An Assessment of the Impact of Disease Activity Criteria on Dosing Interval Assignment in Clinical Trial Patients With nAMD

Faruque Ghanchi, MBBS, MS, MML, FRCS, FRCOphth[1]; Christina Y. Weng, MD, MBA[2]; Audrey Souverain, PharmD, MSc[3]; Ivaylo Stoilov, MD[4]; and Philippe Margaron, PhD[3]

[1] Bradford Teaching Hospitals NHS Foundation Trust and Bradford Ophthalmology Research Network, Bradford, UK; [2] Baylor College of Medicine, Cullen Eye Institute, Houston, TX, USA; [3] F. Hoffmann-La Roche Ltd., Basel, Switzerland; [4] Genentech, Inc., South San Francisco, CA, USA

Purpose

To evaluate the effect of applying different disease activity criteria on dosing interval assignment using data from the phase 3 TENAYA and LUCERNE faricimab trials, and data from the phase 2 CANDELA and phase 3 PULSAR aflibercept trials

Background

- Clinical treatment decisions for patients with neovascular age-related macular degeneration (nAMD) are based on disease activity
- Recent guidance[1] defines nAMD disease activity as:
  - Loss of ≥ 5 letters due to disease activity **OR**
  - Increased disease activity on optical coherence tomography **OR**
  - Macular haemorrhage **OR**
  - Subretinal hyperreflective material
- In clinical trials, disease activity criteria guide dosing regimen allocation and dosing interval adjustment
  - Differences in criteria between trials along with different study designs complicate the comparison of durability outcomes
- Faricimab, a dual angiopoietin-2/vascular endothelial growth factor−A inhibitor, maintained vision and had extended treatment durability and fewer injections vs aflibercept through 2 years in the TENAYA/LUCERNE nAMD trials

Conclusions

In TENAYA/LUCERNE, determination of active disease at weeks 20 and 24 was made based on central subfield thickness (CST) changes OR best-corrected visual acuity (BCVA) changes OR presence of new macular haemorrhage

- Among patients who met the disease activity criteria at week 20, the most commonly met criteria were related to CST changes

In TENAYA/LUCERNE, application of vision AND anatomical criteria would have theoretically resulted in almost all patients being assigned to faricimab every ≥ 12-week dosing at week 20 vs vision OR anatomical criteria

Attention should be paid to which criteria best reflect real-world clinical practice to understand the likelihood of trial results translating to treatment burden reductions

Application of disease activity criteria in clinical trials can have a significant effect on dosing interval adjustment/determination

References

1. Bailey C et al. *Eye (Lond)*. 2022:1-6.
2. Khanani AM et al. *Ophthalmol Sci*. 2021;1(4):100076.
3. Wykoff CC et al. *JAMA Ophthalmol*. 2023;141:834-842.
4. Lanzetta P et al. *Lancet*. 2024;403:1141-1152.

Financial Disclosures

- FG: Consultant: Alimera, Boehringer Ingelheim, Roche; Lecture Fees: Allergan, Heidleberg, Roche
- CYW: Consultant: Alcon, Alimera, Allergan/AbbVie, Dutch Ophthalmic Research Center, Genentech, Inc., Novartis, Opthea, Regeneron, Regenxbio; Research Support: Alimera, Applied Genetic Technologies Corporation, DRCR.net
- AS, PM: Employee: F. Hoffmann-La Roche Ltd.
- IS: Employee: Genentech, Inc.

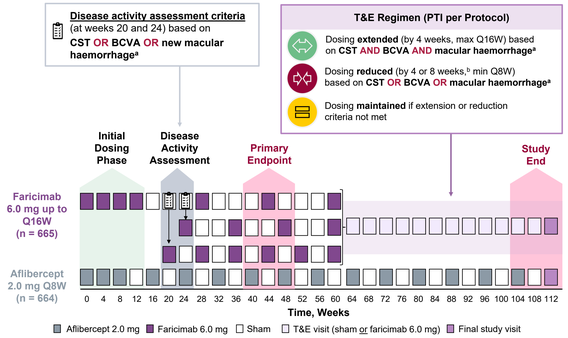
Study and Product Disclosures

- In the UK, faricimab is approved for the treatment of neovascular age-related macular degeneration and diabetic macular oedema. Faricimab is not currently approved for use outside these indications in the UK
- This study includes research conducted on human subjects
- Institutional Review Board approval was obtained prior to study initiation
- Funding was provided by F. Hoffmann-La Roche Ltd, for the study and third-party writing assistance, which was provided by Luke Carey, PhD, CMPP, of Envision Pharma Group
- Roche conducted a factual accuracy check on the final article but any decision to incorporate comments was made solely at the discretion of the authors

Presented at the Royal College of Ophthalmologists Annual Congress
Belfast, UK | 20–23 May 2024

Methods/Results

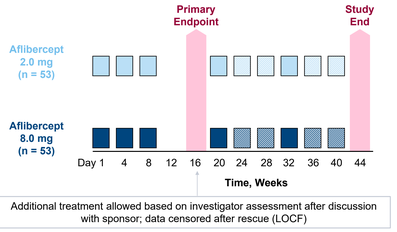
1. TENAYA and LUCERNE[2] Trial Design (Faricimab vs Aflibercept)



T&E regimen in TENAYA (NCT03823287) and LUCERNE (NCT03823300) uses different criteria than those used in the YOSEMITE and RHINE clinical trials. [a] Per the investigator. [b] If ≥ 2 of the reduction criteria were met or 1 criterion included new macular haemorrhage, the interval was reduced to an 8-week interval. BCVA, best-corrected visual acuity; CST, central subfield thickness; max, maximum; min, minimum; PTI, personalised treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

2. CANDELA[3] Phase 2 Trial Design (Aflibercept 2.0 mg vs 8.0 mg)

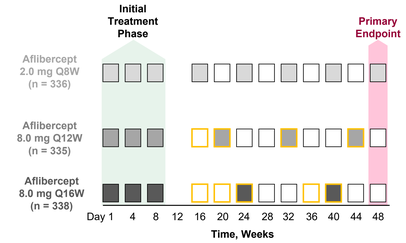
PRN Dosing Criteria[a]
To receive a PRN dose at weeks 24, 28, 36 or 40 patients had to meet either of the following criteria:
BCVA OR anatomical findings considered vision threatening



CANDELA (NCT04126317). [a] Assessed by the study investigator. BCVA, best-corrected visual acuity; LOCF, last observation carried forward; PRN, pro re nata.

3. PULSAR[4] Phase 3 Trial Design (Aflibercept 2.0 mg vs 8.0 mg)

DRM criteria for shortening dosing interval[a]
BCVA AND CRT or new onset foveal neovascularisation or foveal haemorrhage



DRM in year 1
Weeks 16 and 20: Patients on Q12W and Q16W meeting DRM criteria shortened to Q8W

Week 24: Patients on Q16W meeting DRM criteria shortened to Q12W

Weeks 32 and 44 for Q12W and weeks 36[b] and 40 for Q16W: Treatment interval shortened by 4 weeks for patients meeting DRM criteria

Intervals can only be shortened. Minimum interval for all patients was Q8W.

PULSAR (NCT04423718). Note: schematic does not reflect all dosing options once a patient's dosing interval is shortened. [a] All assessments vs week 12. [b] At week 36, patients on Q16W who were previously shortened to Q12W could have been shortened to Q8W. BCVA, best-corrected visual acuity; CRT, central retinal thickness; DRM, dose regimen modification; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks.

4. TENAYA and LUCERNE Disease Activity Criteria: Faricimab nAMD Trials Use Disease Criteria Reflective of Clinical Practice

TENAYA/LUCERNE Disease Activity Criteria
(Active Disease if ***ANY*** Are Met)

- **BCVA loss**
  ≥ 5 letters vs average BCVA over previous 2 scheduled visits **OR**
  ≥ 10 letters vs highest BCVA recorded over previous 2 scheduled visits
  OR
- **CST increase**
  > 50 µm vs average CST over previous 2 scheduled visits **OR**
  ≥ 75 µm vs lowest CST recorded at either of previous 2 scheduled visits
  OR
- **New macular haemorrhage**
  per the investigator and attributable to nAMD

Hypothetical Disease Activity Criteria Based on PULSAR DRM Criteria
(Active Disease if ***BOTH*** Are Met)

- **BCVA loss**
  > 5 letters vs week 16 BCVA
  AND
- **CST increase**
  > 25 µm vs week 16
  OR
  New macular haemorrhage

BCVA, best-corrected visual acuity; CST, central subfield thickness; DRM, dose regimen modification; nAMD, neovascular age-related macular degeneration.

5. CANDELA Disease Activity Criteria

CANDELA PRN Dosing Criteria[a]
(Active Disease if ***ANY*** Are Met)

- **BCVA loss**
  ≥ 5 letters from week 20 due to disease progression
  OR
- **Anatomical findings considered vision threatening**
  (such as worsening or persistent retinal fluid, new or worsening retinal PED, new or persistent haemorrhage, etc.)

[a] Assessed by the study investigator. BCVA, best-corrected visual acuity; PED, pigment epithelial detachment; PRN, pro re nata.

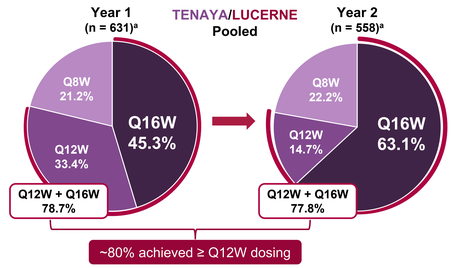
6. PULSAR Disease Activity Criteria

PULSAR DRM Criteria
(Active Disease if ***BOTH*** Are Met)

- **BCVA loss**
  > 5 letters from week 12 due to persistent or worsening AMD
  AND
- **CRT increase**
  > 25 µm from week 12
  OR
  New onset foveal neovascularisation or foveal haemorrhage

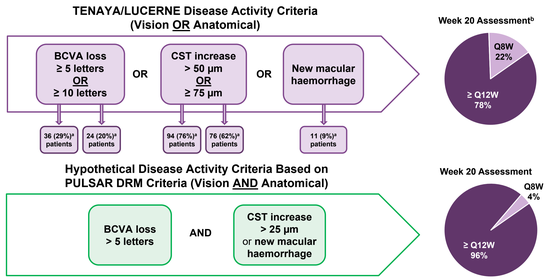
AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CRT, central retinal thickness; DRM, dose regimen modification.

7. TENAYA and LUCERNE Disease Activity Criteria: ~80% of Faricimab-Treated Patients Achieved ≥ Q12W Dosing at the End of the Second Year



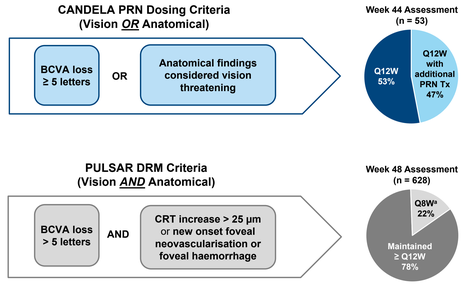
T&E dosing in year 2 allowed more patients to achieve Q16W dosing. [a] Percentages are based on number of patients randomised to the faricimab arm who have not discontinued the study at that visit. Treatment interval at a given visit is defined as the treatment interval decision followed at that visit. Interval at year 2 is calculated using data recorded at week 108. Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks.

8. If Meeting Both Vision AND Anatomical Criteria Had Been Required to Define Active Disease, 96% of Faricimab-Treated Patients in TENAYA and LUCERNE Would Have Been Assigned to ≥ Q12W Dosing at Week 20



This analysis is not intended as a cross-trial comparison and cannot predict whether faricimab-treated patients in TENAYA and LUCERNE would have achieved non-inferiority vs aflibercept 2.0 mg if the treatment regimen had been modified. [a] Proportion based on the number of patients who attended the week 20 visit and had any positive disease activity at week 20 (n = 123). Disease activity criteria are not mutually exclusive (a patient can meet ≥ 1 disease activity criteria). [b] Additional patients with missing week 20 assessments were considered to have met the disease activity criteria and were treated Q8W. BCVA, best-corrected visual acuity; CST, central subfield thickness; DRM, dose regimen modification; Q8W, every 8 weeks; Q12W, every 12 weeks.

9. Proportion of Aflibercept 8.0 mg Patients Achieving ≥ Q12W Dosing Differs Based on PULSAR vs CANDELA Criteria



Cross-trial comparisons are limited by differences in trial design. [a] Patients shortened based on dose regimen modification assessments at some point through week 48. BCVA, best-corrected visual acuity; CRT, central retinal thickness; DRM, dose regimen modification; PRN, pro re nata; Q8W, every 8 weeks; Q12W, every 12 weeks; Tx, treatment.

Faricimab Was Well Tolerated Through Year 2, With a Safety Profile Comparable to Aflibercept