Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials

*Jeffrey S Heier, Arshad M Khanani, Carlos Quezada Ruiz, Karen Basu, Philip J Ferrone, Christopher Brittain, Marta S Figueroa, Hugh Lin, Frank G Holz, Vaibhavi Patel, Timothy Y Y Lai, David Silverman, Carl Regillo, Balakumar Swaminathan, Francesco Viola, Chui Ming Gemmy Cheung, Tien Y Wong, on behalf of the TENAYA and LUCERNE Investigators**

Summary

Background Faricimab is a bispecific antibody that acts through dual inhibition of both angiopoietin-2 and vascular endothelial growth factor A. We report primary results of two phase 3 trials evaluating intravitreal faricimab with extension up to every 16 weeks for neovascular age-related macular degeneration (nAMD).

Methods TENAYA and LUCERNE were randomised, double-masked, non-inferiority trials across 271 sites worldwide. Treatment-naive patients with nAMD aged 50 years or older were randomly assigned (1:1) to intravitreal faricimab 6·0 mg up to every 16 weeks, based on protocol-defined disease activity assessments at weeks 20 and 24, or aflibercept 2·0 mg every 8 weeks. Randomisation was performed through an interactive voice or web-based response system using a stratified permuted block randomisation method. Patients, investigators, those assessing outcomes, and the funder were masked to group assignments. The primary endpoint was mean change in best-corrected visual acuity (BCVA) from baseline averaged over weeks 40, 44, and 48 (prespecified non-inferiority margin of four letters), in the intention-to-treat population. Safety analyses included patients who received at least one dose of study treatment. These trials are registered with ClinicalTrials.gov (TENAYA NCT03823287 and LUCERNE NCT03823300).

Findings Across the two trials, 1329 patients were randomly assigned between Feb 19 and Nov 19, 2019 (TENAYA n=334 faricimab and n=337 aflibercept), and between March 11 and Nov 1, 2019 (LUCERNE n=331 faricimab and n=327 aflibercept). BCVA change from baseline with faricimab was non-inferior to aflibercept in both TENAYA (adjusted mean change 5·8 letters [95% CI 4·6 to 7·1] and 5·1 letters [3·9 to 6·4]; treatment difference 0·7 letters [–1·1 to 2·5]) and LUCERNE (6·6 letters [5·3 to 7·8] and 6·6 letters [5·3 to 7·8]; treatment difference 0·0 letters [–1·7 to 1·8]). Rates of ocular adverse events were comparable between faricimab and aflibercept (TENAYA n=121 [36·3%] *vs* n=128 [38·1%], and LUCERNE n=133 [40·2%] *vs* n=118 [36·2%]).

Interpretation Visual benefits with faricimab given at up to 16-week intervals demonstrates its potential to meaningfully extend the time between treatments with sustained efficacy, thereby reducing treatment burden in patients with nAMD.

Funding F Hoffmann-La Roche.

Introduction

Neovascular age-related macular degeneration (nAMD) remains a leading cause of blindness in adults aged 60 years and older worldwide.[1] Introduction of intravitreal anti-vascular endothelial growth factor (VEGF) therapies has dramatically improved visual outcomes in patients with nAMD.[1,2] Pivotal trials of anti-VEGF treatments in nAMD assessing intravitreal injections administered at 4-week to 12-week intervals have demonstrated meaningful improvements in vision.[3–5] However, these early vision gains are often not maintained long term in real-world clinical practice,[6–8] largely because of under-treatment associated with the burden of frequent monitoring visits and intraocular injections on older patients, their caregivers, and the health-care system.[9–11] Alternative dosing approaches of existing anti-VEGF agents aimed at increasing treatment and monitoring intervals have been evaluated and used, with variable visual results.[10,12–14] Furthermore, selective VEGF neutralisation alone does not address all potential targets or disease mechanisms in nAMD pathophysiology.[15,16] Thus, there is significant interest and need to target additional pathways involved in nAMD beyond the VEGF pathway that might offer longer durability, reduce treatment burden, and potentially improve patient outcomes in clinical practice compared with currently available therapies.

Published **Online** January 24, 2022 https://doi.org/10.1016/S0140-6736(22)00010-1

See **Online/Comment** https://doi.org/10.1016/S0140-6736(22)00105-2

*The TENAYA and LUCERNE Investigators and study sites are listed in the appendix (p 2).

Ophthalmic Consultants of Boston, Boston, MA, USA (J S Heier MD); **Sierra Eye Associates, Reno, NV, USA** (A M Khanani MD); **The University of Nevada, Reno School of Medicine, Reno, NV, USA** (A M Khanani); **Clinica de Ojos Garza Viejo, San Pedro Garza Garcia, Nuevo Leon, Mexico** (C Quezada Ruiz MD); **Genentech, South San Francisco, CA, USA** (C Quezada Ruiz, C Brittain MBBS, H Lin MD); **Roche Products (Ireland), Dublin, Ireland** (K Basu PhD); **Vitreoretinal Consultants of New York, Great Neck, NY, USA** (P J Ferrone MD); **Clinica Baviera, Ramon y Cajal University Hospital, Madrid, Spain** (M S Figueroa MD); **Department of Ophthalmology and GRADE Reading Center, University of Bonn, Bonn, Germany** (F G Holz MD); **Roche Products, Welwyn Garden City, UK** (V Patel BPharm, D Silverman MD); **Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China** (Prof T Y Y Lai MD); **Mid Atlantic Retina, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA, USA** (C Regillo MD); **Hoffmann-La Roche, Mississauga, ON, Canada** (B Swaminathan MSc); **Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico,**

Milan, Italy (Prof F Viola MD)**; Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy** (Prof F Viola)**; Singapore National Eye Centre, Duke-NUS Medical School, National University of Singapore, Singapore** (Prof C M G Cheung MD, Prof T Y Wong MD)

Correspondence to: Dr Jeffrey S Heier, Ophthalmic Consultants of Boston, Boston, MA 02114, USA
JSHEIER@eyeboston.com

See Online for appendix

Research in context

Evidence before this study

Despite the emergence of effective therapy in the form of intravitreal anti-vascular endothelial growth factor (VEGF) injections, neovascular age-related macular degeneration (nAMD) remains a leading cause of severe visual impairment worldwide. A key challenge with currently available anti-VEGF treatments is the need for frequent monitoring and injections to maintain initial vision gains. Furthermore, although anti-VEGF therapy targets pathological neovascularisation, it does not address other features of nAMD pathology. Novel targets beyond the VEGF pathway are therefore required to promote optimal vessel stability for improved patient outcomes.

Angiopoietin-2 (Ang-2) is a ligand that plays a key role in vascular destabilisation and inflammation. Neutralisation of Ang-2 has the potential to restore vascular stability by reducing vascular leakage, neovascularisation, and inflammation, as well as vascular responsiveness, to the effects of VEGF-A. Preclinical studies demonstrated sustained reduction of vascular leakage and inflammation versus VEGF-A inhibition alone. Therefore, targeting two distinct pathways involved in nAMD pathology, through dual Ang-2 and VEGF-A neutralisation, offers a novel therapeutic strategy for nAMD that might further normalise the pathological ocular vasculature compared with anti-VEGF therapy alone. A PubMed search from Jan 1, 2000, to Jan 1, 2021, for reports of clinical trials evaluating intravitreal treatments for nAMD, and dual inhibition of Ang-2 and VEGF-A, did not identify any published studies other than the reports of the phase 2 studies of faricimab in nAMD (AVENUE and STAIRWAY).

Faricimab is the first bispecific antibody designed for intraocular use that acts through inhibition of two distinct pathways by independently and simultaneously binding and neutralising both Ang-2 and VEGF-A. Data from completed phase 2 studies of faricimab support the hypothesis that dual pathway inhibition with faricimab has the potential to provide sustained efficacy through durability of effect beyond anti-VEGF therapy alone in nAMD, and support further evaluation of faricimab in phase 3 trials.

Added value of this study

TENAYA and LUCERNE are the first phase 3 clinical trials to evaluate dual pathway inhibition for the treatment of nAMD, and demonstrate that sustained efficacy can be achieved through combined blockade of Ang-2 and VEGF-A. The primary analysis demonstrated non-inferior visual acuity outcomes with extended faricimab dosing up to every 16 weeks compared with aflibercept, a treatment that targets the VEGF pathway alone, dosed every 8 weeks. Faricimab demonstrated extended durability, with approximately 80% of faricimab-treated patients on extended fixed-dosing intervals of every 12 weeks or more, and nearly 45% of patients on fixed-dosing intervals of every 16 weeks.

Implications of all the available evidence

The primary results of the phase 3 trials support faricimab as a new class of medicine with a dual mechanism of action that addresses multiple pathological features of nAMD beyond neovascularisation alone. The disease control with dual Ang-2 and VEGF-A neutralisation could allow physicians to extend time between treatments without compromising vision outcomes, resulting in less burdensome treatment regimens when compared with currently approved monthly and bimonthly therapies targeting the VEGF pathway alone. The results of these phase 3 trials represent an important step forward in treatment options in nAMD that could optimise patient outcomes.

The angiopoietin-tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (Ang-Tie) pathway, distinct from the VEGF pathway targeted by existing anti-VEGF treatments, plays a key role in maintaining vascular homoeostasis and regulating neovascularisation, inflammation, and leakage.[17] Angiopoietin-2 (Ang-2) is upregulated in the retina and vitreous under pathological conditions, including nAMD.[18] Ang-2 negatively regulates the Ang-Tie pathway by competitively binding to Tie2, inducing endothelial cell activation; destabilisation; elevated expression of molecules such as ICAM-1 and VCAM-1, leading to increased transmigration of macrophages and other inflammatory cells; pericyte detachment; and breakdown of endothelial barrier.[17] In addition, Ang-2 sensitises blood vessels to VEGF-A (member of VEGF family of angiogenic factors) and other pro-angiogenic factors, resulting in vascular leakage and macular neovascularisation (also called choroidal neovascularisation; CNV).[17] Dual pathway inhibition via simultaneous Ang-2 and VEGF-A neutralisation might therefore synergistically promote vascular stability and reduce neovascularisation, hyperpermeability, and concurrent inflammation resulting in fibrosis and cell death leading to atrophy, translating to effects beyond anti-VEGF treatment alone,[16,17] including improved durability compared with therapies targeting the VEGF pathway alone.

Faricimab, the first humanised, bispecific, IgG monoclonal antibody designed for intraocular use via intravitreal injection, independently binds and neutralises both Ang-2 and VEGF-A, enabling dual inhibition of two distinct pathways involved in nAMD pathology.[18,19] Faricimab is engineered using specific heterodimerisation of two different antigen-binding domains. Faricimab's fragment crystallisable (Fc) domain has been optimised to eliminate binding interaction with neonatal Fc and Fc γ receptors, decreasing systemic half-life of the antibody and reducing potential for inflammatory side-effects, respectively.[19]

Safety and efficacy of intravitreal faricimab were evaluated in phase 2 trials in patients with nAMD, demonstrating sustained efficacy on extended 8-week,

12-week, and 16-week dosing intervals, with vision and anatomic gains comparable with ranibizumab every 4 weeks.[20,21] Here, we present primary week 48 outcomes from two phase 3 trials (TENAYA and LUCERNE) to assess faricimab administered at individualised treatment intervals of up to every 16 weeks compared with aflibercept given every 8 weeks in patients with nAMD.

Methods

Study design

The study designs and rationales for TENAYA and LUCERNE (appendix p 8) have been previously described.[22] In brief, TENAYA and LUCERNE were identically designed, multicentre, randomised, active comparator-controlled, double-masked, parallel-group, 112-week trials conducted at 271 clinical sites worldwide (TENAYA 149 sites in 15 countries, LUCERNE 122 sites in 20 countries). Study protocols were approved by appropriate regulatory authorities, applicable institutional review boards, and ethics committees (appendix p 25), and were conducted in accordance with the Declaration of Helsinki and principles of Good Clinical Practice.

Participants

Patients aged 50 years or older at randomisation (day 1) were eligible to participate. One eye per patient was designated the study eye. If both eyes were considered eligible, the eye with worse best-corrected visual acuity (BCVA) at screening was selected as the study eye, unless the investigator deemed the other eye to be more appropriate for study treatment. All participants provided written informed consent.

Key ocular inclusion criteria for the study eye were treatment-naive CNV secondary to nAMD, as assessed by the central reading centre; subfoveal CNV or juxtafoveal or extrafoveal CNV, with subfoveal component related to CNV activity, confirmed on fluorescein angiography, and CNV exudation confirmed on spectral-domain optical coherence tomography (SD-OCT); CNV lesion size of nine or fewer disc areas and CNV component area of 50% or more of total lesion area; and Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA 78–24 letters (20/32–20/320 approximate Snellen equivalent). Full eligibility criteria are provided in the appendix (p 9).

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio (on day 1) to two treatment groups (faricimab up to every 16 weeks or aflibercept every 8 weeks) using identification numbers assigned through an interactive voice-based or web-based response system. From day 1, all study visits occurred every 4 weeks until study end, with a safety assessment visit on day 7 (SD 3). To preserve masking, all patients attended study visits every 4 weeks and received sham injections at non-active dosing visits. Further details are provided in the appendix (p 22).

Procedures

In the primary analysis, study treatment was administered up to week 48. From day 1, patients randomly assigned to the faricimab group initially received intravitreal faricimab 6·0 mg every 4 weeks up to week 12 (four injections) and patients in the aflibercept group received intravitreal aflibercept 2·0 mg, per its international label guidance, every 4 weeks up to week 8 (three injections), followed by fixed 8-week dosing to study end, without allowing rescue or additional treatments during the study.

After the first four monthly doses (day 1, and weeks 4, 8, and 12), patients in the faricimab group were assessed at weeks 20 and 24 for protocol-defined disease activity based on structural and functional criteria and treating physician clinical assessment (appendix p 23). Patients with active disease at week 20 were treated with faricimab and subsequently continued to receive faricimab on fixed 8-week dosing until week 60. After a second disease activity assessment at week 24, patients with active disease (excluding those already on the 8-week regimen) received faricimab and subsequently continued fixed 12-week dosing up to week 60. Patients in the faricimab group who did not have active disease at weeks 20 and 24 received faricimab at week 28 and continued a 16-week regimen up to week 60.

In year 2 of the study, all patients in the faricimab group are scheduled to receive an active dose of faricimab starting at week 60 and will be treated according to a personalised treatment interval (PTI). In the PTI regimen, dosing intervals can be extended in 4-week increments or reduced in 4-week or 8-week increments to a minimum of every 8 weeks, a maximum of every 16 weeks, or maintained based on disease activity assessments at study drug dosing visits. Study treatment will be administered up to week 108, with final visit at week 112.

Key ocular assessments included BCVA, intraocular pressure, slit-lamp biomicroscopy, and dilated indirect ophthalmoscopy at each study visit, and low-luminance BCVA (measured using a 2·0-log-unit Kodak Wratten 2·0 neutral density filter) at day 1 and week 48. Standardised ocular imaging (colour fundus photography, fluorescein angiography, and SD-OCT) was performed at prespecified timepoints. Ocular images were independently assessed by masked evaluators at central reading centres.

Outcomes

The primary efficacy endpoint was change in BCVA from baseline averaged over weeks 40, 44, and 48 (hereafter referred to as primary endpoint visits). Primary efficacy outcome was averaged over three timepoints to limit impact of measurement variability and account for differences in time from last dose received by patients across treatment groups on different dosing intervals. Secondary endpoints reported herein include proportion of faricimab-treated patients on 16-week, 12-week, and 8-week schedules at week 48; change in BCVA over time;

patients gaining BCVA (≥15, ≥10, ≥5, or ≥0 ETDRS letters) over time; patients avoiding BCVA loss (≥15, ≥10, or ≥5 ETDRS letters) over time; patients gaining 15 or more ETDRS letters or achieving BCVA ≥84 ETDRS letters over time; and patients with BCVA Snellen equivalent of 20/40 or better and 20/200 or worse over time. Structural outcomes include change in SD-OCT-measured central subfield thickness (CST; distance between internal limiting membrane and retinal pigment epithelium) from baseline at primary endpoint visits and over time; and change from baseline in total area of CNV lesion and total area of CNV leakage at week 48. Prespecified safety endpoints included incidence and severity of ocular and non-ocular adverse events. Change from baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) composite score at week 48 was included as an exploratory endpoint. A complete list of prespecified endpoints is provided in the appendix (p 11).

Statistical analysis

Primary and secondary efficacy analyses were performed in the intention-to-treat (ITT) population comprising all randomly assigned study participants, grouped by treatment assigned at randomisation. Safety analyses included all randomly assigned participants who received at least one injection of study treatment (faricimab or aflibercept) in the study eye, grouped according to actual treatment received up to week 48.

Sample size calculations were based on the primary endpoint of mean change in BCVA from baseline at primary endpoint visits, and the following assumptions: no difference in mean change from baseline in BCVA between the two treatment groups at primary endpoint visits; SD of 14 ETDRS letters for mean change from baseline in BCVA at primary endpoint visits; two-sample *t* test; 2·5% one-sided type I error rate; and 10% dropout rate. Sample size of approximately 320 patients in each treatment group (ie, N=640 per trial) was estimated to provide more than 90% power to test the primary comparison of non-inferiority of faricimab (up to every 16 weeks) to aflibercept (every 8 weeks) for each trial, using a non-inferiority margin of four ETDRS letters (appendix p 22).

Primary efficacy analysis was performed using a mixed model for repeated measures (MMRM), which included change from baseline at weeks 4–48 as response variable, categorical covariates of treatment group, visit, and visit-by-treatment group interaction and continuous covariate of baseline BCVA (response variable), as well as randomisation stratification factors as fixed effects. An unstructured covariance structure was used. Missing data were implicitly imputed using MMRM, assuming a missing at random mechanism.

For the primary analysis, COVID-19-related intercurrent events (study treatment discontinuation, use of any prohibited systemic treatment or therapy in study eye, missed dose or doses with potential impact on efficacy [ie, immediately preceding and at primary endpoint visits], or death) were handled using a hypothetical strategy where all values were censored after the intercurrent event. For intercurrent events not due to COVID-19 (study treatment discontinuation due to adverse events or lack of efficacy; or use of prohibited systemic treatment or prohibited therapy in study eye), a treatment policy strategy was applied, whereby all observed values were used regardless of occurrence of the intercurrent event. To assess robustness of primary analysis findings, additional sensitivity and supplemental analyses were performed using alternative handling strategies for missing data and intercurrent events (appendix p 24).

Secondary endpoints measured on a continuous scale were analysed using MMRM as described for the primary endpoint. For binary secondary endpoints, proportions of patients in each treatment group and overall differences between treatment groups were estimated using weighted average of observed proportions and differences in observed proportions over the strata defined by randomisation factors of baseline BCVA score (≥74, 73–55, or ≤54 letters), low-luminance deficit (<33 or ≥33 letters), and region using Cochran-Mantel-Haenszel (CMH) weights. CIs were calculated using normal approximation to weighted proportions. Exploratory endpoints were summarised using descriptive statistics.

Safety was assessed through descriptive summaries of ocular and systemic adverse events, deaths, and ocular assessments up to week 48. Adverse events were coded using the Medical Dictionary for Regulatory Activities version 23.1 thesaurus and tabulated by System Organ Class and Preferred Term. Ocular assessments were summarised by timepoint and eye (study *vs* fellow eye).

An independent data monitoring committee monitored safety and conduct of these studies until primary analysis completion. For each unmasked independent data monitoring committee safety review performed before the primary analysis, a nominal type I error penalty of 0·0001 was taken such that efficacy analyses were performed with a family-wise significance level of 0·0497. Consequently, 95% CIs are rounding of 95·03% CIs. Statistical analyses were performed using SAS version 9.4.

TENAYA and LUCERNE are registered with ClinicalTrials.gov (TENAYA NCT03823287 and LUCERNE NCT03823300).

Role of the funding source

F Hoffmann-La Roche participated in study design; collection, analysis, and interpretation of data; writing of the report; and decision to submit for publication.

Results

Between Feb 19 and Nov 19, 2019, in TENAYA and between March 11 and Nov 1, 2019, for LUCERNE, 2001 patients with treatment-naive CNV secondary to nAMD were screened for eligibility (TENAYA n=989, and LUCERNE n=1012). After exclusions, TENAYA enrolled

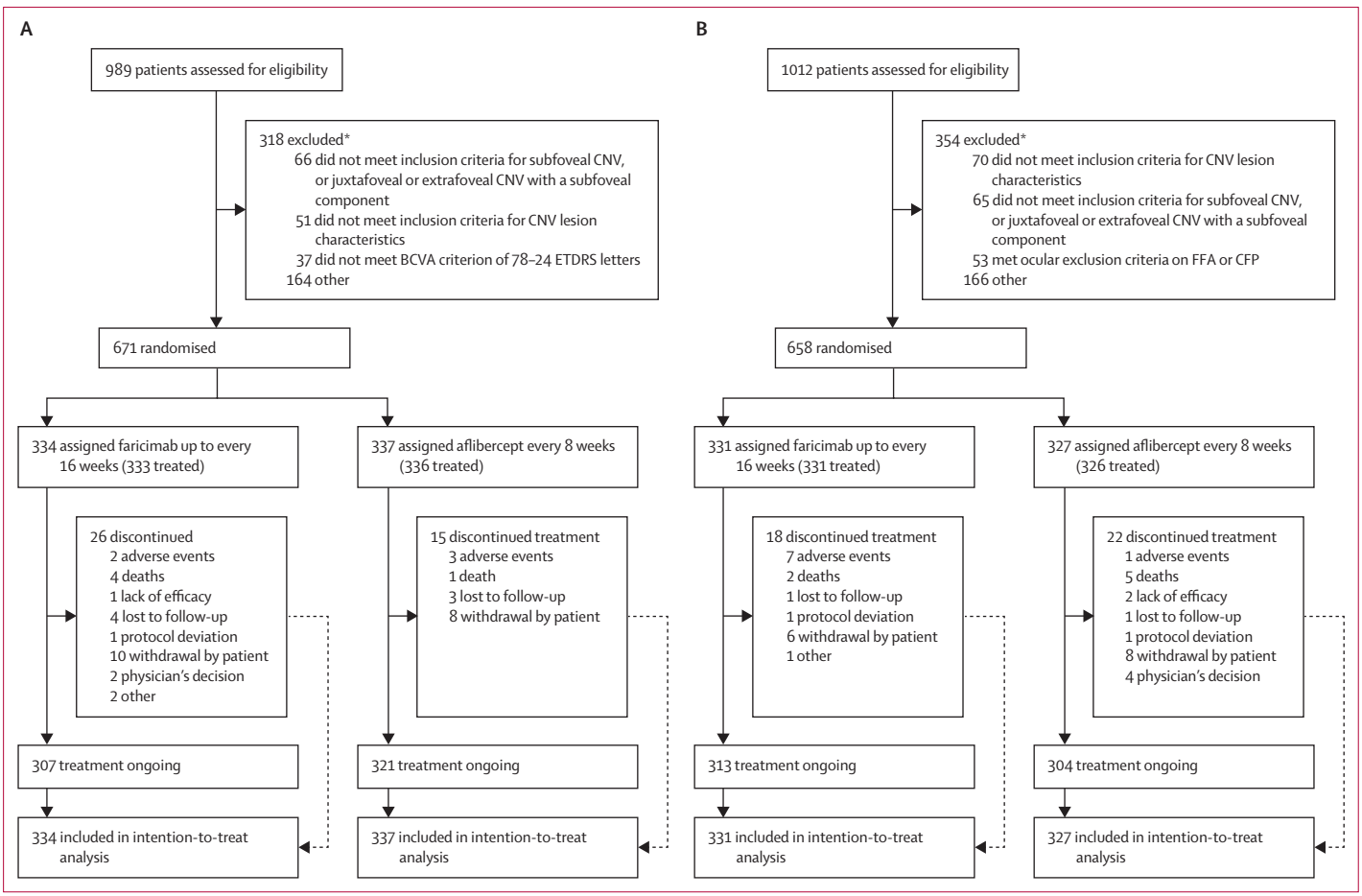

Figure 1: **Trial profile for TENAYA (A) and LUCERNE (B)**
BCVA=best-corrected visual acuity. CFP=colour fundus photograph. CNV=choroidal neovascularisation. ETDRS=Early Treatment Diabetic Retinopathy Study. FFA=fundus fluorescein angiography.
*Primary reason for exclusion; some patients were excluded for more than one reason.

671 patients, who were randomly assigned (1:1) to faricimab 6·0 mg up to every 16 weeks (n=334) or aflibercept 2·0 mg every 8 weeks (n=337; figure 1). LUCERNE enrolled 658 patients, who were randomly assigned (1:1) to faricimab 6·0 mg (n=331) or aflibercept 2·0 mg every 8 weeks (n=327; figure 1).

The proportion of patients discontinuing treatment before week 48 in each group of TENAYA (faricimab group 26 [7·8%], aflibercept group 15 [4·5%]) and LUCERNE (faricimab group 18 [5·4%], aflibercept group 22 [6·7%]) was low, with one patient in the faricimab group of TENAYA and two in the aflibercept group of LUCERNE discontinuing treatment due to lack of efficacy. Overall, 669 (99·7%) patients in TENAYA and 657 (99·8%) patients in LUCERNE received at least one injection of active study treatment and were included in safety analyses.

At least one major protocol deviation was reported for 303 (45·2%) participants in TENAYA and 254 (38·6%) participants in LUCERNE; these were generally well balanced across treatment groups. Most protocol deviations were considered procedural (TENAYA 292 [43·5%], LUCERNE 234 [35·6%]), of which 156 (23·2%) patients in TENAYA and 132 (20·1%) patients in LUCERNE missed at least two loading doses, missed both disease activity assessment visits, or missed visits during weeks 36, 40, 44, or 48 (figure 1).

There were missed visits due to the COVID-19 pandemic, but not all missed visits resulted in a missed dose of study treatment. 58 (17·4%) patients in the faricimab group and 75 (22·3%) patients in the aflibercept group of TENAYA and 55 (16·6%) patients in the faricimab group and 52 (15·9%) patients in the aflibercept group of LUCERNE missed both disease activity assessment visits or missed visits around the primary endpoint (during weeks 36, 40, 44, or 48). 27 (8·1%) patients in the faricimab group and 31 (9·2%) patients in the aflibercept group in TENAYA, and 25 (7·6%) patients in the faricimab group and 21 (6·4%) patients in the aflibercept group in LUCERNE missed at least one dose around the primary endpoint. COVID-19-related study treatment discontinuations were low in TENAYA (faricimab n=3 [0·9%], aflibercept n=1 [0·3%]) and there were none in LUCERNE.

Patient baseline characteristics in TENAYA and LUCERNE were generally well balanced (table 1). Across treatment groups and trials, the mean age was 74·8–76·7 years, mean baseline BCVA was slightly greater in TENAYA (61·3–61·5 ETDRS letters) than in LUCERNE (58·7–58·9 letters), and 24·9–26·0% of patients in TENAYA had baseline BCVA of 54 or fewer letters (Snellen 20/80 or worse) compared with 31·7–32·1% in LUCERNE. Most patients in both trials had baseline BCVA of 73–55 letters (Snellen equivalent 20/40–20/80). Mean baseline CST was 353·1–360·5 µm; mean total CNV lesion area (on fundus fluorescein angiography) was 4·3–4·7 mm², and CNV type and location were also generally well balanced across the two trials. Most patients had occult lesions (42·8–53·0%) located subfoveally (55·2–63·1%).

	TENAYA (N=671)		LUCERNE (N=658)	
	Faricimab up to every 16 weeks (n=334)	Aflibercept every 8 weeks (n=337)	Faricimab up to every 16 weeks (n=331)	Aflibercept every 8 weeks (n=327)
Age, years	75·9 (8·6)	76·7 (8·8)	74·8 (8·4)	76·1 (8·6)
Sex				
Female	191 (57%)	211 (63%)	203 (61%)	188 (57%)
Male	143 (43%)	126 (37%)	128 (39%)	139 (43%)
Ethnicity or race*				
Hispanic or Latino	26 (8%)	26 (8%)	35 (11%)	46 (14%)
White	303 (91%)	302 (90%)	278 (84%)	270 (83%)
Asian	26 (8%)	28 (8%)	38 (11%)	34 (10%)
American Indian or Alaska Native	1 (<1%)	2 (1%)	1 (<1%)	0
Black or African American	0	3 (1%)	2 (1%)	5 (2%)
Region				
USA and Canada	182 (54%)	184 (55%)	135 (41%)	132 (40%)
Rest of the world†	126 (38%)	127 (38%)	161 (49%)	162 (50%)
Asia‡	26 (8%)	26 (8%)	35 (11%)	33 (10%)
BCVA, ETDRS letters	61·3 (12·5)	61·5 (12·9)	58·7 (14·0)	58·9 (13·3)
BCVA categories				
≥74 (20/32 or better)	47 (14%)	52 (15%)	45 (14%)	39 (12%)
73–55 (20/40–20/80)	200 (60%)	201 (60%)	181 (55%)	183 (56%)
≤54 (20/80 or worse)	87 (26%)	84 (25%)	105 (32%)	105 (32%)
CST§, µm	360·5 (124·1)	356·1 (107·0)	353·1 (120·1)	359·0 (131·1)
Intraocular pressure, mm Hg	15·0 (2·8)	15·0 (2·9)	14·9 (3·0)	14·8 (3·0)
Time since AMD diagnosis				
≤1 month	248 (74%)	246 (73%)	221 (67%)	208 (64%)
>1 month	66 (20%)	77 (23%)	96 (29%)	107 (33%)
Phakic	193 (58%)	184 (55%)	190 (57%)	185 (57%)
Presence of IRF	146 (44%)	157 (47%)	142 (43%)	154 (47%)
Presence of SRF	216 (65%)	225 (67%)	221 (67%)	222 (68%)
CNV location by FFA				
Subfoveal	201 (60%)	186 (55%)	209 (63%)	191 (58%)
Juxtafoveal	88 (26%)	88 (26%)	73 (22%)	84 (26%)
Extrafoveal	41 (12%)	55 (16%)	42 (13%)	44 (13%)
CNV lesion type by FFA				
Occult	177 (53%)	174 (52%)	171 (52%)	140 (43%)
Classic	84 (25%)	73 (22%)	98 (30%)	109 (33%)
Minimally classic	32 (10%)	30 (9%)	30 (9%)	31 (9%)
RAP	14 (4%)	27 (8%)	14 (4%)	15 (5%)
Predominantly classic	17 (5%)	19 (6%)	6 (2%)	16 (5%)
Total area of CNV lesion by FFA, mm²	4·7 (4·8)	4·5 (4·1)	4·7 (4·7)	4·3 (4·3)

Data are mean (SD) or n (%). AMD=age-related macular degeneration. BCVA=best-corrected visual acuity. CNV=choroidal neovascularisation. CST=central subfield thickness. ETDRS=Early Treatment Diabetic Retinopathy Study. FFA=fundus fluorescein angiography. ILM=internal limiting membrane. IRF=intraretinal fluid. RAP=retinal angiomatous proliferation. RPE=retinal pigment epithelium. SRF=subretinal fluid. *Not all race categories are listed; therefore, the sums of proportions shown do not equal 100%. †Rest of the world includes Argentina, Australia, Austria, Brazil, Bulgaria, Denmark, France, Germany, Hungary, Israel, Italy, Mexico, the Netherlands, Poland, Portugal, Russia, Spain, Switzerland, Turkey, and the UK. ‡Asia includes Hong Kong, Japan, Singapore, South Korea, and Taiwan. §CST is measured as the distance between the ILM and RPE.

Table 1: **Baseline demographic and ocular characteristics in TENAYA and LUCERNE in the intention-to-treat population**

TENAYA and LUCERNE met their primary endpoints of non-inferiority in mean change from baseline in BCVA in the study eye at primary endpoint visits (average at weeks 40, 44, and 48) with faricimab dosed up to every 16 weeks compared with aflibercept every 8 weeks (figure 2). In the primary analysis (ITT population), adjusted mean gains in BCVA at primary endpoint visits in TENAYA were 5·8 letters (95% CI 4·6 to 7·1) in the faricimab group and 5·1 letters (3·9 to 6·4) in the aflibercept group (treatment difference 0·7 letters [95% CI –1·1 to 2·5]). In LUCERNE, vision gains were 6·6 letters (95% CI 5·3 to 7·8) in the faricimab group and 6·6 letters (5·3 to 7·8) in the aflibercept group (treatment difference 0·0 letters [95% CI –1·7 to 1·8]). Lower bounds of the two-sided 95% CIs for difference in adjusted means of the two treatments were well within the non-inferiority margin of four letters, establishing non-inferiority of faricimab to aflibercept (figure 2). Results were consistent across sensitivity and supplemental analyses, including the per-protocol population, with treatment differences of 0·3 letters (95% CI –1·6 to 2·2) in TENAYA and –0·1 letters (–2·0 to 1·8) in LUCERNE (appendix p 24). At week 48, approximately 80% of faricimab-treated patients in both TENAYA and LUCERNE were on 12-week or 16-week dosing intervals, with 107 (34·0%) patients in TENAYA and 104 (32·9%) patients in LUCERNE on extended dosing regimens of every 12 weeks, and 144 (45·7%) patients in TENAYA and 142 (44·9%) patients in LUCERNE on 16-week dosing (figure 3).

Consistent with the primary endpoint, similar proportions of patients in each group of TENAYA and LUCERNE gained 10 or more or 15 or more ETDRS letters from baseline at primary endpoint visits (appendix p 14). In CMH-weighted estimates, 20·0–20·2% of faricimab-treated patients gained 15 or more letters compared with 15·7–22·2% of patients in the aflibercept group (appendix p 14). More than 95% of patients in the faricimab group in both studies avoided losing 15 letters or more of vision from baseline at primary endpoint visits (appendix p 14). Comparable proportions of patients across treatment groups in both studies demonstrated BCVA Snellen equivalent of 20/40 or better (49·4–57·0%) and 20/200 or worse (6·4–7·9%) at primary endpoint visits (appendix p 14).

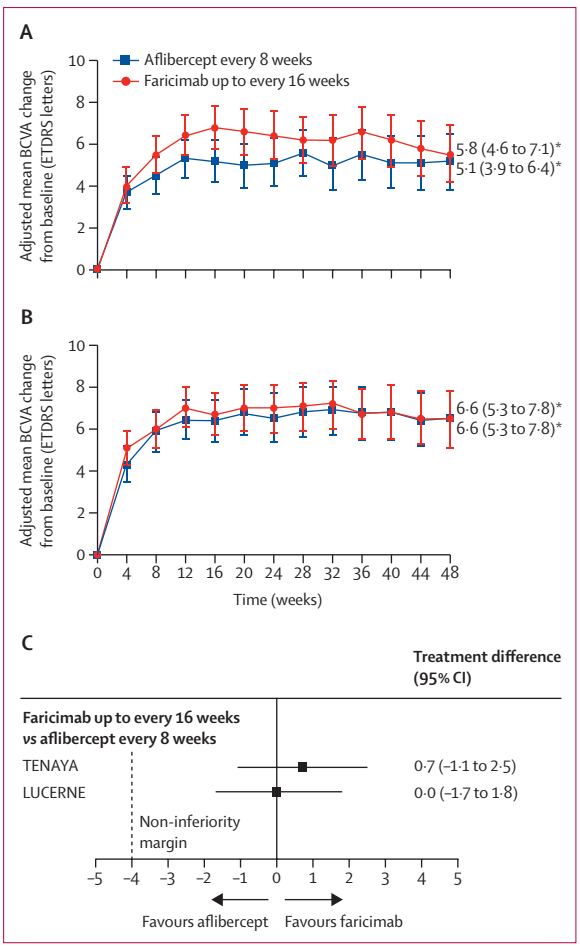

Figure 2: **Adjusted mean change in BCVA (ETDRS letters) from baseline up to week 48 in TENAYA (A) and LUCERNE (B) was non-inferior (C) with faricimab up to every 16 weeks versus aflibercept every 8 weeks**
Primary efficacy outcome is the adjusted mean BCVA change from baseline averaged over weeks 40, 44, and 48. Results are based on MMRM analysis in the ITT population. Missing data were implicitly imputed by the MMRM. Invalid BCVA values were excluded from analysis. 95% CIs are a rounding of 95·03% CIs. BCVA=best-corrected visual acuity. ETDRS=Early Treatment Diabetic Retinopathy Study. ITT=intention to treat. MMRM=mixed model for repeated measures. *Adjusted mean BCVA change from baseline averaged over weeks 40, 44, and 48.

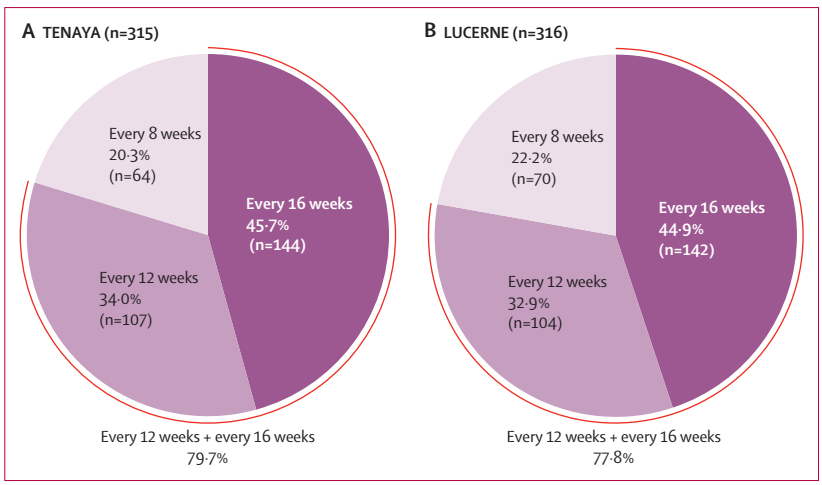

Figure 3: **Proportion of patients in the faricimab group who completed week 48 treatment on 8-week, 12-week, and 16-week fixed-dosing intervals in TENAYA (A) and LUCERNE (B)**
Percentages are based on number of patients randomly assigned to the faricimab group who had not discontinued the study at week 48 (TENAYA n=315, LUCERNE n=316). Treatment interval at week 48 is defined as the treatment interval decision followed at that visit. Red lines indicate the proportion of faricimab-treated patients on 12-week or 16-week dosing intervals at week 48.

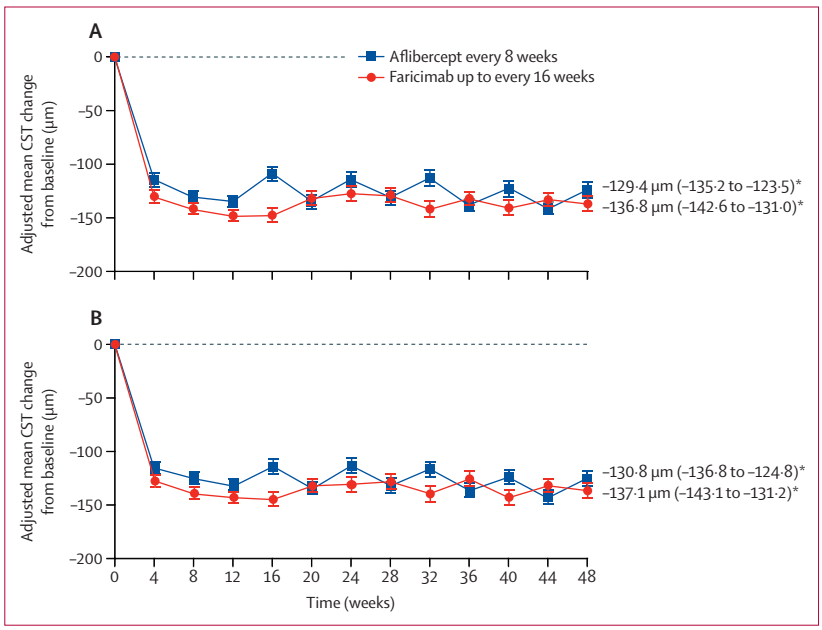

Figure 4: **Adjusted mean change in CST from baseline up to week 48 in TENAYA (A) and LUCERNE (B)**
Adjusted mean CST change from baseline averaged over weeks 40, 44, and 48. Results are based on MMRM analysis in the ITT population. Missing data were implicitly imputed by the MMRM. 95% CIs are a rounding of 95·03% CIs. CST=central subfield thickness. ITT=intention to treat. MMRM=mixed model for repeated measures. *Adjusted mean CST change from baseline averaged over weeks 40, 44, and 48.

In both TENAYA and LUCERNE, anatomical outcomes using SD-OCT supported functional outcomes. Treatment with faricimab dosed up to every 16 weeks resulted in CST reductions from baseline at all timepoints up to week 48, starting at 4 weeks after treatment initiation, and was comparable with aflibercept every 8 weeks (figure 4). Adjusted mean CST change from baseline at primary endpoint visits was –136·8 µm (95% CI –142·6 to –131·0) with faricimab and –129·4 µm (–135·2 to –123·5) with aflibercept in TENAYA (treatment difference –7·4 µm [–15·7 to 0·8]), and –137·1 µm (–143·1 to –131·2) with faricimab and –130·8 µm (–136·8 to –124·8) with aflibercept in LUCERNE (treatment difference –6·4 µm [–14·8 to 2·1]). In both studies, adjusted mean changes in total CNV lesion area and total area of leakage from baseline with faricimab at week 48 were comparable with aflibercept (appendix p 14). Patient-reported vision-related functioning and quality of life, as measured by change from baseline in NEI VFQ-25 composite score from baseline at week 48, was also comparable between treatment groups (appendix p 14).

Key ocular and non-ocular adverse events, as reported by study investigators, are summarised in table 2.

	TENAYA (N=669)		LUCERNE (N=657)	
	Faricimab up to every 16 weeks (n=333)	Aflibercept every 8 weeks (n=336)	Faricimab up to every 16 weeks (n=331)	Aflibercept every 8 weeks (n=326)
Total number of adverse events*	858	812	812	846
Total number of serious adverse events*	47	67	68	122
Patients with ≥1 ocular adverse event†	121 (36%)	128 (38%)	133 (40%)	118 (36%)
Patients with ≥1 ocular serious adverse event†	4 (1%)	6 (2%)	7 (2%)	7 (2%)
Patients with ≥1 non-ocular adverse event	174 (52%)	174 (52%)	172 (52%)	189 (58%)
Patients with ≥1 non-ocular serious adverse event	30 (9%)	34 (10%)	38 (11%)	48 (15%)
Patients with ≥1 treatment-related ocular adverse event†	9 (3%)	9 (3%)	10 (3%)	8 (2%)
Patients with ≥1 treatment-related ocular serious adverse event†	3 (1%)	0	5 (2%)	1 (<1%)
Patients with ≥1 ocular adverse event of special interest†‡	3 (1%)	6 (2%)	5 (2%)	6 (2%)
Patients with ≥1 adverse event of IOI (excluding endophthalmitis)†§	5 (2%)	2 (1%)	8 (2%)	6 (2%)
Iritis	2 (1%)	1 (<1%)	1 (<1%)	1 (<1%)
Uveitis¶	1 (<1%)‖	1 (<1%)	1 (<1%)‖	1 (<1%)‖
Keratic precipitates	1 (<1%)	0	0	0
Vitritis	1 (<1%)	0	2 (1%)	1 (<1%)
Iridocyclitis	0	0	3 (1%)	2 (1%)
Chorioretinitis (viral)	0	0	1 (<1%)‖	0
Post-procedural inflammation	0	0	0	1 (<1%)
Patients with ocular serious adverse event known to be associated with anti-VEGF†				
Endophthalmitis	0	0	0	1 (<1%)
Rhegmatogenous retinal detachment	0	0	0	0
Retinal tear	0	0	0	0
Retinal pigment epithelial tear	2 (1%)	0	2 (1%)	0
Intraocular pressure increased	0	0	1 (<1%)	0
Traumatic cataract	0	0	0	0
Retinal vasculitis and retinal occlusive events†				
Retinal vasculitis	0	0	0	0
Retinal vein occlusion	0	0	0	0
Retinal artery occlusion	0	0	0	0
Retinal artery embolism	0	0	1 (<1%)**	0
Patients with ≥1 APTC†† event	3 (1%)	3 (1%)	4 (1%)	3 (1%)
Death	2 (1%)	1 (<1%)	0	2 (1%)
Non-fatal myocardial infarction	1 (<1%)	1 (<1%)	2 (1%)	1 (<1%)
Non-fatal stroke	0	1 (<1%)	2 (1%)	0

Data are n or n (%). APTC=Anti-Platelet Trialists' Collaboration. BCVA=best-corrected visual acuity. IOI=intraocular inflammation. VEGF=vascular endothelial growth factor. *Total number of adverse events and serious adverse events includes non-ocular and ocular events in the study or fellow eye. †Ocular adverse events and serious adverse events in the study eye only. A full list of ocular adverse events and serious adverse events is provided in the appendix (pp 16–20). ‡Adverse events of special interest includes events associated with severe IOI, events that result in a BCVA decrease of 30 letters or more for more than 1 h, or events that require intervention or surgery to prevent permanent vision loss. For frequency counts by Preferred Term, multiple occurrences of the same adverse event in an individual are counted only once. Includes adverse events with onset up to day 349 (last day of week 48 analysis visit window). A full list of ocular adverse events of special interest is provided in the appendix. §Includes serious and non-serious IOI events. ¶Severe IOI events are reported; all other events were mild or moderate. ‖Severe. **Hollenhorst plaque. ††APTC events were adjudicated by an external committee; all other events were investigator reported.

Table 2: **Summary of key adverse events up to week 48 of TENAYA and LUCERNE (safety-evaluable population)**

Overall, faricimab up to every 16 weeks was well tolerated, as evidenced by low incidence of adverse events leading to study treatment discontinuation up to week 48 in TENAYA (n=3 [0·9%] in both groups) and LUCERNE (faricimab n=8 [2·4%], aflibercept n=1 [0·3%]; appendix p 17). The most common ocular adverse events in the study eye were consistent with those expected in patients with nAMD receiving intravitreal treatment, and incidence of ocular adverse events was comparable between treatment groups in TENAYA (faricimab n=121 [36·3%] *vs* aflibercept n=128 [38·1%]) and LUCERNE (n=133 [40·2%] *vs* n=118 [36·2%]; appendix p 18). Common non-ocular adverse events were generally similar, with no safety

concerns, and occurred at similar rates in both treatment groups across TENAYA and LUCERNE (appendix p 19). Incidence of serious ocular adverse events in the study eye was low and comparable between faricimab and aflibercept groups for both TENAYA (faricimab n=4 [1·2%] *vs* aflibercept n=6 [1·8%]) and LUCERNE (n=7 [2·1%] *vs* n=7 [2·1%]; appendix p 20). Serious intraocular pressure increase observed in one patient in the faricimab group of LUCERNE was transient and determined to be secondary to herpetic uveitis. Rates of other ocular serious adverse events related to commonly associated risks with intravitreal anti-VEGF therapy were absent or low (table 2; appendix p 20). Anti-Platelet Trialists' Collaboration events were low and comparable across groups and studies (TENAYA n=3 [0·9%] in both groups; LUCERNE faricimab n=4 [1·2%] *vs* aflibercept n=3 [0·9%]), and deaths of any type were low (table 2).

Rates of intraocular inflammation were low across both trials. Numerically higher intraocular inflammation events were reported in the faricimab groups (TENAYA n=5 [1·5%], LUCERNE n=8 [2·4%]) compared with aflibercept (TENAYA n=2 [0·6%], LUCERNE n=6 [1·8%]; table 2). Two intraocular inflammation events (one uveitis in TENAYA, one vitritis in LUCERNE) in the faricimab group and one uveitis event (LUCERNE) in the aflibercept group led to a decrease of 30 or more letters in visual acuity score lasting more than 1 h (appendix p 20). However, uveitis cases in the aflibercept group and vitritis cases in the faricimab group were resolved at the time of primary analysis. The remaining case of uveitis in the faricimab group of TENAYA was not resolved at the time of primary analysis but was improving. All patients with intraocular inflammation in the faricimab group and all except one patient (iritis) in the aflibercept group received treatment for the adverse event. There was one report of endophthalmitis in the aflibercept group of LUCERNE, which was culture negative.

Discussion

TENAYA and LUCERNE met their primary endpoint, with mean change from baseline in BCVA at primary endpoint visits with faricimab administered at fixed intervals of up to every 16 weeks non-inferior to aflibercept every 8 weeks. In both trials, faricimab demonstrated sustained efficacy, with nearly half of faricimab-treated patients (approximately 45%) on extended fixed treatment intervals of every 16 weeks at week 48 and four of five patients (approximately 80%) on intervals of every 12 weeks or more. Together, these results demonstrate faricimab's potential, via dual Ang-2 and VEGF-A inhibition, to extend treatment intervals in patients with nAMD and address a key unmet need for effective, more durable therapies that optimise clinical benefits while reducing overall visit and treatment burden.

Overall, results were consistent across both trials, with comparable BCVA outcomes (TENAYA 5·1–5·8 letters *vs* LUCERNE 6·6 letters). Rapid initial BCVA gains were sustained up to week 48 and comparable proportions of faricimab-treated and aflibercept-treated patients gained 15 letters or more in BCVA score or achieved BCVA Snellen equivalent 20/40 or better (BCVA ≥69 letters). About 95% of patients across treatment groups in both trials avoided loss of 15 letters or more in vision—a clinically important endpoint signifying stable maintenance of vision, with the majority of faricimab-treated patients on extended dosing intervals of every 12 weeks or more. Consistent visual outcomes across both trials were supported by anatomical outcomes, with meaningful and comparable reductions in CST from baseline and decreases in CNV size and area of leakage, across treatment groups in both trials.

Previous trials of anti-VEGF agents in nAMD have assessed alternate treatment regimens to monthly dosing aimed at reducing treatment burden, such as as-needed pro re nata[23,24] and treat-and-extend regimens.[14,25] These trials demonstrated that vision outcomes with pro re nata regimens were less than optimal compared with a fixed monthly regimen.[23,24] Treat-and-extend regimens with anti-VEGF offer visual acuity benefits with fewer injections over 1 year compared with monthly dosing or as-needed regimens,[26,27] but might be limited in durability of treatment effect by only targeting the VEGF pathway. Dual inhibition of pathways involving both Ang-2 and VEGF-A might stabilise blood vessels,[16,17] likely contributing to the durability signal observed with faricimab in TENAYA and LUCERNE and might provide added benefits to patients with nAMD by reducing need for frequent clinic visits and injections while ensuring vision gains and maintenance.

Safety of novel therapies for nAMD is important.[28] Faricimab was well tolerated, with an acceptable safety profile. Ocular adverse events were comparable across treatment groups and consistent with those expected with intravitreal anti-VEGF in patients with nAMD.[22,29] In TENAYA and LUCERNE, at week 48, rates of intraocular inflammation were low and on average reported in 2·0% of patients receiving faricimab and 1·2% of patients receiving aflibercept (table 2). Most intraocular inflammation events were resolved or resolving at week 48, except two ongoing cases of uveitis (one in each group).

In TENAYA and LUCERNE, the comparator, aflibercept, was administered every 8 weeks (consistent with its globally approved labelling),[29] representing a well established and effective treatment regimen for nAMD against which to test non-inferiority in BCVA outcome of a new treatment, which was the primary objective of these registrational trials. Consequently, one limitation of the TENAYA and LUCERNE trials is the lack of direct comparison of durability of faricimab relative to the standard of care because the comparator in these studies was administered according to a fixed 8-week dosing regimen without the possibility to extend

treatment intervals, as in the faricimab group.[29] The registrational phase 3 trials of faricimab for nAMD were not designed for head-to-head comparison of faricimab's durability versus aflibercept because extended fixed 12-week or fixed 16-week dosing regimens have not been studied in double-masked phase 3 registrational trials for aflibercept.[4] Fixed 8-week aflibercept dosing, which was used in the pivotal phase 3 trials of aflibercept, was therefore the most appropriate regimen against which to evaluate non-inferiority of a new treatment, especially considering the potential for extended dosing with faricimab at up to 16-week repeating intervals. Another limitation of the TENAYA and LUCERNE trials is the short 1-year follow-up period at the time of the primary analysis. nAMD is a chronic and progressive disease with long-term effects on vision; therefore, the long-term durability benefits of dual Ang-2 and VEGF-A inhibition blockade through faricimab for patients with nAMD remains to be determined and the results presented herein should be interpreted within this context. Finally, the assessment of the potential for faricimab to reduce treatment burden and improve quality of life might also be limited by the fact that at the time of the primary analysis, all patients returned for monthly visits to maintain masking. However, TENAYA and LUCERNE are ongoing trials, and year 2 data, in addition to the long-term follow-up via the 2-year open-label extension study, AVONELLE-X (NCT04777201), will help to address these limitations and further inform faricimab's durability and its long-term effects on visual acuity, retinal morphology, and quality of life.

TENAYA and LUCERNE are large global trials conducted during the COVID-19 pandemic, with potential impact on trial participants, study conduct, and data collection. However, mitigation measures were implemented to minimise impact of COVID-19 on data collection (such as prioritising assessment of critical safety and primary endpoints to ensure continuity of care). In addition, sensitivity and supplemental analyses were performed to test robustness of the primary results. Collectively, these measures ensured interpretability of efficacy and safety data, and conclusively established faricimab's benefit–risk profile.

High treatment and visit burden in nAMD are associated with direct and indirect costs, placing an enormous strain on patients, caregivers, and the health-care system.[9,11] Potential for durable vision outcomes and extended dosing to every 12 weeks or every 16 weeks with dual Ang-2 and VEGF-A inhibition, and a personalised treatment regimen based on individual patient needs, could help to manage and reduce treatment and visit burden on patients, caregivers, and health-care providers, as well as reduce overall costs, to the benefit of patients and payors.

In summary, results from the TENAYA and LUCERNE phase 3 trials evaluating dual Ang-2 and VEGF-A inhibition with intravitreal faricimab, administered at up to 16-week intervals, demonstrated vision benefits and anatomical outcomes comparable with VEGF pathway inhibition alone with aflibercept given at 8-week intervals. Observed extended durability of effect with faricimab, likely driven by vascular-stabilising effects of dual Ang-2 and VEGF pathway inhibition, has the potential to improve patient outcomes in clinical practice beyond targeting the VEGF pathway alone. Disease control afforded by the novel dual pathway inhibition with faricimab could allow extending time between treatments while maximising vision gains, addressing a key clinical unmet need for durable therapies in management of nAMD.

Contributors

CQR, KB, HL, and DS participated in the design of the study. JSH, AMK, PJF, MSF, FGH, TYYL, CR, FV, CMGC, and TYW participated in advisory committees and as study investigators. CQR, KB, CB, HL, VP, DS, and BS provided study oversight. All authors participated in data acquisition, or research execution, or both. All authors also participated in the analysis or interpretation of the data, or both. CQR, KB, CB, HL, VP, DS, and BS vouch for the data and analyses, and for the fidelity of this report to the study protocol and data analysis plan. All authors participated in the drafting and critical review of the study manuscript. All authors had full access to the study data and accept responsibility to submit the manuscript for publication.

Declaration of interests

JSH reports support from Genentech/Roche for the present manuscript; grants from Apellis, AsclepiX, Bayer, Gyroscope, Hemera, Iveric Bio, Kanghong, Kodiak, NGM, Notal Vision, Novartis, Regeneron, Regenxbio, and Stealth, outside the submitted work; and consulting fees from Apellis, AsclepiX, Bayer, Gyroscope, Hemera, Iveric Bio, Kanghong, Kodiak, NGM, Notal Vision, Novartis, Regeneron, Regenxbio, and Stealth. AMK reports grants or contracts to institution from Adverum, Allergan, Chengdu Kanghong, Genentech, Graybug, Novartis, Ophthea, Regenxbio, and Roche, outside the submitted work; consulting fees from Adverum, Allergan, Chengdu Kanghong, Genentech, Graybug, Novartis, Ophthea, Regenxbio, and Roche, outside the submitted work; payment or honoraria for lectures, presentations, or speaker bureaus from Allergan, Genentech, and Novartis, outside the submitted work; and has served on advisory boards for Adverum, Allergan, Chengdu Kanghong, Genentech, Novartis, Ophthea, Regenxbio, and Roche. CQR is an employee of Genentech and reports owning stocks in Roche. KB is an employee of Roche Products (Ireland). PJF reports patient care grants to institution (Vitreoretinal Consultants of New York) for various national clinical trials from Alkeus, Apellis, Chengdu Kanghong, Genentech, Gyroscope, Iveric Bio, Kodiak, NGM, and Regeneron; has served on advisory boards for Allergan and Genentech; and is the president of the American Association of Retinal Specialists (unpaid). CB is an employee of Genentech, and reports owning stocks in Roche. MSF reports consulting fees from Alcon, Bayer, Novartis, Roche, and Zeiss. HL is an employee of Genentech, and has received stock from Genentech/Roche as an employee; has received support from Genentech/Roche to attend meetings as an employee; and is a coauthor on patent application WO202123804 involving the PTI algorithm. FGH reports research grants or contracts to institution from Bayer, Bioeq/Formycon, Kanghong, Novartis, and Roche/Genentech; consulting fees from Bayer, Kanghong, Novartis, and Roche/Genentech; and payment or honoraria for lectures, presentations, or speaker bureaus from Bayer and Novartis. VP is an employee of F Hoffmann-La Roche (UK). TYYL reports grants or contracts to institution from Bayer, Chengdu Kanghong, and Novartis, outside the submitted work; consulting fees from Bayer, Boehringer Ingelheim, Novartis, Oculis, and Roche, outside the submitted work; and payment or honoraria for lectures, presentations, or speaker

bureaus from Bayer, Chengdu Kanghong, Novartis, and Roche, outside the submitted work. DS is an employee of F Hoffmann-La Roche (UK); owns stock and stock options in Roche; and is a coauthor on patent application WO202123804 involving the PTI algorithm. CR reports research support from Allergan, Kodiak, Novartis, and Regeneron, outside the submitted work; and consulting fees from Allergan, Genentech, Kodiak, and Novartis, outside the submitted work. BS is an employee of F Hoffmann-La Roche. FV reports consulting fees from Bayer and Roche; payments for expert testimony from Bayer and Roche; and payments for participation on advisory boards for Bayer and Roche. CMGC reports grants or contracts from Bayer, Boehringer Ingelheim, Novartis, and Topcon, outside the submitted work; consulting fees from Novartis and Roche, outside the submitted work; speaker fees from Allergan, Bayer, Novartis, Roche, Topcon, and Zeiss, outside the submitted work; and support for travel to meetings from Bayer and Topcon. TYW reports clinical trial grants from Aldropika, Allergan, Bayer, Boehringer Ingelheim, Eden Ophthalmic, Genentech, Iveric Bio, Merck, Novartis, Oxurion (ThromboGenics), Roche, Samsung, Shanghai Henlius, and Zhaoke, outside the submitted work; consulting fees from Aldropika, Allergan, Bayer, Boehringer Ingelheim, Eden Ophthalmic, Genentech, Iveric Bio, Merck, Novartis, Oxurion (ThromboGenics), Roche, Samsung, Shanghai Henlius, and Zhaoke, outside the submitted work; payment or honoraria from Allergan, Bayer, Boehringer Ingelheim, Eden Ophthalmic, Genentech, Iveric Bio, Merck, Novartis, Oxurion (ThromboGenics), Roche, Samsung, Shanghai Henlius, and Zhaoke, outside the submitted work; support for travel from Aldropika, Allergan, Bayer, Boehringer Ingelheim, Eden Ophthalmic, Genentech, Iveric Bio, Merck, Novartis, Oxurion (ThromboGenics), Roche, Samsung, Shanghai Henlius, and Zhaoke; and has served on advisory boards of Aldropika, Allergan, Bayer, Boehringer Ingelheim, Eden Ophthalmic, Genentech, Iveric Bio, Merck, Novartis, Oxurion (ThromboGenics), Roche, Samsung, Shanghai Henlius, and Zhaoke.

Data sharing

Qualified researchers can request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available online (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see online (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Acknowledgments

We thank the patients who participated in these trials and their families, the investigators, and staff at all the TENAYA and LUCERNE clinical sites, and the members of the independent data and safety monitoring committee. We thank Aaron Osborne for his contribution to the design of the TENAYA and LUCERNE trials. F Hoffmann-La Roche (Basel, Switzerland) provided support for the study and participated in the study design; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the article for publication. Funding was provided by F Hoffmann-La Roche for third-party writing assistance, which was provided by Dinakar Sambandan of Envision Pharma Group.

Editorial note: The *Lancet* Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

References

1 Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. *Lancet* 2018; **392:** 1147–59.

2 American Academy of Ophthalmology Retina/Vitreous PPP Panel, Hoskins Center for Quality Eye Care. Preferred Practice Pattern®. Age-related macular degeneration. 2019. https://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp (accessed Sept 16, 2020).

3 Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355:** 1419–31.

4 Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology* 2012; **119:** 2537–48.

5 Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology* 2020; **127:** 72–84.

6 Holz FG, Tadayoni R, Beatty S, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. *Br J Ophthalmol* 2015; **99:** 220–26.

7 Ciulla TA, Hussain RM, Pollack JS, Williams DF. Visual acuity outcomes and anti-vascular endothelial growth factor therapy intensity in neovascular age-related macular degeneration patients: a real-world analysis of 49 485 eyes. *Ophthalmol Retina* 2020; **4:** 19–30.

8 Khanani AM, Skelly A, Bezlyak V, Griner R, Torres LR, Sagkriotis A. SIERRA-AMD: a retrospective, real-world evidence study of patients with neovascular age-related macular degeneration in the United States. *Ophthalmol Retina* 2020; **4:** 122–33.

9 Prenner JL, Halperin LS, Rycroft C, Hogue S, Williams Liu Z, Seibert R. Disease burden in the treatment of age-related macular degeneration: findings from a time-and-motion study. *Am J Ophthalmol* 2015; **160:** 725–31.

10 Daien V, Finger RP, Talks JS, et al. Evolution of treatment paradigms in neovascular age-related macular degeneration: a review of real-world evidence. *Br J Ophthalmol* 2021; **105:** 1475–79.

11 Okada M, Mitchell P, Finger RP, et al. Nonadherence or nonpersistence to intravitreal injection therapy for neovascular age-related macular degeneration: a mixed-methods systematic review. *Ophthalmology* 2021; **128:** 234–47.

12 Singer MA, Awh CC, Sadda S, et al. HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology* 2012; **119:** 1175–83.

13 Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 1. *Am J Ophthalmol* 2008; **145:** 239–48.

14 Wykoff CC, Croft DE, Brown DM, et al. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. *Ophthalmology* 2015; **122:** 2514–22.

15 Campochiaro PA. Molecular pathogenesis of retinal and choroidal vascular diseases. *Prog Retin Eye Res* 2015; **49:** 67–81.

16 Heier JS, Singh RP, Wykoff CC, et al. The angiopoietin/Tie pathway in retinal vascular diseases: a review. *Retina* 2021; **41:** 1–19.

17 Joussen AM, Ricci F, Paris LP, Korn C, Quezada-Ruiz C, Zarbin M. Angiopoietin/Tie2 signalling and its role in retinal and choroidal vascular diseases: a review of preclinical data. *Eye* 2021; **35:** 1305–16.

18 Regula JT, Lundh von Leithner P, Foxton R, et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases. *EMBO Mol Med* 2016; **8:** 1265–88.

19 Schaefer W, Regula JT, Bähner M, et al. Immunoglobulin domain crossover as a generic approach for the production of bispecific IgG antibodies. *Proc Natl Acad Sci USA* 2011; **108:** 11187–92.

20 Khanani AM, Patel SS, Ferrone PJ, et al. Efficacy of every four monthly and quarterly dosing of faricimab vs ranibizumab in neovascular age-related macular degeneration: the STAIRWAY phase 2 randomized clinical trial. *JAMA Ophthalmol* 2020; **138:** 964–72.

21 Sahni J, Dugel PU, Patel SS, et al. Safety and efficacy of different doses and regimens of faricimab vs ranibizumab in neovascular age-related macular degeneration: the AVENUE phase 2 randomized clinical trial. *JAMA Ophthalmol* 2020; **138:** 955–63.

22 Khanani AM, Guymer RH, Basu K, et al. TENAYA and LUCERNE: rationale and design for the phase 3 clinical trials of faricimab for neovascular age-related macular degeneration. *Ophthalmol Sci* 2021; **1:** 100076.

23 Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology* 2013; **120:** 1046–56.

24 Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011; **364:** 1897–908.

25 Gillies MC, Hunyor AP, Arnold JJ, et al. Effect of ranibizumab and aflibercept on best-corrected visual acuity in treat-and-extend for neovascular age-related macular degeneration: a randomized clinical trial. *JAMA Ophthalmol* 2019; **137:** 372–79.

26 Augsburger M, Sarra GM, Imesch P. Treat and extend versus pro re nata regimens of ranibizumab and aflibercept in neovascular age-related macular degeneration: a comparative study. *Graefes Arch Clin Exp Ophthalmol* 2019; **257:** 1889–95.

27 Silva R, Berta A, Larsen M, Macfadden W, Feller C, Monés J. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration: results with ranibizumab from the TREND study. *Ophthalmology* 2018; **125:** 57–65.

28 American Society of Retina Specialists. Member update: Novartis-appointed safety review committee reports initial brolucizumab findings. 2020. https://www.brolucizumab.info/sites/brolucizumab_info/files/2020–07/ASRS_SRC_report.pdf (accessed June 25, 2021).

29 Eylea. Prescribing information. Tarrytown, NY: Regeneron Pharmaceuticals, 2021.