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

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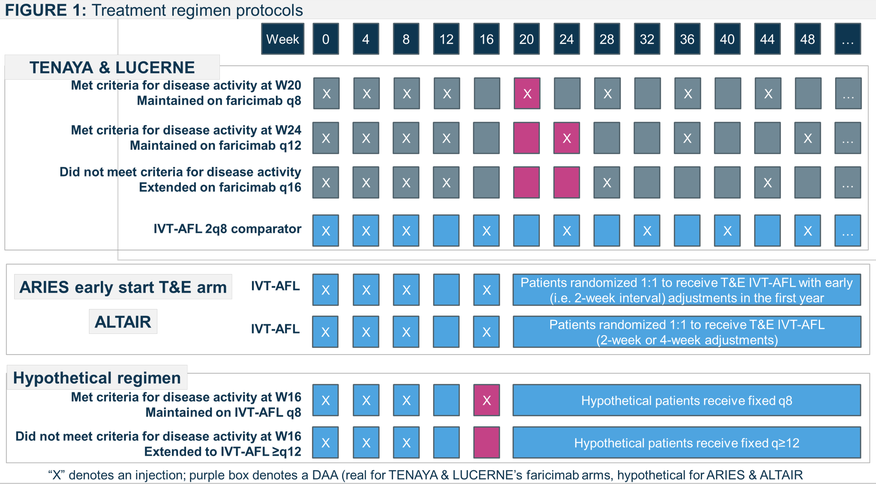
INTRODUCTION

- Study design has a direct impact on outcomes, and cross-comparison studies, including those using hypothetical data, should be conducted with appropriate protocol. Improper cross-trial comparisons should be avoided; different randomization criteria, and differences in baseline populations and methodology can lead to inaccurate comparisons and have limited meaningful implications on clinical practice
- However, cross-comparison analyses may provide insights between drug properties and characteristics when direct comparison data is not yet available
  - ARIES and ALTAIR were Phase 3b/4 studies in patients with nAMD randomized to receive individualized, flexible, proactive treat-and-extend (T&E) regimens of 2 mg aflibercept following 3 initial monthly injections.[1,2] Treatment intervals could be modified based on prespecified criteria reassessed continuously throughout the study at all visits:
    - ARIES: At Week 16, patients were randomized 1:1 to an early-start T&E regimen (extended by 2 weeks or an initial 4-week interval with max of 16 weeks) or late-start T&E arm (IVT-AFL 2q8 until Week 52 followed by T&E; not examined here due to lack of T&E in the first year). Treatment interval extension based on: Absence of IRF, absence of new neovascularisation or hemorrhage, or SRF <50 µm
    - ALTAIR: At Week 16, patients were randomized 1:1 to receive T&E with either 2 or 4-week adjustments. Treatment interval extension/maintenance based on: Absence of new/persistent fluid, loss of <4 EDTRS letters from previous visit in conjunction with no recurrent fluid, no increase in CRT ≥100 µm, and no new-onset neovascularization or macular hemorrhage
  - TENAYA & LUCERNE were Phase 3 trials in patients with nAMD evaluating noninferiority of 6 mg faricimab vs 2 mg IVT-AFL[3,4]
    - The faricimab group received 4 initial monthly injections, then were assigned different fixed treatment intervals until Week (W) 48 based on a disease activity assessment (DAA) at W20 and W24 (**Figure 1**):
      - An increase of >50 µm central subfield thickness (CST) (compared with the average CST) or an increase of ≥75 µm CST (compared with the lowest CST value) at either of the previous 2 scheduled visits
      - Decrease of ≥5 best corrected visual acuity (BCVA) letters (compared with average BCVA) or a decrease of 10 BCVA letters (compared to highest BCVA) at either of the previous 2 scheduled visits
      - Presence of new macular hemorrhage or presence of significant nAMD activity that does not meet any of these criteria
    - Results of DAA:
      - At W20 (8 weeks after the last monthly injection), 20.3–22.2% of patients met the criteria for disease activity and were maintained on 6q8
      - At W24 (12 weeks after the last monthly injection), 32.9–34.0% of patients met the criteria for disease activity and were maintained on 6q12; 44.9–45.7% of patients without disease activity were extended to 6q16
- To demonstrate how study design affects treatment distribution and outcomes, this analysis evaluated the proportion of IVT-AFL-treated patients in ARIES & ALTAIR that would **hypothetically** be assigned to fixed ≥q12 treatment intervals using similar DAA criteria from TENAYA & LUCERNE, and how this compared to their actual intervals at W52

METHODS

FIGURE 1: Treatment regimen protocols



"X" denotes an injection; purple box denotes a DAA (real for TENAYA & LUCERNE's faricimab arms, hypothetical for ARIES & ALTAIR

METHODS (continued)

- A hypothetical DAA was applied to IVT-AFL–treated patients from ARIES & ALTAIR using similar criteria from TENAYA & LUCERNE, including performing this hypothetical DAA 8 weeks after the 3 initial monthly injections, at W16 (**Figure 1**)
  - It was not possible to fully match the conditions in TENAYA & LUCERNE due to important differences in the studies, including the number and timing of initial monthly injections, and the period without injections post-loading (meaning hypothetical assignment in this analysis was limited to either q8 or ≥q12)

❑ DAA per modified TENAYA & LUCERNE criteria. Disease activity 'Yes' at W16 if:
- Decrease of ≥5 BCVA letters from W8 to W16
- Increase of >50µm in CRT from W8 to W16

- This analysis does not attempt to, and cannot, predict the patient's BCVA within this hypothetical scenario

RESULTS

Patient disposition

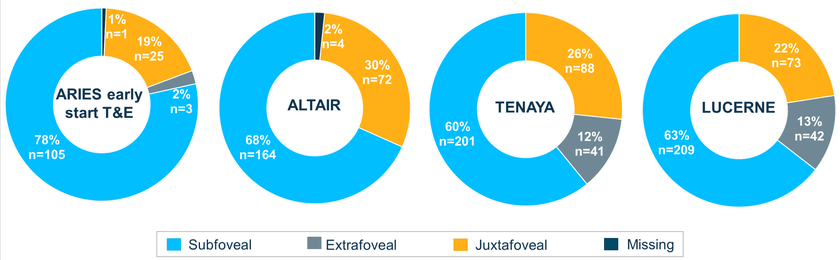
- A total of 134 patients from the early start T&E arm of ARIES and 240 patients from ALTAIR were included in the hypothetical treatment regimen analysis (**Table 1**)
- Differences in inclusion criteria (including CNV lesion size ≤9 disc areas in TENAYA & LUCERNE vs. ≤12 disc areas in ARIES & ALTAIR) resulted in different patient populations between studies
  - At baseline, there were generally fewer patients with subfoveal lesions in TENAYA & LUCERNE compared with ARIES & ALTAIR (**Figure 2**)

TABLE 1: Patient baseline demographics and disease characteristics

	ARIES early start T&E		ALTAIR		TENAYA	LUCERNE
Hypothetical disease activity at W16?	**Yes**	**No**	**Yes**	**No**	[a]	[a]
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)
CNV lesion size, mean (SD), mm²	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)

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

FIGURE 2: CNV location[a]



[a]Central assessment for TENAYA and LUCERNE, investigator assessment for ARIES and ALTAIR. Six patients in ALTAIR were unable to be assigned hypothetical treatment intervals due to missing measurements. BCVA, best corrected visual acuity; CNV, choroidal neovascularization; CRT, central retinal thickness; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; T&E, treat and extend.

Real study outcomes

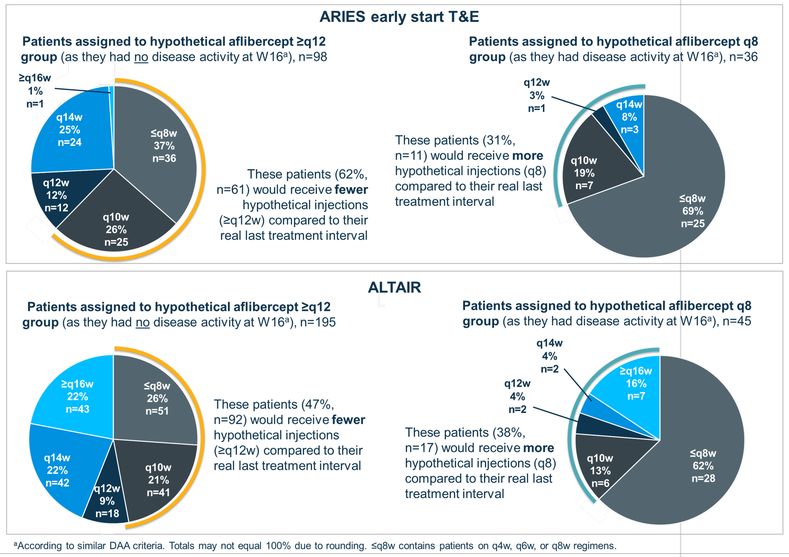
- Continuous assessment of patients on T&E regimens led to a real last treatment interval at W52 of ≥q12 for 31% of ARIES early start T&E patients; and ≥q12 for 48%, and ≥q16 for 21% of ALTAIR patients

Hypothetical outcomes applying TENAYA & LUCERNE similar DAA criteria

- **In total, 73%** (n=98) of patients in ARIES (early start T&E) and **81%** (n=195) of patients in ALTAIR (**Table 1**) had no disease activity at W16 (according to similar DAA criteria) and would have been assigned to treatment intervals of ≥q12. **Figure 3** demonstrates the differences between the real, and the hypothetical, treatment regimens

RESULTS (continued)

FIGURE 3: Real last treatment intervals up to W52 by hypothetical treatment interval assignment



[a]According to similar DAA criteria. Totals may not equal 100% due to rounding. ≤q8w contains patients on q4w, q6w, or q8w regimens.

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 & 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)
  - This was higher than the actual proportion of these ARIES & ALTAIR patients with real last injection intervals of ≥q12 following continuous assessment at W52 (38–49%)
  - This hypothetical treatment regimen would have resulted in a greater proportion of patients on ≥q12 intervals, but a number of patients in ARIES & ALTAIR may have been undertreated if assigned a fixed treatment regimen based on an early assessment until the end of the study
- Continuous monitoring and flexible, personalized T&E regimens can allow refining of the treatment interval by the physician to meet a patient's individual needs
- 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 and inclusion criteria, including how TENAYA & LUCERNE excluded patients with a CNV lesion size greater than 9 DA, whereas ARIES & ALTAIR allowed up to 12 DA
  - It is not possible to know how these hypothetical treatment interval extensions would have impacted visual outcomes – no analyses can predict a patient's visual outcomes within a hypothetical scenario
- A prospective, direct comparison trial using a T&E strategy would provide more information.

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