letters (compared with the highest BCVA) at either of the previous two scheduled visits
- Presence of new macular hemorrhage or presence of significant nAMD activity that does not meet any of these criteria

1. Khanani AM et al. *Ophthalmol Sci*. 2021;17:10076; **2.** Heier JS et al. *Lancet*. 2022;399:729–40.

DAA protocol for ARIES and ALTAIR data in this analysis

A DAA was applied to IVT-AFL–treated patients from ARIES and ALTAIR using similar criteria to that from TENAYA & LUCERNE

This DAA was performed 8 weeks after the three initial monthly injections (i.e. at W16)

The different number of initial monthly injections between studies could not be accounted for in this analysis[a]

This analysis does not attempt to, and cannot, predict what a patient's BCVA might have been within this scenario

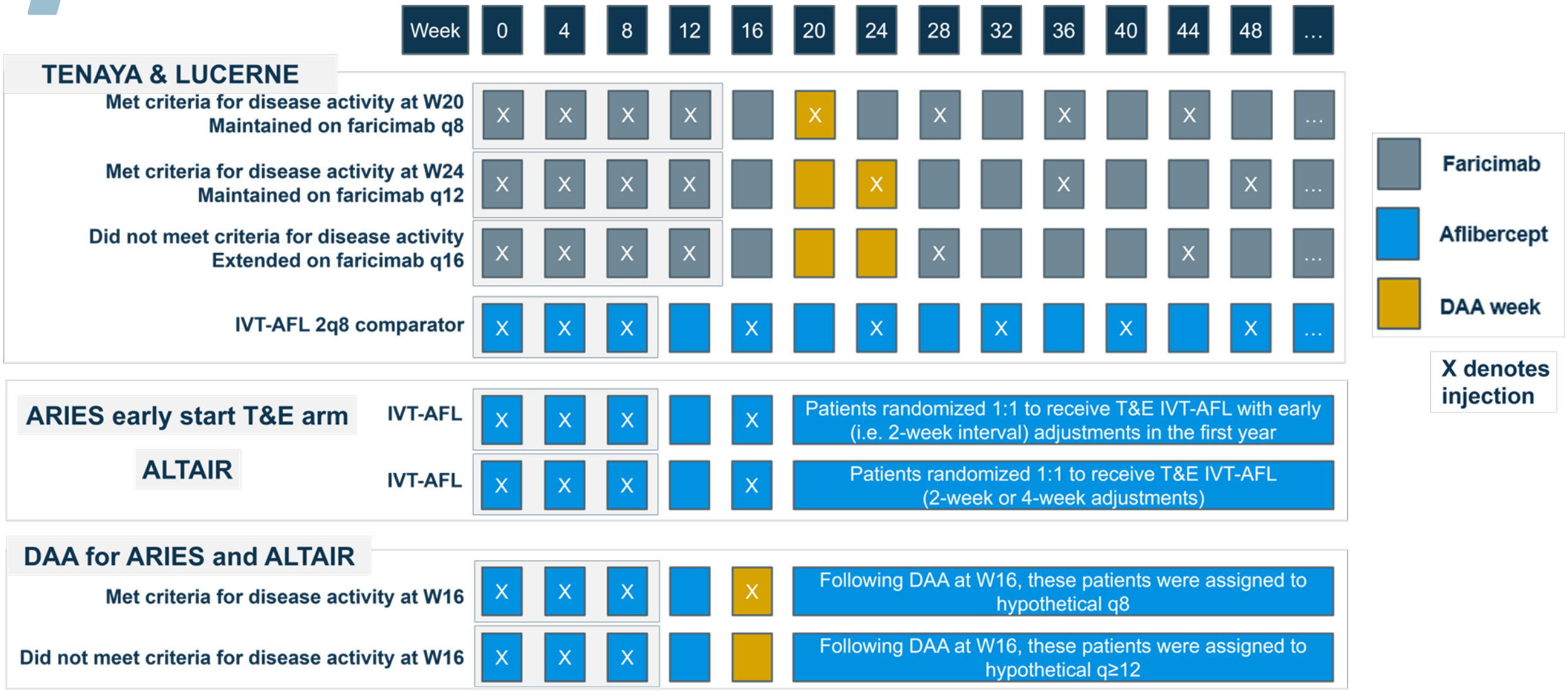
DAA per modified TENAYA & LUCERNE criteria. Disease activity "YES" at W16 if:

- Decrease of ≥5 BCVA letters from W8 to W16
- Increase of >50 µm in CRT from W8 to W16

Disease activity at W16:
If yes = assigned to hypothetical q8
If no = assigned to hypothetical ≥q12

[a]Due to differences in study design, this hypothetical analysis was limited to being able to assign patients from ARIES and ALTAIR to either q8 or ≥q12.

Comparison of treatment regimen protocols



Initial monthly injections highlighted (four for faricimab, three for aflibercept)
"X" denotes an injection; gold boxes denote a DAA (real for the faricimab arms from TENAYA & LUCERNE; and applied to ARIES and ALTAIR data to generate hypothetical assignment).

Baseline demographic and disease characteristics

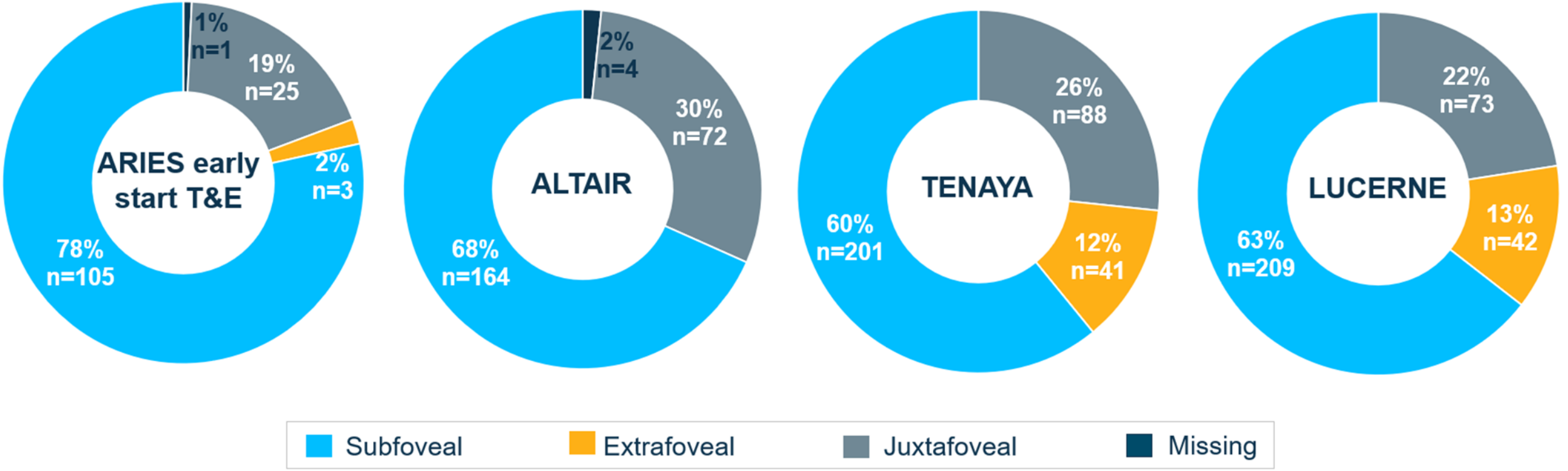
A total of 134 patients from the ARIES early start T&E and 240 patients from ALTAIR were included in this analysis. Differences in inclusion criteria (including CNV lesion size ≤9 disc areas in TENAYA & LUCERNE vs ≤12 disc areas in ARIES and ALTAIR) resulted in different patient populations between studies

	ARIES early start T&E (n=134)		ALTAIR (n=240)		TENAYA (n=334)[a]	LUCERNE (n=331)[a]
Disease activity at W16?	**Yes**	**No**	**Yes**	**No**		
n	36	98	45	195	334	331
Baseline BCVA score, mean (SD), ETDRS letters	61.3 (10.9)	60.6 (12.4)	53.1 (10.2)	55.4 (13.2)	61.3 (12.5)	58.7 (14.0)
Baseline CNV lesion size, mean (SD), mm^2	5.6 (4.3)	4.9 (4.2)	–	–	4.7 (4.8)	4.7 (4.7)
Baseline CRT,[b] mean (SD), µm	482 (131)	456 (131)	382 (139)	378 (140)	361 (124)	353 (120)

Six patients in ALTAIR were unable to be assigned hypothetical treatment intervals due to missing measurements.
[a]Intention-to-treat data (i.e. actual baseline) reported for TENAYA & LUCERNE; [b]CST for TENAYA & LUCERNE. CNV, choroidal neovascularization.

CNV location

At baseline, there were numerically fewer patients with subfoveal lesions and numerically more patients with extrafoveal lesions in TENAYA & LUCERNE compared with ARIES and ALTAIR[a]



Central assessment for TENAYA and LUCERNE, investigator assessment for ARIES and ALTAIR. [a]In TENAYA & LUCERNE, Subfoveal, juxtafoveal, or extrafoveal CNV lesions were included as long as a subfoveal component related to CNV activity was identified on fundus fluorescein angiography or optical coherence tomography.

ARIES and ALTAIR, and TENAYA & LUCERNE real study outcomes

ARIES and ALTAIR

- Continuous assessment of patients on T&E regimens led to an **actual last treatment interval** at W52 of:
  - ≥q12 for 31% of patients in ARIES early start T&E arm
  - ≥q12 for 48% of patients in ALTAIR
  - ≥q16 for 21% of patients in ALTAIR

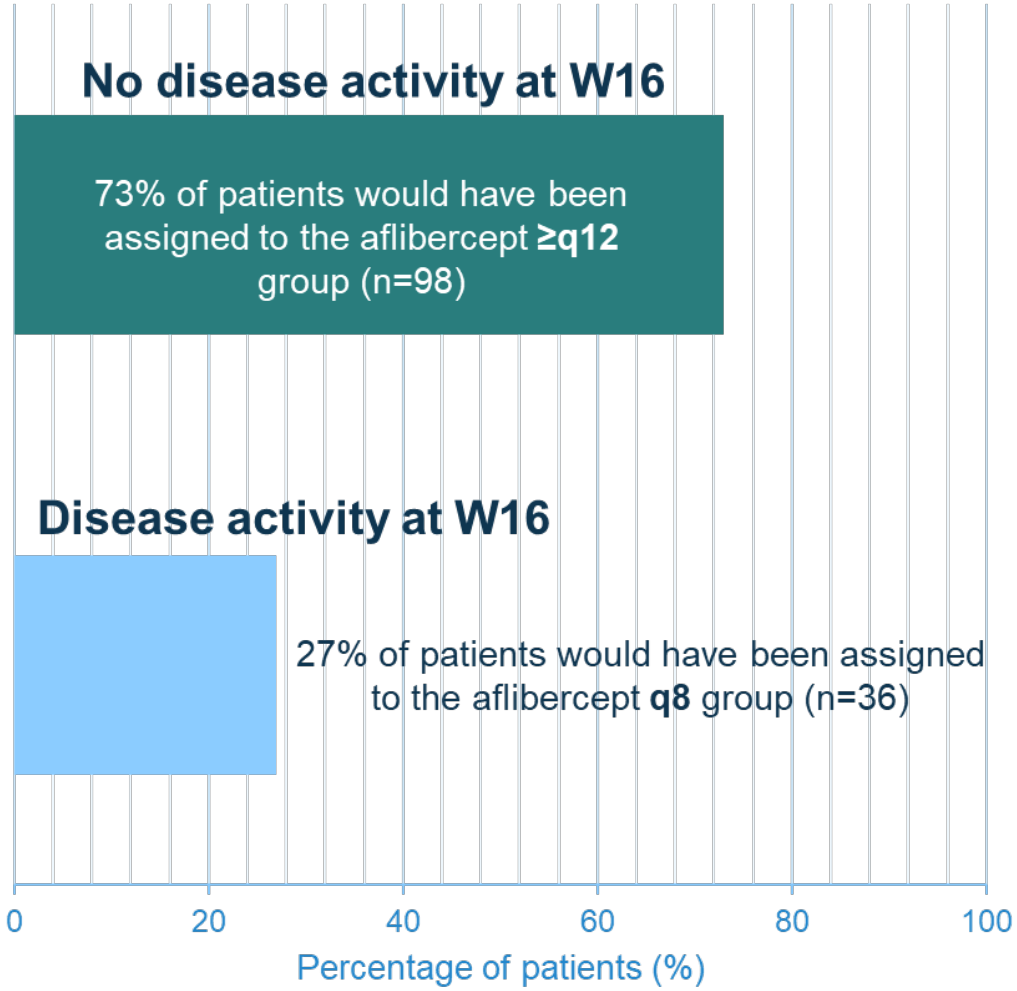
TENAYA & LUCERNE

- At W20 (8 weeks after the last monthly injection):
  - 20–22% of patients met the criteria for disease activity and were maintained on 6q8
- At W24 (12 weeks after the last monthly injection):
  - 33–34% of patients met the criteria for disease activity and were maintained on 6q12
  - 45–46% of patients without disease activity were extended to 6q16

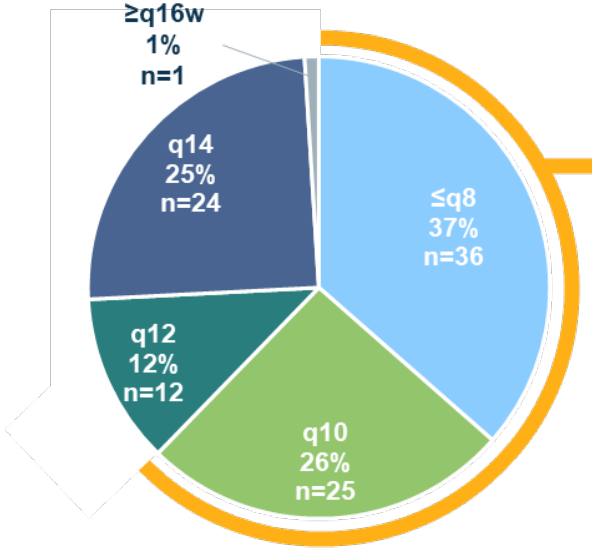
6q8, 6 mg faricimab every 8 weeks; 6q12, 6 mg faricimab every 12 weeks.

ARIES: Actual last treatment interval up to W52 by W16 DAA

Hypothetical treatment interval by W16 DAA

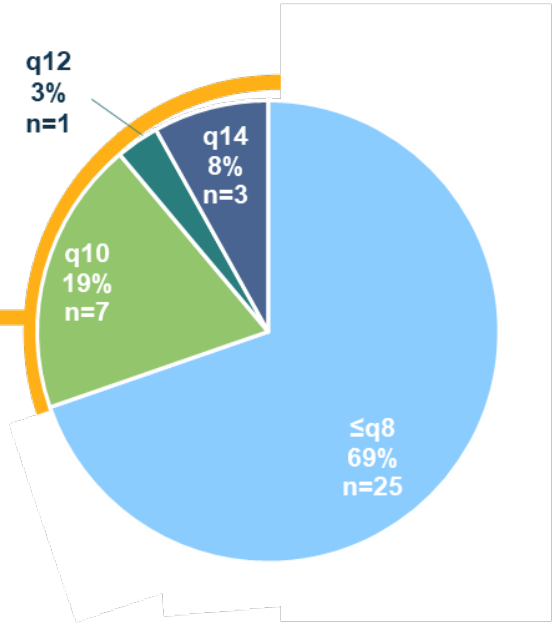


Actual last treatment interval at W52 (by W16 DAA)



These patients (**62%, 61/98**) would have received **fewer** injections if assigned to the hypothetical ≥q12 treatment interval compared with their actual last treatment interval

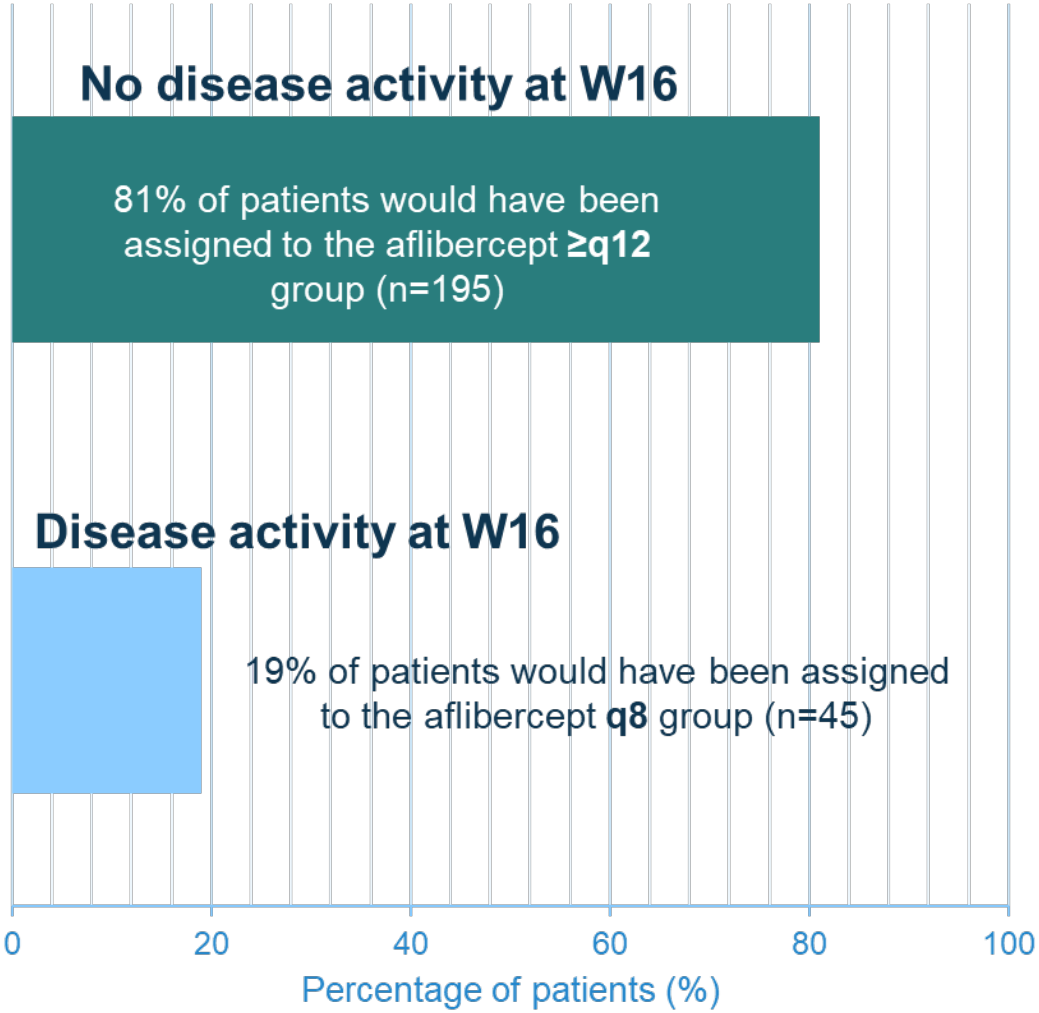
These patients (**31%, 11/36**) would have received **more** injections if assigned to the hypothetical q8 treatment interval compared with the actual last treatment interval



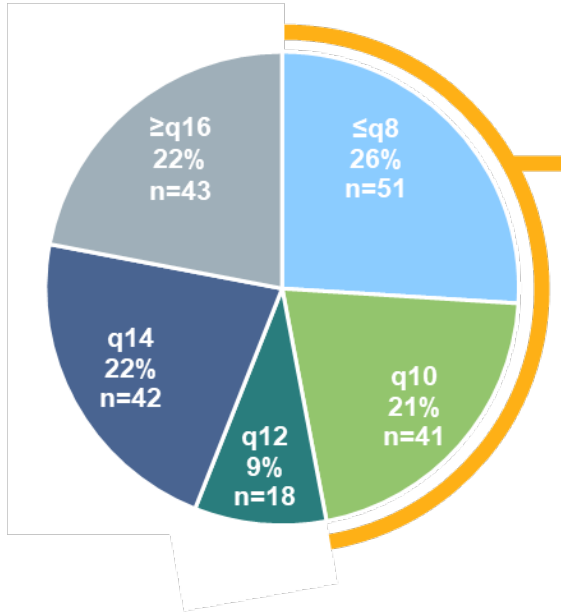
ARIES early start T&E arm. In the pie charts, n=98 and n=36 for no disease activity at W16 and disease activity at W16, respectively.

ALTAIR: Actual last treatment intervals up to W52 by W16 DAA

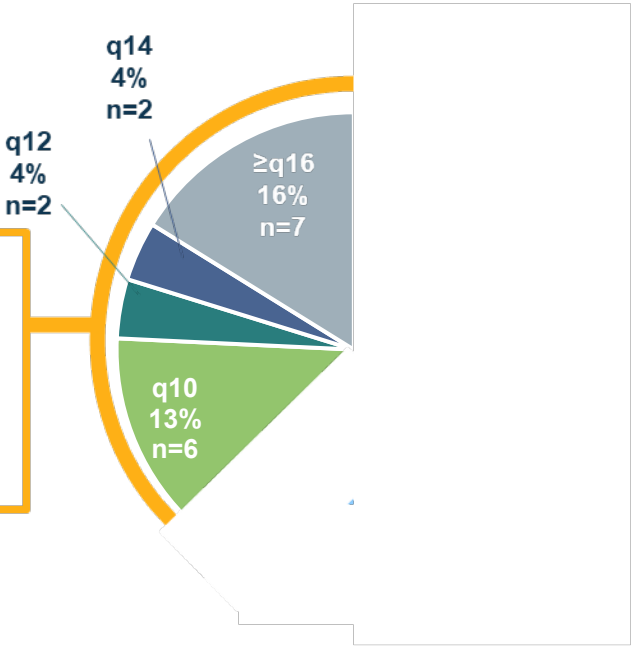
Hypothetical treatment interval by W16 DAA



Actual last treatment interval at W52 (by W16 DAA)



These patients (**47%, 92/195**) would have received **fewer** injections if assigned to the hypothetical ≥q12 treatment interval compared with their actual last treatment interval



These patients (**38%, 17/45**) would have received **more** injections if assigned to the hypothetical q8 treatment interval compared with the actual last treatment interval

In the pie charts, n=195 and n=45 for no disease activity at W16 and disease activity at W16, respectively.

Conclusions

Applying similar DAA criteria from TENAYA & LUCERNE to fix treatment intervals at early assessment**, a high proportion (73–81%) of patients in the T&E ARIES and ALTAIR studies would have been assigned a ≥q12 treatment interval** to W52 (comparable to 78–80% of patients in TENAYA & LUCERNE with the same treatment interval to W48)

These were **higher** than the actual proportion of patients from ARIES and ALTAIR with **real last injection intervals of ≥q12** following continuous assessment at W52

Applying the DAA to assign patients in ARIES and ALTAIR to hypothetical treatment intervals would have resulted in a **greater proportion of patients on ≥q12 intervals**, but a number of patients may have been undertreated if assigned to a fixed treatment interval for the first year of the study based on a W16 assessment

These hypothetical data provide **educational information** outlining the potential **impact of study design** on treatment distribution

The **validity of this model is limited** by cross-comparing trials, and differences in patient populations (baseline characteristics) and inclusion criteria (CNV lesion size)

It is **not possible** to know how these treatment interval extensions may have impacted visual outcomes – **no analyses can predict a patient's visual outcomes within a hypothetical scenario**

Continuous monitoring of functional and anatomic criteria, and flexible, personalized T&E regimens can allow refinement of a treatment interval by a physician to meet a patient's individual needs

A **prospective T&E direct comparison trial** could provide more information