Core Submission Dossier PTJA09

Brolucizumab
for the treatment of neovascular (wet) age-related macular degeneration (wAMD)

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Abbreviations

AAO	American Academy of Ophthalmology
AE	Adverse event
Afli	Aflibercept
AMD	Age-related macular degeneration
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
BCVA	Best-corrected visual acuity
Bev	Bevacizumab
BL	Baseline
Bro	Brolucizumab
CDR	Complementarity-determining regions
CFT	Central field thickness
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Confidence limit
CMT	Central macular thickness
CNV	Choroidal neovascularisation
CRC	Central reading clinic
CRF	Case report form
CrI	Credibility interval
CRT	Central retinal thickness
CSFT/CST	Central subfield thickness
CSR	Clinical study report
DAA	Disease activity assessment
DAs	Disc areas
DIC	Deviance information criterion
DRG	Decision Resources Group
DSU	Decision support unit
eCRF	Electronic case report form
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	EuroQoL-5 Dimensions
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EURETINA	European Society of Retina Specialists
FA	Fluorescein angiography
Fab	Fragment, antigen-binding
FAS	Full analysis set
Fc	Fragment crystallisable
FDA	Food and Drug Administration
HAS	Haute Autorité de Santé
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICD	International Classification of Diseases
ICG	Indocyanine green
ID	Identification
IQR	Interquartile range
IRF	Intraretinal fluid
IRT	Interactive response technology
ITT	Intention-to-treat
IVT	Intravitreal
kDa	Kilodalton
LOCF	Last observation carried forward
logMAR	Logarithm of the minimum angle of resolution
LP	Loading phase

LS	Least square
LSM	Least square mean
LSMD	Least square mean difference
MCMC	Markov Chain Monte Carlo
mg	Milligram
mL	Millilitre
NCT	National clinical trial
NEI	National Eye Institute
NG	NICE guideline
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMPA	The National Medical Products Administration
NR	Not reported
OCT	Optical coherence tomography
OR	Odds ratio
PCV	Polypoidal choroidal vasculopathy
PDS	Port Delivery System
PDT	Photodynamic therapy
PICOS	Population, Intervention, Comparators, Outcomes, Study design
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per-protocol analysis set
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
PRN	Pro re nata
PRNX	Pro re nata and extend
QOL	Quality of life
qXw	One injection every X weeks
RAN	All randomised analysis set
Rani	Ranibizumab
RCT	Randomised controlled trial
REA	Relative Effectiveness Assessment
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SD	Standard deviation
SLR	Systematic literature review
SRF	Subretinal fluid
TEAEs	Treatment-emergent adverse events
TGA	Therapeutic Goods Administration
TREX	Treat-and-extend
TTT	Transpupillary thermotherapy
UK	United Kingdom
USA	United States of America
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VFQ	Visual Function Questionnaire
V_H	Variable domain, heavy-chain
V_L	Variable domain, light-chain
wAMD	Wet age-related macular degeneration

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Submission summary

This submission presents the relative effectiveness of brolucizumab as a treatment for neovascular (wet) age-related macular degeneration (wAMD) in adults versus the currently licensed comparators ranibizumab and aflibercept.

Disease overview

wAMD is an acute onset and rapidly progressing disease characterised by the leaking of fluid from the formation of abnormal blood vessels underneath the macula (choroidal neovascularisation [CNV]).[1-3] CNV is the defining feature in wAMD and occurs in response to abnormally high levels of vascular endothelial growth factor (VEGF). The newly formed blood vessels are fragile and leak fluid, and this progressive exudation from the macula can lead to the separation of Bruch's membrane, retinal pigment epithelium (RPE) and retina, the accumulation of sub-RPE, sub-retinal fluid (SRF) and/or intra-retinal fluid (IRF), and the generalised thickening of the retina (central subfield thickness [CSFT]). Unresolved fluid accumulation consequently leads to the progressive damage of photoreceptors, resulting in severe, irreversible vision loss, metamorphopsia, scotoma, photopsia, dark adaptation difficulties and eventually blindness.[1, 4] The control of fluid accumulation is therefore key to the effective management of wAMD and improving and maintaining vision.

wAMD is the leading cause of severe vision loss and legal blindness in people over the age of 65 in North America, Europe, Australia and Asia, impacting an estimated 20-25 million people worldwide.[5] The impact of wAMD on patients' health-related quality of life (HRQoL), independence and functional ability is substantial and patients with wAMD commonly require caregiver assistance to carry out essential daily activities.[6] The caregiver burden for patients with wAMD is reported to be equivalent to that for conditions such as rheumatoid arthritis and atrial fibrillation, and higher than the burden for colorectal cancer patients.[6, 7]

Clinical pathway of care and unmet need

The aim of wAMD treatment is to resolve the accumulation of retinal fluid and subsequently recover and/or preserve visual function.[8, 9] Early detection of disease onset, prompt therapeutic intervention and continuous follow-up to detect fluid accumulation are critical, as vision loss becomes irreversible with delayed diagnosis and treatment.[8] High-quality clinical guidelines on the treatment of wAMD are available worldwide and include those from EURETINA, AAO and from NICE (NICE clinical guideline NG82).[8, 10] These guidelines recommend the licensed anti-VEGF therapies aflibercept and ranibizumab for the first-line treatment of wAMD, and several studies have demonstrated that both therapies have equal efficacy and similar safety profiles.[11-13]

However, despite a reduction in the incidence of blindness due to wAMD since the availability of aflibercept and ranibizumab,[14, 15] the current management of wAMD is associated with distinct challenges relating to the high monitoring and injection frequency of these therapies. Real-world evidence demonstrates that visual outcomes with current anti-VEGF therapies are related to injection frequency; however, the high treatment burden impacts both patient adherence (due to factors such as injection fear, anxiety and the inconvenience of attending clinic appointments) as well as ophthalmology clinic capacity, which can lead to delay in follow-up of wAMD patients, placing these patients at risk of symptom exacerbation and vision loss.[16-18] Taken together, the high treatment and monitoring burden results in undertreatment, with mean injection frequency of anti-VEGF therapy being lower in real-world practice than in pivotal clinical trials, which can lead to poorer visual outcomes.[16, 19] There is a clear unmet need for a therapy with superior fluid reduction and better drying of the macular that can suppress disease activity for longer than currently available anti-VEGF therapies to enable the administration of less frequent injections immediately after the loading dose phase without compromising visual outcomes.[20]

Brolucizumab

Brolucizumab is the most clinically advanced, first-of-its-kind, humanised single chain antibody fragment (scFv) anti-VEGF therapy.[21] Brolucizumab binds with high affinity to all isoforms of VEGF-A which prevents the ligand-receptor interaction of VEGF receptors VEGFR1 and VEGFR2, thus preventing activation of the VEGF pathway.[22] With a molecular weight of ~26 kDa, brolucizumab has been engineered to achieve more drug per dose than ranibizumab or aflibercept, which can help deliver a long-lasting effect.

The anticipated posology of brolucizumab is 6 mg (0.05 mL solution) administered every 4 weeks (monthly) for the first three doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. A disease activity assessment is suggested 16 weeks (4 months) after treatment start. In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be considered. Physicians may further individualise treatment intervals based on disease activity.

Brolucizumab is currently undergoing review by the EMA; an opinion from the Committee for Medicinal Products for Human Use (CHMP) is expected in December 2019 and the European Commission decision is anticipated in February 2020.

As the first anti-VEGF therapy to have an anticipated licensed q12/q8w dose immediately following the loading phase, brolucizumab addresses the unmet need associated with currently available anti-VEGF therapies, by providing patients and physicians with a therapy with superior fluid reduction and better drying of the macular that suppresses disease activity for a longer duration. In turn, this allows for an earlier extension in the treatment interval immediately following the loading dose phase, and the earlier identification of patients who are able to be maintained on a longer treatment interval. This may allow ophthalmology clinics to run on time and optimise clinic capacity,[20, 23] and will also benefit patients and caregivers by reducing the treatment burden, which may in turn improve patient adherence.

Clinical effectiveness

The efficacy of brolucizumab as a treatment for wAMD has been demonstrated in three large randomised head-to-head trials versus aflibercept; comprising two phase III trials (HAWK and HARRIER) and one phase II trial (OSPREY).[24-26]

Across both the HAWK and HARRIER trials brolucizumab achieved clinically meaningful and consistent visual gains with a majority of patients maintained on a q12w dosing interval immediately following the loading dose phase. The clinical evidence demonstrated that treatment with brolucizumab required fewer injections on average to achieve a similar improvement in BCVA versus aflibercept, with a majority of patients maintained on a q12w dosing interval immediately following the loading dose phase. In addition, brolucizumab was statistically significantly superior to aflibercept in terms of improvements in CSFT, retinal fluid (IRF and/or SRF) and disease activity. The ability to reduce fluid accumulation better than aflibercept, and sustain it, in turn allows for a longer dosing interval immediately following the loading dose phase. The safety profile of brolucizumab is also comparable to the safety profile of aflibercept; the overall incidence of ocular and non-ocular AEs was balanced across all treatment groups in both HAWK and HARRIER trials and no new, previously unreported types of AEs were identified compared with other anti-VEGF therapies.[24, 25]

Comparative effectiveness

In the absence of head-to-head data for brolucizumab versus ranibizumab, an NMA was performed to assess the efficacy and safety of brolucizumab versus the relevant comparators ranibizumab and aflibercept. 14 trials were included in the analysis and standard pairwise meta-

analyses based on direct comparisons were carried out between pairs of treatments where possible. Regimen-based baseline pooling was conducted for the mean change in BCVA, patients gaining at least 15 ETDRS letters, patients losing at least ETDRS 15 letters, injection frequency, and the incidence of AEs. Molecule-based baseline pooling was conducted for treatment discontinuation as well as AEs.

The results of the NMA demonstrated brolucizumab to be associated with comparable efficacy versus aflibercept and ranibizumab in terms of change in BCVA from Baseline to one and two years. The NMA also demonstrated brolucizumab to be statistically significantly superior to all aflibercept and ranibizumab regimens at decreasing retinal thickness from Baseline to one year. Results of the arm-based baseline pooling for injection frequency demonstrated brolucizumab to be associated with one of the lowest injection frequencies across year one and the lowest injection frequency in year two versus all aflibercept and ranibizumab regimens. Taken together, the results of the NMA further support the comparable efficacy of brolucizumab in terms of improvements in BCVA and as well as the superior improvements in CSFT reduction and reduced injection frequency requirements versus currently licensed anti-VEGF therapies ranibizumab and aflibercept.

Summary

Brolucizumab provides comparable visual gains in terms of change in BCVA versus ranibizumab and aflibercept, whilst providing statistically significantly superior anatomical outcomes in terms of greater reductions in CSFT. Compared with aflibercept, treatment with brolucizumab also led to significantly fewer patients with disease activity, and significantly fewer patients with IRF and/or SRF.[24, 25] This is achieved with 56% (HAWK) and 51% (HARRIER) of brolucizumab 6 mg-treated patients maintained on a q12w dosing interval immediately after loading up to Week 48.[24, 25] Brolucizumab is therefore able to provide equivalent visual gains in terms of BCVA to current standard of care, at a reduced injection frequency, offering a solution to the current patient and healthcare system burdens contributed to by ranibizumab and aflibercept.

1 Description and technical characteristics of the technology

Summary of the characteristics of the technology

- Wet age-related macular degeneration (wAMD) is an acute onset and rapidly progressing disease characterised by the leaking of fluid from the formation of abnormal blood vessels underneath the macula.[1, 3] This phenomenon, known as choroidal neovascularisation (CNV), is the defining feature in wAMD and occurs in response to abnormally high levels of VEGF[2].
- Brolucizumab is a humanised monoclonal single chain Fv (scFv) inhibitor of VEGF-A designed specifically for the treatment of wAMD.[21, 27] An scFv comprises only the variable domains of the monoclonal antibody (joined by a short flexible linker peptide) that are responsible for binding to its receptor. As such, an scFv is an autonomous binding agent that is no longer dependent on a heavy molecular support structure and still retains full binding capacity to its target[21, 28].
- Brolucizumab binds with high affinity to all isoforms of VEGF-A, which prevents the ligand-receptor interaction of VEGF-A with the receptors VEGFR1 and VEGFR2.[27] This prevents activation of the VEGF pathway, thereby reducing pathological neovascularisation and decreasing vascular permeability, resulting in less fluid leakage and the preservation of visual function.[27]
- Brolucizumab has a smaller molecular size than both of the current gold standard treatments for wAMD, ranibizumab and aflibercept, allowing more drug per dose. The smaller size of brolucizumab may also facilitate rapid and more effective penetration of the different retinal layers, resulting in faster elimination from the systemic system with a similar ocular half-life to currently available licensed anti-VEGF therapies.[21, 29] Taken together, these features of brolucizumab contribute to better fluid resolution which enable brolucizumab to be administered less frequently immediately after the loading dose phase than currently available licensed anti-VEGF therapies.[21, 29]
- The anticipated posology of brolucizumab is 6 mg (0.05 mL solution) administered every 4 weeks (monthly) for the first three doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. A disease activity assessment is suggested 16 weeks (4 months after treatment start). In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be considered. Physicians may further individualise treatment intervals based on disease activity.[27]
- A marketing authorisation application for brolucizumab for the treatment of wAMD was submitted to the EMA via the centralised procedure on the 6th February 2019, with a confirmed procedure start of 28th February 2019. An opinion from the CHMP is expected in December 2019 and the European Commission decision is anticipated in February 2020.

1.1 Characteristics of the technology

1. **In Table 1 provide an overview of the technology.**

Table 1: Features of the technology

Non-proprietary name	Brolucizumab
Proprietary name	Beovu
Marketing authorisation holder	Novartis Europharm Limited
Class	Anti-vascular endothelial growth factor (VEGF)
Active substance(s)	Brolucizumab

Pharmaceutical formulation(s)	120 mg/mL solution for injection in pre-filled syringe 120 mg/mL solution for injection
ATC code	S01LA06
Mechanism of action	The VEGF pathway regulates the development of blood vessels. Increased signalling through the VEGF pathway is associated with the pathological manifestations of wAMD such as CNV and retinal oedema,[30] with VEGF-A emerging as the most important regulator of angiogenesis.[31] Brolucizumab is a humanised monoclonal single chain Fv (scFv) antibody fragment with a molecular weight of ~26 kDa. It is administered via intravitreal injection where it binds with high affinity to all isoforms of VEGF-A, which prevents the ligand-receptor interaction of VEGF-A with the receptors VEGFR1 and VEGFR2, thus preventing activation of the VEGF pathway.[22, 32] By inhibiting VEGF-A binding, brolucizumab suppresses endothelial cell proliferation, thereby reducing pathological neovascularisation and decreasing vascular permeability, resulting in less fluid leakage and the preservation of visual function.

Abbreviations: ATC: anatomical therapeutic chemical; CHMP: Committee for Medicinal Products for Human Use; CNV: choroidal neovascularisation; EMA: European Medicines Agency; scFv: single-chain antibody fragment; VEGF: vascular endothelial growth factor; wAMD: wet age-related macular degeneration.
Source: Brolucizumab draft SmPC.[33]

2. In Table 2, summarise the information about administration and dosing of the technology.

Table 2: Administration and dosing of the technology

Method of administration	Brolucizumab is administered via intravitreal injection
Doses	The recommended dose is 6 mg (0.05 mL)
Dosing frequency	The anticipated posology of brolucizumab is 6 mg (0.05 mL solution) administered every 4 weeks (monthly) for the first three doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. A disease activity assessment is suggested 16 weeks (4 months) after treatment start. In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be considered. Physicians may further individualise treatment intervals based on disease activity.
Average length of a course of treatment	Treatment is continuous. If visual and anatomical outcomes indicate that the patient is not benefitting from continued treatment, brolucizumab should be discontinued.
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	No dosage adjustments are necessary

Abbreviations: qXw: one injection every X weeks.
Source: Brolucizumab draft SmPC.[33]

3. State the context and level of care for the technology (for example, primary healthcare, secondary healthcare, tertiary healthcare, outside health institutions or as part of public health or other).

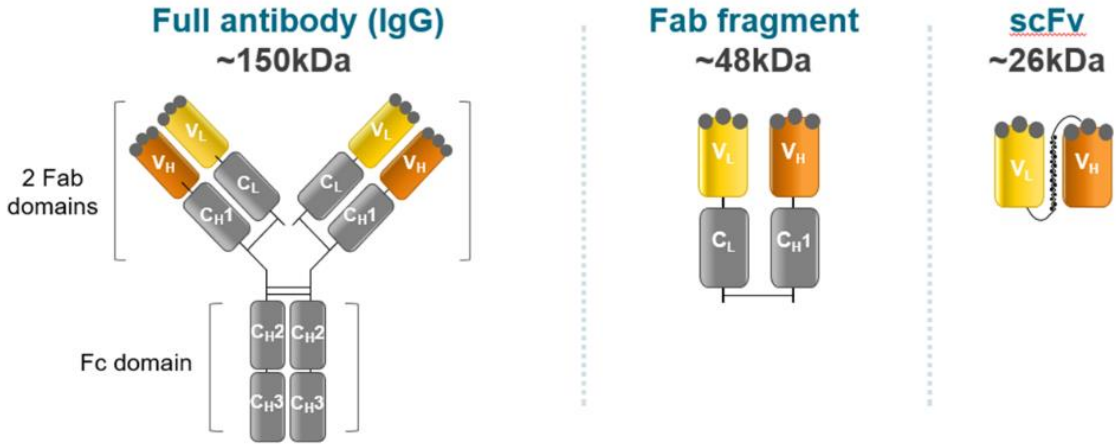
The setting of care for brolucizumab may vary between countries across Europe. Intravitreal injections are administered by qualified ophthalmologists at either an outpatient or day case visit in a hospital or clinic setting.

4. State the claimed benefits of the technology, including whether the technology should be considered innovative.

Brolucizumab is a humanised scFv inhibitor of VEGF-A designed specifically for the treatment of wAMD. Brolucizumab brings innovation to the wAMD treatment pathway as the most clinically advanced, humanised scFv inhibitor of VEGF-A.[21, 34]

An scFv is an autonomous binding agent that is no longer dependent on a heavy molecular support structure and still retains full binding capacity to its target. It comprises only the variable domains of the monoclonal antibody (joined by a short flexible linker peptide) that are responsible for binding to its receptor,[28] and advantages of scFvs may include effective tissue penetration and administration of more drug in a single injection (Figure 1). To date, no other scFv inhibitor of VEGF-A has been approved for commercial use in ophthalmology.[21, 32, 35-37]

Figure 1: Structure of a full monoclonal antibody, Fab fragment and scFv



Abbreviations: C_H: constant domain, heavy-chain; C_L: constant domain, light-chain; Fab: fragment, antigen-binding; Fc: fragment crystallizable; Ig: immunoglobulin; kDa: kilodalton; scFv: single-chain antibody fragment; V_H: variable domain, heavy-chain; V_L: variable domain, light-chain.

The licensed anti-VEGF therapies ranibizumab and aflibercept comprise the current standard of care for wAMD across Europe[8, 10, 38, 39] With a molecular weight of ~26 kDa, brolucizumab has been engineered to achieve more drug per dose than ranibizumab or aflibercept (Figure 2). Whilst the ocular half-lives of ranibizumab and aflibercept are similar,[40] the smaller size brolucizumab may facilitate the drug to more rapidly and effectively distribute from the vitreous to the retina, resulting in faster elimination from the systemic system with a similar ocular half-life to currently available licensed anti-VEGF therapies.[21, 29] Taken together, these advantages of brolucizumab contribute to better fluid resolution, which in turn enables brolucizumab to be administered at less frequent intervals immediately following the loading phase than currently available licensed anti-VEGF therapies ranibizumab and aflibercept. Brolucizumab can be administered every 12 weeks immediately following the initial loading dose phase.

Figure 2: Comparison of anti-VEGF treatments

	Aflibercept	Ranibizumab	Brolucizumab
Format	VEGFR1/2-Fc fusion protein	Fab fragment	single-chain antibody fragment
Molecular structure			
Molecular weight	97-115 kDa	~48 kDa	26 kDa

Abbreviations: C_H: constant domain, heavy-chain; C_L: constant domain, light-chain; Fc: fragment crystallizable; kDa: kilodalton; V_H: variable domain, heavy-chain; V_L: variable domain, light-chain; VEGFR: vascular endothelial growth factor receptor.

1.2 Regulatory status of the technology

1. **Complete Table 3 with the marketing authorisation status of the technology.**

Please refer to Table 3 for details of the marketing authorisation status of brolucizumab worldwide.

2. **State any other indications not included in the assessment for which the technology has marketing authorisation.**

The current wAMD assessment is the first indication for brolucizumab. No other indications have been submitted for regulatory approval.

3. **State any contraindications or groups for whom the technology is not recommended.**

Brolucizumab is contraindicated in patients with:

- Hypersensitivity to the active substance or to the following excipients: sodium citrate, sucrose, polysorbate 80, water for injections
- Active or suspected ocular or periocular infections
- Active intraocular inflammation.[33]

4. **List the other countries in which the technology has marketing authorisation.**

Approval from the US Food and Drug Administration (FDA) for brolucizumab for the treatment of wAMD was received on 7th October 2019. Please see Table 3 for details of the marketing authorisation status of brolucizumab in other countries.

Table 3: Regulatory status of the technology

Country	Organisation issuing approval	Verbatim wording of the (expected) indication(s)	(Expected) Date of approval	Launched (yes/no). If no include proposed date of launch
European countries				
Member States of the European Union (EU) and the European Economic Area (EEA)	EMA	Beovu is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD)	February 2020	No (date to be confirmed)
Switzerland	Swissmedic	Beovu is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD)	March 2020	No (date to be confirmed)
Other countries				
USA	FDA	Beovu is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD)	7 October 2019	Yes
Canada	Health Canada	Beovu is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD)	March 2020	No (date to be confirmed)
Australia	Therapeutic Drugs Administration (TGA)	Beovu is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD)	March 2020	No (date to be confirmed)
Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	Age-related macular degeneration (AMD) with subfoveal choroidal neovascularization (CNV)	June 2020	No (date to be confirmed)

Abbreviations: AMD: age-related macular degeneration; CNV: choroidal neovascularisation; EEA: European Economic Area ; EMA: European Medicines Agency; EU: European Union; FDA: Food and Drug Administration; NMPA: The National Medical Products Administration; PMDA: Pharmaceuticals and Medical Devices Agency; TGA: Therapeutic Drugs Administration.

2 Health problem and current clinical practice

Summary of issues relating to the health problem and current clinical practice

- AMD is a chronic eye disease characterised by the progressive degeneration of the macula, the area of the retina responsible for sharp, central vision. Left untreated, AMD can lead to rapid, irreversible vision loss. wAMD develops in only 10%–20% of all AMD cases, however, it is responsible for around 80%–90% of the vision loss associated with AMD. wAMD is the leading cause of severe vision loss and legal blindness in people over the age of 65 in Europe, and the size of the wAMD population (≥60 years) in Europe has been estimated to be approximately 1.7 million people.
- wAMD is an acute onset and rapidly progressing disease, characterised by the leaking of fluid from abnormal blood vessels growing beneath the macula (choroidal neovascularisation [CNV]) which occurs in response to abnormally high levels of vascular endothelial growth factor (VEGF). Fluid accumulation results in generalised thickening of the retina, which unresolved, can lead to the progressive damage of photoreceptors and severe, irreversible vision loss.
- The vision loss associated with wAMD has a profound negative impact on patient health-related quality of life (HRQoL), independence and functional ability. This results in patients utilising considerable resources from the healthcare system and community in order to function adequately in society. The wAMD-associated caregiver burden can be substantial and is reported to be equivalent to that for conditions such as rheumatoid arthritis and atrial fibrillation, and higher than the burden for colorectal cancer patients.
- Current management of wAMD is associated with challenges related to the injection frequency of currently licensed anti-VEGF therapies. This high injection frequency impacts patient adherence and places a burden on ophthalmology clinic capacity, which can put patients at risk of undertreatment and symptom exacerbation. To reduce this treatment burden, physicians tend to adopt flexible treatment regimens, including pro re nata (PRN), with treatment administered on an 'as-needed' basis, and treat-and-extend (T&E). In practice this means that in some cases physicians are waiting for signs of disease activity, such as retinal fluid, to return before providing further treatment, leading to sub-optimal treatment outcomes. There is a clear unmet need for a therapy that suppresses disease activity and fluid accumulation for longer than currently available licensed anti-VEGF therapies, and allows for the prediction of patients that can be maintained on a longer treatment interval, enabling the administration of less frequent injections without reducing visual outcomes.
- As the first anti-VEGF therapy to have a licensed q12/q8w dose immediately following the loading phase, brolucizumab addresses the unmet need associated with currently available licensed anti-VEGF therapies. The early identification of patients who are able to receive dosing at longer intervals may lead to better patient adherence and a reduced risk of under-treatment, leading to improved visual outcomes, patient independence and HRQoL.
- Brolucizumab is anticipated to be used in clinical practice in accordance with its full licensed indication, for the treatment of wAMD. Therefore, the relevant comparators to brolucizumab in this position are the licensed anti-VEGF therapies ranibizumab and aflibercept.

2.1 Overview of the disease or health condition

1. Define the disease or health condition in the scope of this assessment.

AMD is a chronic eye disease characterised by the progressive degeneration of the macula, the area of the retina responsible for sharp, central vision. Left untreated, AMD can lead to rapid,

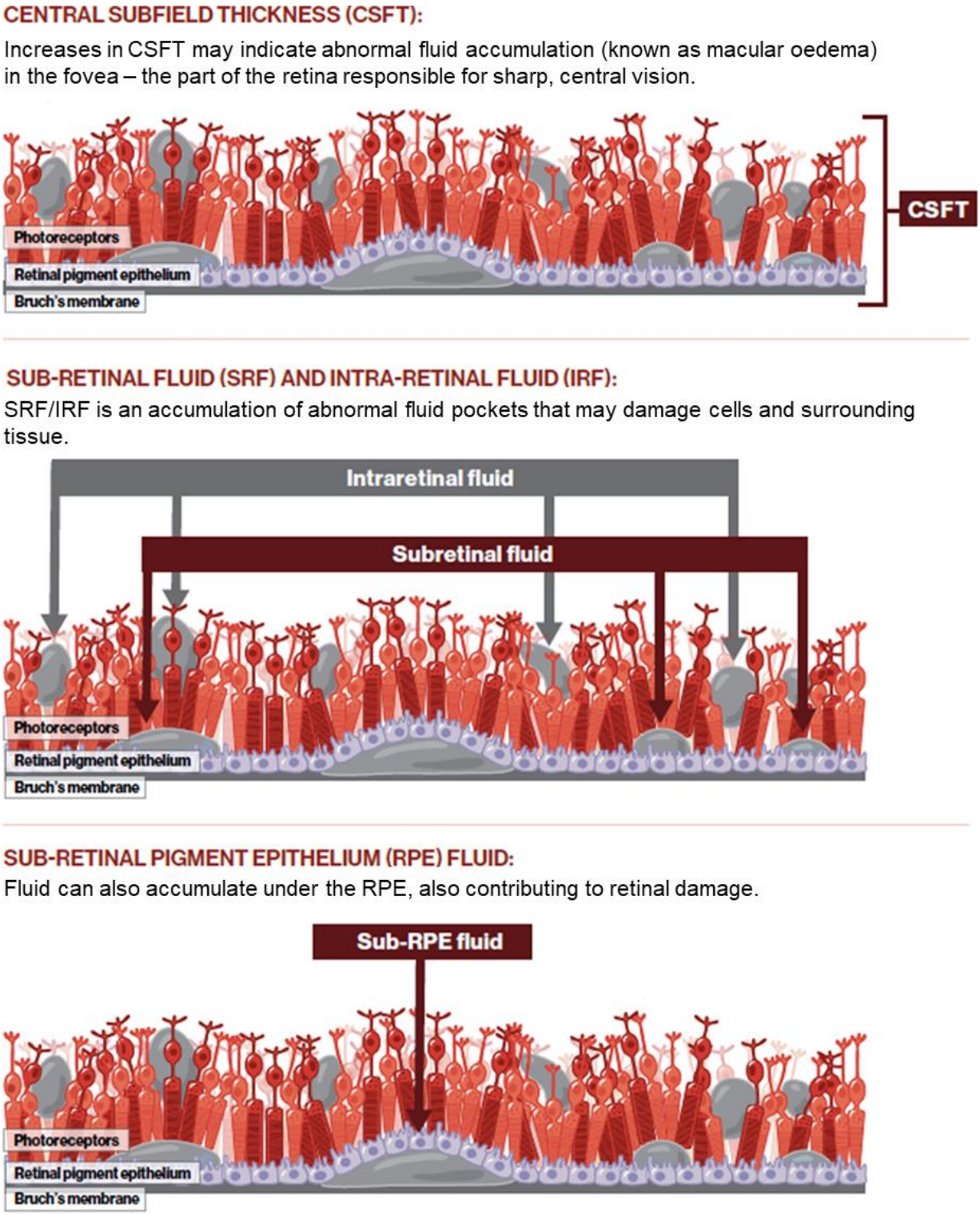
irreversible vision loss and globally, 8.7% of all cases of blindness are attributed to AMD.[41, 42] The late stages of disease progression in AMD (late AMD) are classified into two types: geographic atrophy/non-exudative (dry) and neovascular/exudative (wet), i.e. wAMD, the indication relevant to this appraisal. Dry AMD is more frequent than wAMD, occurring in 80–90% of all cases. Although wAMD develops in only 10%–20% of all AMD cases, it is responsible for around 80%–90% of the vision loss associated with AMD.[3, 43]

The ICD-9 and ICD-10 disease codes for wAMD are detailed in Section 7.1 of the Appendices, in Table 70 and Table 71 respectively.

Pathophysiology

wAMD is an acute and rapidly progressing disease characterised by the leaking of fluid from the formation of abnormal blood vessels underneath the macula.[1-3] This phenomenon, known as choroidal neovascularisation (CNV), is the defining feature in wAMD and occurs in response to abnormally high levels of VEGF.[2] The newly formed blood vessels are fragile and leak fluid, and progressive exudation from the macula can lead to the separation of Bruch's membrane, retinal pigment epithelium (RPE) and retina, and the accumulation of sub-RPE, subretinal fluid (SRF) and/or intraretinal fluid (IRF).[4] This leads to the generalised thickening of the retina (central subfield thickness [CSFT]) and the generation of cystic spaces (Figure 3).[4, 8] Unresolved fluid accumulation consequently leads to the disruption to the anatomical architecture of the retina ultimately leads to progressive, severe, and irreversible vision loss due to photoreceptor degeneration.[44] Patients may also experience metamorphopsia, scotoma, photopsia, dark adaptation difficulties, and eventually, irreversible vision loss.[8, 45-47] The control of fluid accumulation is therefore key to the effective management of wAMD and maintaining and improving vision.

Figure 3: Fluid accumulation in wAMD



Abbreviations: CSFT: central subfield thickness; SRF: subretinal fluid; IRF: intraretinal fluid; RPE: subretinal pigment epithelium.
Source: HAWK and HARRIER Fact Sheet.[48]

Diagnosis and monitoring of disease activity

Early detection of disease onset, prompt therapeutic intervention and continuous follow-up to detect fluid accumulation are critical for patients with wAMD, as vision loss becomes irreversible with delayed diagnosis and treatment.[8] Basic visual function tests such as Snellen's chart, the

Amsler grid and the Early Treatment Diabetic Retinopathy Study chart (ETDRS) are the most commonly used tools to determine the symptomatic impact of wAMD on patients' best-corrected visual acuity (BCVA).[8] For definitive diagnosis of disease, current clinical guidelines recommend the use of fundus angiography (FA) and optical coherence tomography (OCT), with FA used to detect fluid leakage, and OCT used for detailed imaging of pathophysiological changes.[8, 38, 49] For the follow-up and regular monitoring of the anatomical signs of disease activity, OCT is recommended.[8, 38, 49] In the past, time domain OCT was predominantly used to diagnose wAMD, but advances in OCT scanning techniques including spectral domain OCT (SD-OCT) and OCT angiography (OCT-A) are more commonly being used. While reimbursement decisions for wAMD therapies focus on BCVA outcomes, the real-world economic impact of anti-VEGF therapies is based on disease activity which drives (re)-treatment decisions and ultimately injection frequency, and these advances in diagnostic techniques will enable clinicians to visualise anatomical changes in even more detail to aid the earlier detection of fluid accumulation.[8]

2. Present an estimate of prevalence and/or incidence for the disease or health condition including recent trends.

Prevalence

wAMD is the leading cause of severe vision loss and legal blindness in people over the age of 65 in Europe, North America, Australia and Asia, and impacts an estimated 20–25 million people worldwide.[8, 50] Prevalence reports have estimated that wAMD affects approximately 1.7 million people in Europe.[51, 52]

A comprehensive meta-analysis of AMD epidemiology data with a focus on ethnic and geographic variations was published in 2014 and included 129,664 patients (aged 30–97 years) with 12,727 AMD cases from 39 publications. For wAMD, the global prevalence in adults aged 45–85 years (based on a pooled estimate of eight studies) was estimated to be 0.46% (95% CrI, 0.18–1.08).[42] The prevalence of late AMD was estimated to be highest in people of European ancestry (0.5%; 95% CrI, 0.26–1.08).[42]

Globally, the prevalence of late AMD has been estimated at around 11.26 million for 2020, increasing to 18.57 million by 2040.[42] The prevalence of late AMD in Europe in 2014 was 2.57 million. This has been estimated to rise to 2.84 million in 2024, 3.46 million in 2034 and 3.69 million in 2040.[42] In developed nations, the projected increase in population ageing is a contributing factor to the projected increase in wAMD prevalence, with the proportion of the population aged ≥ 60 years projected to increase 35% in Europe.[53]

Incidence

Recently published country-specific data on the incidence of wAMD are extremely limited. A study by Buitendijk et al. from 2013 estimated the incidence of late AMD in Europe to be between 2.9–3.7 per 1000 person years.[54] For gender specific rates, a study of the UK population from 2012 estimated the annual incidence of wAMD at 2.3 per 1000 women (95% CrI 2.4% to 6.8%) and 1.4 per 1000 men (95% CrI 0.8% to 2.4%).[55] It is anticipated that these rates are reflective of other European countries.

3. Describe the symptoms and burden of the disease or health condition for patients.

Symptoms

The early and intermediate stages of AMD usually occur without symptoms, with minimal or no vision loss.[56] As the disease progresses into late AMD, the symptoms of wAMD include reduced VA, blurred vision and image distortion. [46, 47, 57, 58]

Table 4: Common signs and symptoms of wAMD

Sign/Symptom	Description
Reduced VA	Reduced ability to see fine detail.[46]
Blurred vision	Blurriness in the visual field.[47]
Reduced contrast sensitivity	Reduced ability to differentiate between light/colour of two close objects, a practical example being reading at varying levels of illumination.[57]
Metamorphopsia	Image distortion leading to wavy vision.[47, 58]
Scotoma	Appearance of a blind spot, usually central, in the visual field.[47]
Photopsia	Quick, flashing, white lights.[45]
Difficulties in dark adaptation	The ability of the eye to adapt to recover sensitivity in low light following exposure to bright light.[46]

Abbreviations: VA: visual acuity; wAMD: wet age-related macular degeneration.

Patient and caregiver burden

wAMD is a debilitating, chronic disease that significantly impacts patients' HRQoL, independence and functional ability. Several studies have shown overall HRQoL to be significantly associated with the degree of visual impairment suffered.[59-61] Patients with wAMD commonly have difficulty carrying out activities of daily living, including reading, driving, meal preparation and self-care activities such as dressing, bathing and toileting.[6] As a result, wAMD patients have also been shown to be significantly more likely to develop anxiety and depression than those without wAMD.[59, 60]

Despite the success of licensed anti-VEGF therapies in reducing the incidence of wAMD-related blindness, wAMD is still associated with a visual morbidity burden due to vision loss.[62] wAMD patients are associated with an increased risk of vision-related comorbidities and falls and fractures, the need to access community support services, nursing home placement and increased mortality.[63-65]

The impaired ability to perform daily activities increases the likelihood of patients requiring caregiver assistance, and approximately 50% of patients with wAMD require caregiver support with instrumental daily activities such as telephone usage and food preparation.[6] As a result, the wAMD-associated caregiver burden can be substantial, and is reported to be equivalent to that for conditions such as rheumatoid arthritis and atrial fibrillation, and higher than the burden for colorectal cancer patients.[6]

Finally, the administration of currently available licensed anti-VEGF therapies involves high treatment frequency and regular monitoring, which contributes substantially to the patient and caregiver burden of the disease. Several studies have demonstrated reduced patient adherence as a result of the treatment burden associated with currently licensed anti-VEGF therapies, due to factors such as injection fear, anxiety and the inconvenience of attending regular clinic appointments.[23, 66]

2.2 *Target population*

1. Describe the target population and the proposed position of the target population in the patient pathway of care.

Brolucizumab is anticipated to be used in clinical practice in accordance with its full licensed indication, for the treatment of wAMD.

A summary of the clinical pathway of care for wAMD is shown in Figure 4, including the positioning of brolucizumab.

2. Provide a justification for the proposed positioning of the technology and the definition of the target population.

The proposed target population for brolucizumab is consistent with the anticipated marketing authorisation for brolucizumab, and the patient populations of the pivotal clinical trials for brolucizumab in this indication (HAWK and HARRIER).[24, 25, 27]

Brolucizumab is expected to replace the licensed anti-VEGF therapies ranibizumab and aflibercept, which are both recommended as first-line treatments for wAMD across Europe.

3. Estimate the size of the target population. Include a description of how the size of the target population was obtained and whether it is likely to increase or reduce over time.

A report prepared for the European Society of Retina Specialists (EURETINA) in 2017 estimated the size of the wAMD population (≥60 years) in Europe to be approximately 1.7 million people.[51] This estimate is further corroborated in a recent Disease Landscape and Forecast report by Decision Resources Group (DRG), estimating the total number of prevalent cases of wAMD in Europe to be 1.798 million in 2019 (1.724 million in 2017).[52]

The report by DRG provided estimates of the total prevalent cases up to 2026, as summarised in Table 5.[52] The wAMD population size is likely to increase over time, with population ageing a contributing factor, as the proportion of the population aged ≥ 60 years is projected to increase by 35% in Europe.[53]

Table 5: Estimates for European wAMD population sizes

Country (Year)	Estimated wAMD population size (prevalent cases, thousands)		
	2020	2023	2026
Europe	1,828	1,932	2,044
France	395	411	440
Germany	550	580	600
Italy	334	358	376
Spain	211	222	237
United Kingdom	338	361	391

Numbers reflect rounding. Estimates include both males and females ≥40 years. Data last updated June 2017.
Abbreviations: wAMD: wet age-related macular degeneration.
Source: DRG, 2019[52]

2.3 Clinical management of the disease or health condition

1. Describe the clinical pathway of care for different stages and /or subtypes of the disease being considered in the assessment.

The aim of wAMD treatment is to resolve the accumulation of retinal fluid and subsequently recover and/or preserve visual function, whilst slowing disease progression.[8, 9] Early detection of disease onset, prompt therapeutic intervention and continuous follow-up to detect fluid accumulation are critical, as vision loss becomes irreversible with delayed diagnosis and treatment.[8] Various diagnostic tools including SD-OCT (spectral domain optical coherence tomography) and fluorescein angiography (FA) are used to confirm diagnosis of late wAMD.[8, 38]

High-quality European and international clinical guidelines on the treatment of wAMD are available from EURETINA, NICE, HAS and AAO.[8, 10, 38, 39] These guidelines are summarised in Table 6, alongside recommendations from the key national guidelines across Europe. The recommendations made in these local guidelines may support, or be used in preference to, the recommendations made within the EURETINA guidelines. All the guidelines recommend the licensed anti-VEGF therapies ranibizumab and aflibercept for the first-line treatment of wAMD, and both therapies have also been assessed and recommended for reimbursement for the treatment of wAMD by NICE and HAS.[39, 67, 68] The guidelines from EURETINA and NICE recommend that photodynamic therapy (PDT) may be offered in particular patient subgroups, or as an adjunct to anti-VEGF therapy only as second-line treatment.[10] A summary of the clinical pathway of care for wAMD is shown in Figure 4.

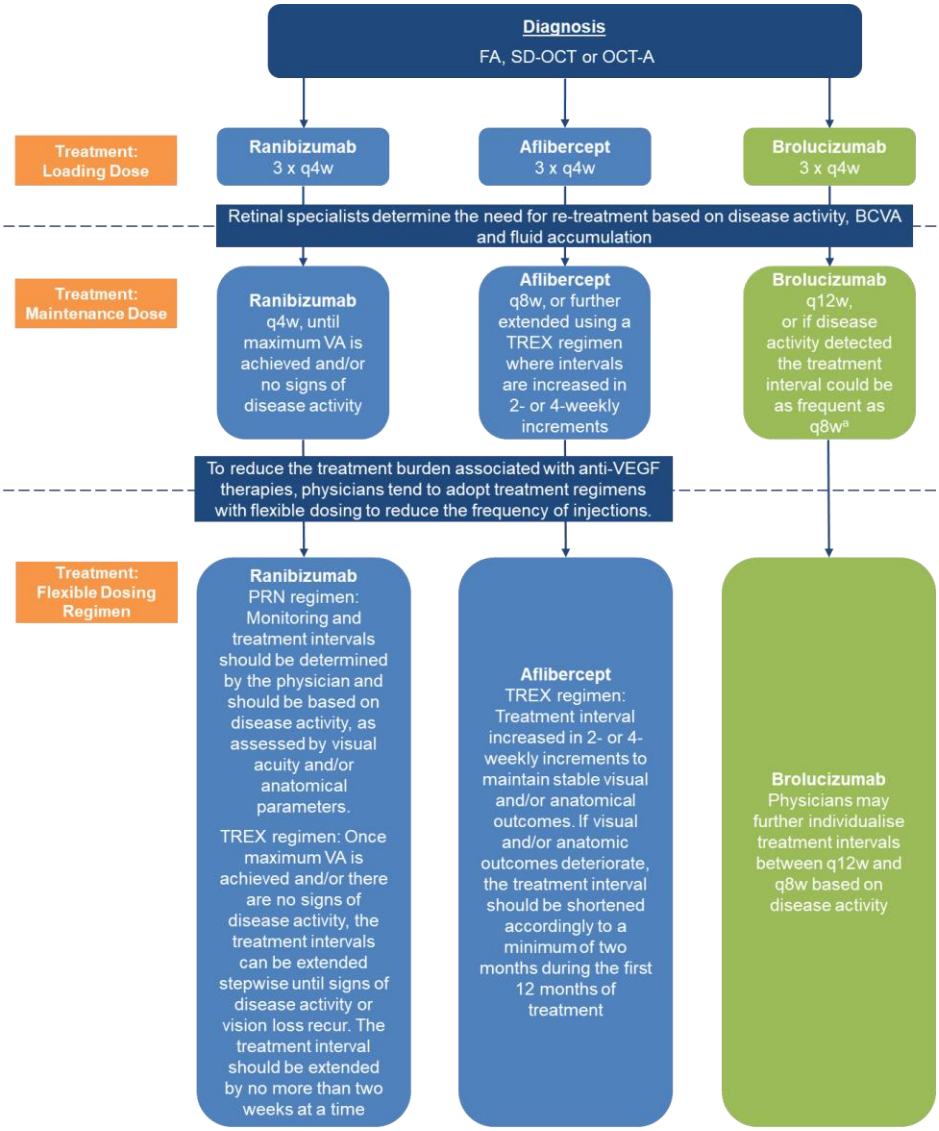
The development of the licensed anti-VEGF therapies, ranibizumab and aflibercept, has revolutionised the management of wAMD and several studies have demonstrated that both therapies have equal and similar safety profiles.[11-13] However, the current management of wAMD is still associated with distinct challenges relating to the high monitoring and injection frequency of these therapies. Real-world evidence demonstrates that visual outcomes with currently licensed anti-VEGF therapies are related to injection frequency; however, the high treatment burden impacts both patient adherence (due to factors such as injection fear, anxiety and the inconvenience of attending clinic appointments) as well as ophthalmology clinic capacity, which can lead to delay in follow-up of wAMD patients, placing these patients at risk of symptom exacerbation and vision loss.[16-18] Taken together, the high injection burden results in undertreatment, with mean injection frequency of anti-VEGF therapy is lower in real-world practice than in pivotal clinical trials.[16, 19]

To reduce the treatment burden associated with currently licensed anti-VEGF therapies, the adoption of flexible treatment regimens is now more common, including pro re nata (PRN) and treat-and-extend (T&E). With a PRN regimen, patients are monitored frequently (as often as every month) and treatment is administered reactively on an ‘as-needed’ basis based on disease activity, as assessed by VA and/or anatomical parameters, including the accumulation of sub-RPE, sub-retinal and/or intra-retinal fluid and CSFT increases secondary to the presence of fluid.[69] In practice, this means that clinicians are waiting for disease activity to return before receiving additional treatment. If clinical capacity is not available to enable regular monitoring, patients may experience a delay with their treatment and therefore experience poorer outcomes. With a T&E regimen, the treatment interval may be extended in a stepwise manner until signs of disease activity or visual impairment recur, at this point the interval is shortened and only re-extended when the disease activity/visual impairment is controlled. Whilst the use of flexible treatment regimens may help to reduce the treatment burden of these therapies, as visual outcomes with currently licensed anti-VEGF therapies are related to injection frequency, these

flexible treatment regimens may, in turn, be associated with reduced visual outcomes when compared with fixed, continuous regimens.[16-18]

The limitations associated with currently licensed anti-VEGF therapies are therefore two-fold: a risk of undertreatment leading to symptom exacerbation and vision decline, and a need to maintain visual and anatomical outcomes whilst reducing the burden on ophthalmology clinic capacity. There is a clear unmet need for a therapy to suppress disease activity (fluid accumulation and CSFT) for longer than currently available licensed anti-VEGF therapies, enabling the administration of less frequent injections immediately after the loading dose phase without reducing visual outcomes. Furthermore, the earlier identification of patients who are able to be maintained on a longer treatment interval is critical, to enable ophthalmology clinics to plan ahead with regards to clinic capacity. In turn, this may lead to better patient adherence and a reduced risk of undertreatment, leading to improved visual outcomes, patient independence and HRQoL.

Figure 4: Clinical pathway for wAMD



[a]A disease activity assessment is suggested 16 weeks (4 months) after treatment initiation.[35]
Abbreviations: BCVA: best-corrected visual acuity; FA: fluorescein angiography; OCT-A: Optical coherence tomography angiography; qXw: one injection every X weeks; SD-OCT: spectral domain optical coherence tomography; T&E: treat-and-extend; VA: visual acuity; VEGF: vascular endothelial growth factor; wAMD: wet age-related macular degeneration.
Source: Ranibizumab SmPC;[70] Aflibercept SmPC;[71] Brolucizumab Draft SmPC.[33]

Table 6: Summary of available guidelines for diagnosis and management of wAMD

Country/ region	Are there guidelines available for this region?	Name of society/organisation issuing guidelines	Date of issue or last update	Summary of recommendations (Level of evidence/grade of recommendation for the indication under assessment)
USA	Yes	AAO	January 2015	• Aflibercept and ranibizumab recommended • PDT with verteporfin may be used for macular or occult CNV • For juxtafoveal CNV: PDT with verteporfin may be considered in select cases (off-label) • For extrafoveal classic CNV and juxtapapillary CNV: laser photocoagulation surgery
Europe	Yes	EURETINA	September 2014	• Aflibercept and ranibizumab recommended • For peripapillary CNV: PDT or laser photocoagulation may be used • For extrafoveal CNV in pregnant women: laser photocoagulation may be used
France	Yes	HAS	October 2017	• Aflibercept and ranibizumab recommended as first-line treatments in the management of patients with AMD and subfoveal CNV[a] • Laser photocoagulation is recommended in extra-foveolar forms only • PDT with verteporfin is only recommended in cases of contraindication or non-response to repeated anti-VEGFs
Germany	Yes	DOG	October 2015	• For AMD, aflibercept and ranibizumab are the available approved anti-VEGF therapies, and are considered equal based on their therapeutic effect[a] • PDT should be considered only in PCV • Therapy should be individualized based on features identified through SD-OCT (including the presence of fluid, change in retinal thickness,

		BVA, RG, DOG	November 2014	intraretinal cysts and sub-RPE fluid) • PRN, T&E and fixed-dose regimens can be applied depending on a patient's individual need • In the case of the initial loading phase or the following maintenance therapy showing no effect on morphology, a switch to another anti-VEGF is recommended
Italy	Yes	Fondazione BIETTI	October 2008	• Considering only clinical evidence, anti-VEGF therapy should be used. However, clinical evidences are applicable only in high frequency regimens, which are difficult to obtain in real clinical practice • Anti-VEGF therapy should have a loading phase • Anti-VEGF is strongly recommended in comparison to PDT; however, no recommendation is given regarding which anti-VEGF is preferred
Spain	Yes	SERV	January 2014	• Aflibercept and ranibizumab recommended[a]
UK	Yes	NICE	January 2018	• Aflibercept and ranibizumab recommended • PDT not to be offered as a monotherapy: PDT as an adjunct to anti-VEGF only recommended in second-line treatment, in the context of an RCT
Belgium	Yes	BRS	July 2019	• Aflibercept and ranibizumab recommended and considered equal based on their therapeutic effect.[a] • Current recommended treatment protocol: loading phase with 3 monthly injections followed by a T&E protocol up to a maximum interval of 12 weeks
Finland	YES	FMAD	June 2016	• Aflibercept and ranibizumab recommended for all patients and are considered equal based on their therapeutic effect.[a]
Poland	Yes	PTO	November 2014	• Aflibercept and ranibizumab recommended • PDT may be considered as an alternative if patients cannot receive intraocular injections
Portugal	Yes	DGS	2008	• Ranibizumab and aflibercept are recommended[a] • PRP and laser are also recommended
Croatia	No	N/A	N/A	N/A

Greece	No	N/A	N/A	N/A
Latvia	No	N/A	N/A	N/A
Lithuania	No	N/A	N/A	N/A
Slovakia	No	N/A	N/A	N/A
Slovenia	No	N/A	N/A	N/A
Switzerland	No	N/A	N/A	N/A

[a]Within these guidelines, the off-license use of bevacizumab is also recommended for the treatment of wAMD. As an unlicensed treatment, these recommendations have not been added within the main body of the table, as unlicensed medicines have not undergone rigorous regulatory scrutiny to enable a favourable efficacy/safety analysis to be made.

Abbreviations: AAO: American Academy of Ophthalmology; BRS: Belgian Retina Society; BVA: Berufsverband der Augenärzte; CNV: choroidal neovascularisation; DGS: Direção Geral de Saúde; DOG: Deutsche Ophthalmologische Gesellschaft; EURETINA: European Society of Retina Specialists; FMAD: Finnish Medical Association Duodecim; HAS; haute autorité de santé; NICE: National Institute for Health and Care Excellence; PCV: Polypoidal choroidal vasculopathy; PDT: photodynamic therapy; PRN: pro re nata: PTO: Polskie Towarzystwo Okulistyczne; RCT: randomised controlled trial; RPE: retinal pigment epithelium ; SD-OCT: Spectral domain optical coherence tomography; RG: Retinologische Gesellschaft; SERV: Spanish Society for Retina and Vitreous; T&E: Treat and extend; UK: United Kingdom; USA: United States of America; VEGF: vascular endothelial growth factor; wAMD: wet age-related macular degeneration.

Source: AAO, 2015;[38] BVA, RG, DGS[72], BRS, 2019;[73] DOG, 2014;[74] DOG, 2015;[75] FMAD 2016,[76] EURETINA 2014;[8] Finland[77], Fondazione BIETTI, 2008;[78] HAS, 2017;[39] NICE, 2018;[10] PTO, 2014;[79] SERV, 2014[80].

2.4 Comparators in the assessment

1. On the basis of the alternatives presented, identify the technologies to be used as comparator(s) for the assessment.

Relevant comparators

Brolucizumab is anticipated to be used in clinical practice in accordance with its full licensed indication, for the treatment of wAMD. Therefore, the relevant comparators to brolucizumab in this position are the licensed anti-VEGF therapies ranibizumab and aflibercept.

The EUnetHTA guidelines for the choice of appropriate comparators state that "under ideal circumstances the comparator for a REA applicable across European countries should be the reference treatment according to up to date high-quality clinical practice guidelines at European or international level with good quality evidence on the efficacy and safety profile from published scientific literature".[81] Both ranibizumab and aflibercept hold EU market authorisation in the indication of wAMD, with aflibercept included as the active comparator in the pivotal HAWK and HARRIER phase III clinical trials for brolucizumab in this indication. These treatments are both recommended for the first-line treatment of wAMD in high-quality European and international clinical guidelines from EURETINA, NICE, HAS and the AAO.[8, 10, 38, 39] These therapies therefore represent the gold standard of care in this indication across Europe, and are the therapies most likely to be replaced by the introduction of brolucizumab.

Unlicensed bevacizumab

Unlicensed bevacizumab is not considered a relevant comparator to this assessment. The EUnetHTA guidelines recommend that the comparator for assessment should hold "an EU marketing authorisation or another form of recognised regulatory approval for the respective indication and line of treatment".[81] Bevacizumab is only licensed by the EMA for applications in oncology and is manufactured for intravenous administration; bevacizumab is therefore not licensed or formulated for intraocular use.[82]

The purpose of EU marketing authorisation from the EMA is "To protect public health and ensure the availability of high quality, safe and effective medicines".[83] The Regulation (EC) number 726/2004 of the European Parliament and of the Council of the 31st March 2004 lays down the procedures to be used for the authorisation, and subsequent supervision and pharmacovigilance of medicinal products for human use.[84] Pharmacovigilance activities ensure a "rapid withdrawal from the market of any medicinal product presenting a negative risk-benefit balance under normal conditions of use".[84] As an unlicensed product in wAMD, the use of bevacizumab in clinical practice to treat this condition is not subject to these supervision activities. Additionally, there is no generalised risk management plan (RMP) or global patient registry in place, in order to monitor the intravitreal use of bevacizumab specifically. Therefore, the safety of intravitreal bevacizumab treatment cannot be confirmed. The use of off-label products where alternative on-label treatments are available poses unacceptable risks for patient safety, as stated by the EFPIA, EUCOPE and EuropaBio.[85]

The risks for patient safety associated with off-label treatment use are evident through the legal necessity for informed patient consent prior to the use of off-label treatment. The study of 'Off-label use of medicinal products' conducted by the European Commission found that, whilst the policy for "dealing with off-label use is not harmonised" across EU Member States, "informed consent [is] needed in many".[86] EURETINA also state in their wAMD guidelines that the decision to use bevacizumab should be "legally and medically – based on an individual agreement between a treating physician and patient", and must include discussion of risks.[8]

Finally, the Directive 2001/83/EC of the European Parliament and of the Council of the 6th November 2001 states that, "In general, clinical trials shall be done as 'controlled clinical trials' if possible, randomised and as appropriate versus placebo and versus an *established medicinal product of proven therapeutic value*; any other design shall be justified".[87] As an off-label product, bevacizumab cannot be considered to have proven therapeutic value in the indication of wAMD. For these reasons, bevacizumab cannot be considered an appropriate clinical comparator for brolucizumab.

3 Current use of the technology

Summary of issues relating to current use of the technology

Brolucizumab is not currently licensed in any European countries. It is currently undergoing HTA in the UK by NICE, with final guidance anticipated in Q2 2020.

3.1 Current use of the technology

1. **Describe the experience of using the technology, for example the health conditions and populations, and the purposes for which the technology is currently used. Include whether the current use of the technology differs from that described in the (expected) authorisation.**

Not applicable.

2. **Indicate the scale of current use of the technology, for example the number of people currently being treated with the technology, or the number of settings in which the technology is used.**

Not applicable.

3.2 Reimbursement and assessment status of the technology

1. **Complete Table 7 with the reimbursement status of the technology in Europe.**

Table 7: Overview of the reimbursement status of the technology in European countries

Country and issuing organisation	Status of recommendation (positive/negative/ongoing/not assessed)	If positive, level of reimbursement*
NICE, UK	Ongoing. Final guidance is anticipated in Q2 2020.	N/A

Abbreviations: NICE: National Institute for Health and Care Excellence; UK: United Kingdom.

4 Investments and tools required

Summary of issues relating to the investments and tools required to introduce the technology

- No additional training, premises, equipment or conditions are required prior to and during treatment with brolucizumab, beyond those currently used in the standard care of wAMD patients with the licensed anti-VEGF therapies aflibercept and ranibizumab.

- The anticipated posology for brolucizumab is such that treatment is able to be administered according to a q12/q8w interval immediately following the loading dose phase. In addition, data from HAWK and HARRIER trials indicates that clinicians will be able to predict which patients will be able to be maintained on a longer treatment interval. It is therefore anticipated that fewer monitoring and treatment visits will be required for patients treated with brolucizumab.

4.1 Requirements to use the technology

1. If any special conditions are attached to the regulatory authorisation more information should be provided, including reference to the appropriate sections of associated documents (for example, the EPAR and SPC). Include:

- **conditions relating to settings for use, for example inpatient or outpatient, presence of resuscitation facilities**
- **restrictions on professionals who can use or may prescribe the technology**
- **conditions relating to clinical management, for example patient monitoring, diagnosis, management and concomitant treatments.**

Brolucizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections. The intravitreal injection procedure should be carried out under aseptic conditions which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Sterile paracentesis equipment should be available as a precautionary measure. The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure. Adequate anaesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

No additional training or conditions are required prior to and during treatment with brolucizumab, beyond those currently used in the standard care of wAMD patients with licensed anti-VEGF therapies. Additionally, it is anticipated that fewer monitoring visits will be required for patients treated with brolucizumab.

2. Describe the equipment required to use the technology.

Sterile paracentesis equipment should be available as a precautionary measure for the intravitreal injection procedure. This equipment is similarly required for the treatment of patients with the current standard of care licensed anti-VEGF therapies.

3. Describe the supplies required to use the technology.

Brolucizumab will be available in a pre-filled syringe or as a solution for injection. The solution for injection will require a syringe to be used for administration. Each pre-filled syringe and vial is for singe use only and should only be used for the treatment of a single eye.

The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Adequate anaesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

These supplies are similarly required for the treatment of patients with the current standard of care licensed anti-VEGF therapies.

The anticipated posology for brolucizumab is such that treatment is able to be administered according to a q12/q8w treatment interval immediately following the loading dose phase. In addition, data from HAWK and HARRIER trials indicates that clinicians will be able to predict which patients will be able to be maintained on a longer treatment interval. Among patients with no q8w need during the initial q12w cycle, the estimate of the probability for a patient to be maintained on q12w regimen up to the DAA at Week 44 was 80.9% (HAWK) in the brolucizumab 3 mg arm, and 85.4% (HAWK) and 81.7% (HARRIER) in the brolucizumab 6 mg arms (See Section 5). It is therefore anticipated that fewer monitoring and treatment visits will be required for patients treated with brolucizumab which in turn will result in cost savings to the healthcare system.

5 Clinical effectiveness and safety

Summary of the clinical effectiveness

- The evidence base for brolucizumab comprises two phase III randomised head-to-head trials versus aflibercept (HAWK and HARRIER) and one phase II randomised head-to-head trial versus aflibercept (OSPREY; presented in Appendix 7.4). The primary hypothesis of both trials was non-inferiority in terms of mean change in BCVA from Baseline to Week 48 with fewer injections. Across both the HAWK and HARRIER trials brolucizumab achieved clinically meaningful and consistent visual gains with a majority of patients maintained on a q12w dosing interval immediately following the loading dose phase.
- **HAWK and HARRIER:** The hypothesis of non-inferiority of brolucizumab 6 mg to aflibercept 2 mg was confirmed for the primary endpoint of mean change in BCVA from Baseline to Week 48 in HAWK and HARRIER with highly significant p- values. At Week 48, the mean change in BCVA from Baseline was 6.6 versus 6.8 letters, and 6.9 versus 7.6 letters, for brolucizumab 6 mg versus aflibercept 2 mg in HAWK and HARRIER, respectively ($p<0.0001$ for both comparisons, non-inferior 4-letter margin). More than 50% (56% in HAWK and 51% in HARRIER) of brolucizumab 6 mg patients were exclusively maintained on a q12w regimen immediately following the loading dose phase through to Week 48, and for those on a q12w regimen at Week 48 there was a >75% probability of maintaining on this regimen at Week 96.
- **HAWK and HARRIER:** Brolucizumab was statistically significantly superior to aflibercept in terms of improvements in central subfield retinal thickness (CSFT), retinal fluid (intraretinal fluid [IRF] and/or subretinal fluid [SRF]) and disease activity. 30% fewer patients receiving brolucizumab had disease activity at Week 16 compared to those receiving aflibercept. At Week 16, the probability of disease activity in patients treated with brolucizumab 6 mg was significantly lower than that for aflibercept 2 mg (24.0% versus 34.5% in HAWK, $p=0.0013$; and 22.8% versus 32.1% in HARRIER, $p=0.0021$). Significantly fewer patients receiving brolucizumab had IRF and/or SRF at Week 16 and Week 48, with differences maintained to Week 96. At Week 16, the proportion of patients with IRF and/or SRF was 33.9% for brolucizumab 6 mg versus 52.2% for aflibercept 2 mg in HAWK ($p<0.0001$), and 29.4% versus 45.1% in HARRIER ($p<0.0001$). At Week 48, the proportion of patients with IRF and/or SRF was 31.2% for brolucizumab 6 mg versus 44.7% for aflibercept 2 mg in HAWK ($p=0.0002$), and 25.8% versus 43.9% in HARRIER ($p<0.0001$). Brolucizumab showed a superior reduction in CSFT compared with aflibercept at Week 16 and Week 48, with differences maintained at Week 96.
- **Network meta-analysis (NMA):** An NMA was performed to assess the efficacy and safety of brolucizumab versus the relevant comparators ranibizumab and aflibercept. 14 trials were included in the analysis and standard pairwise meta-analyses based on direct comparisons were carried out between pairs of treatments where possible. Regimen-based baseline pooling was conducted for the mean change in BCVA, patients gaining at least 15 ETDRS letters, patients losing at least ETDRS 15 letters, injection frequency, and the incidence of AEs. Molecule-based baseline pooling was conducted for treatment discontinuation as well as AEs.
- The base case NMA demonstrated brolucizumab to be associated with comparable efficacy versus ranibizumab and aflibercept in terms of change in BCVA from Baseline to one and two years. The NMA also demonstrated brolucizumab to be statistically significantly superior to all ranibizumab and aflibercept regimens at decreasing retinal thickness from Baseline to one year.
- Results of the arm-based baseline pooling for injection frequency also demonstrated brolucizumab to be associated with one of the lowest injection frequencies across year one and year two versus most ranibizumab and aflibercept regimens, and results of the baseline pooling for serious AEs demonstrated brolucizumab to be associated with a comparable safety profile to both ranibizumab and aflibercept.

Summary of safety

- The overall safety profile of brolucizumab was comparable to the safety profile of aflibercept and no new, previously unreported types of safety events were identified compared with previous trials of licensed anti-VEGF therapies
- The mean number of active injections administered to patients on the brolucizumab treatment arms was between 1 and 1.5 injections fewer than the number administered on the aflibercept arms
- The overall incidence of ocular and non-ocular AEs was balanced across all treatment groups in both HAWK and HARRIER trials and comparable to previous clinical trials of brolucizumab
- The proportion of patients experiencing ≥1 ocular AE was 218 (60.9%), 220 (61.1%) and 201 (55.8%) patients in the brolucizumab 3 mg, brolucizumab 6 mg and aflibercept 2 mg arms, respectively in HAWK, and 174 (47.0%) and 176 (47.7%) patients in the brolucizumab 6 mg and aflibercept 2 mg arms, respectively in HARRIER
- In HAWK, conjunctival haemorrhage was the most frequently reported ocular AE, occurring in 39 (10.9%), 29 (8.1%), and 32 (8.9%) patients in the brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept 2 mg arms, respectively. In HARRIER, the most frequently reported ocular AE in the brolucizumab 6 mg arm was reduced VA, occurring in 32 (8.6%) patients; in the aflibercept 2 mg arm, cataract was the most frequently reported AE
- Non-ocular AEs were predominantly mild or moderate in severity. The most frequent non-ocular adverse events were typical of those reported in a wAMD population and there were no notable differences between arms. In HAWK up to Week 96, 60 patients (16.8%) in the brolucizumab 3 mg arm, 48 patients (13.3%) in the brolucizumab 6 mg arm, and 72 patients (20.0%) in the aflibercept 2 mg arm experienced at least 1 severe non-ocular AE. In HARRIER, up to Week 96, 37 patients (10.0%) in the brolucizumab 6 mg arm and 44 patients (11.9%) in the aflibercept 2 mg arm experienced at least 1 severe non-ocular AE.

5.1 Identification and selection of relevant studies

A systematic literature (SLR) review was conducted to identify relevant evidence of the efficacy and safety of brolucizumab versus comparator therapies for the treatment of wAMD. The SLR was conducted in line with the NICE guide to the methods of technology appraisal.[88]

1. State the databases and trial registries searched and, when relevant, the platforms used to do this.

The electronic databases searched were EMBASE, Medline, Medline-in-Process and the Cochrane Library. In addition to the PICOS framework, the search terms used for EMBASE, Medline, and Medline-in-Process were developed according to methods NICE used in their SLR and NMA in wAMD.[49, 89, 90] The search terms used for Cochrane Library were adapted from a previously conducted SLR and NMA for ranibizumab in wAMD.[91]

In addition to the searches of electronic databases, hand searches were also conducted, in order to capture data from recent studies not yet published. Hand searches were run for the following:

- Congress proceedings:
    - American Society of Retinal Specialists
    - The American Macular Degeneration Foundation
    - European Society of Retina Specialists

- The Retina International World Congress of Ophthalmology
- The Association for Research and Vision in Ophthalmology
- American Academy of Ophthalmology
- The Royal Australian and New Zealand College of Ophthalmologists
- Asia-Australia Controversies in Ophthalmology
- The Royal College of Ophthalmologists

- Clinical trial registries:
  - US National Library of Medicine
  - EU Clinical Trials Register

2. State the date the searches were done and any limits (for example date, language) placed on the searches.

The electronic database searches were conducted on 12th and 13th June 2019. Searches were limited to records published in English. No date limits were placed on the searches.

Hand searches of congress proceedings were limited to 2015–2019. This is because most congress abstracts are expected to lead to full publications within two to three years, so the full publications of any studies published at congresses prior to 2015 were likely to be captured in the electronic searches. Where possible, congress searches were filtered to include only congress proceedings and scientific communications. Similarly, hand searches of clinical trials were limited to trials that were completed. The search terms used for the hand searches are presented in Table 76 in Appendix 7.2.

3. Include as an appendix the search terms and strategies used to interrogate each database or registry.

The search terms and strategies employed for each electronic database are presented in Table 73, Table 74 and Table 75 in Appendix 7.2. The search terms used for the hand searches of congress proceedings and clinical trial registries are presented in Table 76 in Appendix 7.2.

4. In Table 8, state the inclusion and exclusion criteria used to select studies and justify these.

The titles and abstracts of studies identified from the search strategy, where available, were reviewed according to the pre-specified inclusion/exclusion criteria presented in Table 8.

Table 8: Eligibility criteria for the SLR

Topic	Inclusion criteria	Exclusion criteria
Population	• Patients 18 years and older with wAMD (also known as neovascular AMD)	• PCV (if >10% of population)
Intervention/ Comparators	• Brolucizumab • Ranibizumab (Lucentis®) • Aflibercept (Eylea®) • Photodynamic therapy with verteporfin (Visudyne) • Laser photocoagulation therapy	• Intervention or comparator of interest not included in any arm of trial

Topic	Inclusion criteria	Exclusion criteria
	• Macular surgeries	
Outcomes	• Visual acuity (VA) (ETDRS letters or logMAR or Snellen equivalent) • Other measures of VA (blindness and ≥15 letter gain/loss) • Central retinal thickness • HRQoL • Severe ocular and systemic adverse events • Treatment discontinuation • Injection and monitoring frequencies	• Outcomes which do not measure efficacy, safety or HRQoL
Study Type	• Randomised controlled trials (RCTs) or cross-over RCTs (if data presented at the time of cross-over) of 44 weeks or longer • Open-label extension studies of RCTs	• SLRs • Observational or real-world evidence studies • Single arm trials • Non-randomised trials • Post-hoc analyses • Case studies • Reviews
Publication Type	• Peer reviewed published in journals or retrieved via hand searches on relevant congress websites	• Letters, editorials and conference abstracts
Language	• English	• Languages other than English
Publication Date	• No restriction on electronic searches • Hand searches from conferences between 2015 and 2019	• Not applicable
Countries	• No restriction	• Not applicable

Abbreviations: ETDRS: Early Treatment Diabetic Retinopathy Study; HRQoL: health-related quality of life; logMAR: logarithm of the minimum angle of resolution; PCV: Polypoidal choroidal vasculopathy RCT: randomised controlled trial; SLR: Systematic literature review; wAMD: wet AMD; VA: Visual acuity.

Articles that were identified as potentially relevant on the basis of their titles and abstracts were reviewed in full and selected according to the same list of pre-specified inclusion/exclusion criteria detailed above. Parallel screening was undertaken by a second reviewer and any discrepancies were resolved by discussion. Identified studies were independently extracted by an analyst.

Population

The subtype of wAMD polypoidal choroidal vasculopathy (PCV) has multiple unique epidemiological and clinical characteristics, natural history and treatment outcomes. Studies that enrolled patients with PCV, where PCV patients comprised >10% of the total population, were

therefore excluded. This threshold was based on the assumption that a small proportion of PCV patients is considered to have a negligible impact on study results.

Intervention and comparators

Brolucizumab was the primary intervention of interest in the SLR. Publications were also included if they contained relevant comparators to brolucizumab. Licensed comparators to brolucizumab for the treatment of wAMD include ranibizumab and aflibercept. PDT is also licensed for the treatment of wAMD and may be offered in particular patient subgroups, or as an adjunct to anti-VEGF therapy only as second-line treatment, thus studies of PDT were included within the SLR. Studies of macular surgeries, including laser photocoagulation therapy, were also included due to their importance in the wAMD treatment algorithm.[10]

Outcomes

The focus of the research question was on collecting efficacy, safety, and HRQoL data from wAMD clinical trials. Table 9 summarises the endpoints that were included in the SLR.

Table 9: Outcomes included in the SLR

Efficacy	• Visual acuity (VA) according to ETDRS letters, logMAR chart, or Snellen chart • Other measures of VA including blindness and ≥15 letter gain/loss • Central retinal thickness
Safety	• Severe ocular and systemic adverse events • Treatment discontinuation
HRQoL and other	• HRQoL according to disease specific instruments • HRQoL according to generic instruments EQ-5D, SF-36, SF-6D, and SF-12 • Injection frequency

Abbreviations: ETDRS: Early Treatment Diabetic Retinopathy Study; HRQoL: health-related quality of life; logMAR: logarithm of the Minimum Angle of Resolution; SLR: systematic literature review; VA: visual acuity.

Monitoring frequency was not included in the review as it was not consistently published in the included trials.

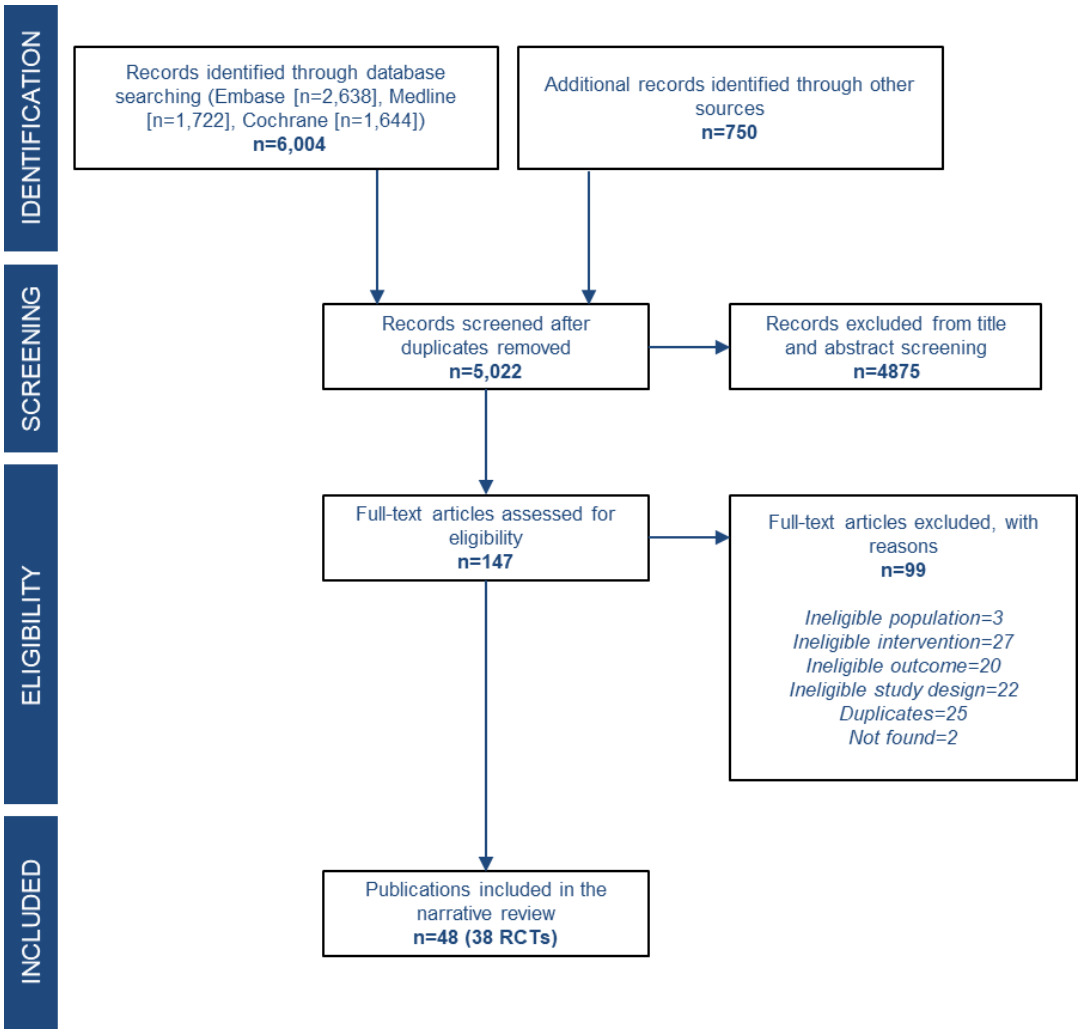
5. Provide a flow chart showing the number of studies identified and excluded.

A total of 6,004 citations were captured from the electronic database searches. After removal of duplicates, 5,022 citations remained. The screening of these titles and abstracts led to the review of 147 publications to assess their eligibility for inclusion in the SLR.

After exclusion of publications not meeting the selection criteria, 48 publications, reporting on 38 unique RCTs, were included in the SLR, as shown in the PRISMA diagram in Figure 5.

An overview of the trials included and excluded in the SLR is provided in Table 77 and Table 78 in Appendix 7.2.

Figure 5: PRISMA diagram



Abbreviations: NMA: network meta-analysis; RCTs: randomised controlled trials.

5.2 Relevant studies

6. In Table 10 provide a list of the relevant studies identified.

Of the publications identified in the SLR, three RCTs compared brolucizumab to a relevant comparator: HAWK (NCT02307682), HARRIER (NCT02434328) and OSPREY (NCT01796964). The available documentation for these studies is summarised in Table 10.

Table 10: List of relevant studies identified in the SLR

Study reference/ID	Available documentation	Status (ongoing/complete)
HAWK (NCT02307682)	HAWK CSR[24] Dugel et al. 2019[27]	Complete
HARRIER (NCT02434328)	HARRIER CSR[25] Dugel et al. 2019[27]	Complete
OSPREY (NCT01796964)	OSPREY CSR[26] Dugel et al. 2017[50]	Complete

Abbreviations: CSR: clinical study report; ID: identification.

5.3 Main characteristics of studies

1. **In Table 12, describe the main characteristics of the studies.**

Trial design and methodology

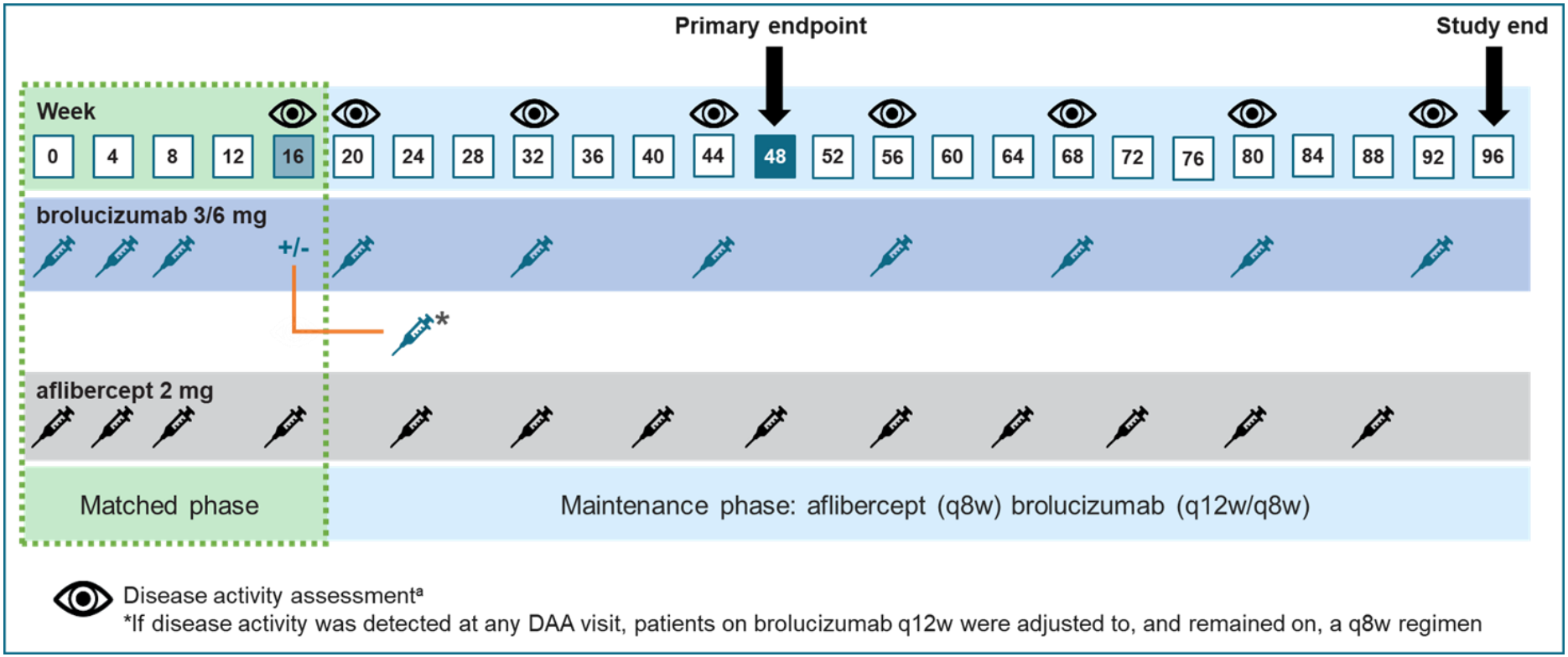
Both the HAWK and HARRIER trials were phase III, two-year, international, multicentre, randomised controlled trials comparing the efficacy and safety of brolucizumab versus aflibercept 2 mg. HAWK investigated the use of brolucizumab at doses of 3 mg and 6 mg whereas HARRIER investigated brolucizumab 6 mg alone. The phase II OSPREY trial also compared brolucizumab 6 mg with aflibercept 2 mg and provides supportive evidence of the efficacy and safety of brolucizumab in this indication. Together, these trials represent the pivotal evidence base for brolucizumab in this indication and details of these trials have been presented in the main body of this submission.

The study populations of both trials consisted of anti-VEGF treatment naïve patients aged ≥50 years of age with active CNV due to AMD. Included patients had to have a Baseline BCVA in the study eye of between 78 and 23 letters (inclusive), assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) testing.

A schematic of the study design of the HAWK and HARRIER trials is presented in Figure 6. Both trials primarily followed the same study design, differing only in the dosing of brolucizumab (HAWK investigated the use of brolucizumab at doses of 3 mg and 6 mg whereas HARRIER investigated brolucizumab 6 mg alone) and in the number of scheduled Disease Activity Assessment (DAA) visits and potential dosing interval adjustments (from Week 20, DAAs were conducted every 12 weeks in both trials; in HARRIER, additional DAAs occurred at Weeks 28, 40, 52, 64, 76 and 88).

Both studies included screening visits (2–14 days prior to Baseline) and a Baseline visit (Day 0), followed by monthly post-Baseline study visits from Week 4 until Week 96. After confirmation of eligibility at Baseline, patients were randomised to receive either brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg via IVT injection in a 1:1:1 ratio in HAWK, and randomised to receive either brolucizumab 6 mg or aflibercept 2 mg via IVT injection in a 1:1 ratio in HARRIER. Monthly loading dose injections were given for the first 3 months (Day 0, Week 4, and Week 8) across all arms of both trials, followed by maintenance dosing.

Figure 6: HAWK and HARRIER trial design



[a]The maintenance dosing regimen for brolucizumab is denoted as 'q12/q8w' whereby the treatment interval could be adjusted according to the patient's individual treatment need based on disease activity. All patients were allocated to q12w dosing and only re-allocated to q8w dosing if disease activity was detected via disease activity assessments (DAAs). DAAs were performed by masked Investigators at pre-specified visits. Once patients were adjusted to a q8w interval, they stayed on that interval until the end of the study (Week 96/Exit). Presence of disease activity was determined at the discretion of the masked Investigator and supported by protocol guidance based on functional and anatomical criteria. Additional DAAs occurred at Weeks 28, 40, 52, 64, 76, and 88 in HARRIER only, due to a health authority request. HAWK was initiated on 8th December 2014 and completed on 28th March 2018. HARRIER was initiated on 28th July 2015 and completed on 7th March 2018.
Abbreviations: DAA: disease activity assessment; q8w: 8-week dosing interval; q12w: 12-week dosing interval.
Source: HAWK CSR;[24] HARRIER CSR.[25]

Maintenance dosing for aflibercept in both trials was administered at 8-week intervals (q8w). This was in line with the marketing authorisation for aflibercept in this indication.[71]

Maintenance dosing for brolucizumab in both trials was 'q12/q8w', where the treatment interval could be adjusted according to the patient's individual treatment need, from 12- to 8-week intervals, based on DAA. DAAs were performed by masked Investigators at pre-specified visits.

For patients receiving brolucizumab, the third brolucizumab loading injection (at Week 8) was followed by a 12-week interval, to identify patients' individual anti-VEGF therapy need. During this interval, DAAs were performed after 8 and 12 weeks. If disease activity was identified by the Investigator at either of these DAAs, the dosing interval was adjusted to q8w. Once patients were adjusted to a q8w interval, they remained on that interval until the end of the study (Week 96/Exit) and could not return to a q12w interval.

Whilst disease activity identification was at the discretion of the masked Investigator, the protocols provided guidance based on anatomical and functional parameters of disease activity. After Week 16 (first DAA), guidance was based on BCVA decline due to wAMD activity when compared with Week 12 (Table 11). Ultimately, the masked Investigator made the final treatment decisions based on clinical judgement, with anatomical assessments such as OCT and FA also used in clinical practice for treatment decisions.

Table 11: DAA criteria for HAWK and HARRIER

Study week(s)	DAA criteria
Week 16	• Decrease in BCVA of ≥ 5 letters compared with baseline • Decrease in BCVA of ≥ 3 letters and CSFT increase ≥ 75 µm compared with Week 12 • Decrease in BCVA of ≥ 5 letters due to wAMD disease activity compared with Week 12 • New or worse IRF/intraretinal cysts compared with Week 12
Weeks 20, 28[b], 32, 40[b], and 44	• Decrease in BCVA of ≥ 5 letters due to wAMD disease activity compared with Week 12
Weeks 52[b], 56, 64[b], 68, 76[b], 80, 88[b], and 92	• Decrease in BCVA of ≥ 5 letters due to wAMD disease activity compared with Week 48

[a]DAA criteria used to assign brolucizumab q12w or q8w dosing were developed based on findings from predictive data modelling combined with clinically meaningful vision and anatomical parameters of disease activity. Dynamic criteria identified in analyses of the PIER, EXCITE and CATT studies support DAA at Week 16 for early determination of patients suited to q8w dosing and to minimise patient reassignment at later time points. Subsequent DAA visits coincide with q12w dosing visits to allow reassignment to q8w dosing if patients experience BCVA decline due to wAMD at these time points. [b]Additional DAA visits included in the HARRIER study due to a health authority request.
Key: BCVA: best-corrected visual acuity; CSFT: central subfield thickness; DAA: disease activity assessment; IRF: intraretinal fluid; wAMD: wet age-related macular degeneration.
Source: HAWK CSR;[24] HARRIER CSR.[25]

The primary hypothesis of both trials was non-inferiority in terms of mean change in BCVA from Baseline to Week 48 with fewer injections. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% confidence interval (CI) for the corresponding treatment difference (brolucizumab [6 mg or 3 mg] − aflibercept 2 mg) was greater than −4 letters.

The main characteristics of these studies are described in Table 12. Details of the trial design, methodology and results of the phase II OSPREY trial have been presented separately to HAWK and HARRIER, in Appendix 7.4.

Table 12: Characteristics of the relevant studies

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
HAWK (NCT02307682)	To compare the efficacy and safety of brolucizumab with aflibercept to treat wAMD	A two-year, randomised, double-masked, multicentre, three-arm phase III study (212 study centres across 11 countries)	**Key inclusion criteria:** • Patients ⩾50 years of age at time of screening • Active CNV lesions secondary to AMD that affected the central subfield in the study eye at time of screening • Total area of CNV (including both classic and occult components) must have comprised >50% of the total lesion area in the study eye at time of screening, confirmed by the CRC • IRF and/or SRF affecting the central subfield of the study eye at time of screening, confirmed by the	**Intervention:** • Brolucizumab 3 mg (N=358) • Brolucizumab 6 mg (N=360) **Comparator:** • Aflibercept 2 mg (N=360)	Change in BCVA from Baseline to Week 48	• Change in BCVA from Baseline averaged over the period Week 36 to Week 48 • The proportion of patients receiving q12w in the brolucizumab treatment arms (up to Week 48) • The predictive value of the first (“initial”) q12w cycle for maintenance of q12w treatment up to Week 48 in the brolucizumab treatment arms • Change in BCVA from Baseline to Week 96 • Anatomical parameters of disease activity including: CSFT, neurosensory retinal thickness, CNV area, and the presence of SRF, IRF/intraretinal cysts and sub-RPE fluid
HARRIER (NCT02434328)		A two-year, randomised, double-masked, multicentre, two-arm phase III study (147 study centres across 29 countries)		**Intervention:** • Brolucizumab 6 mg (N=370) **Comparator:** • Aflibercept 2 mg (N=369)		

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
			CRC • BCVA between 78 and 23 letters, inclusive, in the study eye at time of screening and Baseline using ETDRS testing			• The presence of "q8w treatment need", including assessment of q12w status for patients in the brolucizumab treatment arms • Visual function-related quality of life, as assessed by the NEI VFQ-25 • The safety and tolerability of brolucizumab relative to aflibercept
OSPREY (NCT01796964)	To compare the efficacy and safety of brolucizumab with aflibercept to treat wAMD	A randomised, double-masked, multicentre, two-arm phase II study	**Key inclusion criteria:** • Patients ⩾50 years of age at time of screening • Untreated and active CNV lesion due to AMD in the study eye • Confirmed evidence of leakage on FA and SRF, IRF, or sub-RPE fluid as assessed by SD-OCT in the study	**Intervention:** • Brolucizumab 6 mg (N=44) **Comparator:** • Aflibercept 2 mg (N=45)	Change in BCVA from Baseline to Week 12	• Change in BCVA from Baseline to Week 16 • Change in BCVA from Baseline by visit • Change in BCVA from Baseline averaged over the periods of Week 4 to Week 16, Week 4 to Week 24, Week 4 to Week 40, and Week 4 to Week 56 • Change in BCVA from Week 12

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
			eye • Total area of CNV (including both classic and occult components) must have comprised >50% of the total lesion area in the study eye • Subretinal blood, if present, must have spared the fovea and must have been ⩽ 50% of the lesion in the study eye • BCVA between 78 and 23 letters, inclusive, in the study eye at time of screening and Baseline using ETDRS testing • Patient's fellow eye must have had a BCVA of 20 letters			averaged over the periods of Week 16 to Week 24, Week 16 Week 40, and Week 16 to Week 56 • One-month BCVA changes following no treatment for one-month • One-month BCVA changes following treatment by visit • Two-months BCVA changes following no treatment for one month in brolucizumab treatment group • CSFT change from Baseline by visit

Abbreviations: BCVA: best-corrected visual acuity; CNV: choroidal neovascularisation; CRC: central reading center; CSFT: central subfield thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; FA: fluorescein angiography; IRF: intraretinal fluid; NEI: National Eye Institute; RPE: retinal pigment epithelium; qXw: one injection every X weeks; SD-OCT: spectral domain optical coherence tomography; SRF: subretinal fluid; VFQ-25: visual function questionnaire 25; wAMD: wet age-related macular degeneration.
Source: HAWK CSR;[24] HARRIER CSR;[25] OSPREY CSR;[26] Dugel et al 2017;[50] Dugel et al 2019.[27]

2. For each study provide a flow diagram of the numbers of patients moving through the trial.

Flow diagrams of the patient disposition in the HAWK and HARRIER trials are presented in Figure 7 and Figure 8.

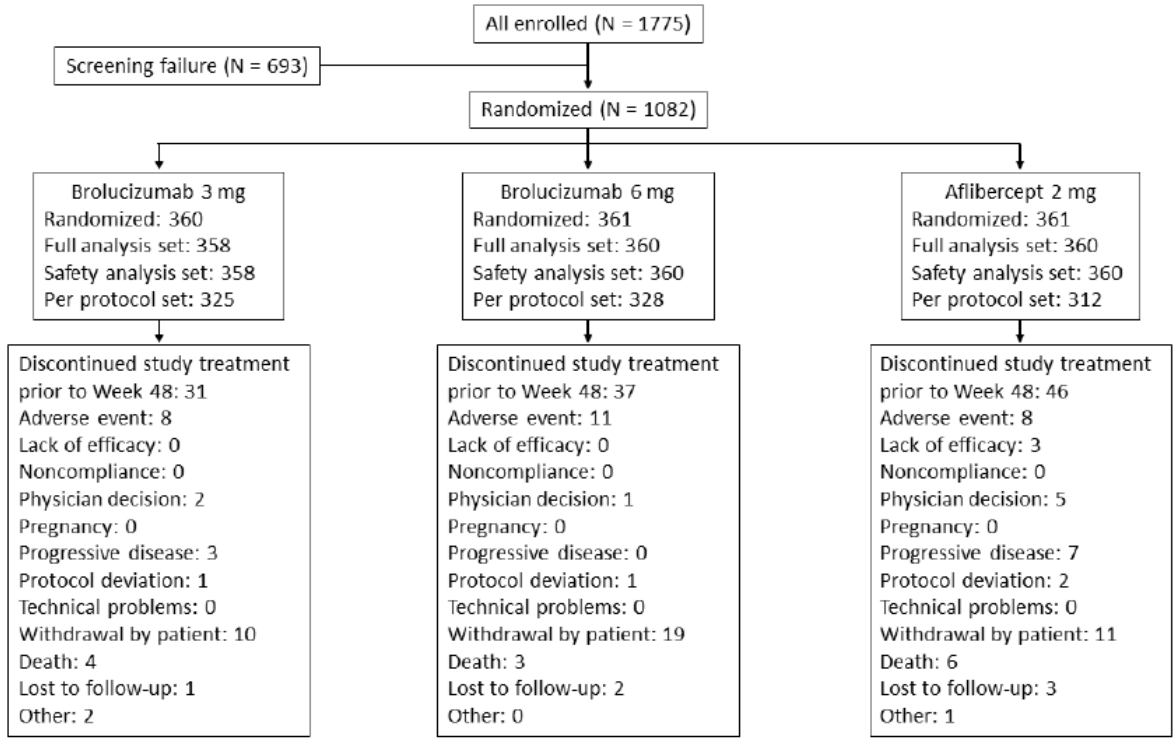
In HAWK, a total of 1775 patients were screened, of which there were 693 screen failures. The most common reasons for screening failure were related to the anatomical diagnostic/severity criteria for the study: 227 patients with no active CNV lesion secondary to AMD, 217 patients with total area of CNV ≤50% of the total lesion area, 139 patients with BCVA >78 or <23 letters at screening and/or Baseline, and 112 patients with no IRF or SRF affecting the central subfield.

Overall in HAWK, 1082 patients were randomised 1:1:1 to brolucizumab 3 mg (n=360), brolucizumab 6 mg (n=361) and aflibercept 2 mg (n=361), of which 1078 patients (99.6%) received study treatment and 994 patients (91.9%) completed the Week 48 visit. In total, 114 patients (10.5%) discontinued study treatment prior to Week 48. The most common reasons for study treatment discontinuation were patient withdrawal, and adverse events. Study treatment discontinuations due to patient withdrawal occurred in 19 patients (5.3%) in the brolucizumab 6 mg arm, 10 patients (2.8%) in the brolucizumab 3 mg arm, and 11 patients (3.0%) in the aflibercept 2 mg arm. Study treatment discontinuations due to adverse events occurred in 11 patients (3.0%) in the brolucizumab 6 mg arm, 8 patients (2.2%) in the brolucizumab 3 mg arm, and 8 patients (2.2%) in the aflibercept 2 mg arm.

In HARRIER, a total of 1048 patients were screened, of which there were 305 screen failures. The most common reasons for screen failures were related to not meeting the anatomical diagnostic/severity criteria for the study: 82 patients with no active CNV lesion secondary to AMD, 118 patients with total area of CNV ≤ 50% of the total lesion area, 62 patients with subretinal blood affecting the central subfield and/or ≥50% of the lesion, 51 patients with central subfield affected by fibrosis or GA, 27 patients had no IRF or SRF affecting the central subfield, and 20 patients had total area of fibrosis <50% of the total lesion.

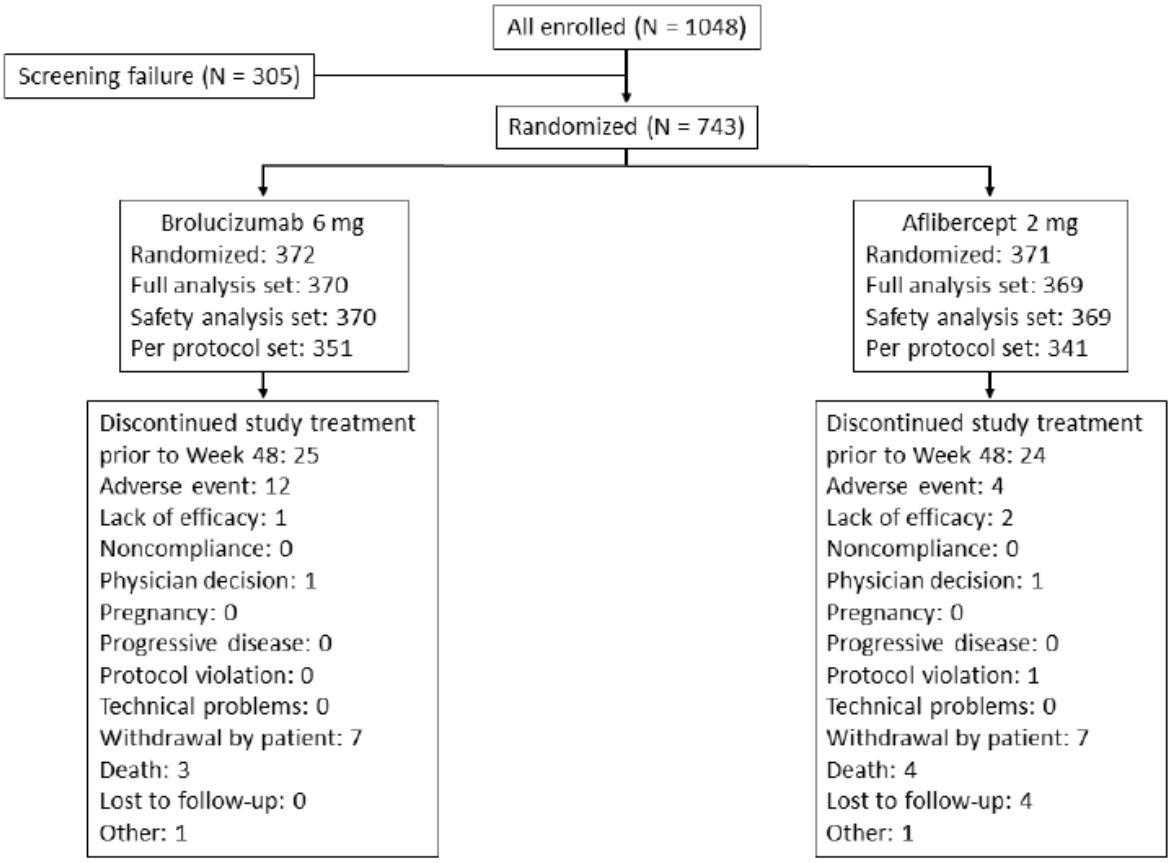
Overall in HARRIER, 743 patients were randomised 1:1 to brolucizumab 6 mg (n=372) and aflibercept 2 mg (n=371), of which 739 patients (99.5%) received study treatment and 706 patients (95.0%) completed the week 48 visit. In total, 49 patients (6.6%) discontinued study treatment prior to Week 48. The most common reasons for study treatment discontinuation were AEs, occurring in 3.2% of patients in the brolucizumab 6 mg arm and 1.1% of patients in in the aflibercept 2 mg arm (brolucizumab 6 mg: 3.2%; aflibercept 2 mg: 1.1%).

Figure 7: Patient disposition in the HAWK trial



Source: Dugel et al 2019.[27]

Figure 8: Patient disposition in the HARRIER trial



Source: Dugel et al 2019.[27]

3. For each study provide a comparison of patients (including demographic, clinical and social information [if applicable]) in treatment arms at baseline.

Baseline demographics and disease characteristics of the patients included in the HAWK and HARRIER trials are presented in Table 13.

The demographic and disease characteristics of patients were similar between treatment arms in both trials. The mean age of patients included in HAWK was 76.5 years (range: 50 to 97 years), and in HARRIER was 75.1 years (range: 50 to 95 years), with majority being ≥75 years old (HAWK: 60.9%; HARRIER: 56.4%) at the time of study entry. A greater percentage of the patients were female than male (HAWK: 56.5%; HARRIER: 57.1%), and the patients were predominantly white (HAWK: 81.1%; HARRIER: 92.2%). In the HAWK trial, 14.3% of patients were of Japanese ancestry. The majority of the patients (HAWK: 75.0%; HARRIER: 70.8%) had unilateral wAMD with occult CNV lesions (HAWK: 57.7%; HARRIER: 50.3%) at Baseline.

Table 13: Baseline characteristics of patients in the HAWK and HARRIER trials (FAS)

Trial name	HAWK			HARRIER	
Characteristic	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Age (years)					
Mean (SD)	76.7 (8.28)	76.7 (8.95)	76.2 (8.80)	74.8 (8.58)	75.5 (7.87)
Median (range)	78.0 (50–96)	78.0 (51–97)	77.0 (51–96)	75.0 (50–94)	76.0 (52–95)
Min–Max	50–96	51–97	51–96	50–94	52–95
Age category (years) – n (%)					
<50	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
50-64	31 (8.7)	35 (9.7)	37 (10.3)	44 (11.9)	28 (7.6)
65-74	103 (28.8)	103 (28.6)	112 (31.1)	124 (33.5)	126 (34.1)
75-84	162 (45.3)	155 (43.1)	148 (41.1)	150 (40.5)	167 (45.3)
≥85	62 (17.3)	67 (18.6)	63 (17.5)	52 (14.1)	48 (13.0)
Sex – n (%)					
Male	148 (41.3)	155 (43.1)	166 (46.1)	160 (43.2)	157 (42.5)
Female	210 (58.7)	205 (56.9)	194 (53.9)	210 (56.8)	212 (57.5)
Race – n (%)					
White	302 (84.4)	285 (79.2)	287 (79.7)	340 (91.9)	341 (92.4)
Asian	44 (12.3)	61 (16.9)	53 (14.7)	22 (5.9)	23 (6.2)
Other	9 (2.5)	9 (2.5)	17 (4.7)	5 (1.4)	4 (1.1)
Multiple	1 (0.3)	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Black or African American	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)
American Indian or Alaska Native	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity – n (%)					

Not Hispanic or Latino	323 (90.2)	329 (91.4)	319 (88.6)	321 (86.8)	322 (87.3)
Hispanic/Latino	32 (8.9)	29 (8.1)	40 (11.1)	23 (6.2)	25 (6.8)
Unknown	2 (0.6)	1 (0.3)	1 (0.3)	18 (4.9)	17 (4.6)
Not reported	1 (0.3)	1 (0.3)	0 (0.0)	8 (2.2)	5 (1.4)
Japanese ancestry – n (%)					
Japanese	41 (11.5)	60 (16.7)	53 (14.7)	NR	NR
Non-Japanese	317 (88.5)	300 (83.3)	307 (85.3)	NR	NR
Time since diagnosis of wAMD (months) – n (%)					
<1	155 (43.3)	159 (44.2)	154 (42.8)	136 (36.9)	139 (37.7)
1–3	183 (51.1)	184 (51.1)	190 (52.8)	191 (51.8)	197 (53.4)
>3	20 (5.6)	17 (4.7)	16 (4.4)	42 (11.4)	33 (8.9)
Unilateral versus bilateral wAMD – n (%)					
Unilateral	269 (75.1)	271 (75.3)	268 (74.4)	268 (72.4)	255 (69.1)
Bilateral	89 (24.9)	89 (24.7)	92 (25.6)	102 (27.6)	114 (30.9)
BCVA (letters read)					
Mean (SD)	61.0 (13.57)	60.8 (13.66)	60.0 (13.92)	61.5 (12.59)	60.8 (12.93)
Median (range)	64.5 (23–85)	64.0 (23–85)	63.0 (16–83)	64.0 (22–78)	64.0 (23–79)
Min–Max	23–85	23–85	16–83	22–78	23–79
BCVA (letters read) – n (%)					
≤55	109 (30.4)	101 (28.1)	116 (32.2)	102 (27.6)	107 (29.0)
56-70	138 (38.5)	157 (43.6)	153 (42.5)	171 (46.2)	170 (46.1)
≥71	111 (31.0)	102 (28.3)	91 (25.3)	97 (26.2)	92 (24.9)
CSFT total (µm)					
Mean (SD)	61.0 (13.57)	60.8 (13.66)	60.0 (13.92)	473.6 (171.39)	465.3 (151.21)
Median (range)	427 (168–1392)	417 (217–1204)	425 (215–1082)	434 (200–1192)	442 (206–1319)
Min–Max	168–1392	217–1204	215–1082	200–1192	206–1319
CSFT total (µm) – n (%)					

<400	157 (43.9)	157 (43.6)	146 (40.6)	148 (40.0)	130 (35.2)
≥400	201 (56.1)	203 (56.4)	214 (59.4)	222 (60.0)	239 (64.8)
Type of CNV – n (%)					
Predominantly classic	122 (34.1)	113 (31.4)	116 (32.3)	154 (41.6)	144 (39.5)
Minimally classic	32 (8.9)	39 (10.8)	34 (9.5)	33 (8.9)	34 (9.3)
Occult	204 (57.0)	208 (57.8)	209 (58.2)	183 (49.5)	187 (51.2)
Area of lesion associated with CNV (mm^2)					
Mean (SD)	4.5 (4.7)	4.6 (4.1)	4.4 (3.7)	2.6 (2.8)	2.9 (4.0)
Median (range)	3.2 (0–28)	3.4 (0–20)	3.7 (0–19)	1.5 (0–14)	1.6 (0–34)
Min–Max	0–28	0–20	0–19	0.022–13.9	0–33.6
Presence of fluid – n (%)					
SRF	244 (68.2)	250 (69.4)	245 (68.1)	251 (67.8)	268 (72.6)
IRF/cyst	196 (54.7)	194 (53.9)	194 (53.9)	149 (40.4)	139 (37.7)
SRF and/or IRF	330 (92.2)	334 (92.8)	336 (93.3)	330 (89.2)	332 (90.0)
Sub-RPE fluid	147 (41.1)	168 (46.7)	158 (43.9)	125 (33.8)	127 (34.4)
PCV (Japanese patients only)	20 (50.0)	39 (66.1)	30 (56.6)	NR	NR

Abbreviations: BCVA: best-corrected visual acuity; CSFT: central subfield thickness; CNV: choroidal neovascularisation; FAS: full analysis set; IRF: intraretinal fluid; PCV: polypoidal choroidal vasculopathy; RPE: retinal pigment epithelium; SD: standard deviation; SRF: subretinal fluid.
Source: HAWK CSR;[24] HARRIER CSR;[25] Dugel et al. 2019.[27]

5.4 Individual study results (clinical outcomes)

1. Describe the relevant endpoints, including the definition of the endpoint, and method of analysis.

Relevant endpoints

The key clinical endpoints assessed in the pivotal HAWK and HARRIER phase III clinical trials of brolucizumab versus aflibercept were as follows:

- Average change in BCVA (treated eye) from Baseline to Week 48
- Average change in BCVA from Baseline over the period Week 36 to Week 48
- Proportion of patients receiving q12w in the brolucizumab treatment arms (up to Week 48)
- Predictive value of the first ("initial") q12w cycle for maintenance of q12w treatment in the brolucizumab treatment arms (up to Week 48)
- Average change in BCVA (treated eye) from Baseline to Week 96
- Changes in anatomical parameters of disease activity from Baseline, including: CSFT, retinal fluid and CNV area
- Change in CSFT-neurosensory area (CSFTns) from Baseline to each postbaseline visit
- Visual function-related QoL, assessed through the NEI VFQ-25

Methods of analysis

Definitions of the study populations analysed in HAWK and HARRIER are presented in Table 14.

Table 14: Trial populations used for the analysis of outcomes in HAWK and HARRIER

Analysis set	Description
All enrolled analysis set	• All patients who signed an informed consent and were assigned a subject number. This analysis set was used to summarise subject disposition and pre-treatment AEs
All randomised analysis set (RAN)	• All patients who were randomised in the IRT • This analysis set was used to summarise protocol deviations, analysis restrictions, medical history, and prior medications
Full analysis set (FAS)	• All randomised patients who received at least 1 intravitreal injection of study treatment • The FAS served as the primary analysis set for all efficacy analyses, with LOCF imputation of missing/censored (after start of alternative anti-VEGF treatment) BCVA values. • The FAS represented the analysis set that was as close as possible to the intent-to-treat principle of including all randomised patients
Safety analysis set (SAF)	• All patients who received at least 1 intravitreal injection
Per protocol analysis set (PPS)	• Subset of the FAS that excluded patients with protocol deviations and violations of analysis requirements that were expected to majorly affect the validity of the assessment of efficacy at Week 48

Abbreviations: AE: adverse event; BCVA: best-corrected visual acuity; RAN: randomised analysis set; FAS: full analysis set; IRT: interactive response technology; LOCF: last observation carried forward; SAF: safety analysis set; PPS: per protocol analysis set; VEGF: vascular endothelial growth factor.
Source: HAWK CSR;[24] HARRIER CSR.[25]

The primary and key secondary endpoints were analysed using the FAS and PPS. The statistical analyses used in the HAWK and HARRIER trials for the primary and first key secondary endpoint, alongside sample size calculations and methods for handling missing data are presented in Table 15. No formal statistical hypotheses were tested for the additional secondary and exploratory endpoints.

Table 15: Statistical methods for primary analyses of the HAWK and HARRIER trials

Trial name	HAWK	HARRIER
Hypothesis objective	• The primary hypothesis was non-inferiority in terms of mean change in BCVA from Baseline to Week 48 (margin: 4 letters) with fewer injections • The first key secondary efficacy endpoint was the average change in BCVA from Baseline over the period of Week 36 through Week 48 • The statistical hypotheses for the primary and first key secondary efficacy endpoints were intended to demonstrate the non-inferiority of brolucizumab to aflibercept	
Statistical analysis	• Non-inferiority was demonstrated (i.e. the null hypothesis was rejected) if the lower limit of the 2-sided 95% CI for the corresponding treatment difference (brolucizumab [6 mg or 3 mg] − aflibercept 2 mg) was greater than −4 ETDRS letters	
Sample size, power calculation	• A sample size of 297 patients per treatment arm was considered sufficient to demonstrate non-inferiority (margin = 4 letters) of brolucizumab 3 mg/6 mg versus aflibercept 2 mg with respect to the change in BCVA from Baseline to Week 48 at a 2-sided alpha level of 0.05 with a power of approximately 90%, assuming equal efficacy and a common SD of 15 letters • A power of at least 90% was expected for the first key secondary efficacy endpoint, assuming that averaging over the 4 time points would not lead to an increase in the SD • To account for a dropout rate of 10%, a total of 330 patients were planned for randomisation into each treatment arm (i.e. a total of 990 and 660 randomised patients in the HAWK and HARRIER trials, respectively)	
Data management, patient withdrawals	• Patients could voluntarily withdraw from the study for any reason at any time. A patient could be considered withdrawn if he or she stated an intention to withdraw, failed to return for visits, or became lost to follow-up for any other reason • If premature withdrawal occurred for any reason, the Investigator was obliged to determine the primary reason for the subject's premature withdrawal from the study and record this information on the Study Completion eCRF. Patients who withdrew or were withdrawn from the study should have completed all procedures indicated at the Week 96 visit. Patients who were prematurely withdrawn from the study were not replaced • Patients could voluntarily discontinue study treatment for any reason at any time. Patients who discontinued study treatment were not considered withdrawn from the study. Rather, these patients were expected to continue with the study visits and procedures if such procedures did not pose a risk to the well-being of the patients • For patients who were lost to follow-up (i.e., those patients whose status was unclear because they failed to appear for study visits without stating an intention to withdraw), the Investigator was required to show due diligence by documenting in the source documents all	

	steps taken to contact the subject, e.g., dates of telephone calls, registered letters.

Abbreviations: BCVA: best-corrected visual acuity; eCRF: electronic case report form; SD: standard deviation.

2. Provide a summary of the study results for each relevant comparison and outcome.

Given their similarities in trial design and methodology, the clinical results of the HAWK and HARRIER trials have been presented together.

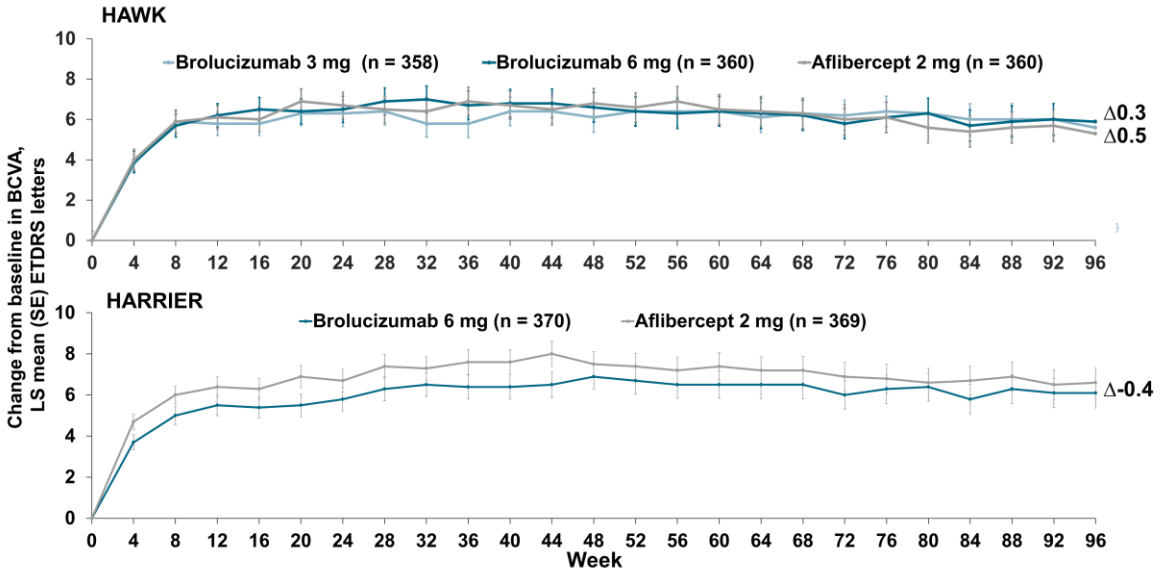
Primary endpoint

Change in BCVA from Baseline to Week 48

Brolucizumab achieved clinically meaningful and consistent visual gains, meeting the primary endpoint of non-inferiority with respect to change in BCVA from Baseline to Week 48 in both the HAWK and the HARRIER trials

The results from both HAWK and HARRIER showed a rapid improvement in change in BCVA from Baseline during the loading phase which was maintained up to Week 96, with no relevant differences observed between treatment arms (Figure 9). No relevant fluctuations or treatment arm differences in BCVA changes from Baseline were noted.

Figure 9: LS-mean change (SE) in BCVA (letters) from Baseline to Week 96 (FAS-LOCF)



Mean differences in BCVA (brolucizumab–aflibercept, Δ). Note this figure displays both the primary endpoint and the additional secondary endpoint of change in BCVA from Baseline to each post-Baseline visit.
Abbreviations: BCVA: best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; FAS: full analysis set; LOCF: last observation carried forward; LS: least squares; q8w: every 8 weeks; q12w: every 12 weeks; SE: standard error.
Source: HAWK CSR;[24] HARRIER CSR;[25] Dugel et al. 2019.[27]

In HAWK, treatment with brolucizumab resulted in an LS-mean estimate of the change in BCVA from Baseline to Week 48 of 6.1 letters in the brolucizumab 3 mg arm (95% CI: 4.8–7.5) and 6.6 letters in the brolucizumab 6 mg arm (95% CI: 5.2–8.0), versus 6.8 letters (95% CI: 5.4–8.2) in the aflibercept 2 mg arm (p<0.0001, non-inferiority 4-letter margin). In HARRIER, the LS-mean estimate of the change in BCVA from Baseline to Week 48 was 6.9 letters (95% CI: 5.7–8.1) in

the brolucizumab 6 mg arm versus 7.6 letters (95% CI: 6.4–8.8) in the aflibercept 2 mg arm (Table 16).

The results from both trials for the primary endpoint analysis using the FAS were consistent with the corresponding supporting analysis using the PPS (Table 16). All analyses were conducted with LOCF imputation of missing/censored (after start of alternative anti-VEGF treatment) BCVA values.

Treatment with brolucizumab required fewer injections on average to achieve a similar improvement in BCVA, with a majority of patients maintained on a q12w dosing interval immediately following the loading dose phase.

Data on the number of injections received by patients in each arm of the HAWK and HARRIER trials are presented in Section 5.5. Treatment with brolucizumab was associated with a fewer number of injections required versus aflibercept over 2 years. Based on the results of the primary endpoint, treatment with brolucizumab provided comparable efficacy to aflibercept with respect to change in BCVA, which was achieved by administering fewer injections over a 2-year period. The differences in the number of active injections between brolucizumab and aflibercept were driven by differences in the injection schedules, with a majority of brolucizumab 6 mg patients maintained on a q12w dosing schedule immediately following the loading dose phase.

Table 16: BCVA (letters read): summary statistics and ANOVA for change from Baseline to Week 48 for the study eye (FAS-LOCF and PPS-LOCF)

Trial name	HAWK			HARRIER	
FAS population	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Change in BCVA from Baseline to Week 48					
Mean (SD)	5.9 (13.49)	6.4 (14.40)	7.0 (13.16)	6.9 (11.47)	7.6 (12.47)
Median (range)	7.0 (-57, 51)	7.5 (-69, 52)	8.0 (-57, 54)	8.0 (-57, 38)	8.0 (-37, 50)
95% CI for mean	4.5, 7.3	4.9, 7.9	5.6, 8.3	5.8, 8.1	6.3, 8.9
LSM (Pairwise ANOVA) (brolucizumab 3 mg versus aflibercept 2 mg)					
LSM (SE)	6.1 (0.69)	-	6.8 (0.69)	-	-
95% CI for LSM	4.8, 7.5	-	5.4, 8.1	-	-
LSMD (SE)	-0.6 (0.98)			-	-
95% CI for LSMD	-2.5, 1.3			-	-
p-value for treatment difference (2-sided)	0.5237			-	-
p-value for non-inferiority (4 letter margin) (1-sided)	0.0003			-	-
LSM (Pairwise ANOVA) (brolucizumab 6 mg versus aflibercept 2 mg)					
LSM (SE)	-	6.6 (0.71)	6.8 (0.71)	6.9 (0.61)	7.6 (0.61)
95% CI for LSM	-	5.2, 8.0	5.4, 8.2	5.7, 8.1	6.4, 8.8
LSMD (SE)	-	-0.2 (1.00)		-0.7 (0.86)	
95% CI for LSMD	-	-2.1, 1.8		-2.4, 1.0	
p-value for treatment difference (2-sided)	0.8695			0.4199	
p-value for non-inferiority (4 letter margin) (1-sided)	<0.0001			0.0001	
PPS population	**Brolucizumab 3 mg (n=325)**	**Brolucizumab 6 mg (n=328)**	**Aflibercept 2 mg (n=312)**	**Brolucizumab 6 mg (n=351)**	**Aflibercept 2 mg (n=341)**
Change in BCVA from Baseline to Week 48					
Mean (SD)	6.3 (13.37)	6.6 (14.68)	7.4 (12.71)	7.0 (11.24)	7.8 (12.49)
Median (range)	7.0 (-56, 51)	8.0 (-69, 52)	8.0 (-57, 51)	8.0 (-57, 38)	8.0 (-35, 50)

95% CI for mean	4.9, 7.8	5.0, 8.2	6.0, 8.8	5.8, 8.2	6.5, 9.1
LSM (pairwise ANOVA) (brolucizumab 3 mg versus aflibercept 2 mg)					
LSM (SE)	6.5 (0.71)	-	7.2 (0.73)	-	-
95% CI for LSM	5.1, 7.9	-	5.7, 8.6	-	-
LSMD (SE)	-0.6 (1.02)			-	-
95% CI	-2.6, 1.4			-	-
p-value for treatment difference (2-sided)	0.5355			-	-
p-value for non-inferiority (4 letter margin) (1-sided)	0.0005			-	-
LSM (pairwise ANOVA) (brolucizumab 6 mg versus aflibercept 2 mg)					
LSM (SE)	-	6.9 (0.74)	7.1 (0.76)	7.0 (0.62)	7.8 (0.63)
95% CI for LSM	-	5.4, 8.3	5.7, 8.6	5.8, 8.2	6.6, 9.0
LSMD (SE)	-	-0.3 (1.06)		-0.8 (0.88)	
95% CI	-	-2.4, 1.8		-2.5, 1.0	
p-value for treatment difference (2-sided)	0.7844			0.3771	
p-value for non-inferiority (4 letter margin) (1-sided)	0.0003			0.0001	

Abbreviations: ANOVA: analysis of variance; BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; LOCF: last observation carrier forward; LSM: least squares mean; LSMD: least squares mean difference; PPS: per protocol set; SD: standard deviation; SE: standard error.
Source: HAWK CSR;[24] HARRIER CSR;[25] Dugel et al. 2019.[27]

Key secondary endpoints

Average change in BCVA from Baseline over the period Week 36 to Week 48

Brolucizumab demonstrated a non-inferior change in BCVA from Baseline over the period of Week 36–48 in both HAWK and HARRIER versus aflibercept

Both studies confirmed the hypothesis of non-inferiority of brolucizumab to aflibercept for the key secondary endpoint of mean BCVA change from Baseline over the period of Week 36 through to Week 48. This endpoint was assessed in order to account for differences in the dosing intervals between treatment arms following the matched loading dose phase, where the time from last dose received and Week 48 was not the same between the treatment arms. Outcomes of this analysis therefore demonstrated that non-inferiority with brolucizumab versus aflibercept was not due to differences in time between last dose received and Week 48.

In the HAWK trial, the LS-mean estimate of the change in BCVA from Baseline to the period of Week 36 to Week 48 was 6.2 letters in the brolucizumab 3 mg arm (95% CI: 4.9–7.5), 6.7 letters in the brolucizumab 6 mg arm (95% CI: 5.4–8.0), and 6.7 letters for the aflibercept 2 mg arm (95% CI: 5.4–8.1). In HARRIER, the LS-mean estimate of the change in BCVA from Baseline to the period of Week 36 to Week 48 was 6.5 letters in the brolucizumab 6 mg arm (95% CI: 5.4–7.7) and 7.7 letters for the aflibercept 2 mg arm (95% CI: 6.6–8.9). The results from both trials for the primary endpoint using the FAS were consistent with the corresponding analysis using the PPS (Table 17).

Table 17: Best-corrected visual acuity (letters read): summary statistics and ANOVA for average change from Baseline over the period Week 36 through Week 48 (FAS-LOCF and PPS-LOCF)

Trial name	HAWK			HARRIER	
FAS population	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Change in BCVA from Baseline over the period Week 36 through Week 48					
Mean (SD)	6.0 (13.37)	6.5 (13.85)	6.9 (12.61)	6.6 (11.10)	7.7 (11.81)
Median (range)	7.0 (-64, 54)	7.3 (-67, 50)	7.6 (-53, 52)	7.5 (-58, 37)	8.3 (-38, 47)
95% CI for mean	4.6, 7.4	5.1, 8.0	5.6, 8.2	5.4, 7.7	6.5, 8.9
LSM (Pairwise ANOVA) (brolucizumab 3 mg versus aflibercept 2 mg)					
LSM (SE)	6.2 (0.67)	-	6.7 (0.67)	-	-
95% CI for LSM	4.9, 7.5	-	5.4, 8.0	-	-
LSMD (SE)	-0.5 (0.95)			-	-
95% CI for LSMD	-2.4, 1.3			-	-
p-value for treatment difference (2-sided)	0.5829			-	-
p-value for non-inferiority (4 letter margin) (1-sided)	0.0001			-	-
LSM (Pairwise ANOVA) (brolucizumab 6 mg versus aflibercept 2 mg)					
LSM (SE)	-	6.7 (0.68)	6.7 (0.68)	6.5 (0.58)	7.7 (0.58)
95% CI for LSM	-	5.4, 8.0	5.4, 8.1	5.4, 7.7	6.6, 8.9
LSMD (SE)	-	0.0 (0.96)		-1.2 (0.82)	
95% CI for LSMD	-	-1.9, 1.9		-2.8, 0.5	
p-value for treatment difference (2-sided)	0.9791			0.1582	
p-value for non-inferiority (4 letter margin) (1-sided)	<0.0001			0.0003	
PPS population	**Brolucizumab 3 mg (n=325)**	**Brolucizumab 6 mg (n=328)**	**Aflibercept 2 mg (n=312)**	**Brolucizumab 6 mg (n=351)**	**Aflibercept 2 mg (n=341)**
Change in BCVA from Baseline over the period Week 36 through Week 48					
Mean (SD)	6.4 (13.11)	6.8 (13.98)	7.3 (12.20)	6.7 (10.96)	7.9 (11.79)
Median (range)	7.3 (-56, 54)	7.6 (-67, 50)	8.0 (-53, 52)	7.5 (-58, 37)	8.5 (-33, 47)

95% CI for mean	(5.0, 7.9)	(5.2, 8.3)	(5.9, 8.7)	(5.5, 7.8)	(6.6, 9.1)
LSM (pairwise ANOVA) (brolucizumab 3 mg versus aflibercept 2 mg)					
LSM (SE)	6.7 (0.69)	-	7.1 (0.70)	-	-
95% CI for LSM	5.3, 8.0	-	5.7, 8.4	-	-
LSMD (SE)	-0.4 (0.99)			-	-
95% CI	-2.3, 1.5			-	-
p-value for treatment difference (2-sided)	0.6869			-	-
p-value for non-inferiority (4 letter margin) (1-sided)	0.0001			-	-
LSM (pairwise ANOVA) (brolucizumab 6 mg versus aflibercept 2 mg)					
LSM (SE)	-	7.0 (0.71)	7.1 (0.72)	6.7 (0.59)	7.9 (0.60)
95% CI for LSM	-	5.6, 8.4	5.6, 8.5	5.5, 7.8	6.7, 9.0
LSMD (SE)	-	-0.1 (1.01)		-1.2 (0.84)	
95% CI	-	-2.0, 1.9		-2.8, 0.5	
p-value for treatment difference (2-sided)	0.9553			0.1625	
p-value for non-inferiority (4 letter margin) (1-sided)	<0.0001			0.0004	

Abbreviations: ANOVA: analysis of variance; BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; LOCF: last observation carrier forward; LSM: least squares mean; LSMD: least squares mean difference; PPS: per protocol set; SD: standard deviation; SE: standard error.
Source: HAWK CSR;[24] HARRIER CSR;[25] Dugel et al. 2019.[27]

Proportion of q12w treatment status at Week 48 for patients randomised to brolucizumab ("maintaining on q12w")

Over 50% of brolucizumab 6mg-treated patients were exclusively maintained on a q12w dose interval (loading through Week 48), requiring a lower frequency of injections than those treated with aflibercept

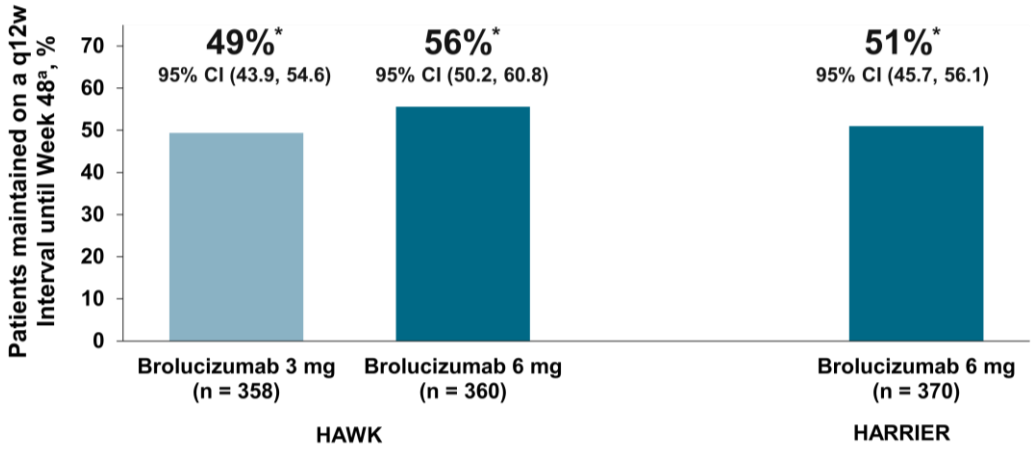
The third brolucizumab loading injection (at Week 8) was followed by a 12-week interval, to identify patients' individual anti-VEGF therapy need. During this interval, DAAs were performed after 8 and 12 weeks. If disease activity was identified by the Investigator at either of these DAAs, the dosing interval was adjusted to q8w. Once patients were adjusted to a q8w interval, they remained on that interval until the end of the study (Week 96/Exit) and could not return to a q12w interval.

Patients without disease activity during the initial q12w cycle following the loading dose phase were considered to be suitable for q12w and continued on this treatment frequency. Based on the assumption of stable treatment need, subsequent monitoring of the adequacy of the q12w treatment frequency was limited to an assessment of disease activity at the end of each q12w cycle, representing the most likely trough in terms of disease control.

Thus, patients remaining on q12w at Week 48 had no detectable disease activity at any of the DAAs from Baseline to Week 48. If disease activity was identified by the Investigator at any DAA, the dosing interval was adjusted to q8w and patients remained on a q8w interval until the end of the study (Week 96/Exit).

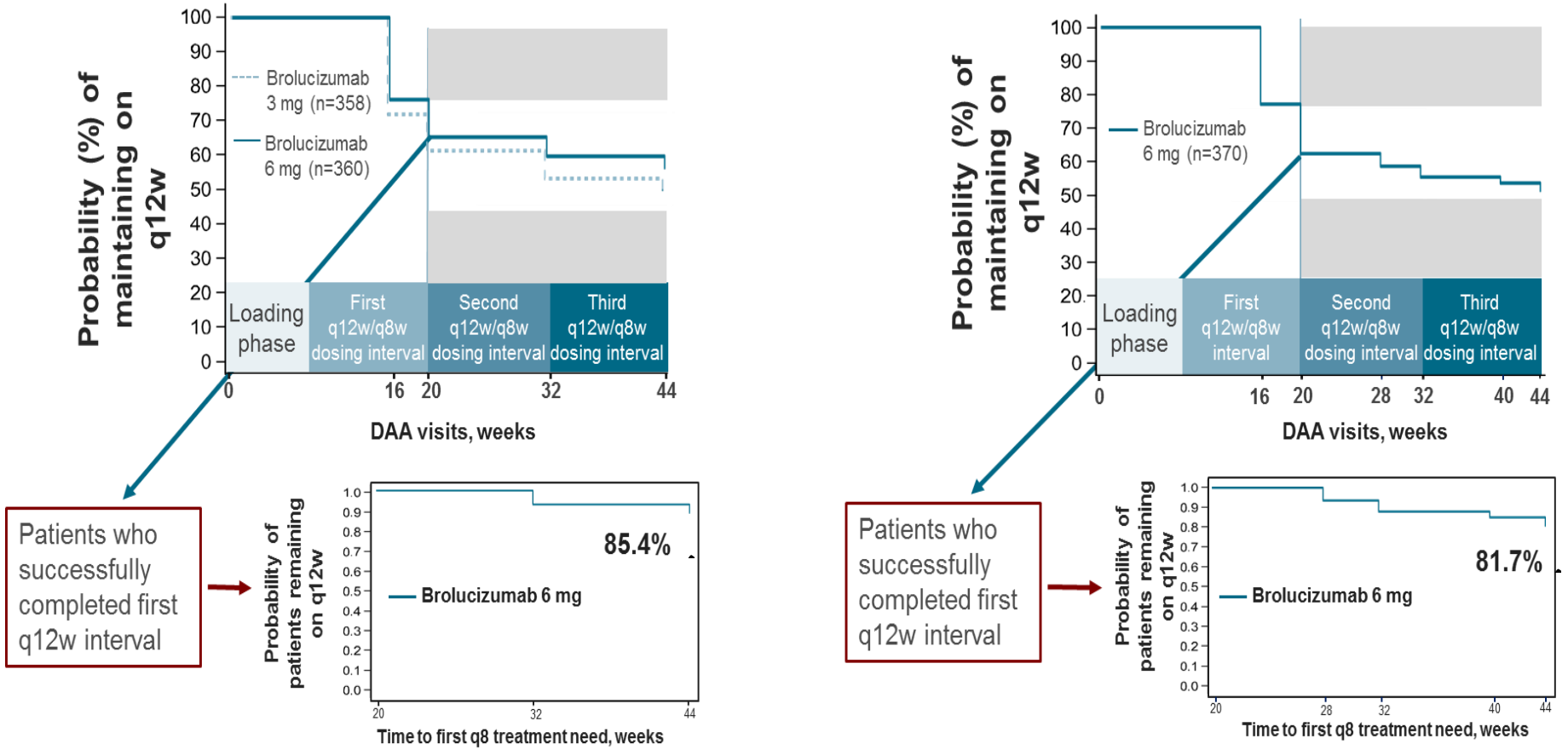
Overall, the brolucizumab 6 mg arm showed a higher proportion of patients maintained on a q12w regimen compared to the brolucizumab 3 mg arm across all subgroups. The estimated proportion of patients remaining on the q12w dosing interval up to Week 48 was 49.4% in the brolucizumab 3 mg arm (HAWK), and 55.6% (HAWK) and 51.0% (HARRIER) in the brolucizumab 6 mg arms (Figure 10). This estimate was based on the "efficacy/safety" approach, where censored data attributable to a lack of efficacy and/or safety were imputed with "q8w need=yes" at the next DAA visit.

Figure 10: Proportion of patients maintained on a q12w interval until Week 48 in HAWK and HARRIER



FAS "Efficacy/Safety approach". The numbers are based on estimated percentages from Kaplan Meier analysis.
*In case of missing/confounded data due to lack of efficacy and/or safety a 'q8w-need' is allocated, otherwise censoring is applied.
Abbreviations: CI: confidence interval; q12w: one injection every 12 weeks.
Source: Monés et al. 2018.[92]

Figure 11: Probability of patients who successfully completed the first q12w interval remaining on the q12w interval until Week 48 in HAWK and HARRIER



FAS "Efficacy/Safety approach". The numbers are based on estimated percentages from Kaplan-Meier analysis. *In case of missing / confounded data due to lack of efficacy and safety a 'q8-need' is allocated, otherwise censoring is applied. Note at previous congresses, the q12w dosing results were reported using 'Efficacy only' approach (87.1% and 82.5% of brolucizumab 6 mg patients in HAWK and HARRIER, respectively).
Abbreviations: DAA: disease activity assessment; FAS: full analysis set; qXw: one injection every X weeks.
Source: HAWK CSR;[24] HARRIER CSR.[25]

Predictive value of the initial q12w cycle for maintenance of q12w treatment

A high predictive value was associated with the initial q12w cycle for patients treated with brolucizumab, with over 80% of brolucizumab 6 mg patients who successfully completed the first q12w interval remaining on q12w interval until Week 48, allowing ophthalmology clinics to plan ahead with regards to clinic capacity.

Among patients with no q8w need during the initial q12w cycle, the estimate of the probability for a patient to be maintained on q12w regimen up to Week 48 was 80.9% (HAWK) in the brolucizumab 3 mg arm, and 85.4% (HAWK) and 81.7% (HARRIER) in the brolucizumab 6 mg arms, based on the “efficacy/safety” approach (Figure 11). Additionally, the majority of q8w need up to Week 48 was identified during the initial q12w cycle (brolucizumab 3 mg: 77%, [HAWK]; brolucizumab 6 mg: 79% [HAWK], 77% [HARRIER]).

Additional secondary endpoints: anatomical outcomes

Change in CSFT from Baseline

Brolucizumab shows a significantly superior reduction in CSFT from Baseline to Week 16 and Week 48, with differences maintained at Week 96

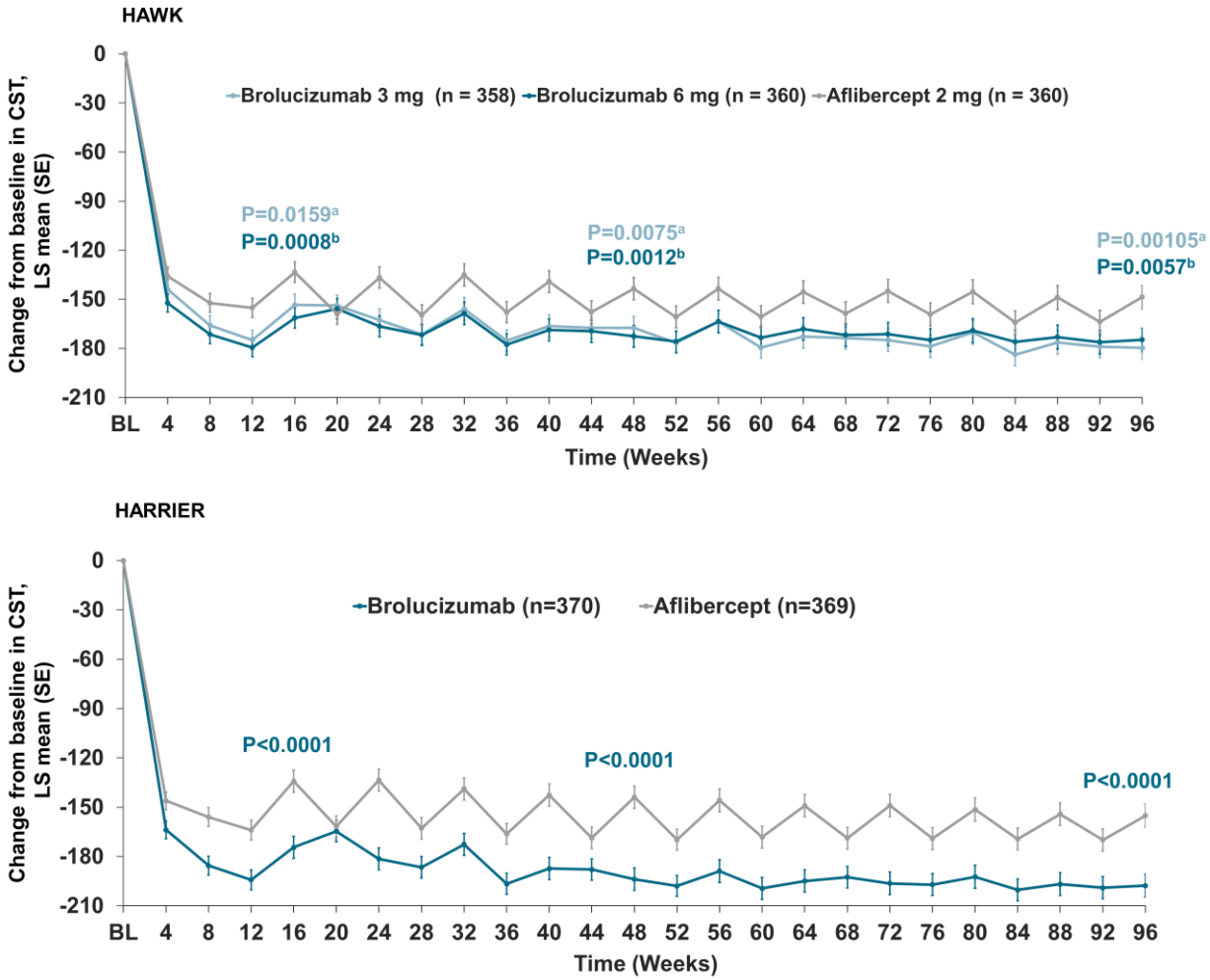
An increase in CSFT in wAMD is an important measure of abnormal fluid accumulation and oedema and may result in reduced vision. Reduction in CSFT therefore indicates better control of disease activity.

Greater reductions in total CSFT were observed for brolucizumab 6 mg versus aflibercept 2 mg at Week 16 and Week 48 in HAWK (p=0.0008 and p=0.0012 respectively) and HARRIER (p<0.0001 for both time points) (Figure 12).[93] These superior reductions were reaffirmed by the results from Week 96 for both HAWK (p=0.0115) and HARRIER (p<0.0001).[93] Greater reductions were consistently observed for the brolucizumab 6 mg arm, with the exception of Week 20, which was the end of the initial q12w cycle. The pattern of observed fluctuations followed the treatment schedule with peak reductions occurring 4 weeks after the last active injection and troughs at the end of a treatment interval.

In HAWK, hypothesis testing at Week 16 and Week 48 revealed statistically significant superiority for brolucizumab 6 mg compared to aflibercept 2 mg (differences at Week 16: -28 µm, and at Week 48: -29 µm). Averaging changes from Baseline over the period from Week 36 to Week 48 revealed a difference of -22.4 µm. In HARRIER, averaging across all post-Baseline visits revealed about a 30 µm greater reduction for brolucizumab 6 mg compared with aflibercept 2mg. The greater reductions at Week 16: 40 µm, at Week 48: 50 µm and for the average change over the period Week 36 to Week 48: 36 µm were all assessed with 2-sided p-values of <0.0001.[27]

At Week 96, absolute reductions in CSFT from Baseline were –175 µm for brolucizumab 6 mg versus –149 µm for aflibercept 2 mg in HAWK (p=0.0057) and 198 µm versus –155 µm, respectively, in HARRIER (p<0.0001).

Figure 12: Plot of LS-mean change (+/– SE) of central subfield thickness-total (µm) from Baseline by visit through Week 96 (FAS-LOCF)



[a]Brolucizumab 3 mg versus aflibercept 2 mg; [b]brolucizumab 6 mg versus aflibercept 2 mg.
Prespecified secondary endpoint in HARRIER. 1-sided p values for HARRIER. 2-sided p-values at Week 96. P-values are descriptive.
Abbreviations: BL: baseline; FAS: full analysis set; LOCF: last observation carried forward; LS: least squares; SE: standard error.
Source: HAWK CSR;[24] HARRIER CSR;[25] Singh et al. 2019.[93]

Change in CSFTns from Baseline to each postbaseline visit

In both HAWK and HARRIER, a rapid reduction in CSFTns was observed in all treatment arms following the first treatment administration and maintained through Week 48 and Week 96. The time courses did not suggest any relevant differences between the brolucizumab and aflibercept treatment arms in the retina thickness measured from apical outer segment tip to inner limiting membrane.

A summary of the LS mean change (± SE) from Baseline to Week 48 is presented in Table 18 for HAWK and HARRIER. Full results up to Week 96 are presented in Figure 13 for HAWK and Figure 14 for HARRIER.

Table 18: CSFTns (µm): summary statistics and ANOVA for change from Baseline to Week 48 for the study eye (FAS-LOCF) in HAWK and HARRIER

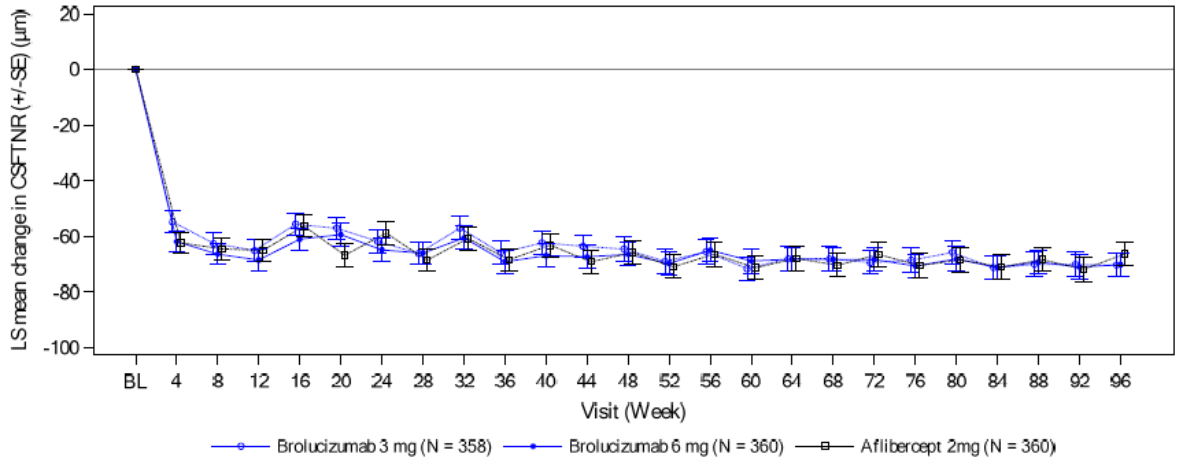
Trial name	HAWK			HARRIER	
FAS population	**Brolucizumab 3 mg (n=358)**	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Descriptive statistics					
Mean (SD)	65.9 (95.06)	-66.6 (98.72)	-64.5 (92.74)	-56.2 (100.12)	-42.9 (92.89)
SE	5.02	5.20	4.89	5.20	4.84
Median (range)	-39.0 (-495, 166)	-38.0 (-681, 159)	-33.5 (-485, 91)	-21.5 (-552, 99)	-16.0 (-434, 344)
95% CI for mean	(-75.8 , -56.0)	(-76.8 , -56.3)	(-74.1 , -54.9)	(-66.4, -46.0)	(-52.4 , -33.3)
LSM (Pairwise ANOVA) (brolucizumab 3 mg versus aflibercept 2 mg)					
LSM (SE)	-64.6 (4.07)	-	-65.9 (4.06)	-	-
95% CI for LSM	(-72.6, -56.6)	-	(-73.8, -57.9)	-	-
LSM (Pairwise ANOVA) (brolucizumab 6 mg versus aflibercept 2 mg)					
LSM (SE)	-	-65.8 (4.18)	-65.3 (4.18)	-53.0 (3.79)	-46.0 (3.79)
95% CI for LSM	-	(-74.0, -57.6)	(-73.5, -57.1)	(-60.4, -45.6)	(-53.5, -38.6)
LSM difference (Pairwise ANOVA) (brolucizumab - aflibercept)					
Difference (SE)	1.3 (5.75)	-0.5 (5.92)	-	-7.0 (5.36)	-
95% CI for treatment difference	(-10.0, 12.6)	(-12.1, 11.1)	-	(-17.5, 3.6)	-
p-value for treatment difference (2-sided)	0.8228	0.9318	-	0.1945	-

n is the number of subjects with data used in the model. 95% CI for the mean are based on t-distribution. Analysed using ANOVA model with baseline CSFT-neurosensory retina categories (<250, ≥250 µm), age categories (<75, ≥75 years) and treatment as fixed effect factors. CSFT assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.

Abbreviations: ANOVA: analysis of variance; CI: confidence interval; CSFTns: central subfield thickness-neurosensory retina; FAS: full analysis set; LOCF: last observation carried forward; LSM: least squares mean; SD: standard deviation; SE: standard error.

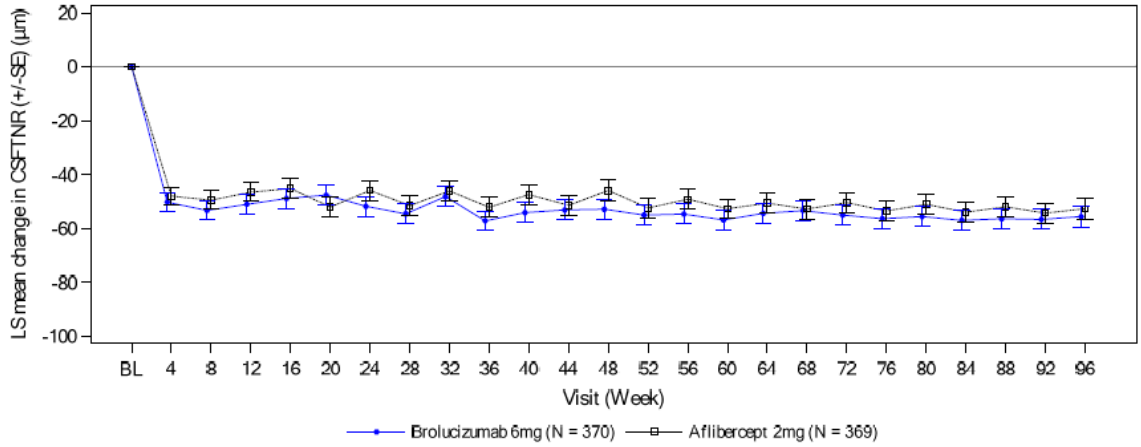
Source: HAWK CSR;[24] HARRIER CSR.[25]

Figure 13: CSFTns (µm): LS mean change (± SE) from Baseline by visit (FAS-LOCF) in HAWK



LS mean and SE estimates are based on an ANOVA model with baseline CSFT-neurosensory retina categories (<250, ≥250 µm) age categories (<75, ≥75 years) and treatment as fixed effect factors. CSFT assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.
Abbreviations: ANOVA: analysis of variance; CSFTns: central subfield thickness-neurosensory retina; FAS: full analysis set; LOCF: last observation carried forward; LS: least squares; SE: standard error.
Source: HAWK CSR.[24]

Figure 14: CSFTns (µm): LS mean change (± SE) from baseline by visit (FAS-LOCF) in HAWK



LS mean and SE estimates are based on an ANOVA model with baseline CSFT-neurosensory retina categories (<250, ≥250 µm) age categories (<75, ≥75 years) and treatment as fixed effect factors. CSFT assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.
Abbreviations: ANOVA: analysis of variance; CSFTns: central subfield thickness-neurosensory retina; FAS: full analysis set; LOCF: last observation carried forward; LS: least squares; SE: standard error.
Source: HARRIER CSR.[25]

Presence of SRF and/or IRF (central subfield) from Baseline to each post Baseline visit

Significantly fewer patients receiving brolucizumab had SRF and/or IRF at Week 16 and Week 48 compared to patients receiving aflibercept, and this was maintained at Week 96

The increase in VEGF seen in wAMD causes increased retinal fluid accumulation and oedema, which may cause functional deterioration and lead to vision loss due to disruption of the retinal

architecture. Therefore, SRF and IRF are important measures of both fluid accumulation and disease activity, with reductions in fluid indicating better control of disease activity.

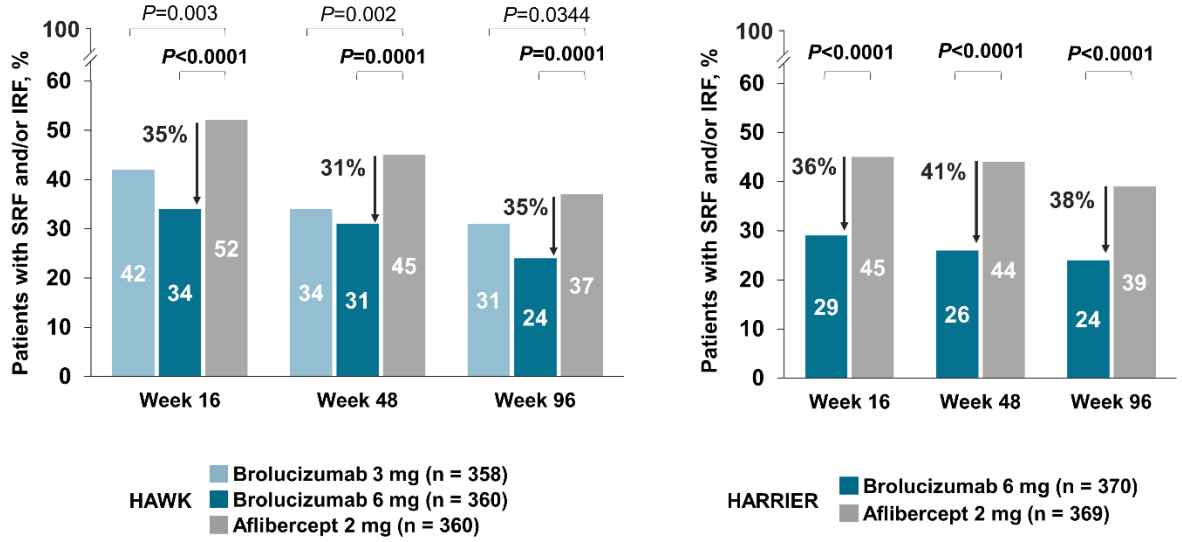
In both HAWK and HARRIER, consistently lower proportions of patients with SRF and/or IRF were observed for the brolucizumab 6 mg arm compared with the aflibercept 2 mg arm up to Week 96. At Week 16, the proportion of patients with IRF and/or SRF was 33.9% for brolucizumab 6 mg versus 52.2% for aflibercept 2 mg in HAWK (p<0.0001), and 29.4% versus 45.1% in HARRIER (p<0.0001). At Week 48, the proportion of patients with IRF and/or SRF was 31.2% for brolucizumab 6 mg versus 44.6% for aflibercept 2 mg in HAWK (p=0.0002), and 25.8% versus 43.9% in HARRIER (p<0.0001) (Table 19).

Table 19: Proportion of patients with presence of SRF and/or IRF at Week 16 and Week 48 (FAS-LOCF)

Trial name	HAWK			HARRIER	
Time point	Brolucizumab 3 mg, mean (n)	Brolucizumab 6 mg, mean (n)	Aflibercept 2 mg, mean (n)	Brolucizumab 6 mg, mean (n)	Aflibercept 2 mg, mean (n)
Week 16					
Mean (%)	41.8	33.9	52.2	29.4	45.1
Difference (%)	-10.2	-18.2	-	-15.7	-
95% CI for difference (%)	(-17.3, -2.5)	(-25.3, -10.9)	-	(-22.9, -9.0)	-
p-value	0.0059	<0.0001	-	<0.0001	-
Week 48					
Mean	34.1	31.2	44.6	25.8	43.9
Difference	-10.5	-13.5	-	-18.1	-
95% CI for difference	(-17.4, -3.3)	(-20.7, -6.1)	-	(-24.9, -11.8)	-
p-value	0.0039	0.0002	-	<0.0001	-

Abbreviations: FAS: full analysis set; IRF: intraretinal fluid; LOCF: last observation carried forward; SRF: subretinal fluid.
Source: Dugel et al. 2019.[27]

Figure 15: Proportion of patients with the presence of SRF and/or IRF at Weeks 16, 48 and 96 in HAWK and HARRIER (FAS-LOCF)



Prespecified secondary endpoint in both HAWK and HARRIER. Confirmatory superiority analysis at Week 16 and Week 48 in HAWK only. 1-sided p-values for HAWK and HARRIER. For confirmatory superiority testing in HAWK, 1-sided p-values below the adjusted significance level (to account for multiplicity) of P<0.01 (for IRF and/or SRF) are regarded as statistically significant. 2-sided p-values for both HAWK and HARRIER at Week 96; P-values are descriptive.
Abbreviations: FAS: full analysis set; IRF: intraretinal fluid; LOCF: last observation carried forward; SRF: subretinal fluid.
Source: HAWK CSR;[24] HARRIER CSR;[25] Singh et al. 2019.[93]

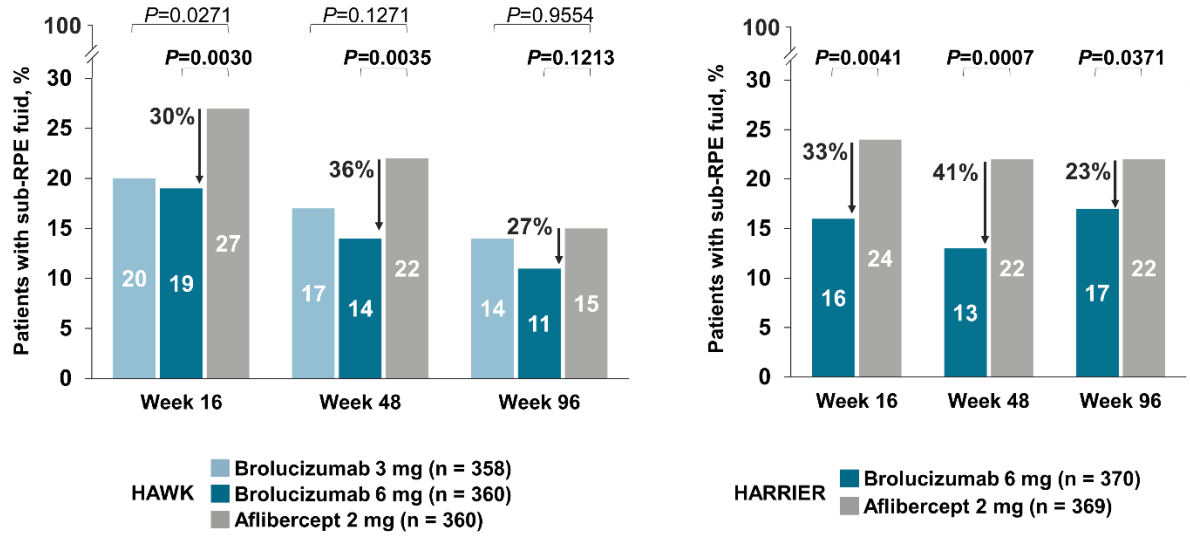
Presence of sub-RPE fluid (central subfield) at each post Baseline visit

Fewer patients on brolucizumab had sub-RPE fluid at Weeks 16, 48 and 96 versus aflibercept

An increase in sub-RPE fluid in wAMD is an important measure of abnormal fluid accumulation and oedema and may result in reduced vision. Therefore, reductions in sub-RPE fluid indicate better disease control.

Fewer patients on brolucizumab 6 mg had sub-RPE fluid versus aflibercept at Week 16 (p=0.003) and Week 48 (p=0.0035) in HAWK and HARRIER (Week 16, p=0.0041; Week 48, p=0.0007).[27, 93] A lower proportion of patients with sub-RPE fluid for the brolucizumab 6 mg arm compared with the aflibercept 2 mg arm was maintained up to Week 96.

Figure 16: Proportion of patients with the presence of sub-RPE fluid by visit at Weeks 16, 48 and 96 in HAWK and HARRIER (FAS-LOCF)



Prespecified secondary endpoint in both HAWK and HARRIER. 2-sided p values for both HAWK and HARRIER. P-values are descriptive.
Abbreviations: FAS: full analysis set; LOCF: last observation carried forward; RPE: retinal pigment epithelium.
Source: HAWK CSR;[24] HARRIER CSR;[25] Singh et al. 2019.[93]

Change in CNV lesion size from Baseline to Week 12, 48 and 96

Treatment with brolucizumab was associated with superior efficacy in CNV lesion size outcomes versus aflibercept

Superior efficacy was observed for brolucizumab 6 mg in terms of CNV lesion size reduction. At Week 12 and Week 48, the number of patients with presence of CNV lesions (lesion size >0 mm^2) was lower for brolucizumab 6 mg patients compared to aflibercept 2 mg.

From Baseline to Week 12, the mean change in CNV lesion size was -3.3 mm^2, -3.8 mm^2 and -3.2 mm^2 (brolucizumab 3 mg, brolucizumab 6 mg, aflibercept 2 mg respectively) in HAWK; and -2.2 mm^2 and -2.5 mm^2 (brolucizumab 6 mg and aflibercept 2 mg respectively) in HARRIER. The

difference between the brolucizumab 6 mg and aflibercept 2 mg arms was assessed with a p-value of 0.0024 (HAWK) and 0.0859 (HARRIER).

Similarly, from Baseline to Week 48, the mean change in CNV lesion size was -3.9 mm^2, -4.0 mm^2 and -3.5 mm^2 in HAWK; and -2.3 mm^2 and -2.5 mm^2 in HARRIER. The difference between the brolucizumab 6 mg and aflibercept 2 mg arms was assessed with a p-value of 0.0344 (HAWK) and 0.1207 (HARRIER). For Baseline to Week 96, the mean change in CNV lesion size was -3.9 mm^2, -4.1 mm^2 and -3.5 mm^2 in HAWK; and -2.5 mm^2 and -2.7 mm^2 in HARRIER. The difference between the brolucizumab 6 mg and aflibercept 2 mg arms was assessed with a p-value of 0.0022 (HAWK) and 0.0366 (HARRIER).

Additional secondary endpoints: disease activity

Brolucizumab was statistically significantly superior to aflibercept in disease activity parameters; 30% fewer patients receiving brolucizumab had disease activity compared to those receiving aflibercept at Week 16

For disease activity, the prespecified 1-sided alpha for confirmatory testing of superiority was set to 0.01 within the hierarchical testing approach. A Week 16 matched regimen phase comparison of the presence of disease activity revealed probabilities of: 28.1% (HAWK) for brolucizumab 3 mg; 24.0% (HAWK) and 22.7% (HARRIER) for brolucizumab 6mg; 34.5% (HAWK) and 32.2% (HARRIER) for aflibercept 2mg. Across both trials, 30% fewer patients receiving brolucizumab had disease activity at Week 16 compared to those receiving aflibercept, and statistically significant differences in disease activity were seen between brolucizumab 6 mg and aflibercept 2 mg (HAWK: p=0.0013; HARRIER: p=0.0021).

The overall presence of disease activity from Week 16 through Week 96 (adjusting for differences in time since last active injection) was 63% higher in the aflibercept 2 mg arm compared to the brolucizumab arm (13.6% versus 22.2%) in HAWK, and 25% higher (15.7% versus 19.6%) in HARRIER (Table 20).

Table 20: Overall presence of disease activity across all DAAs

Endpoint/categories	Brolucizumab (overall[a])	Aflibercept 2 mg (8-week)
HAWK		
Number of DAAs performed	2360	1177
Number of disease activity identified by the Investigator	322 (13.6%)	261 (22.2%)
Both, functional and anatomical post hoc disease activity criteria met	121 (5.1%)	101 (8.6%)
HARRIER		
Number of DAAs performed	4494	2266
Number of disease activity identified by the Investigator	707 (15.7%)	444 (19.6%)
Both, functional and anatomical post hoc disease activity criteria met	152 (3.4%)	144 (6.4%)

[a]Combined results for all patients treated with brolucizumab in HAWK (6 mg and 3 mg treatment arms) and HARRIER (6 mg). For aflibercept 2 mg, DAAs performed 8 weeks after the last injection were considered to adjust for the differences in time since last injection.
Abbreviations: DAA: disease activity assessment.
Source: HAWK CSR;[24] HARRIER CSR.[25]

In HAWK, a total of 7,018 DAAs were performed by masked Investigators, with 1,084 cases of disease activity identified across all treatment arms. Qualitative analysis revealed that in 71.4%

of cases, anatomical signs of disease activity were present either alone (35.8%) or in combination with function (35.6%). In the HARRIER trial, a total of 9,005 DAAs were performed by masked Investigators, with 1,421 cases of disease activity identified across all treatment arms. Qualitative analysis revealed that in 67.7% of cases, anatomical signs of disease activity were present either alone (41.9%) or in combination with function (25.8%). With fluid present in the majority of cases of disease activity, this emphasises the importance of monitoring fluid as a symptom of recurring disease activity as reflected in high-quality European and International clinical guidelines.[8, 10] This also highlights the importance of the superior fluid control displayed by brolucizumab in comparison to aflibercept, as superior control of fluid suggests greater control of disease activity.

Additional secondary endpoints: functional outcomes

Change in BCVA from Baseline to each post-Baseline visit

Results from both HAWK and HARRIER showed brolucizumab 6 mg in the HAWK trial to be advantageous compared to aflibercept (2 mg) in terms of the proportion of patients gaining ≥15 BCVA letters or reaching a BCVA of ≥84 letters at both the 48- and 96-week time point (Table 21). Overall, no relevant differences were identified between brolucizumab (3 mg or 6 mg) and aflibercept (2 mg) in terms of the proportion of patients who lost ≥15 letters at any post Baseline visit up to Week 48, and Week 96.

Table 21: Selected secondary endpoints related to BCVA at, and up to, Week 48 and Week 96 (FAS-LOCF)

Trial name	HAWK		HARRIER
Secondary BCVA endpoint	**Brolucizumab 3 mg – aflibercept 2 mg difference (95% CI), p value**	**Brolucizumab 6 mg – aflibercept 2 mg difference (95% CI), p value**	**Brolucizumab 6 mg – aflibercept 2 mg difference (95% CI), p value**
Analysis at Week 48			
Mean change from Baseline (Week 4 – Week 48)	-0.4 (-1.9, 1.1), p=0.6275	0.0 (-1.5, 1.6), p=0.9647	-1.1 (-2.4, 0.3), p=0.1191
Mean change from Baseline (Week 12 – Week 48)	-0.4 (-2.0, 1.2), p=0.6185	0.1 (-1.6, 1.8), p=0.9235	-1.1 (-2.5, 0.4), p=0.1429
≥15 letters gained from Baseline/BCVA of ≥84 letters at Week 48	-0.2 (-6.8, 6.1), p=0.9480	8.2 (2.2, 15.0), p=0.0136	-0.6 (-7.1, 5.8), p=0.8600
≥15 letters loss from Baseline at Week 48	0.3 (-3.2, 3.9), p=0.8583	0.9 (-2.7, 4.3), p=0.6198	-1.0 (-3.9, 2.2), p=0.5079
BCVA of ≥73 letters at Week 48	-3.5 (-9.5, 2.3), p=0.2455	-2.4 (-8.6, 3.6), p=0.4442	0.4 (-5.4, 6.1), p=0.8922
Analysis at Week 96			
Mean change from Baseline at Week 96	0.3 (-1.9, 2.5), p=0.8062	0.5 (-1.6, 2.7), p=0.6326	-0.4 (-2.5, 1.6), p=0.6708
Mean change from Baseline (Week 84 – Week 96)	0.4 (-1.7, 2.5), p=0.7242	0.4 (-1.7, 2.5), p=0.7289	-0.6 (-2.5, 1.4), p=0.5532
Mean change from Baseline (Week 4 – Week 96)	-0.1 (-1.8, 1.6), p=0.8892	0.0 (-1.7, 1.8), p=0.9554	-0.8 (-2.4, 0.7), p=0.2915
Mean change from Baseline (Week 12 – Week 96)	-0.1 (-1.9, 1.7), p=0.8974	0.1 (-1.7, 1.9), p=0.9379	-0.8 (-2.4, 0.8), p=0.3228
≥15 letters gained from Baseline/BCVA of ≥84 letters at Week 96	5.5 (-1.2, 12.3), p=0.1023	7.2 (1.4, 13.8), p=0.0313	-2.4 (-8.8, 4.1), p=0.4765
≥15 letters loss from Baseline at Week 96	1.1 (-2.9, 4.9), p=0.5769	0.7 (-3.6, 4.6), p=0.7210	-0.4 (-3.8, 3.3), p=0.8377
BCVA of ≥73 letters at Week 96	1.7 (-4.7, 7.8), p=0.5950	2.3 (-3.8, 9.0), p=0.4820	-2.0 (-8.1, 4.1), p=0.5295

Abbreviations: BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; LOCF: last observation carried forward.
Source: HAWK CSR;[24] HARRIER CSR;[25] Khanani et al. 2018.[94]

Post-hoc analyses: time to dry analysis

Sustained drying of the retina is an indicator of better disease control and may be associated with improved long-term visual outcomes. Retreatment decisions in routine clinical practice are commonly made based on OCT, and sustained dryness is therefore potentially associated with reduced treatment burden.

Post-hoc analyses of the HAWK and HARRIER trials were conducted to assess the time to achieve sustained dryness and the cumulative incidence rate (%) of sustained dryness up to Week 96. Time to first sustained dryness was evaluated using the Kaplan-Meier method and a proportional hazard analysis. Sustained dryness was defined as ≥2 consecutive and ≥3 consecutive fluid-free (IRF and SRF) visits. The cumulative incidence (the number of new cases with sustained dryness up to a specified timepoint, divided by the number of population that is at risk of the event) was calculated using the Kaplan-Meier analysis, whereby the risk event was to have ≥2 consecutive or ≥3 consecutive fluid-free (IRF and SRF) visits.

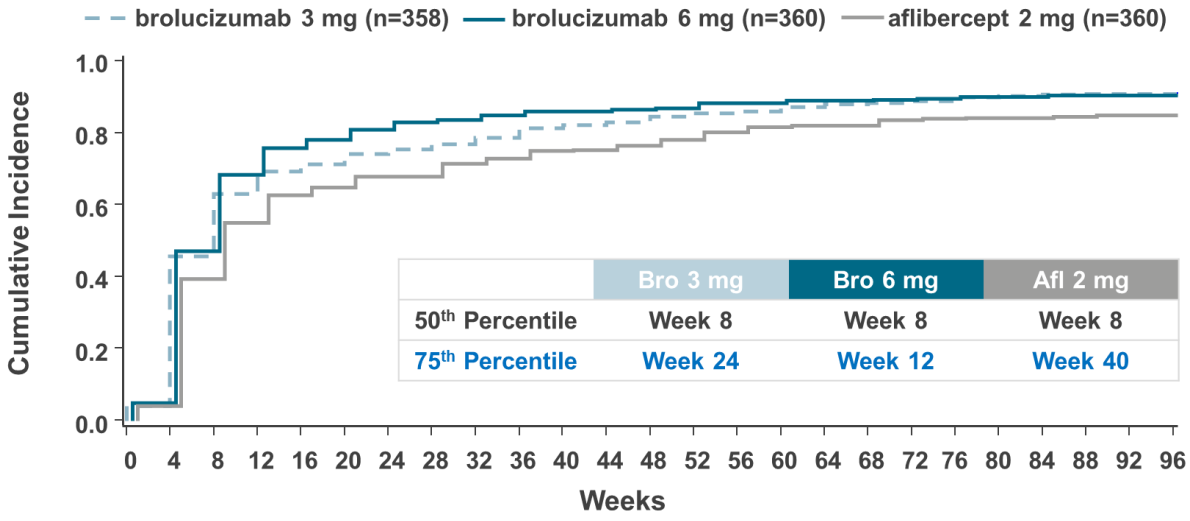
Results of these analyses up to Week 96 are presented in Figure 17 and Figure 18 for HAWK and Figure 19 and Figure 20 for HARRIER.

Compared with aflibercept, brolucizumab achieved first time to fluid-free faster, and more patients treated with brolucizumab achieved sustained dryness, which was then sustained in all cases until Week 96.

The 50th percentile for sustained dryness was achieved earlier for patients on brolucizumab (3 mg and 6 mg) with most achieving ≥2/≥3 fluid free visits by Week 8/8 in HAWK and Week 4/4 in HARRIER compared to aflibercept (HAWK: ≥2/≥3 visits: Week 8/12; HARRIER: Week 4/8]). The 75th percentile was also achieved earlier with brolucizumab compared to aflibercept ≥2/≥3 visits: HAWK-[brolucizumab 3 mg - Week 24/36, brolucizumab 6 mg - Week 12/32, aflibercept - Week 40/not achieved]; HARRIER: brolucizumab 6 mg - Week 8/20, aflibercept – Week 16/not achieved.

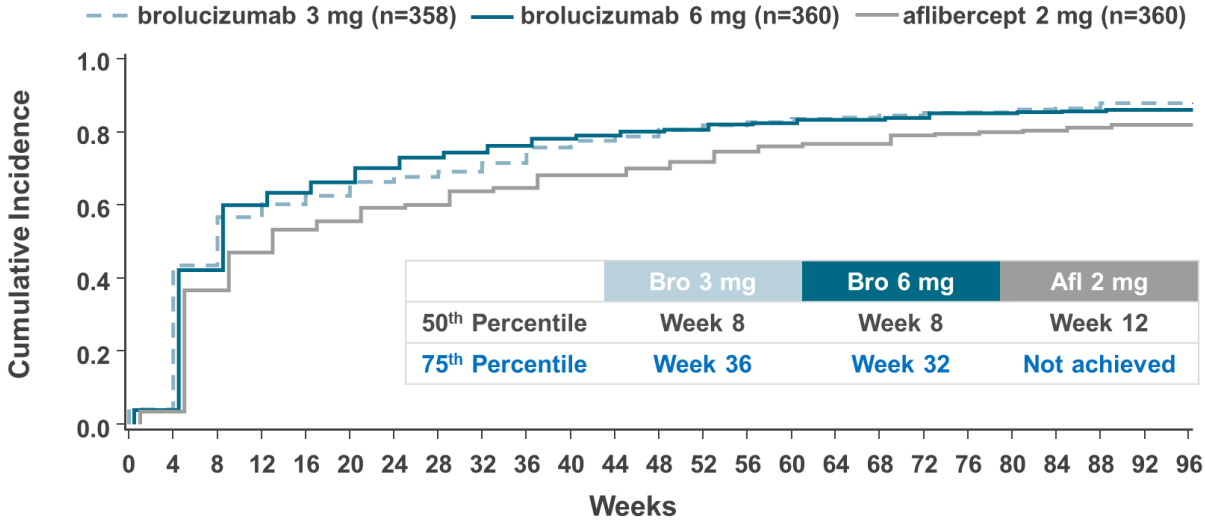
These results are consistent with the superior fluid outcomes seen for brolucizumab at Weeks 16 and 48, which were then maintained through to Week 96.

Figure 17: Time to sustained dryness: ≥2 consecutive fluid free (IRF and SRF) visits until Week 96 in HAWK



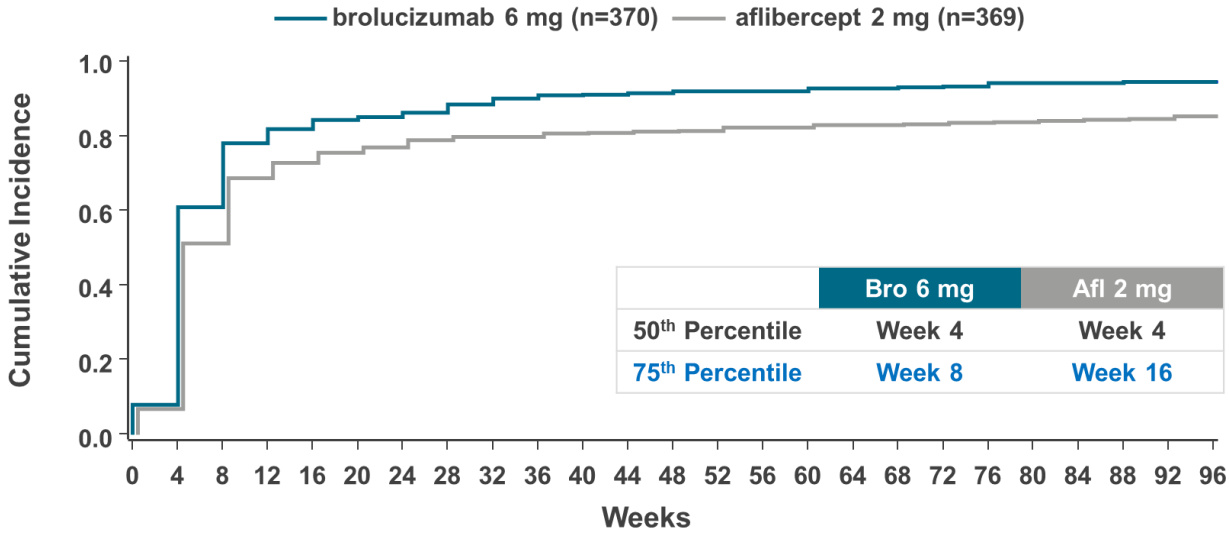
Abbreviations: IRF: intraretinal fluid; SRF: subretinal fluid.
Source: Regillo et al. 2019.[95]

Figure 18: Time to sustained dryness: ≥3 consecutive fluid free (IRF and SRF) visits until Week 96 in HAWK



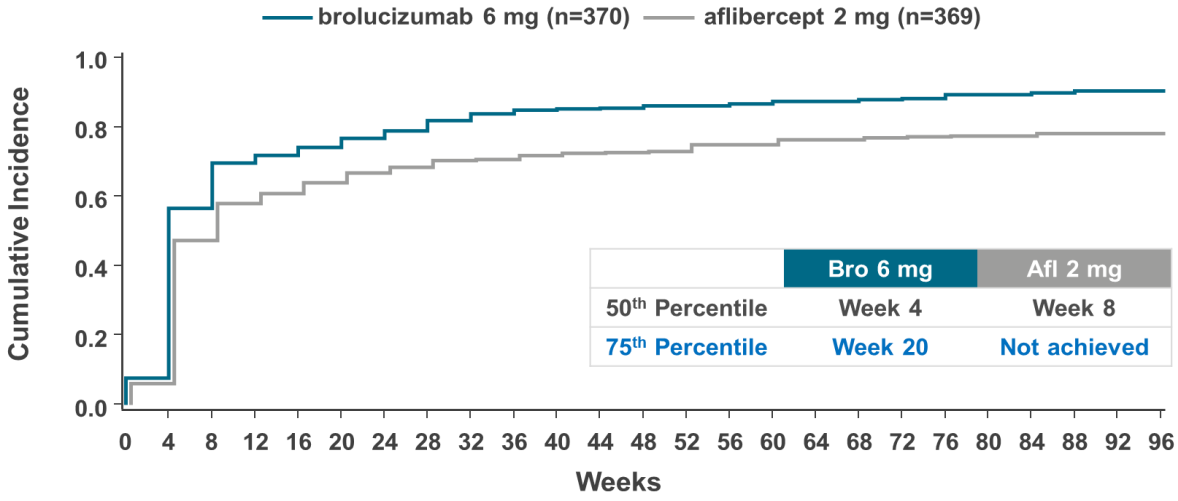
Abbreviations: IRF: intraretinal fluid; SRF: subretinal fluid.
Source: Regillo et al. 2019.[95]

Figure 19: Time to sustained dryness: ≥2 consecutive fluid free (IRF and SRF) visits until Week 96 in HARRIER



Abbreviations: IRF: intraretinal fluid; SRF: subretinal fluid.
Source: Regillo et al. 2019.[95]

Figure 20: Time to sustained dryness: ≥3 consecutive fluid free (IRF and SRF) visits until Week 96 in HARRIER



Abbreviations: IRF: intraretinal fluid; SRF: subretinal fluid.
Source: Regillo et al. 2019.[95]

Cumulative incidence was calculated using the Kaplan-Meier method, and results are presented in Table 22 and Table 23. The cumulative incidence rate (%) in study eyes with sustained dryness was greater for brolucizumab compared with aflibercept at Week 48 [HAWK: ≥2/≥3 visits (brolucizumab 3 mg; 82.9/77.6, brolucizumab 6 mg; 86.5/79.1, aflibercept; 76.5/68.3); HARRIER: ≥2/≥3 visits (brolucizumab 6 mg; 91.5/85.9, aflibercept; 81.4/73.0)]. Similar findings were observed for patients at Week 96 [HAWK: ≥2/≥3 visits (brolucizumab 3 mg; 90.8/87.9, brolucizumab 6 mg; 90.4/86.1, aflibercept; 84.8/82.0); HARRIER: ≥ 2/≥ 3 visits (brolucizumab 6 mg; 94.5/91.2, aflibercept; 85.4/78.8)].

Table 22: Cumulative incidence of ≥2 consecutive fluid free (IRF and SRF) visits

	HAWK			HARRIER	
	Brolucizumab 3 mg (n=358)	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Week 48					
Cumulative incidence rate (%)	**82.9**	**86.5**	**76.5**	**91.5**	**81.4**
Hazard ratio (95% CI)*	1.21 (1.03, 1.43)	1.39 (1.18, 1.63)	-	1.35 (1.15, 1.58)	-
P-value	0.0230	0.0001	-	0.0002	
Week 96					
Cumulative incidence rate (%)	**90.8**	**90.4**	**84.8**	**94.5**	**85.5**
Hazard ratio (95% CI)*	1.22 (1.04, 1.43)	1.33 (1.14, 1.56)	-	1.37 (1.17, 1.60)	
P-value	0.0130	0.0004		<0.0001	

Abbreviations: CI: confidence interval**;** IRF: intraretinal fluid; SRF: subretinal fluid.
Source: Regillo et al. 2019.[95]

Table 23: Cumulative incidence of ≥3 consecutive fluid free (IRF and SRF) visits

	HAWK			HARRIER	
	Brolucizumab 3 mg (n=358)	**Brolucizumab 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Brolucizumab 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**
Week 48					
Cumulative incidence rate (%)	77.6	79.1	68.3	85.9	73.0
Hazard ratio (95% CI)*	1.27 (1.06, 1.51)	1.34 (1.12, 1.59)	-	1.40 (1.19, 1.65)	-
P-value	0.0080	0.0010	-	<0.0001	-
Week 96					
Cumulative incidence rate (%)	87.9	86.1	82.0	91.2	78.8
Hazard ratio (95% CI)*	1.24 (1.05, 1.45)	1.24 (1.06, 1.46)	-	1.43 (1.21, 1.67)	-
P-value	0.0104	0.0080	-	<0.0001	-

Abbreviations: CI: confidence interval**;** IRF: intraretinal fluid; SRF: subretinal fluid.
Source: Regillo et al. 2019.[95]

Patient-reported outcomes

Results for vision-related QoL for HAWK and HARRIER are presented below, with QoL assessed via the NEI VFQ-25 instrument.

These results have not been provided separately for patients who received treatment for their first-affected eye and those who received treatment for their second-affected eye. Both worst eye VA and best eye VA have been shown to contribute independently to vision-related QOL when assessed via the NEI VFQ-25, the instrument used within the HAWK and HARRIER studies.[96] Therefore, the effect of treating the first-affected or second-affected eye on vision-related QoL, when assessed using the NEI VFQ-25, should be considered as equally relevant.

Studies investigating vision-related QoL in wAMD have provided evidence of a strong correlation between VA in the best eye and QoL.[97] However, both worst eye VA and best eye VA will contribute to overall QoL, with loss of binocular vision reducing QOL, due to impacts on key aspects of vision such as depth perception. It is therefore unethical to consider separate treatment approaches for each eye, or to consider withholding treatment from the first-affected eye. The withholding of treatment from an eye could also result in considerable anxiety and depression for a patient, due to the knowledge that the sight in this eye may deteriorate as a result of absence of treatment.

Initiating treatment in the first eye to present clinically is supported by high-quality European and international clinical guidelines for the treatment of wAMD (as summarised in Section 2.3), which refer to the treatment of the disease in general, and do not differentiate treatment recommendations for the first or second eye to be affected.[8, 10, 38] Indeed, in the NICE appraisal of ranibizumab (TA155), the NICE Committee evaluated whether “it would be appropriate to consider recommending treatment in the better-seeing eye only: that is, not to treat where

patients present with only one eye affected" and the Committee noted that "it would be unacceptable, and clinically inappropriate, not to treat the first eye that comes to clinical attention".[67]

Consequently, the number of patients and vision-related QoL results have not been presented separately for patients who received treatment for the first-affected eye and second-affected eye.

Change in vision-related QoL (VFQ-25)

Brolucizumab achieved a similar improvement in HRQoL compared with aflibercept, with a majority of patients maintained on a q12w dosing interval

VFQ-25 is a patient-reported instrument widely used to measure vision-related HRQoL in wAMD. A positive change in VFQ-25 score indicates benefit.

Both trials (HAWK and HARRIER) showed a similar change in VFQ-25 score from Baseline for both brolucizumab (6 mg and 3 mg) and aflibercept (2 mg) treatment groups. At Week 96, the mean change from Baseline in the VFQ-25 was 3.8 for brolucizumab (6 mg) versus 2.8 for aflibercept in HAWK, and 3.8 versus 2.6 in HARRIER.

The FAS-observed and FAS-LOCF analysis of VFQ-25 showed no relevant differences between treatment arms in terms of mean composite score (Table 24). Similar results were seen for all 11 individual VFQ-25 subscales including general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, colour vision, and peripheral vision.

Table 24: HAWK and HARRIER: mean change in VFQ-25 composite scores from Baseline (FAS-observed)

Trial name	HAWK			HARRIER	
Time point	**Brolucizumab 3 mg, mean (n)**	**Brolucizumab 6 mg, mean (n)**	**Aflibercept 2 mg, mean (n)**	**Brolucizumab 6 mg, mean (n)**	**Aflibercept 2 mg, mean (n)**
Week 24	4.4 (n=342)	4.0 (n=341)	3.5 (n=333)	3.9 (n=354)	3.5 (n=355)
Week 48	4.3 (n=328)	4.1 (n=324)	4.5 (n=317)	4.8 (n=347)	3.6 (n=346)
Week 72	4.4 (n=306)	3.9 (n=303)	4.0 (n=298)	5.0 (n=342)	3.2 (n=334)
Week 96	3.8 (n=310)	3.8 (n=301)	2.8 (n=296)	3.8 (n=370)	2.6 (n=369)

Abbreviations: FAS: full analysis set; VFQ-25: visual function questionnaire-25.
Source: HAWK CSR;[24] HARRIER CSR.[25]

5.5 Individual study results (safety outcomes)

1. **Describe the relevant endpoints, including the definition of the endpoint and methods of analysis (table 14).**

The relevant endpoints for safety outcomes considered in this submission are include:

- Treatment exposure
- Ocular and non-ocular adverse events (AEs)
- Serious ocular and non-ocular AEs
- Deaths, other serious adverse events, and other significant adverse events leading to treatment discontinuation
- AEs of special interest

2. **For the technology, and the comparator, tabulate the total number of adverse events, frequency of occurrence (as a %), absolute and relative risk and 95% CI reported in each of the clinical studies. Categorise the adverse events by frequency, severity and system organ class.**

Given their similarities in trial design and methodology, details of the safety results of the HAWK and HARRIER trials have been presented together.

The results presented below are for safety data from Baseline to Week 96. Safety results from Baseline to Week 48 are presented in Appendix 7.3.

Treatment exposure

Over 96 weeks, the mean number of active injections administered in the brolucizumab treatment arms of HAWK and HARRIER was between 1 and 1.5 fewer than the number administered in the aflibercept arms.

The number of active injections administered overall from Baseline to Week 96 is presented in Table 25. In HAWK, overall from Baseline to Week 96, the mean number of active injections administered was 10.5 in the brolucizumab 3 mg arm, 10.2 in the brolucizumab 6 mg arm, and 11.3 in the aflibercept 2 mg arm. The majority of brolucizumab 3 mg and 6 mg patients (34.1% and 39.2%, respectively) received 10 active injections during the study. The majority of aflibercept 2 mg subjects (67.5%) received 13 active injections during the study.

In HARRIER, overall from Baseline to Week 96, the mean number of active injections administered was 10.9 in the brolucizumab 6 mg arm and 12.1 in the aflibercept 2 mg arm (Table 12-5). The majority of aflibercept 2 mg subjects (78.6%) received 13 active injections during the study. In the brolucizumab 6 mg arm, approximately one-third of the subjects (34.1%) received 13 injections and one-third of the subjects (34.3%) 10 active injections. The differences in the number of active injections between the brolucizumab 6 mg and aflibercept 2 mg arms were driven by differences in the dosing intervals, with a majority of brolucizumab 6 mg patients on a q12w dosing interval immediately following the loading dose phase.

Table 25: Extent of exposure to study treatment: number of active injections from Baseline to Week 96 (SAF)

Trial name	HAWK			HARRIER	
Extent of exposure	Brolucizumab 3 mg, (N=358) n (%)	Brolucizumab 6 mg, (N=360) n (%)	Aflibercept 2 mg, (N=360) n (%)	Brolucizumab 6 mg, (N=370) n (%)	Aflibercept 2 mg, (N=369) n (%)
Descriptive statistics					
N	358	360	360	370	369
Mean (SD)	10.5 (2.55)	10.2 (2.74)	11.3 (3.21)	10.9 (2.38)	12.1 (2.32)
Median	10.0	10.0	13.0	11.0	13.0
Min, Max	2, 13	1, 13	1, 13	1, 13	1, 14

Abbreviations: SAF: safety analysis set; SD: standard deviation.
Source: HAWK CSR;[24] HARRIER CSR.[25]

Ocular adverse events

The number of patients with ≥1 AE in the study eye at Week 48 was similar across all treatment arms but higher in HAWK (brolucizumab 3 mg: 175 patients [48.9%]; brolucizumab 6 mg: 179 [49.7%]; aflibercept 2 mg: 170 [47.2%]) than HARRIER (brolucizumab 6 mg: 122 [33.0%]; aflibercept 2 mg: 119 [32.2%]). In HAWK, conjunctival haemorrhage was the most frequently ocular AE in the brolucizumab arms (brolucizumab 3 mg: 30 patients [8.4%]; brolucizumab 6 mg: 23 patients [6.4%]) and VA reduced was the most frequent in the aflibercept arm (24 patients [6.7%]). In HARRIER, VA reduced was the most frequently reported AE, which occurred in 20 patients (5.4%) in each treatment arm.[27] These data are presented in Appendix 7.3.

At Week 96, the number of patients with ≥1 AE in the study eye was higher than at Week 48 and remained similar across treatment arms and higher in HAWK (brolucizumab 3 mg: 218 patients [60.9%]; brolucizumab 6 mg: 220 [61.1%]; aflibercept 2 mg: 201 [55.8%]) than HARRIER (brolucizumab 6 mg: 174 [47.0%]; aflibercept 2 mg: 176 [47.7%]) (Table 26). Conjunctival haemorrhage remained the most frequent ocular AE across all treatment arms in HAWK, and in HARRIER, VA reduced and cataract were the most frequent AEs in the brolucizumab and aflibercept arms, respectively.[93] The majority of ocular AEs were of mild or moderate severity in HAWK (96.1%) and HARRIER (94.9%).

Data relating to ocular AEs in the study eye suspected to be related to the study drug can be found in the CSRs for HAWK and HARRIER.

Table 26: Ocular adverse events up to Week 96 (greater than or equal to 2% in any treatment group) by preferred term for the study eye (SAF)

Trial name	HAWK			HARRIER	
Preferred term	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Number of patients with at least one event	218 (60.9)	220 (61.1)	201 (55.8)	174 (47.0)	176 (47.7)
Conjunctival haemorrhage	39 (10.9)	29 (8.1)	32 (8.9)	17 (4.6)	19 (5.1)
VA reduced	34 (9.5)	22 (6.1)	29 (8.1)	32 (8.6)	26 (7.0)
Vitreous floaters	26 (7.3)	22 (6.1)	16 (4.4)	15 (4.1)	5 (1.4)
Retinal haemorrhage	14 (3.9)	21 (5.8)	20 (5.6)	12 (3.2)	4 (1.1)
Cataract	18 (5.0)	20 (5.6)	13 (3.6)	11 (3.0)	43 (11.7)
Vitreous detachment	24 (6.7)	19 (5.3)	19 (5.3)	10 (2.7)	8 (2.2)
Dry eye	20 (5.6)	19 (5.3)	26 (7.2)	10 (2.7)	11 (3.0)
Eye pain	28 (7.8)	18 (5.0)	21 (5.8)	13 (3.5)	19 (5.1)
Posterior capsule opacification	16 (4.5)	14 (3.9)	11 (3.1)	-	-
Intraocular pressure increased	16 (4.5)	13 (3.6)	15 (4.2)	14 (3.8)	15 (4.1)
Blepharitis	8 (2.2)	13 (3.6)	12 (3.3)	13 (3.5)	5 (1.4)
Retinal pigment epithelial tear	5 (1.4)	12 (3.3)	4 (1.1)	8 (2.2)	5 (1.4)
Vision blurred	16 (4.5)	11 (3.1)	10 (2.8)	-	-
Visual impairment	15 (4.2)	10 (2.8)	14 (3.9)	-	-
Eye irritation	10 (2.8)	10 (2.8)	11 (3.1)	-	-
Punctate keratitis	11 (3.1)	9 (2.5)	10 (2.8)	-	-
Conjunctivitis	3 (0.8)	9 (2.5)	3 (0.8)	15 (4.1)	8 (2.2)
Iritis	3 (0.8)	9 (2.5)	1 (0.3)	0 (0.0)	1 (0.3)
Uveitis	6 (1.7)	8 (2.2)	1 (0.3)	3 (0.8)	0 (0.0)
Visual field defect	9 (2.5)	7 (1.9)	5 (1.4)	-	-
Corneal abrasion	6 (1.7)	7 (1.9)	10 (2.8)	-	-

Macular fibrosis	10 (2.8)	5 (1.4)	4 (1.1)	-	-
Dry age-related macular degeneration	7 (2.0)	5 (1.4)	3 (0.8)	-	-
Foreign body sensation in eyes	8 (2.2)	4 (1.1)	9 (2.5)	-	-
Lacrimation increased	7 (2.0)	4 (1.1)	5 (1.4)	-	-
Lenticular opacities	7 (2.0)	1 (0.3)	4 (1.1)	13 (3.5)	12 (3.3)

Abbreviations: SAF: safety analysis set.
Source: HAWK CSR;[24] HARRIER CSR;[25] Singh et al. 2019.[93]

Non-ocular adverse events

The number of patients with ≥1 non-ocular AE at Week 48 was similar across all treatment arms in HAWK (brolucizumab 3 mg: 242 patients [67.6%]; brolucizumab 6 mg: 232 [64.5%]; aflibercept 2 mg: 258 [71.7%]) and HARRIER (brolucizumab 6 mg: 219 [59.2%]; aflibercept 2 mg: 211 [57.2%]). These data are presented in Appendix 7.3.

At Week 96, the number of patients with ≥ 1 non-ocular AE was similar across all treatment arms in HAWK (brolucizumab 3 mg: 301 patients [84.1%]; brolucizumab 6 mg: 289 patients [80.3%]; aflibercept 2 mg: 303 patients [84.2%]) and across both treatment arms in HARRIER trial (brolucizumab 6 mg: 282 patients [76.2%]; aflibercept 2 mg: 272 patients [73.7%]) (Table 27).[93] In both trials, nasopharyngitis was the most frequently reported non-ocular AE across all treatment arms at Week 48 and Week 96. Across all treatment arms, the vast majority of ocular AEs up to Week 96 were of mild or moderate severity in HAWK (96.1%) and HARRIER (94.9%).

Additionally, at Week 96 the number of patients with ≥1 non-ocular AE in the study eye suspected to be related to the study drug was 11 in HAWK (brolucizumab 3 mg: 6 patients [1.7%]; brolucizumab 6 mg: 2 patients [0.6%]; aflibercept 2 mg: 3 patients [0.8%]) and 5 in HARRIER (brolucizumab 6 mg: 4 patients [1.1%]; aflibercept 2 mg: 1 patients [0.3%]).

Table 27: Non-ocular adverse events up to Week 96 (≥2% in any treatment group) by preferred term for the study eye (SAF)

Trial name	**HAWK**			**HARRIER**	
Preferred term	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Number of patients with at least one event	301 (84.1)	289 (80.3)	303 (84.2)	282 (76.2)	272 (73.7)
Nasopharyngitis	44 (12.3)	38 (10.6)	44 (12.2)	43 (11.6)	31 (8.4)
Pneumonia	17 (4.7)	32 (8.9)	20 (5.6)	7 (1.9)	13 (3.5)

Urinary tract infection	41 (11.5)	27 (7.5)	41 (11.4)	16 (4.3)	19 (5.1)
Hypertension	33 (9.2)	25 (6.9)	24 (6.7)	28 (7.6)	25 (6.8)
Upper respiratory tract infection	17 (4.7)	18 (5.0)	16 (4.4)	6 (1.6)	14 (3.8)
Influenza	17 (4.7)	17 (4.7)	20 (5.6)	24 (6.5)	27 (7.3)
Arthralgia	19 (5.3)	15 (4.2)	21 (5.8)	14 (3.8)	13 (3.5)
Pain in extremity	14 (3.9)	15 (4.2)	10 (2.8)	9 (2.4)	4 (1.1)
Back pain	26 (7.3)	14 (3.9)	17 (4.7)	16 (4.3)	28 (7.6)
Diarrhoea	11 (3.1)	14 (3.9)	13 (3.6)	10 (2.7)	6 (1.6)
Cough	20 (5.6)	13 (3.6)	17 (4.7)	12 (3.2)	8 (2.2)
Bronchitis	13 (3.6)	13 (3.6)	22 (6.1)	23 (6.2)	21 (5.7)
Constipation	11 (3.1)	13 (3.6)	13 (3.6)	-	-
Nausea	17 (4.7)	12 (3.3)	12 (3.3)	-	-
Headache	10 (2.8)	12 (3.3)	13 (3.6)	12 (3.2)	8 (2.2)
Contusion	7 (2.0)	12 (3.3)	12 (3.3)	-	-
Chronic obstructive pulmonary disease	6 (1.7)	12 (3.3)	12 (3.3)	-	-
Arthritis	4 (1.1)	12 (3.3)	13 (3.6)	-	-
Sinusitis	17 (4.7)	11 (3.1)	14 (3.9)	-	-
Fall	18 (5.0)	10 (2.8)	7 (1.9)	-	-
Musculoskeletal pain	4 (1.1)	10 (2.8)	4 (1.1)	-	-
Seasonal allergy	3 (0.8)	10 (2.8)	9 (2.5)	-	-
Osteoarthritis	14 (3.9)	9 (2.5)	11 (3.1)	19 (5.1)	7 (1.9)
Blood pressure increased	9 (2.5)	9 (2.5)	9 (2.5)	2 (0.5)	11 (3.0)
Cardiac failure congestive	6 (1.7)	9 (2.5)	6 (1.7)	-	-
Atrial fibrillation	13 (3.6)	8 (2.2)	15 (4.2)	5 (1.4)	10 (2.7)
Dizziness	9 (2.5)	8 (2.2)	6 (1.7)	5 (1.4)	9 (2.4)
Gamma-glutamyltransferase increased	8 (2.2)	8 (2.2)	7 (1.9)	-	-
Herpes zoster	6 (1.7)	8 (2.2)	8 (2.2)	-	-
Dental caries	6 (1.7)	8 (2.2)	7 (1.9)	-	-
Basal cell carcinoma	5 (1.4)	8 (2.2)	6 (1.7)	-	-

Neck pain	2 (0.6)	8 (2.2)	3 (0.8)	-	-
Anaemia	12 (3.4)	7 (1.9)	15 (4.2)	5 (1.4)	8 (2.2)
Gastroesophageal reflux disease	11 (3.1)	7 (1.9)	3 (0.8)	-	-
Oedema peripheral	4 (1.1)	7 (1.9)	8 (2.2)	-	-
Dyspnoea	9 (2.5)	6 (1.7)	8 (2.2)	-	-
Vomiting	7 (2.0)	6 (1.7)	5 (1.4)	-	-
Anxiety	13 (3.6)	5 (1.4)	10 (2.8)	-	-
Insomnia	11 (3.1)	5 (1.4)	10 (2.8)	-	-
Laceration	9 (2.5)	5 (1.4)	6 (1.7)	-	-
Cystitis	9 (2.5)	5 (1.4)	4 (1.1)	17 (4.6)	5 (1.4)
Benign prostatic hyperplasia	8 (2.2)	5 (1.4)	5 (1.4)	-	-
Depression	7 (2.0)	5 (1.4)	7 (1.9)	-	-
Blood uric acid increased	7 (2.0)	4 (1.1)	4 (1.1)	-	-
Dehydration	4 (1.1)	4 (1.1)	8 (2.2)	-	-
Coronary artery disease	9 (2.5)	3 (0.8)	3 (0.8)	-	-
Asthenia	7 (2.0)	3 (0.8)	2 (0.6)	-	-
Blood urea increased	10 (2.8)	2 (0.6)	5 (1.4)	-	-
Haematoma	7 (2.0)	2 (0.6)	4 (1.1)	-	-
Muscle strain	4 (1.1)	1 (0.3)	10 (2.8)	-	-
Hypercholesterolaemia	-	-	-	13 (3.5)	8 (2.2)
Sciatica	-	-	-	9 (2.4)	8 (2.2)
Pharyngitis	-	-	-	2 (0.5)	12 (3.3)
Syncope	-	-	-	8 (2.2)	8 (2.2)

Abbreviations: SAF: safety analysis set.
Source: HAWK CSR;[24] HARRIER CSR.[25]

Serious ocular adverse events

At Week 48, a total of 19 patients experienced ≥1 ocular SAE in the study eye in HAWK (brolucizumab 3 mg: 5 patients [1.4%]; brolucizumab 6 mg: 11 patients [3.1%]; aflibercept 2 mg: 3 patients [0.8%]) and 13 patients in HARRIER (brolucizumab 6 mg: 9 patients [2.4%]; aflibercept 2 mg: 4 patients [1.1%]).[27] In HAWK, the most frequently reported ocular SAEs in the study eye were endophthalmitis and uveitis in the brolucizumab arms and VA reduced in the aflibercept arms. In HARRIER, the most frequently reported ocular SAEs in the study eye was uveitis in the brolucizumab arm;

in the aflibercept arm none of the SAEs were reported in more than 1 patient each. These data are presented in Appendix 7.3 and are comparable to the safety profiles reported for licensed anti-VEGF therapies in previous trials.

At Week 96, the number of patients who experienced ≥1 ocular SAE in the study eye increased to 24 patients experienced in HAWK (brolucizumab 3 mg: 7 patients [2.0%]; brolucizumab 6 mg: 12 patients [3.3%]; aflibercept 2 mg: 5 patients [1.4%]) and 19 patients in HARRIER (brolucizumab 6 mg: 13 patients [3.5%]; aflibercept 2 mg: 6 patients [1.6%]) (Table 28).[93] In HAWK, the most frequently reported ocular SAEs were endophthalmitis and VA reduced in the brolucizumab and aflibercept arms, respectively. In HARRIER, the most frequently reported ocular SAE in the brolucizumab arm was uveitis; none of the SAEs in the aflibercept arm were reported in more than 1 patient each.

Table 28: Serious ocular adverse events up to Week 96 by preferred term for the study eye (SAF)

Trial name	HAWK			HARRIER	
Preferred term	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Number of patients with at least one event	7 (2.0)	12 (3.3)	5 (1.4)	13 (3.5)	6 (1.6)
Endophthalmitis	3 (0.8)	3 (0.8)	0 (0.0)	1 (0.3)	1 (0.3)
Uveitis	1 (0.3)	2 (0.6)	0 (0.0)	3 (0.8)	0 (0.0)
Retinal detachment	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
VA reduced	0 (0.0)	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)
Macular hole	0 (0.0)	1 (0.3)	1 (0.3)	-	-
Cataract	0 (0.0)	1 (0.3)	0 (0.0)	-	-
Retinal artery thrombosis	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Retinal depigmentation	0 (0.0)	1 (0.3)	0 (0.0)	-	-
Retinopathy proliferative	0 (0.0)	1 (0.3)	0 (0.0)	-	-
Vitritis	0 (0.0)	1 (0.3)	0 (0.0)	-	-
Retinal artery occlusion	3 (0.8)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.3)
Glaucoma	1 (0.3)	0 (0.0)	0 (0.0)	-	-
Cataract subscapular	0 (0.0)	0 (0.0)	1 (0.3)	-	-
Retinal tear	-	-	-	2 (0.5)	1 (0.3)
Retinal pigment epithelial tear	-	-	-	2 (0.5)	0 (0.0)
Anterior chamber inflammation	-	-	-	1 (0.3)	0 (0.0)
Blindness	-	-	-	1 (0.3)	0 (0.0)

Cataract traumatic	-	-	-	1 (0.3)	0 (0.0)
Dacryocystitis	-	-	-	1 (0.3)	0 (0.0)
Retinal artery embolism	-	-	-	1 (0.3)	0 (0.0)
Dry age-related macular degeneration	-	-	-	0 (0.0)	1 (0.3)

Abbreviations: SAF: safety analysis set.
Source: HAWK CSR;[24] HARRIER CSR;[25] Singh et al. 2019.[93]

Serious non-ocular adverse events

At Week 48, a total of 162 patients experienced ≥1 non-ocular SAE in HAWK (brolucizumab 3 mg: 47 patients [13.1%]; brolucizumab 6 mg: 47 patients [13.1%]; aflibercept 2 mg: 68 patients [18.9%]) and 78 patients in HARRIER (brolucizumab 3 mg: 35 patients [9.5%]; aflibercept 2 mg: 43 patients [11.7%]).[27] In HAWK, the most frequently reported non-ocular SAEs in the study eye were pneumonia and cerebrovascular accident. In HARRIER, the most frequently reported non-ocular SAEs were rectal haemorrhage, cholecystitis acute, gastroenteritis, and pulmonary oedema in the brolucizumab arm and pneumonia in the aflibercept arm. These data are presented in Appendix 7.3.

At Week 96, a total of 283 patients experienced ≥1 non-ocular SAE in HAWK (brolucizumab 3 mg: 88 patients [24.6%]; brolucizumab 6 mg: 85 patients [23.6%]; aflibercept 2 mg: 110 patients [30.6%]) and 154 patients in HARRIER (brolucizumab 6 mg: 69 patients [18.6%]; aflibercept 2 mg: 85 patients [23.0%]) (Table 29).[93] The most frequently reported non-ocular SAE was pneumonia across all treatment arms in HAWK. In HARRIER, the most frequently reported non-ocular SAEs were lower limb fracture and syncope in the brolucizumab 6 mg arm and pneumonia in the aflibercept 2 mg arm.

Table 29: Serious non-ocular adverse events up to Week 96 (≥3 patients in any treatment group) by preferred term (SAF)

Trial name	**HAWK**			**HARRIER**	
Preferred term	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Number of patients with at least one event	88 (24.6)	85 (23.6)	110 (30.6)	69 (18.6)	85 (23.0)
Pneumonia	7 (2.0)	10 (2.8)	9 (2.5)	2 (0.5)	8 (2.2)
Cardiac failure congestive	4 (1.1)	6 (1.7)	4 (1.1)	-	-
Chronic obstructive pulmonary disease	1 (0.3)	6 (1.7)	4 (1.1)	2 (0.5)	1 (0.3)
Atrial fibrillation	4 (1.1)	4 (1.1)	2 (0.6)	-	-
Cerebrovascular accident	3 (0.8)	4 (1.1)	3 (0.8)	0 (0.0)	4 (1.1)

Sepsis	3 (0.8)	4 (1.1)	1 (0.3)	-	-
Septic shock	0 (0.0)	3 (0.8)	0 (0.0)	-	-
Urinary tract infection	4 (1.1)	2 (0.6)	2 (0.6)	-	-
Hyponatraemia	4 (1.1)	2 (0.6)	1 (0.3)	-	-
Syncope	3 (0.8)	2 (0.6)	3 (0.8)	3 (0.8)	2 (0.5)
Myocardial infarction	1 (0.3)	2 (0.6)	3 (0.8)	2 (0.5)	0 (0.0)
Femur fracture	0 (0.0)	2 (0.6)	4 (1.1)	2 (0.5)	0 (0.0)
Coronary artery disease	6 (1.7)	1 (0.3)	3 (0.8)	-	-
Cholelithiasis	4 (1.1)	1 (0.3)	2 (0.6)	2 (0.5)	0 (0.0)
Transient ischaemic attack	3 (0.8)	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.5)
Non-cardiac chest pain	1 (0.3)	1 (0.3)	3 (0.8)	-	-
Subdural haematoma	1 (0.3)	1 (0.3)	3 (0.8)	-	-
Influenza	3 (0.8)	0 (0.0)	1 (0.3)	-	-
Intestinal obstruction	1 (0.3)	0 (0.0)	3 (0.8)	-	-
Lower limb fracture	-	-	-	3 (0.8)	0 (0.0)
Cardiac failure	-	-	-	2 (0.5)	2 (0.5)
Ischaemic stroke	-	-	-	2 (0.5)	1 (0.3)
Prostate cancer	-	-	-	2 (0.5)	1 (0.3)
Rectal haemorrhage	-	-	-	2 (0.5)	1 (0.3)
Benign prostatic hyperplasia	-	-	-	2 (0.5)	0 (0.0)
Cholecystitis acute	-	-	-	2 (0.5)	0 (0.0)
Gastroenteritis	-	-	-	2 (0.5)	0 (0.0)
Inguinal hernia	-	-	-	2 (0.5)	0 (0.0)
Joint dislocation	-	-	-	2 (0.5)	0 (0.0)
Pulmonary oedema	-	-	-	2 (0.5)	0 (0.0)
Bronchitis	-	-	-	1 (0.3)	2 (0.5)
Femoral neck fracture	-	-	-	1 (0.3)	2 (0.5)
Osteoarthritis	-	-	-	1 (0.3)	2 (0.5)
Pulmonary embolism	-	-	-	1 (0.3)	2 (0.5)
Death	-	-	-	0 (0.0)	3 (0.8)
Arrhythmia	-	-	-	0 (0.0)	2 (0.5)

Cerebrovascular disorder	-	-	-	0 (0.0)	2 (0.5)
Fall	-	-	-	0 (0.0)	2 (0.5)
Humerus fracture	-	-	-	0 (0.0)	2 (0.5)

Abbreviations: SAF: safety analysis set.
Source: HAWK CSR;[24] HARRIER CSR;[25] Dugel et al. 2019;[27] Singh et al. 2019.[93]

Adverse events of special interest

The following section presents details of adverse events of special interest which were defined in the HAWK and HARRIER trial protocols and identified by the investigator. A full list of the AEs of special interests can be found in the HAWK and HARRIER CSRs.

In the brolucizumab arms of HAWK, the following AEs of potential relevance to intravitreal anti-VEGF therapy were more frequently reported than in the aflibercept arm.

Intraocular inflammation in the study eye was reported in 17 subjects (4.7%) in the brolucizumab 3 mg arm, 21 subjects (5.8%) in the brolucizumab 6 mg and two subjects (0.6%) in the aflibercept 2 mg arm. The majority of events were mild and moderate (96.2%), with only one subject (0.3%) in the brolucizumab 3 mg arm and one subject (0.3%) in the brolucizumab 6 mg arm with severe intraocular inflammation. Most of the events were treated with topical corticosteroids (65.6%) and resolved without sequelae (80.8%).

Endophthalmitis was reported in four subjects (1.1%) in the brolucizumab 3 mg arm, 4 subjects (1.1%) in the brolucizumab 6 mg and zero subjects in the aflibercept 2 mg arm. It should be noted that the incidence of endophthalmitis was considered related to the intravitreal procedure rather than related to drug, and the incidence of endophthalmitis in HAWK was similar to that reported in other clinical trials.[98]

RPE tears in the study eye was reported in five subjects [1.4%] in the brolucizumab 3 mg arm, 12 subjects [3.3%] in the brolucizumab 6 mg and four subjects [1.1%] in the aflibercept 2 mg arm. The incidence of RPE tears in the study eye in HAWK falls within the range reported for wAMD patients treated with VEGF inhibitors.

In the brolucizumab arm of the HARRIER trial, the following AEs of potential relevance to intravitreal injection were more frequently reported than in the aflibercept arm.

Intraocular inflammation in the study eye was reported in 11 subjects (3.0%) in the brolucizumab 6 mg arm and five subjects (1.4%) in the aflibercept 2 mg arm. While rates of intraocular inflammation were higher in the brolucizumab arm than the aflibercept arm, rates were in line with those previously reported in clinical trials. In the brolucizumab 6 mg arm, the majority of the events were mild or moderate (86.7%), with only two events reported as severe. Most of the events were treated with topical corticosteroids (43.4% of concomitant treatment administered) and were resolved without sequelae (86.7% of events).

Endophthalmitis in the study eye was observed in one patient in the brolucizumab 6 mg arm and one patient in the aflibercept 2 mg arm.

Deaths, other serious adverse events, and other significant adverse events leading to treatment discontinuation

At Week 48, 14 patients had died in HAWK (brolucizumab 3 mg: 4 patients [1.1%]; brolucizumab 6 mg: 4 patients [1.1%]; aflibercept 2 mg: 6 patients [1.7%]) and 7 patients in HARRIER (brolucizumab 6 mg: 3 patients [0.8%]; aflibercept 2 mg: 4 patients [1.1%]). No deaths were considered to be related to study treatment by the Investigator. In HAWK, 183 patients had experienced ≥1 SAE, and 40 led to premature study discontinuation (brolucizumab 3 mg: 11 patients [3.1%]; brolucizumab 6 mg: 12 patients [3.3%]; aflibercept 2 mg: 17 patients [4.7%]); the majority of these were related to ocular AEs in the study eye (72.5%). In HARRIER, 90 patients had experienced ≥1 SAE, and 16 led to premature study discontinuation (brolucizumab 6 mg: 12 patients [3.2%]; aflibercept 2 mg: 4 patients [1.1%]); the majority of these were also related to ocular AEs in the study eye (75.0%). 303 and 168 patients had experienced ≥1 SAE in HAWK and HARRIER respectively and 55 and 29 had led to premature study discontinuation. The

majority of premature study discontinuations were related to ocular AEs in the study eye in both trials. These data are presented in Appendix 7.3.

At Week 96, 29 patients had died in HAWK (brolucizumab 3 mg: 9 patients [2.5%]; brolucizumab 6 mg: 8 patients [2.2%]; aflibercept 2 mg: 12 patients [3.3%]) and 11 in HARRIER (brolucizumab 6 mg: 4 patients [1.1%]; aflibercept 2 mg: 7 patients [1.9%]) (Table 30).[93] No deaths were suspected to be related to study treatment by the Investigator in HARRIER. In HAWK, in the second year in the brolucizumab 3 mg treatment arm, one SAE with a fatal outcome (cerebrovascular accident) was considered to be related to the study treatment by the Investigator.

Table 30: Deaths, SAE or AE leading to permanent study treatment discontinuation up to Week 96 (SAF)

Trial name	HAWK			HARRIER	
Patients with serious or significant AE	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Death	9 (2.5)	8 (2.2)	12 (3.3)	4 (1.1)	7 (1.9)
SAE	94 (26.3)	95 (26.4)	114 (31.7)	79 (21.4)	89 (24.1)
Study eye	7 (2.0)	12 (3.3)	5 (1.4)	13 (3.5)	6 (1.6)
Fellow eye	0 (0.0)	4 (1.1)	1 (0.3)	0 (0.0)	0 (0.0)
Non-ocular	88 (24.6)	85 (23.6)	110 (30.6)	69 (18.6)	85 (23.0)
AE leading to permanent study treatment discontinuation	17 (4.7)	16 (4.4)	22 (6.1)	20 (5.4)	9 (2.4)
Study eye	14 (3.9)	11 (3.1)	12 (3.3)	13 (3.5)	6 (1.6)
Fellow eye	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-ocular	3 (0.8)	5 (1.4)	10 (2.8)	8 (2.2)	3 (0.8)

Abbreviations: AE: adverse event; SAE: serious adverse event**;** SAF: safety analysis set.
Source: HAWK CSR;[24] HARRIER CSR;[25] Dugel et al. 2019;[27] Singh et al. 2019.[93]

5.6 Subgroups

1. Describe which subgroup(s) were analysed in the clinical trials of the technology under assessment.

The pre-planned subgroups for analysis in HAWK and HARRIER were:

- Age category (<75 years and ≥75 years)
- Sex (male and female)
- Baseline BCVA categories (≤55, 56–70, and ≥ 71 letters)
- Baseline CSFT category (<400 and ≥400 µm)
- Baseline lesion type (predominantly classic, minimally classic, occult)
- Baseline CNV lesion size (<1.3 mm2, 1.3–3.9 mm2, >3.9 mm2)
- Baseline lesion size by lesion type
- Baseline fluid status (IRF, SRF, sub-RPE fluid)

The following pre-planned subgroups were analysed in HAWK only:

- Japanese ethnicity: Japanese versus non-Japanese
- Baseline polyp status (present/absent) from ICG assessment at Screening (study centres in Japan only)

2. State which papers are relevant to the subgroup analyses.

Results of the subgroup analyses of the HAWK and HARRIER trials have not yet been published. Details of the subgroup analyses can be found in the HAWK and HARRIER CSRs.

3. Specify the methods of subgroup analysis used in the clinical trials.

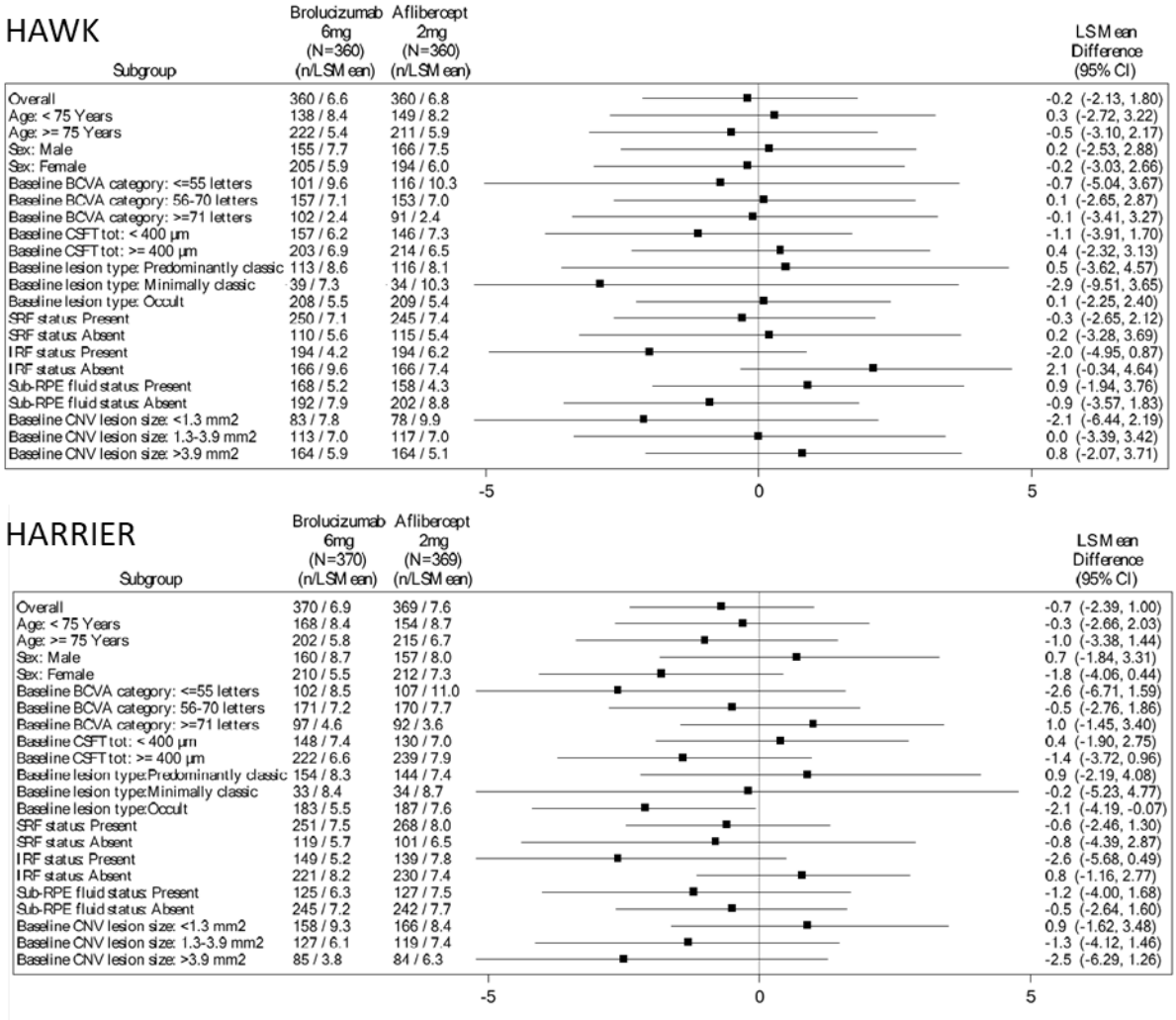
Subgroup analyses were conducted using the same model and analysis strategies described for the primary and key secondary analyses but fitted by category for each of the subgroups. Subgroup variables that were used as fixed effects in the model were removed from the model statement for the subgroup analysis.

4. Give the results of the subgroup analyses from the clinical trials.

Change in BCVA from Baseline to Week 48

The results of the subgroup analyses for the primary endpoint of change in BCVA from Baseline to Week 48 showed a relevant improvement in BCVA from Baseline across all brolucizumab subgroups, irrespective of baseline disease characteristics/demographics (Figure 21). Additionally, the differences between treatments were not suggestive of relevant subgroup-specific effects for either brolucizumab dose compared with aflibercept 2 mg.

Figure 21: Forest plot of summary statistics and ANOVA for change in BCVA from Baseline to Week 48 by subgroups of interest (FAS-LOCF)

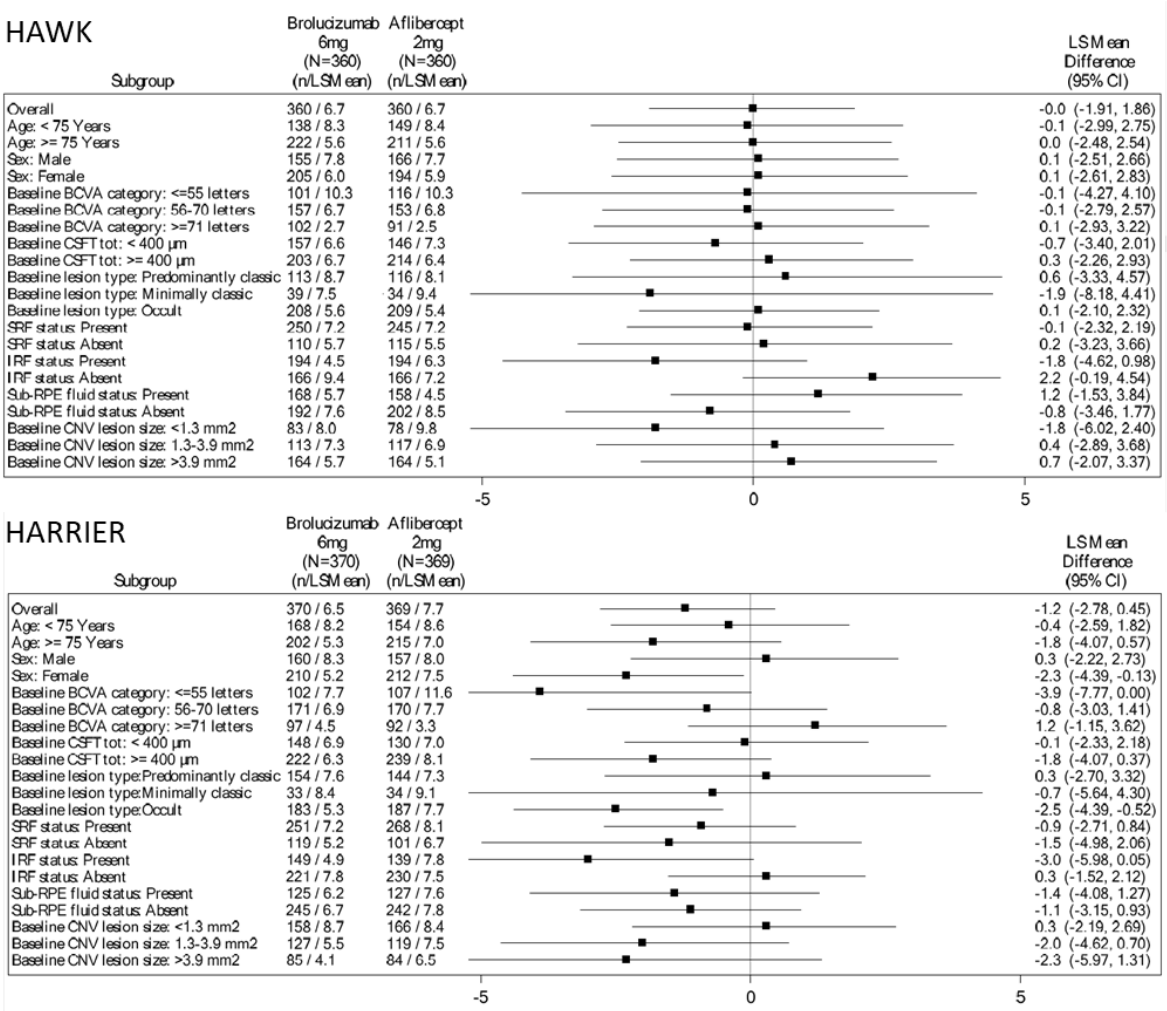


Abbreviations: ANOVA: analysis of variance; BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; LOCF: last observation carried forward; LSM: least squares mean.
Source: HAWK CSR;[24] HARRIER CSR.[25]

Average change in BCVA from Baseline over the period Week 36 to Week 48

Similar to primary efficacy endpoint, subgroup analyses were conducted for the first key secondary endpoint. Overall, results of the subgroup analyses up to Week 48 confirmed relevant improvements for all subgroups in all treatments groups and were not suggestive of relevant differences in treatment effect for either brolucizumab dose (HAWK: 6 mg and 3 mg; HARRIER: 6 mg) compared with aflibercept 2 mg (Figure 22).

Figure 22: Forest plot of summary statistics and ANOVA for change in BCVA from Baseline over the period of Week 36 through Week 48 by subgroups of interest (FAS-LOCF)



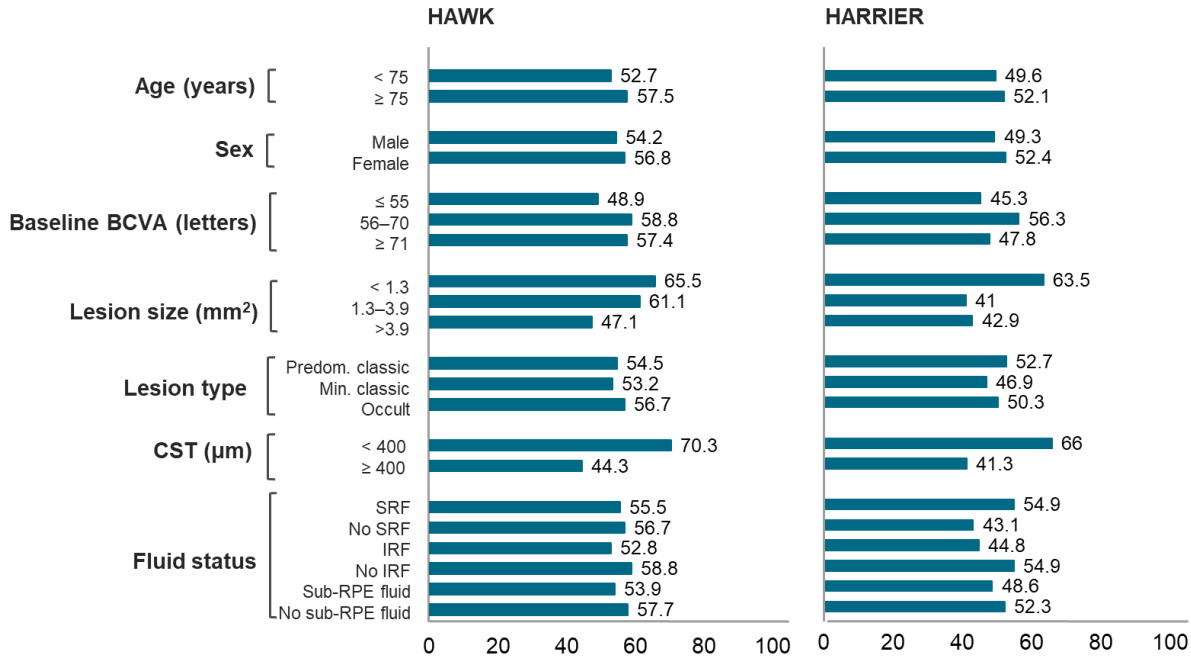
Abbreviations: ANOVA: analysis of variance; BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; LOCF: last observation carried forward; LSM: least squares mean.
Source: HAWK CSR;[24] HARRIER CSR.[25]

Proportion of patients maintained on q12w dosing interval until Week 48 by Baseline characteristics

Subgroup analyses related to the q12w treatment status at Week 48 suggested that, irrespective of subgroup parameters, >40% of patients qualified for q12w in all subgroups in the brolucizumab arms of both HAWK and HARRIER trials. Overall, the brolucizumab 6 mg arm demonstrated a higher probability of maintaining on a q12w regimen compared to the brolucizumab 3 mg arm across all subgroups.

Baseline characteristics were not predictive for patients maintaining on a q12w dosing interval until Week 48. The most differentiating parameter identified in both trials which impacted the potential of maintaining on the q12w regimen, was baseline CSFT status (Figure 23).

Figure 23: Proportion of patients maintained on q12w dosing interval until Week 48 (FAS)

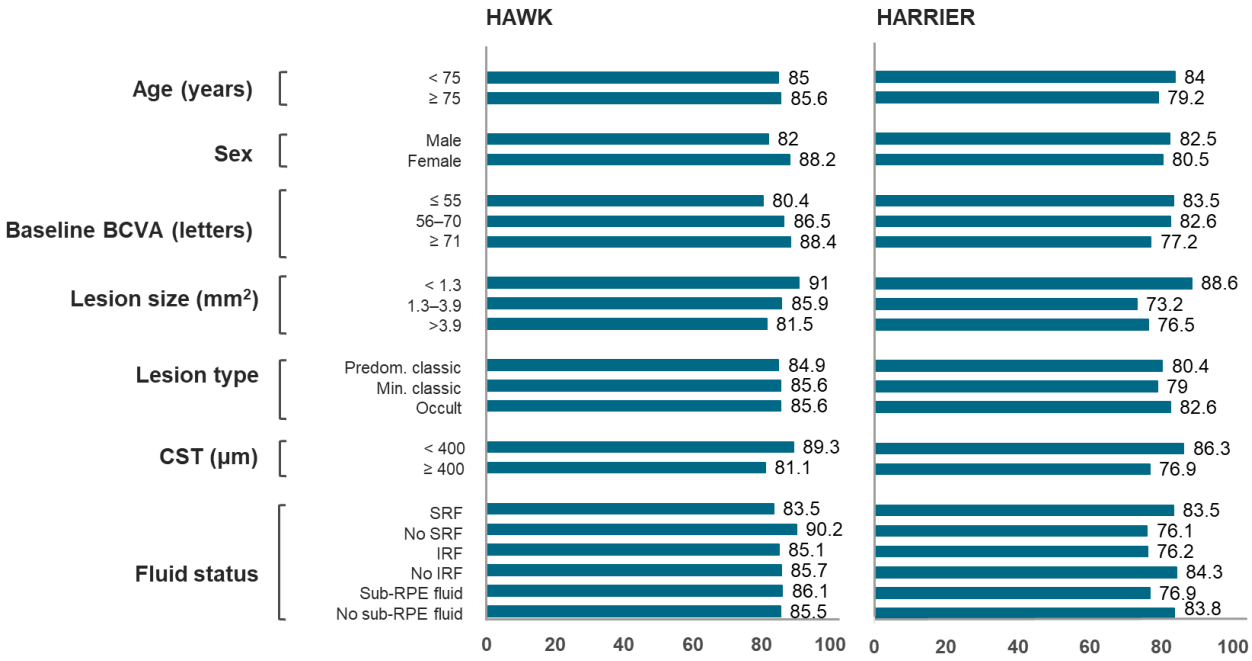


Predefined subgroup analysis, FAS "Efficacy/Safety approach". The numbers are based on estimated percentages from Kaplan Meier analysis.
Abbreviations: BCVA: best-corrected visual acuity; CST: central subfield thickness; q12w: one injection every 12 weeks.
Source: Monés et al. 2018.[92]

Predictive value of the initial q12w cycle

Subgroup analyses revealed high q12w potential for all subgroups in patients receiving brolucizumab across both HAWK (>80% in 6 mg treatment group) and HARRIER (>70%), based on the proportion of patients who successfully completed the first q12w interval (i.e. no disease activity at Week 20) (Figure 24). In the Japanese ancestry subgroup, the observed proportion of patients who successfully completed the first q12w interval (i.e. no disease activity at Week 20) and were maintained on a q12w dosing interval at Week 48 was 86.7%. Similar results were observed in the subgroup analysis for patients in the brolucizumab 3 mg treatment group.

Figure 24: Proportion of patients who successfully completed the first q12w interval remaining on the q12w interval until Week 48, by Baseline characteristics (FAS)



Predefined subgroup analysis, FAS "Efficacy/Safety approach". The numbers are based on estimated percentages from Kaplan Meier analysis.
Abbreviations: BCVA: best-corrected visual acuity; CST: central subfield thickness; q12w: one injection every 12 weeks.
Source: Monés et al. 2018.[92]

5.7 Methods of evidence synthesis

In the absence of head-to-head data for brolucizumab versus ranibizumab, a network meta-analysis (NMA) was performed to assess the relative effectiveness of brolucizumab versus the relevant comparators to this appraisal: aflibercept and ranibizumab.

1. **State the type of synthesis (for example, narrative, meta-analysis, indirect or mixed treatment comparison).**

Feasibility assessment

Following the identification of relevant studies from the clinical SLR, a feasibility assessment was first conducted to assess the feasibility of performing an NMA to estimate the relative effectiveness brolucizumab and the relevant comparators to this appraisal: ranibizumab and aflibercept.

The eligibility criteria for the NMA were based on the PICOS criteria reported in

Table 31 below. These criteria were applied to the studies identified from the clinical SLR to attain the studies relevant to the NMA. The same criteria were also applied to establish the feasibility of conducting baseline pooling analysis to estimate the absolute treatment effect for treatment regimens with more than one trial.

If a comparator of interest was evaluated against PDT, or sham IVT, the trial was included only if it helped connect the networks to another comparator of interest.

Table 31: PICOS framework for the NMA

Topic	Description
Population	• Patients ≥18 years old with wAMD (also known as neovascular AMD)[a]
Intervention	• Brolucizumab
Comparators	• Ranibizumab (Lucentis®) • Aflibercept (Eylea®)
Outcomes	• Mean change in BCVA • Mean change in CRT • Proportion of patients gaining at least 15 ETDRS letters • Proportion of patients losing at least 15 ETDRS letters • Overall discontinuation • Injection frequencies[b] • Adverse events[b]
Study type	• RCTs of 44 weeks or longer, cross-over RCTs (if data presented at the time of cross-over) • Open-label extension studies of RCTs

[a]Studies that enrolled patients with uncommon manifestations of wAMD, including PCV, were excluded if these subtypes comprised greater than 10% of the total population.
[b]These outcomes were evaluated through baseline pooling analysis only.
Abbreviations: BCVA: best corrected visual acuity; CRT: central retinal thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; NMA: network meta-analysis; PCV: polypoidal choroidal vasculopathy; RCT: randomised controlled trial; wAMD: wet age-related macular degeneration.

2. State the outcomes included in the synthesis and the time point for the collection of outcome data. Justify the inclusion and exclusion of outcomes and the time point.

Outcome measures

The following table summarises the outcomes tested for feasibility and evaluated within the NMAs to estimate the relative treatment effect and within the baseline pooling analysis to estimate the absolute treatment effect for treatment regimens with more than one trial. Molecule-based pooling refers to pooling treatments by their molecule alone (i.e. ranibizumab, brolucizumab, and aflibercept). The following outcomes represent the gold standard in terms of measuring the effectiveness of therapies for wAMD.

Table 32: Type of analyses with outcome description

Outcome and time points	Definition	NMA	Baseline pooling
BCVA, mean change	Mean change in BCVA according to ETDRS letters		Regimen-based
Baseline→Year One		X	X
Baseline→Year Two		X	X
Discontinuation	Treatment discontinuation		Regimen-based
Baseline→Year One		X	X
Baseline→Year Two		X	X
Injection frequency	Annualised number of injections		Regimen-based
Baseline→Year One		O	X

Baseline→Year Two		O	X
Retinal thickness	Mean change in retinal thickness: Central retinal thickness (CRT), central macular thickness (CMT), central subfield thickness (CSFT), and central foveal thickness (CFT) will be considered as the same endpoint, as confirmed by Novartis's medical expert		NA
Baseline→Year One		X	O
Baseline →Year Two		X	O
Proportions gaining/losing 15 letters	Proportion of patients gaining or losing at least 15 ETDRS letters		Regimen-based
Baseline→Year One		X	X
Baseline →Year Two		X	X
Ocular adverse events	SAE: cataract, endophthalmitis, intraocular inflammation, retinal detachment, retinal pigment epithelial tear, retinal tear Overall AE: endophthalmitis		Regimen-based & molecule-based
Baseline→Year One		O	X
Baseline→Year Two		O	X
Systemic adverse events	SAE: Gastrointestinal event, stroke		Molecule-based
Baseline→Year One		O	X
Baseline→Year Two		O	X

X – Analysed; O – Not of interest/not feasible.
Abbreviations: AE: adverse events; BCVA: best-corrected visual acuity; CFT: central foveal thickness; CMT: central macular thickness; CRT: central retinal thickness; CSFT: central subfield thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; NA: not applicable; NMA: network meta-analysis; SAE: serious adverse event.

The outcomes were analysed at both one and two years. The NICE NMA in wAMD[49] also considered outcomes at one and two years and indicated that outcomes for the interval 1–2 years can be inferred from Baseline to one year and Baseline to two years[49]. However, some trials reported results within several weeks of 12 and 24 months. Equivalence was therefore assumed between 48 and 52 weeks for results to be considered at 12 months, and between 96 and 104 weeks for results at 24 months.

3. State whether any syntheses of subgroup data are being presented. Justify the subgroups chosen.

Not applicable.

4. State the comparators included in the synthesis, indicate with justification whether any comparators have been added to the synthesis (for example, to help create a network of evidence) or excluded from the synthesis (for example, because of an absence of data).

Included comparators

Among the studies included in the SLR, only studies investigating EU licensed and NICE recommended treatments and doses were included in the NMA. Table 33 presents the list of licensed treatments and doses as well as their respective NICE recommendations.[10]

Table 33: EMA-approved and NICE-recommended doses and regimens for each comparator of interest

Treatment	Approved dose	EMA regimen	NICE Guideline NG82[10]
Aflibercept	2 mg	Monthly injections for 3 months after which the treatment interval is extended to bi-monthly injections. Dependent on the physician's judgment the treatment interval of 2 months may be maintained or further extended using a treat-and extend dosing regimen[71]	Recommended as an option for the treatment of wAMD
Ranibizumab	0.5 mg	Monthly injections until no sign of disease activity (3 or more monthly injections may be needed), followed by as needed based on disease activity[49]	Recommended, within its marketing authorisation, as an option for the treatment of wAMD
Verteporfin PDT	2 mg/mL **Light dose:** 50 J/cm^2	Initial injection, followed by as needed: if CNV leakage detected[99]	Not recommended. In addition, PDT not recommended as an adjunct to anti-VEGF as first-line treatment, and only as second-line treatment in a randomised controlled trial

Abbreviations: CNV: choroidal neovascularisation; EMA: European Medicines Agency; J: joule; NICE: National Institute of Health and Care Excellence; PDT: photodynamic therapy; VEGF: vascular endothelial growth factor; wAMD: wet age-related macular degeneration.

A table summarising the treatments and doses excluded from the NMA, with reasons for exclusion, is provided below in Table 34. After applying the exclusion criteria, the following treatments were considered in the base case analysis:

- Interventions of interest: Brolucizumab 6 mg (and 3 mg)
- Licensed and recommended comparators: Ranibizumab 0.5 mg, Aflibercept 2 mg

Table 34: Summary of excluded treatments and doses in the NMA with reasons for exclusion

Excluded from the NMA	Reason for exclusion
Ranibizumab 0.3 mg	Not an EMA licensed dose in wAMD
Bevacizumab 1.25 mg	Not an EMA licensed treatment in wAMD
Ranibizumab 2 mg	Not an EMA licensed dose in wAMD
Aflibercept 4 mg	Not an EMA licensed dose in wAMD
Aflibercept 0.5 mg	Not an EMA licensed dose in wAMD
TTT + Ranibizumab	Not an EMA licensed treatment in wAMD
PDT	Not recommended as treatment for wAMD by NICE[10]
PDT + Ranibizumab 0.3 mg	Ranibizumab 0.3 mg is not an EMA licensed dose

PDT + Ranibizumab 0.5 mg	Not recommended as first-line therapy in wAMD by NICE, and only as a second-line therapy in the context of a randomised controlled trial[10]
Macular surgeries	No trials identified in the SLR
Laser photocoagulation therapy	Used as a potential strategy to slow the progression of wAMD

Abbreviations: AMD: age-related macular degeneration; EMA: European Medicines Agency; NICE: The National Institute for Health and Care Excellence; NMA: network meta-analysis; PDT: photodynamic therapy; SLR: systematic literature review; TTT: transpupillary thermotherapy; wAMD: wet age-related macular degeneration.

Regimens of included treatments

Different treatment regimens were also taken into account in the NMA using an attribute-based approach as done in the NICE NMA in wAMD.[49] Each treatment was evaluated separately by its treatment regimen, including if a loading phase was used. The following abbreviations were used to identify the treatments by their dose and regimen:

- LP: loading phase of three initial monthly injections
- PRN (pro re nata): treatment administered as needed
- PRNX: PRN with the potential to extend the assessment interval
- TREX (treat-and-extend): treat with the potential to extend the treatment interval (when no signs of exudation are present)
- qXw: injections that are administered on a fixed schedule every X weeks, i.e. q4w, q8w, or q12w

The list of included treatments and their regimens considered is reported below in Table 35.

Table 35: List of included treatments and regimens

Treatment	Included regimens
Ranibizumab 0.5 mg	Rani 0.5q4w Rani 0.5PRN LP → Rani 0.5PRNX LP → Rani 0.5q8w LP → Rani 0.5PRN LP → Rani 0.5q12w LP → Rani 0.5TREX
Brolucizumab 6 mg	LP → Bro 6q8w → q12w[a] LP → Bro 6q12/q8w[a]
Brolucizumab 3 mg	LP → Bro 3q12/q8w[a]
Aflibercept 2 mg	LP → Afli 2q8w Afli 2q4w LP → Afli 2PRN LP (2q12w) → Afli 2PRN LP → Afli 2TREX

[a]Bro 6q8 → q12 indicates bi-monthly injections until week 40 and every 12 weeks to week 56 (evaluated in OSPREY).[50] Bro q12/q8w indicates injections every 12 weeks unless there were signs of disease progression, in which case the patient switched to bi-monthly injections (evaluation in HAWK and HARRIER).
The treatment names have been shortened and are followed by their dose and then regimen.
Abbreviations: LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata dosing regimen with the potential to extend the assessment interval; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

5. **Where a quantitative approach is used, list the studies informing the synthesis showing the comparisons made by the studies. Justify any exclusions from the synthesis (see tables 27 and 28).**

Feasibility assessment results

Given the data availability and homogeneous populations of the identified trials, conducting NMAs for the efficacy and safety of brolucizumab was determined to be feasible and was conducted on all outcomes of interest.

As part of the feasibility assessment, 23 RCTs were excluded from the base case NMA altogether. Seven RCTs were excluded from the base case NMA because they included a treatment that is currently unlicensed by the EMA. Six RCTs were excluded for including licensed treatments that are not recommended by NICE for the treatment of wAMD.[49] Other reasons for exclusion were that the dose considered was not the licensed dose (n=5), the time of assessment was not in the specified ranges of 48–52 and 96–104 weeks (n=1), and the treatment doses were not reported (n=2). Among the trials included in the base case and sensitivity analyses, CLEAR-IT 2 and FLUID did not connect to any of the networks. CLEAR-IT 2 evaluated Afli 2PRN with two different loading phases and FLUID evaluated Rani 0.5TREX according to two different TREX regimens (relaxed versus intensive). As such, they were excluded from the analyses, and therefore Afli 2PRN was not evaluated.

Finally, VIEW 1&2 were pooled in the NMAs as the trials are similarly designed and use the same inclusion/exclusion criteria. The main difference between these trials is that they were conducted on different sites, suggesting that any differences can be attributed to random variability. In addition, NICE used the pooled analysis for VIEW 1&2 in their NMA in wAMD.[49] As such, these two trials were considered as one in the networks.

A total of 14 trials were therefore included in the base case NMA: CAN-TREAT, CATT, OSPREY, HARRIER, HAWK, SALUTE, RABIMO, RIVAL, HARBOR, PIER, MARINA, VIEW1&2 pooled, TREND and TREX-AMD.

Inconsistency assessment results

Table 36 displays the results for the inconsistency assessment for the closed loop containing the HAWK and HARRIER trials. None of the results were inconsistent between the direct and indirect comparison for the difference between LP → Afli 2q8w and LP → Bro 6q12/q8w.

Table 36: Results from the inconsistency assessment for all NMA endpoints

Endpoint	Difference (SE) – Direct versus indirect comparison	Z-score	P-value
Change in BCVA			
1 year	0.23 (1.19)	0.19	0.846
2 years	0.59 (1.34)	0.44	0.662
Change in retinal thickness			
1 year	10.18 (11.79)	0.86	0.388
2 years	8.59 (12.41)	0.69	0.489
Patients gaining ≥ 15 letters			
1 year	0.21 (0.26)	0.81	0.420
2 years	0.22 (0.25)	0.86	0.387
Patients losing ≥ 15 letters			
1 year	0.18 (0.26)	0.35	0.727
2 years	0.08 (0.43)	0.18	0.855

Discontinuation			
1 year	-0.11 (0.40)	-0.28	0.781
2 years	0.01 (0.30)	0.02	0.982

Abbreviations: BCVA: best-corrected visual acuity; NMA: network meta-analysis; SE: standard error.

Base case NMA

The base case NMA included studies with treatment-naïve patients (naïve to any anti-VEGF treatment) and mixed prior therapy patients (treatment naïve and previously treated with an anti-VEGF). All trials that were connected via common comparators to brolucizumab, were included in the analyses.

An overview of the trials included in the base case NMA is presented below in Table 37.

Table 37: Overview of trials included in the NMA

Trial ID	Author, year	Time of assessment (months)	Trial name	Sample size	Phase	Blinding status	Intervention	Comparator	Included in the base case NMA?
1	Dugel 2017	12	OSPREY	90	2	Double-blind	LP → Bro 6q8w → q12w	LP→Afli 2q8w	Included
2	Dugel 2019	96 weeks	HARRIER	739	3	Double-blind	LP → Bro 6q12/q8w	LP→Afli 2q8w	Included
3	Dugel 2019	96 weeks	HAWK	1078	3	Double-blind	LP → Bro 6q12/q8w LP → Bro 3q12/q8w	LP→Afli 2q8w	Included
4	Martin 2011 / Martin 2012	12 / 24	CATT	1143	NR	Single-blind	Rani 0.5q4w Rani 0.5PRN	Bev 1.25q4w Bev 1.25PRN	Included
5	Eldem 2015	12	SALUTE	77	4	Open-label	LP → Rani 0.5PRNX	LP→ Rani 0.5PRN	Included
6	Feltgen 2017	12	RABIMO	40	4	Open-label	LP→ Rani 0.5q8w	LP→Rani 0.5PRN	Included
7-8	Heier 2012 / Yuzawa 2015 / Schmidt-Erfurth 2014	12 / 96 weeks	VIEW 1&2 / VIEW 1&2 Pooled	1217	3	Double-blind	Afli 0.5q4w→PRN Afli 2q4w→PRN LP→Afli 2q8w→PRN	Rani 0.5q4w→PRN	Included
9	Ho 2014	24	HARBOR	1089	3	Double-blind	Rani 0.5q4w Rani 2q4w	LP→Rani 0.5PRN LP→Rani 2PRN	Included
10	Gillies 2019 / Hunyor 2018	12 / 24	RIVAL	278	3	Double-blind	LP→Rani 0.5TREX	LP→Afli 2TREX	Included
11	Kertes 2019	24	CAN-TREAT	580	NR	Open-label	LP→Rani 0.5TREX	Rani 0.5q4w	Included
12	Regillo 2008	12	PIER	184	3b	Double-blind	LP→Rani 0.5q12w LP→Rani 0.3q12w	Sham IVT	Included
13	Rosenfeld 2006/ Chang 2007	24	MARINA	716	3	Double-blind	Rani 0.5q4w Rani 0.3q4w	Sham IVT	Included
14	Silva 2017	12	TREND	650	3b	Single-blind	LP→Rani 0.5TREX	Rani 0.5q4w	Included
15	Wykoff 2015/2017	12 / 24	TREX-AMD	60	3b	Open-label	LP→Rani 0.5TREX	Rani 0.5q4w	Included
16	Antoszyk 2007	24	FOCUS	162	1/2	Single-blind	Vert PDT q4w	Rani 0.5q4w	Excluded (Not recommended by NICE and does not help connect networks)
17	Berg 2015/2016	12 / 24	LUCAS	441	NR	Double-blind	Bev 1.25TREX	LP→Rani 0.5TREX	Excluded (Not a licensed treatment)
18	Boyer 2009	12	SAILOR	2378	3b	Single-blind	LP→Rani 0.3PRN	LP→Rani 0.5PRN	Excluded (Not a licensed dose)

Trial ID	Author, year	Time of assessment (months)	Trial name	Sample size	Phase	Blinding status	Intervention	Comparator	Included in the base case NMA?
19	**Brown 2009 / Bressler 2009/2013**	24	ANCHOR	423	3	Double-blind	Vert PDT PRN	Rani 0.3q4w Rani 0.5q4w	Excluded (Not a licensed dose and not recommended by NICE and does not help connect networks)
20	**Campochiaro 2019a**	9	LADDER	220	2	Open-label	PDS + Rani 10PRN, 40PRN, 100PRN	Rani 0.5q4w	Excluded (No follow-up time of interest)
21	**Guymer 2019**	24	FLUID	349	4	Single-blind	LP→Rani 0.5TREX (relaxed)	LP→Rani 0.5TREX (intensive)	Excluded (Not connected to the network)
22	**Hatz 2014**	12	NR	40	3	Double-blind	Vert PDT + Rani 0.3PRN	LP→Rani 0.3PRN	Excluded (Not a licensed dose)
23	**Heier 2011**	12	CLEAR-IT 2	157	2	Double-blind	LP (w0-12) → Afli 0.5PRN LP (w0-12) → Afli 2PRN	LP (q12, w0-12) → Afli 0.5PRN LP (q12w, w0-12) → Afli 2PRN LP (q12w, w0-12) → Afli 4PRN	Excluded (Not connected to the network)
24	**Kaiser 2012**	12	DENALI	286	3b	Double-blind	Vert PDT + Rani 0.5q4w	Rani 0.5q4w	Excluded (Not recommended as first-line therapy in wAMD by NICE)
25	**Kodjikian 2013**	12	GEFAL	501	NR	Double-blind	LP → Bev 1.25PRN	LP → Rani 0.5PRN	Excluded (Not a licensed treatment)
26	**Krebs 2013 (1)**	12	NR	44	NR	Single-blind	Vert PDT + Rani 0.5q4w	Rani 0.5q4w	Excluded (Not recommended as first-line therapy in wAMD by NICE)
27	**Krebs 2013 (2)**	12	NR	317	NR	Double-blind	LP → Bev 1.25PRN	LP → Rani 0.5PRN	Excluded (Not a licensed treatment)
38	**Larsen 2012**	12	MONT BLANC	255	2	Double-blind	Vert PDT + Rani 0.5q4w	Rani 0.5q4w	Excluded (Not recommended as first-line therapy in wAMD by NICE)
29	**Li 2017**	12	SIGHT	304	3	Double-blind	LP→Afli 2q8w	Vert PDT PRN	Excluded (Not recommended by NICE and does not help connect networks)
30	**Mori 2017**	12	NR	58	NR	NR	LP → Afli PRN	LP → Afli q8w	Excluded (Doses not reported)
31	**Nunes 2019**	12	NR	45	NR	Open-label	LP → Bev 1.25PRN LP (q2w) → Bev 1.25PRN	LP → Rani 0.5PRN	Excluded (Not a licensed treatment)

Trial ID	Author, year	Time of assessment (months)	Trial name	Sample size	Phase	Blinding status	Intervention	Comparator	Included in the base case NMA?
32	**Schauwvliegh e 2016**	12	BRAMD	327	NR	Double-blind	Bev 1.25q4w	Rani 0.5q4w	Excluded (Not a licensed treatment)
33	**Schmidt-Erfurth 2011**	12	EXCITE	233	3b	Double-blind	LP → Rani 0.3q12w	LP → Rani 0.5q12w Rani 0.3q4w	Excluded (Not a licensed dose)
34	**Scholler 2014**	12	NR	55	NR	Open-label	LP → Rani 0.5PRN	LP → Bev 1.25PRN	Excluded (Not a licensed treatment)
35	**Söderberg 2012**	24	NR	92	NR	Double-blind	LP → Rani 0.5PRN	TTT + Rani 0.5PRN	Excluded (Not a licensed treatment)
36	**Subramanian 2010**	24	NR	22	NR	Double-blind	Bev 1.25q4ww	Rani	Excluded (Dose not reported)
37	**Tano 2010**	12/24	EXTEND-I	76	1/2	Open-label	Rani 0.3q4w	Rani 0.5q4w	Excluded (Not a licensed dose)
38	**Weingessel 2015**	12	NR	34	NR	NR	Vert PDT + Rani 0.5PRN	LP→Rani 0.5PRN	Excluded (Not recommended as first-line therapy in wAMD by NICE)

[a]The LADDER trial (Campochiaro 2019) should be interpreted with caution as the main objective of the trial was to assess the effect of the PDS, it was included in the SLR as it does still report relevant outcomes.
Abbreviations: ID: identification; IVT: intravitreal; LP: loading phase of three initial monthly injections; NR: not reported; PDS: port delivery system; PDT: photodynamic therapy; PRN: pro re nata dosing regimen; PRNX: PRN and extend dosing regimen; qXw: one injection every X weeks; SLR: systematic literature review; TREX: treat-and-extend dosing regimen; TTT: transpupillary thermotherapy; wAMD: wet age-related macular degeneration.

6. **Describe the methods used to synthesise the evidence.**

   - **Meta-analysis: state methods and models used and justify these. If Bayesian methods are used, justify the priors chosen.**
   - **Indirect or mixed treatment comparisons: state the statistical model, software and whether a fixed or random effects model has been used. Justify the choice of methods. If Bayesian methods are used, justify the priors chosen.**
   - **Narrative review: give details of the methods used**.

The NMA was conducted using a Bayesian framework, which preserved the randomisation of each trial.[100]

Baseline pooling

Baseline pooling was conducted to estimate the absolute treatment effect for treatment regimens with more than one trial. The following outcomes were considered:

- Mean change in BCVA
- Proportion of patients gaining at least 15 ETDRS letters
- Proportion of patients losing at least 15 ETDRS letters
- Overall discontinuation
- Injection frequency
- AEs (intraocular inflammation, endophthalmitis, retinal detachment, retinal tear, retinal pigment epithelial tear, and cataract)

Regimen-based pooling was conducted for the mean change in BCVA, patients gaining at least 15 letters, patients losing at least 15 letters, injection frequency, and adverse events. Molecule-based pooling was conducted for discontinuation as well as AEs. Full details of the baseline pooling methodology are presented in Appendix 7.6.

Direct comparisons

Standard pairwise meta-analyses based on direct comparisons were carried out between pairs of treatments when possible, where two treatments were compared in two or more clinical trials. Direct pairwise comparisons were conducted to assess the heterogeneity between studies when there was more than one study comparing the same treatments.

The NMA was conducted using a Bayesian framework, which preserved the randomisation of each trial. The relative goodness of fit of the models was assessed using the deviance information criterion (DIC). Both fixed-effects and random-effects models were developed and the one associated with the lowest DIC was selected.[88] Full details of the methodology of the NMA, and any assumptions that were adopted, are presented in Appendix 7.6.

The programming language used for the indirect treatment comparisons is included in Appendix 7.6.

7. Discuss the extent to which the studies may be considered (1) homogeneous as a group and (2) representative of the target population and treatments.

The potential sources of heterogeneity in the studies included within the NMA were investigated and discussed with clinicians, based on the descriptive statistics. Overall, the studies were considered largely homogenous, and representative of the target population and treatments. There was homogeneity among the trials included in the NMAs for the following baseline characteristics:

- Age
- Sex (proportion of males)
- Visual acuity (ETDRS),
- Retinal thickness (CRT, CMT, CSFT, CFT)
- CNV lesion size in disc areas (DAs) and mm^2
- CNV lesion type (predominantly classic, minimally classic, and occult)

An overview of the baseline demographics, baseline disease characteristics and efficacy and safety results for the studies included in the base case NMA is included in Appendix 7.5.

Potential sources of heterogeneity identified between the studies included: outcome measures and previous treatment use.

Outcome measures

For continuous outcomes, only mean changes were included in the analyses. SALUTE reported both the mean and median change in BCVA, as shown in Table 38. Given the difference between the mean and median, there was reason to believe that the data were skewed for this endpoint. There was also little evidence to validate the distribution of change in retinal thickness. Therefore, a conservative approach was made to only include mean change from Baseline and not include median change, to avoid making assumptions that the two were equivalent. This led to the exclusion of one trial (RABIMO) for mean change in BCVA and two trials for mean change in retinal thickness (RABIMO and SALUTE), where only median values were reported. Both trials had small sample sizes (RABIMO, n=40 and SALUTE=77), which could also explain the skewness of the data. Finally, NICE did not include median changes in their NMA in wAMD, so this approach was consistent with their analysis.[49]

Table 38: Comparison of mean and median change in BCVA for SALUTE

	LP → Rani 0.5PRN	LP → Rani 0.5PRNX
Number of patients	39	38
Change in BCVA – one year		
Mean (SD)	3.2 (20.9)	7.7 (15.9)
Median (IQR)	6 (19)	9 (16)

Abbreviations: BCVA: best-corrected visual acuity; IQR: interquartile range; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; SD: standard deviation.

Previous treatment use

Among the trials included in the base case, 13 of them were conducted on treatment-naïve patients (defined as patients who are naïve to other anti-VEGFs), whereas two of them did not report any

inclusion or exclusion criteria related to prior anti-VEGF therapy. The studies that did not report prior therapies (PIER and MARINA) were conducted when pegaptanib was the only authorised anti-VEGF. PIER indicated that between 54.1 and 58.3% of patients had “any prior therapy for AMD”, but did not mention the use of pegaptanib in these percentages. Similarly, the MARINA trial mentioned that between 57.9 to 58.8% of patients had been previously treated; among which 1.2 to 3.4% had been treated with “other therapy”, i.e. not laser photocoagulation, nutritional supplements, triamcinolone acetonide, prednisolone ophthalmic, or diclofenac sodium. PIER and MARINA, while not treatment-naïve by definition, are therefore likely to be predominantly treatment-naïve given the lack of authorised anti-VEGF treatments at the time. As such, these analyses included both trials with treatment-naïve patients only and MARINA and PIER.

Table 39 below presents the trials included in the base case, classified by mixed/not reported patient groups and treatment-naïve patient groups.

Table 39: Trials included in the base case and/or sensitivity analyses by prior treatment and regimen administered

	PRN: 5 trials	PRNX: 1 trial	TREX: 4 trials	Continuous: 14 trials
Mixed patients: 2 trials				Regillo 2008 (PIER)
				Rosenfeld 2006 (MARINA)
Treatment-naïve patients: 13 trials	Ho 2014 (HARBOR)	Eldem 2015 (SALUTE)	Wykoff 2015/2016 (TREX-AMD)	Martin 2011/Martin 2012 (CATT)
	Martin 2011/Martin 2012 (CATT)		Silva 2017 (TREND)	Dugel 2017 (OSPREY)
	Eldem 2015 (SALUTE)		Kertes 2019 (CAN-TREAT)	Dugel 2019 (HARRIER)
	Feltgen 2017 (RABIMO)		Hunyor 2018/Gillies 2019 (RIVAL)	Dugel 2019 (HAWK)
				Heier 2012 (VIEW 1&2)
				Schmidt-Erfurth 2014 (VIEW 1&2 Pooled)
				Feltgen 2017 (RABIMO)
				Silva 2017 (TREND)
				Wykoff 2015/2016 (TREX-AMD)
				Kertes 2019 (CAN-TREAT)

				Ho 2014 (HARBOR)

Studies in bold include the intervention of interest. *Trials in italics compare two different treatment regimens.*
Abbreviations: PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; TREX: treat-and-extend dosing regimen.

8. State how heterogeneity in the relative treatment effects was assessed and give evidence of the degree of heterogeneity in each of the pairwise comparisons.

For each pairwise comparison, the Cochran's Q test and the I^2 statistic were calculated. Heterogeneity was suspected if:

- The Cochran's Q test was significant with a significance level of 10%, or
- I^2 was higher than 50%[101]

Forest plots were generated for each comparison, to illustrate heterogeneity (included within Section 5.8).

9. If network meta-analysis is used, state how consistency between direct and indirect comparisons was assessed. Highlight any inconsistencies in comparisons.

Direct comparisons

Standard pairwise meta-analyses based on direct comparisons were carried out between each pair of treatments when possible, i.e. when the two treatments were compared in two or more clinical trials. Direct pairwise comparisons were conducted to assess the heterogeneity between studies when there was more than one study comparing the same treatments.

The inverse variance-weighted method was used to analyse binary and continuous outcomes, which is the standard approach.[102] The weights used to pool the different studies are the inverse of the variance of the study outcomes. Moreover, the weighted least squares method was used to estimate the between study variance in random-effect models, which is the commonly used method.[102]

In the case of binary outcomes, the inverse variance-weighted method cannot be implemented if one or more arms in one or more studies reported zero events. The presence of zero(s) in the analysis of an outcome was handled using the continuity correction and the Mantel-Haenszel method, as recommended in the Cochrane handbook.[103]

10. State how publication bias was assessed and give evidence to justify whether or not publication bias is presumed to be present.

The randomised clinical trials included in the NMA were qualitatively assessed through the Centre for Review of Dissemination (CDR) for assessing risk of bias in randomised trials.

Overall evidence was of moderate to high quality. The greatest risk of bias was due to insufficient information identified in the publication during the quality assessment. The majority of studies did not have unexpected imbalances in drop-outs between groups.

The results of this quality assessment are presented in Appendix 7.7.

11. Describe the sensitivity analyses done. If the conclusions are sensitive to outliers or influential studies, present the sensitivity analyses as part of the results of evidence synthesis.

Several sensitivity analyses were conducted to test the assumptions adopted within the based case NMA (summarised in Appendix 7.6).

Networks of evidence

Retinal thickness can be measured using different imaging techniques. Optical coherence tomography (OCT) is often used to scan the retinal area, with two types of OCT commonly used: time-domain (TD) and spectral-domain (SD).[8] A sensitivity analysis around the definition of SD-OCT was considered, in order to assess heterogeneity. However, in removing studies without an SD-OCT measurement, the VIEW 1&2 pooled would be excluded which is the main connecting study for brolucizumab to the other treatments. As the network would become disconnected, it was not possible to run this sensitivity analysis.

A sensitivity analysis was conducted including trials that reported only the median change in BCVA and retinal thickness. In addition, the following two sensitivity analyses were conducted based on clinical expert opinion:

- The RIVAL study was excluded from visual acuity outcomes (mean change in BCVA, and patients gaining and losing at least 15 letters) as patients in RIVAL had the highest mean BCVA at Baseline, and the results from this study appeared to be outlying values
- The PIER and MARINA studies were excluded, as these two trials compared an active treatment to sham IVT, which could have introduced bias into the relative efficacy results versus results from studies comparing anti-VEGF treatments

Time of assessment

A sensitivity analysis was performed that extrapolates results prior to 52 weeks and 104 weeks. Given that time equivalence was assumed between 48 and 52 weeks for 1-year results and between 96 and 104 weeks for 2-year results, this analysis made it possible to identify if the results are highly influenced by this assumption.

Methodological analyses

The following methodological sensitivity analyses were run to test the effects of chosen model specifications:

- A sensitivity analysis was conducted regarding trials with imputed standard error from the Baseline and final value: rather than a correlation of 0.5, a correlation of 0.7 between the Baseline and the final value was assumed
- Two sensitivity analyses were conducted regarding trials with imputed standard error from the mean standard deviation of the other trials:
    - The minimum standard deviation instead of the mean
    - The maximum standard deviation instead of the mean

The sensitivity analyses performed showed that the results of the NMA were robust and not significantly affected by the assumptions made. Full details of the results of these analyses are included in Appendix 7.8.

5.8 Results of evidence synthesis

1. State the effects of the technology versus the comparator(s) on mortality.

Not applicable. Mortality outcomes were not assessed in the HAWK and HARRIER trials, or as part of the NMA.

2. State the effects of the technology versus the comparator(s) on the following aspects of morbidity:

- **severity and frequency of symptoms and findings**
- **progression of disease**
- **body functions.**

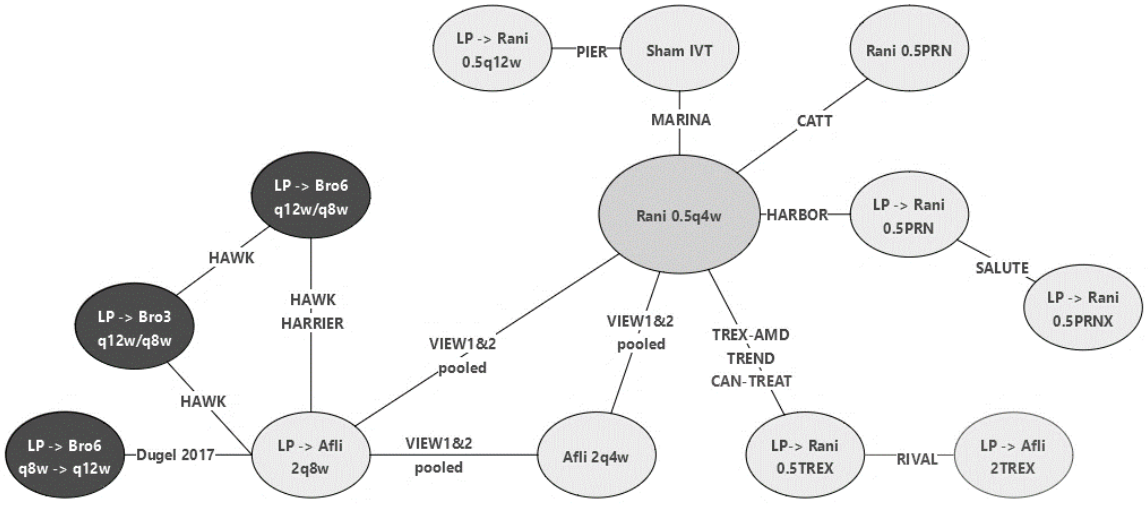
The results of the NMA for mean change in BCVA, the proportion of patients gaining or losing at least 15 ETDRS letters, mean change in central retinal thickness and frequency of injections, are presented in this section.

Mean change in BCVA (Baseline to one year)

At one year, the base case NMA demonstrated brolucizumab to be associated with comparable efficacy to aflibercept and ranibizumab in terms of mean change in BCVA from Baseline

The network for mean change in BCVA from Baseline to one year is displayed in Figure 25. A total of 13 studies were included in the analysis.

Figure 25: Network for mean change in BCVA from Baseline to one year



Abbreviations: BCVA: best-corrected visual acuity; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

The pairwise meta-analysis results are reported in Table 40. VIEW 1&2 were similarly designed trials and used the same inclusion/exclusion criteria, with the main difference being that the trials were conducted on different sites. This suggests that the heterogeneity is due to random variability. In addition, Schmidt-Erfurth 2014 reported the pooled results for VIEW 1&2.[98] These trials were therefore pooled in the NMA and considered one trial. This is the same approach that NICE used in their NMA in wAMD.[49]

For the heterogeneity identified between LP → Rani 0.5TREX and Rani 0.5q4w, baseline characteristics were assessed and were similar across the three trials. The heterogeneity is therefore likely due to the inherent variability of the follow-up treatment intervals in the TREX regimen and cannot be controlled for.

Table 40: Summary of direct comparison results for mean change in BCVA from Baseline to one year

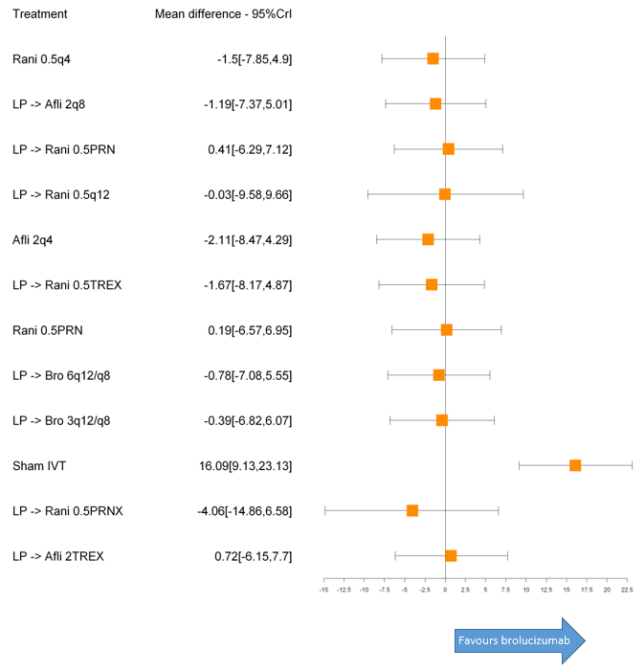
Comparison	Trials	Mean Difference [95% CI]		I-square	p-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP → Rani 0.5TREX vs Rani 0.5q4w	TREND TREX-AMD CAN-TREAT	0.17 [-1.21; 1.54]	0.31 [-3.18; 3.8]	77.77%	0.011[b]
Rani 0.5q4w vs LP→ Afli 2q8[a]	VIEW 1 VIEW 2	0.36 [-1.28; 2.00]	0.36 [-1.28; 2.00]	0.00%	0.858
Rani 0.5q4w vs Afli 2q4w[a]	VIEW 1 VIEW 2	-0.26 [-1.81; 1.29]	-0.47 [-4.98; 4.04]	88.03%	0.004[b]
LP → Afli 2q8w vs Afli 2q4w[a]	VIEW 1 VIEW 2	-0.70 [-2.26; 0.87]	-0.83 [-5.04; 3.39]	86.14%	0.007[b]
LP → Afli 2q8w vs LP → Bro 6q12/q8w	HARRIER HAWK	0.43 [-0.85; 1.71]	0.43 [-0.85; 1.71]	0.00%	0.763

*Direct comparisons come from VIEW 1&2, which were pooled in the NMA.
[b]Statistically significant at 5%.
Abbreviations: BCVA: best-corrected visual acuity; CI: confidence interval; LP: loading phase; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

This section presents results from the fixed-effects model of the NMA. The DIC of the fixed-effects model was higher than that of the random-effects model (112.23 versus 108.36) but since the random-effects model encountered convergence issues due to the fact that the prior distribution dominated the posterior for the random-effects SD, the fixed-effects model was chosen.

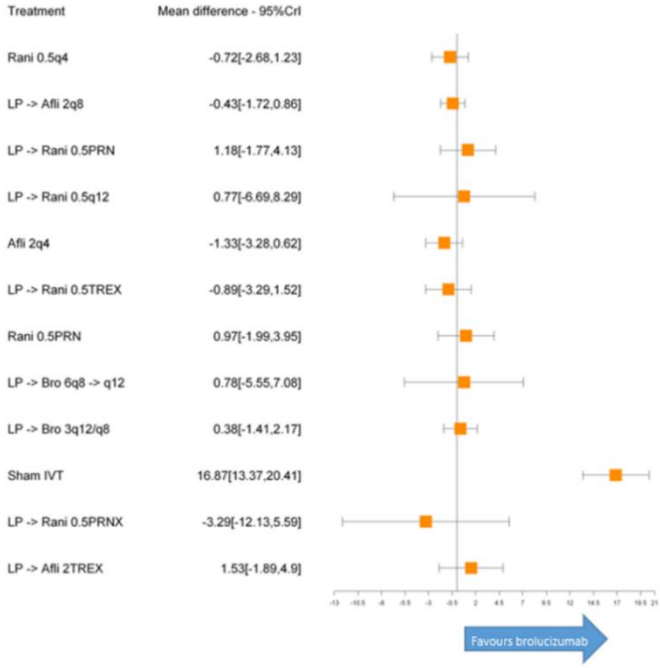
The indirect comparisons obtained through the NMA are reported in Figure 26 (LP → Bro 6q8w → q12w versus each comparator), and Figure 27 (LP → Bro 6q12/q8w versus each comparator). Brolucizumab showed comparable efficacy to ranibizumab and aflibercept for mean change in BCVA from Baseline to one year, with none of the treatment effects for this endpoint significant at a 95% credibility level. Additionally, results for mean change in BCVA at one year indicated that brolucizumab was statistically significantly superior to sham IVT.

Figure 26: Forest plot of the NMA results comparing the difference in mean change in BCVA from Baseline to one year between LP → Bro 6q8w → q12w and each comparator (fixed-effects)



Abbreviations: BCVA: best-corrected visual acuity; CrI: credibility interval; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Figure 27: Forest plot of the NMA results comparing the difference in mean change in BCVA from Baseline to one year between LP → Bro 6q12/q8w and each comparator (fixed-effects)



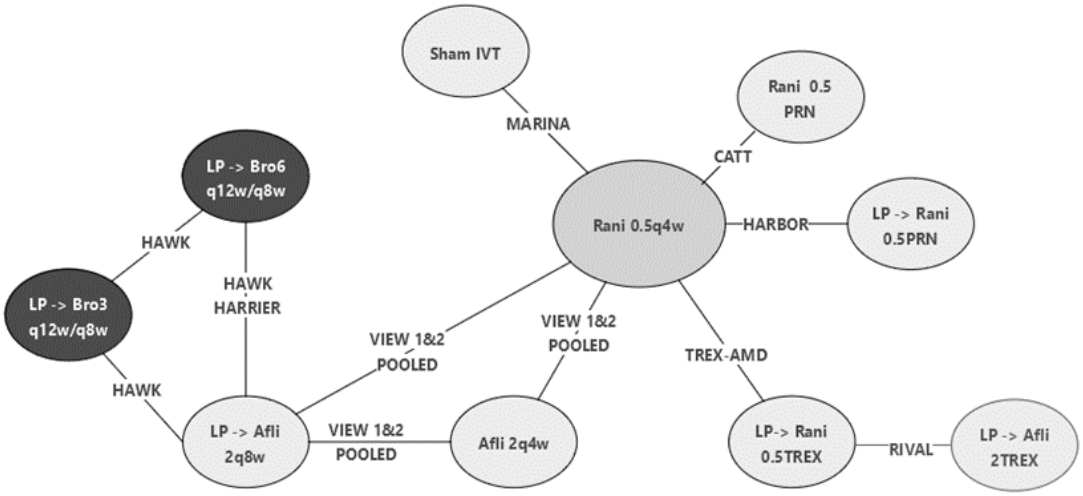
Abbreviations: BCVA: best-corrected visual acuity; CrI: credibility interval; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Mean change in BCVA (Baseline to two years)

At two years, the base case NMA demonstrated brolucizumab to be associated with comparable efficacy to aflibercept and ranibizumab in terms of mean change in BCVA from Baseline

The network for mean change in BCVA at two years is displayed in Figure 28. Eight studies were included in the analysis.

Figure 28: Network for mean change in BCVA from Baseline to two years



Abbreviations: BCVA: best corrected visual acuity; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

One direct comparison needed to be evaluated for heterogeneity for the mean change in BCVA at two years. This was between LP → Afli 2q8w and LP → Bro 6q12/q8w, which was shared by HAWK and HARRIER. No heterogeneity was present for the comparison, with an I-square value of 0% and a Cochran test p-value of 0.47. The result from the direct comparison is presented in Table 41.

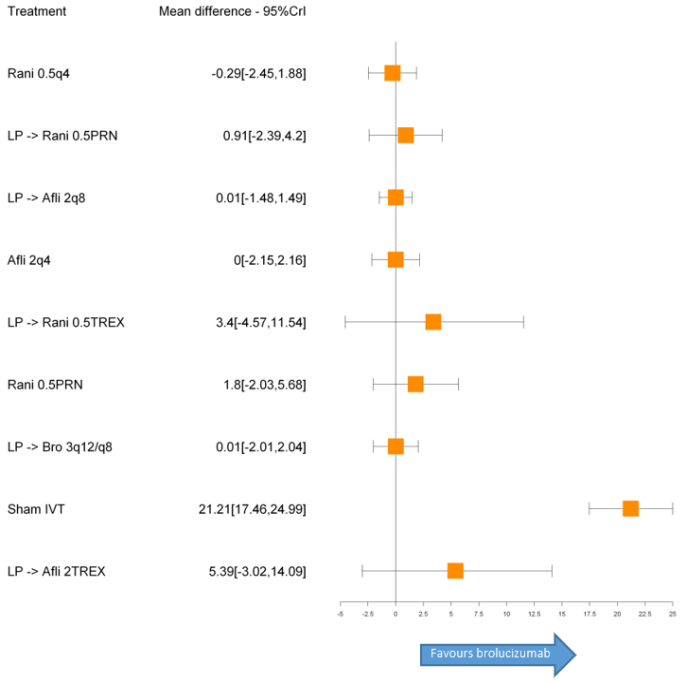
Table 41: Summary of direct comparison results for mean change in BCVA from Baseline to two years

Comparison	Trials	Mean Difference [95% CI]		I-square	p-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP → Bro 6q12/q8w vs LP → Afli 2q8w	HARRIER HAWK	0.01 [-1.46;1.49]	0.01 [-1.46;1.49]	0.00%	0.467

Abbreviations: BCVA: best-corrected visual acuity; CI: confidence interval; LP: loading phase; qXw: one injection every X weeks.

This section presents the results from the fixed-effects model of the NMA because the DIC was lower than that of the random-effects model (65.93 versus 66.31). The indirect comparisons obtained through the NMA are reported in Figure 29 (LP → Bro 6q12/q8w versus each comparator). Brolucizumab showed comparable efficacy to ranibizumab and aflibercept for mean change in BCVA from Baseline to two years, with none of the treatment effects for this endpoint significant at a 95% credibility level. Additionally, the results for mean change in BCVA at two years indicated that brolucizumab was statistically significantly superior to sham IVT.

Figure 29: Forest plot of the NMA results comparing the difference in mean change in BCVA from Baseline to two years between LP → Bro 6q12/q8w and each comparator (fixed-effects)



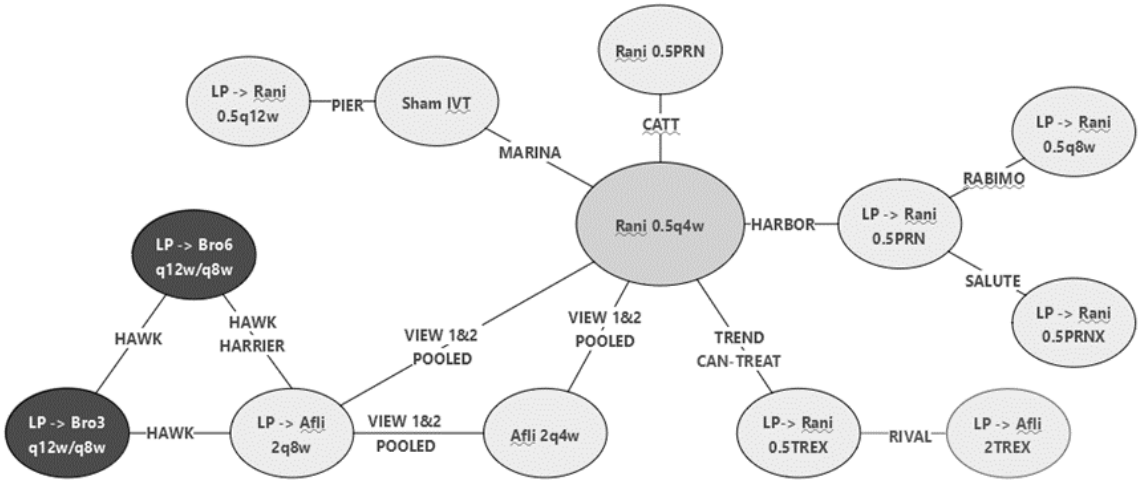
Abbreviations: BCVA: best corrected visual acuity; CrI: credibility interval; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Patients losing at least 15 letters (Baseline to one year)

At one year, the base case NMA demonstrated brolucizumab to be associated with comparable efficacy to aflibercept and ranibizumab for odds of losing at least 15 letters from Baseline

The network for the proportion of patients losing at least 15 letters by one year is displayed in Figure 30. A total of twelve studies were included in the analysis.

Figure 30: Network for patients losing at least 15 letters from Baseline to one year



Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

The pairwise meta-analysis results are reported in Table 42. Each direct comparison included two trials. No significant heterogeneity was reported in any of the comparisons, with an I-square value from 0% to 64.04% obtained for pairwise result.

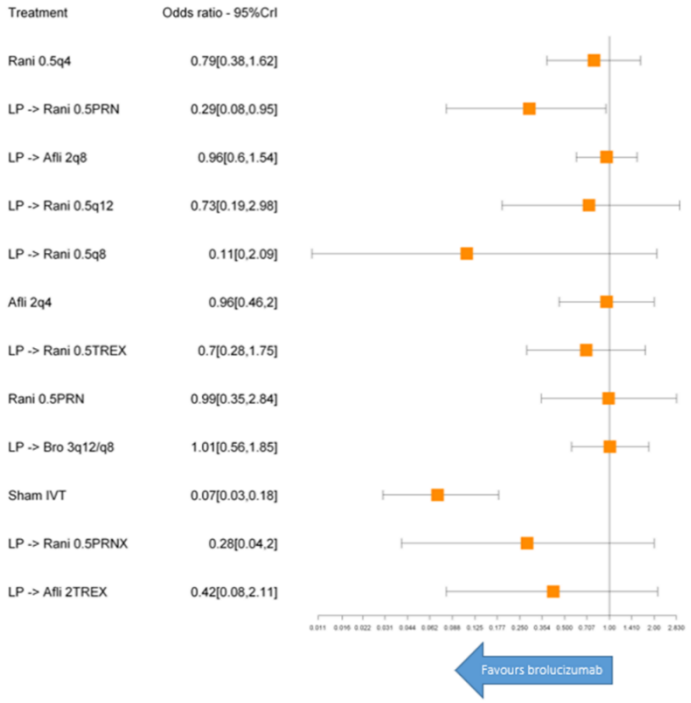
Table 42: Summary of direct comparison results for odds of losing at least 15 letters from Baseline to one year

Comparison	Trials	Mean Difference [95% CI]		I-square	p-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP → Afli 2q8w vs Rani 0.5q4w[a]	VIEW 1 VIEW 2	0.83 [0.50; 1.38]	0.83 [0.50; 1.38]	0.0%	0.826
Afli 2q4w vs Rani 0.5q4w[a]	VIEW 1 VIEW 2	0.91 [0.55; 1.50]	0.91 [0.55; 1.50]	0.0%	0.530
LP → Afli 2q8w vs Afli 2q4w	VIEW 1 VIEW 2	1.10 [0.66; 1.84]	1.10 [0.66; 1.84]	0.0%	0.698
LP → Bro 6q12/q8w vs LP → Afli 2q8w	HARRIER HAWK	0.97 [0.61; 1.55]	0.97 [0.61; 1.55]	0.0%	0.390
LP → Rani 0.5TREX vs Rani 0.5q4w	TREND CAN-TREAT	1.12 [0.63;1.98]	1.06 [0.39;2.85]	64.0%	0.095

[a]Direct comparisons come from VIEW 1&2, which were pooled in the NMA.
Abbreviations: CI: confidence interval; LP: loading phase; TREX: treat-and-extend dosing regimen.

This section presents the results from the fixed-effects model of the NMA because the DIC was lower than that of the random-effects model (161.1 versus 161.2). The indirect comparisons obtained through the NMA are reported in Figure 31 (LP → Bro 6q12/q8w versus each comparator). Brolucizumab (LP → Bro 6q12/q8w) had significantly lower odds of losing at least 15 letters from Baseline to one year than sham IVT and LP → Rani 0.5 PRN; none of the other results were significant based on the 95% credible intervals.

Figure 31: Forest plot of the NMA results comparing the odds of losing at least 15 letters from Baseline to one year between LP → Bro 6q12/q8w and each comparator (fixed-effects)



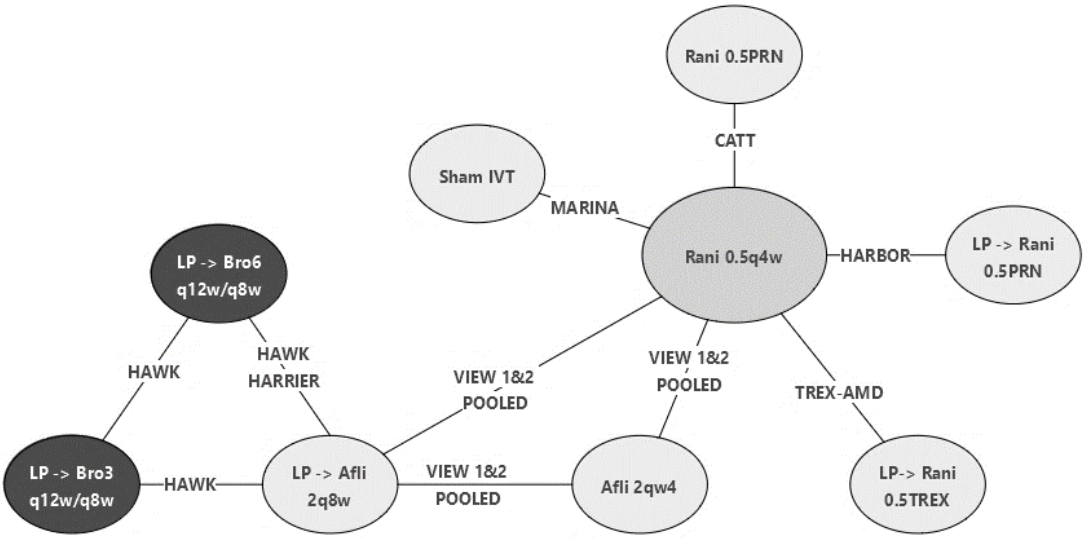
Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; PRN: pro re nata and extend dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Patients losing at least 15 letters (Baseline to two years)

At two years, the base case NMA demonstrated brolucizumab to be associated with comparable efficacy to aflibercept and ranibizumab for odds of losing at least 15 letters from Baseline

The network for the proportion of patients losing at least 15 letters by two years is displayed in Figure 32. A total of seven studies were included in the analysis.

Figure 32: Network for patients losing at least 15 letters from Baseline to two years



Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

The pairwise meta-analysis results are reported in Table 43. One direct comparison needed to be evaluated for heterogeneity for the odds of losing at least 15 letters at two years. This was between LP → Afli 2q8w and LP → Bro 6q12/q8w, which was shared by HAWK and HARRIER. No heterogeneity was present for the comparison, with an I-square value of 0% and Cochran test p-value of 0.69.

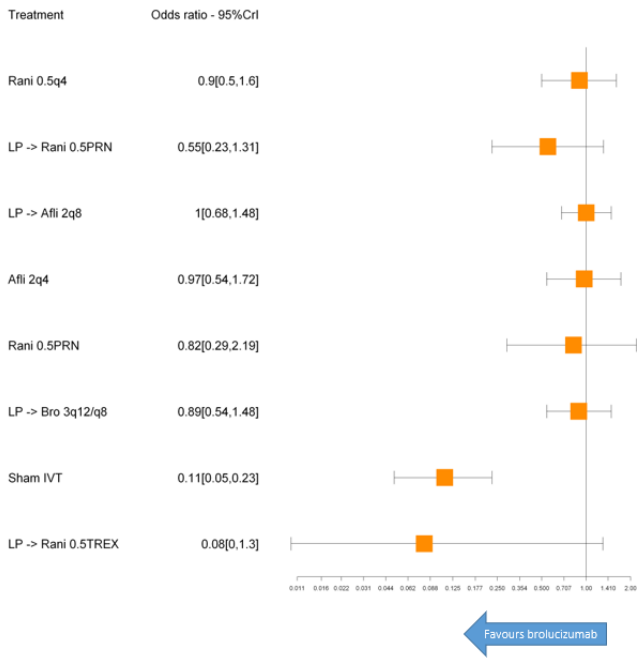
Table 43: Summary of direct comparison results for odds of losing at least 15 letters from Baseline to two years

Comparison	Trials	Mean Difference [95% CI]		I-square	p-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP → Bro 6q12/q8w vs LP → Afli 2q8w	HARRIER HAWK	1.00 [0.68; 1.47]	1.00 [0.68; 1.47]	0.0%	0.686

Abbreviations: CI: confidence interval; LP: loading phase.

This section presents the results from the fixed-effects model of the NMA because the DIC was lower than that of the random-effects model (106.6 versus 107.7). The indirect comparisons obtained through the NMA are reported in Figure 33 (LP → Bro 6q12/q8w versus each comparator). Brolucizumab (LP → Bro 6q12/q8w) had significantly lower odds of losing at least 15 letters from Baseline to two years than sham IVT; none of the other results were significant based on the 95% credible intervals.

Figure 33: Forest plot of the NMA results comparing the odds of losing at least 15 letters from Baseline to two years between LP → Bro 6q12/q8w and each comparator (fixed-effects)



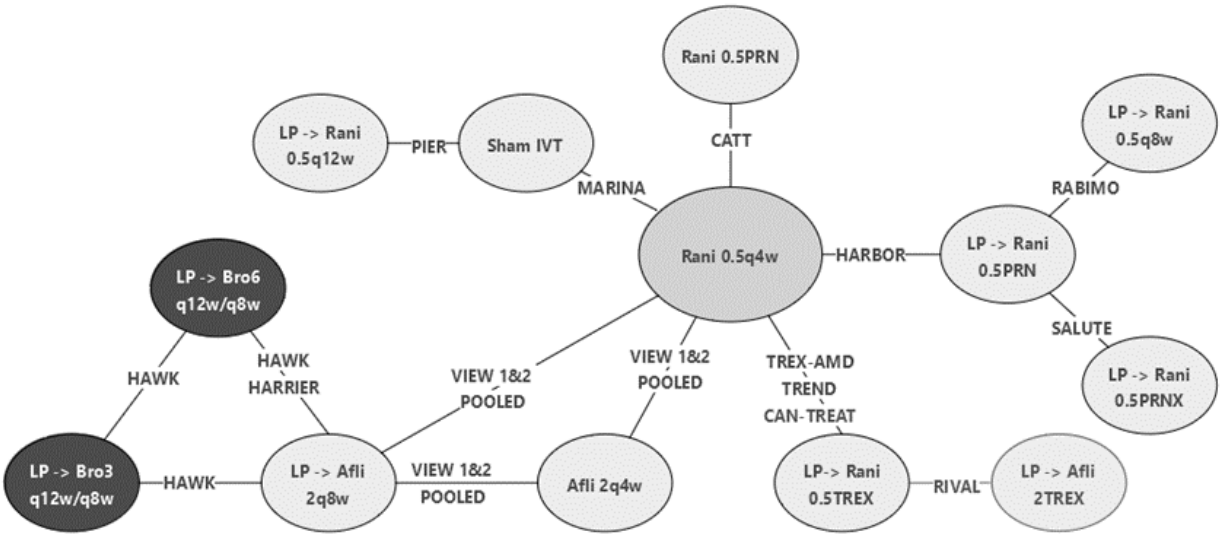
Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Patients gaining at least 15 letters (Baseline to one year)

At one year, the base case NMA demonstrated brolucizumab to be associated with comparable efficacy to aflibercept and ranibizumab for odds of gaining at least 15 letters from Baseline

The network for the proportion of patients gaining at least 15 letters by one year is displayed in Figure 34. A total of thirteen studies were included in the analysis.

Figure 34: Network for patients gaining at least 15 letters from Baseline to one year



Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

The pairwise meta-analysis results are reported in Table 44. Significant heterogeneity was present in the direct comparison between Afli 2q4w and Rani 0.5q4w (trials VIEW 1 and VIEW 2). Another comparison had an I-square value of greater than 50%, between LP → Afli 2q4w and Afli 2q4w, as well as the direct comparison in HAWK and HARRIER.

In addition, Schmidt-Erfurth 2014 reported the pooled results for VIEW 1&2.[98] These trials were therefore pooled in the NMA and considered one trial. This is the same approach that NICE used in their NMA in wAMD.[49]

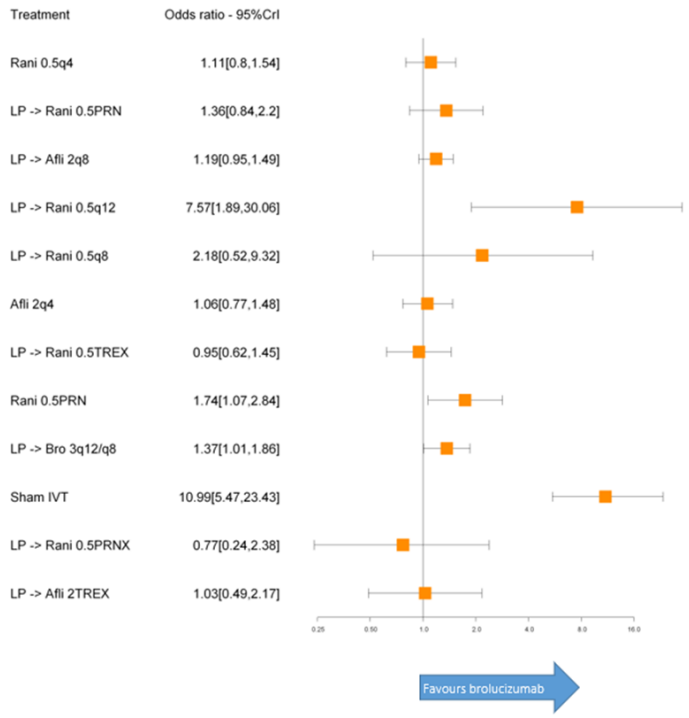
Table 44: Summary of direct comparison results for odds of gaining at least 15 letters from Baseline to one year

Comparison	Trials	Mean Difference [95% CI]		I-square	p-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP → Rani 0.5TREX vs Rani 0.5q4w	TREND TREX-AMD	1.18 [0.90; 1.54]	1.18 [0.90; 1.54]	0.0%	0.489
LP → Afli 2q8w vs Rani 0.5q4w[a]	VIEW 1 VIEW 2	0.93 [0.73; 1.19]	0.93 [0.73; 1.19]	0.0%	0.676
Afli 2q4w vs Rani 0.5q4w[a]	VIEW 1 VIEW 2	1.05 [0.82; 1.33]	1.04 [0.64; 1.71]	76.3%	0.040
LP → Afli 2q8w vs Afli 2q4w	VIEW 1 VIEW 2	1.12 [0.88;1.43]	1.12 [0.75; 1.65]	62.3%	0.103
LP → Bro 6q12/q8w vs LP → Afli 2q8w	HARRIER HAWK	1.19 [0.95; 1.49]	1.19 [0.79; 1.80]	69.7%	0.069

[a]Direct comparisons come from VIEW 1&2, which were pooled in the NMA.
Abbreviations: CI: confidence interval; LP: loading phase; TREX: treat-and-extend dosing regimen.

This section presents the results from the fixed-effects model of the NMA because the DIC was lower than that of the random-effects model (120.1 versus 201.0). The indirect comparisons obtained through the NMA are reported in Figure 35 (LP → Bro 6q12/q8w versus each comparator). Brolucizumab (LP → Bro 6q12/q8w) had significantly greater odds of gaining at least 15 letters from Baseline to one year than sham IVT, Rani 0.5PRN, LP → Bro 3q12/q8w and LP → Rani 0.5q12w; none of the other results were significant based on the 95% credible intervals.

Figure 35: Forest plot of the NMA results comparing the odds of gaining at least 15 letters from Baseline to one year between LP → Bro 6q12/q8w and each comparator (fixed-effects)



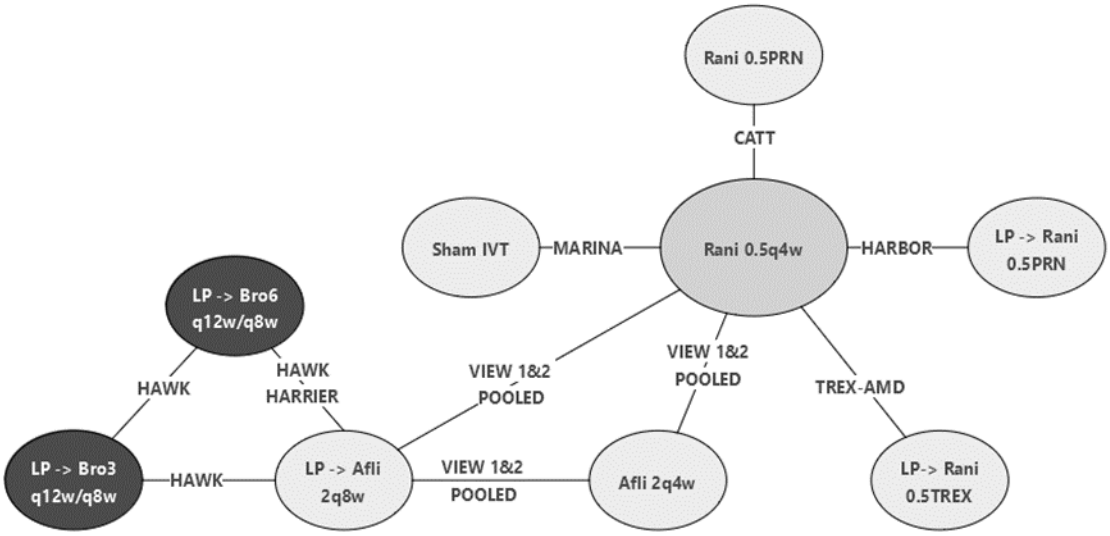
Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Patients gaining at least 15 letters (Baseline to two years)

At two years, the base case NMA demonstrated brolucizumab to be associated with comparable efficacy to aflibercept and ranibizumab for odds of gaining at least 15 letters from Baseline

The network for the proportion of patients gaining at least 15 letters by two years is displayed in Figure 36. A total of seven studies were included in the analysis.

Figure 36: Network for patients gaining at least 15 letters from Baseline to two years



Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Only one direct comparison needed to be evaluated for heterogeneity for the patients gaining at least 15 letters between Baseline and two years. This was between LP → Afli 2q8w and LP → Bro 6q12/q8w, which was shared by HAWK and HARRIER. Relatively high heterogeneity was present, with an I-square value of 72.4% and Cochran test p-value of 0.06. The results from the direct comparison are presented in Table 45. The source of the heterogeneity was examined for both comparisons by assessing certain characteristics at Baseline. However, the source of this heterogeneity was not clearly identifiable from these analyses.

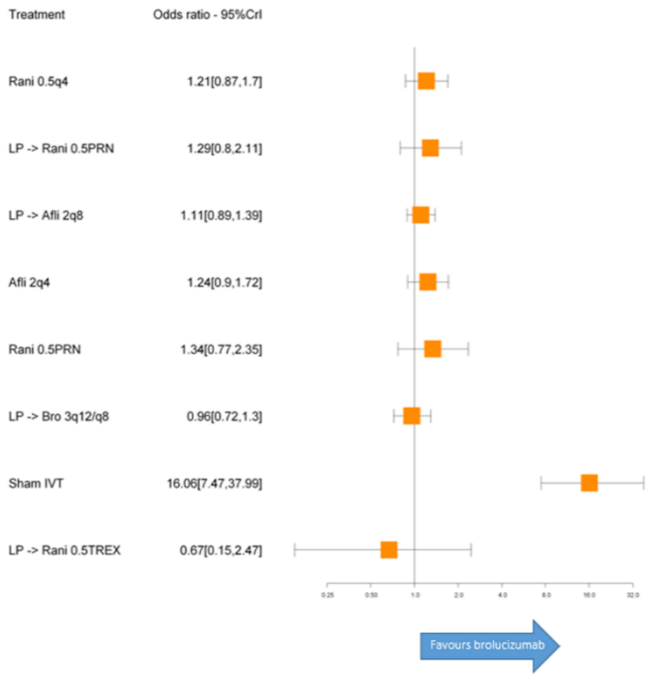
Table 45: Summary of direct comparison results for odds of gaining at least 15 letters from Baseline to two years

Comparison	Trials	Mean Difference [95% CI]		I-square	p-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP → Bro 6q12/q8w vs LP → Afli 2q8w	HARRIER HAWK	1.11 [0.89; 1.39]	1.12 [0.73; 1.71]	72.4%	0.057

Abbreviations: CI: confidence interval; LP: loading phase.

This section presents the results from the fixed-effects model of the NMA because the DIC was lower than that of the random-effects model (124.9 and 123.3). The indirect comparisons obtained through the NMA are reported in Figure 37 (LP → Bro 6q12/q8w versus each comparator). Brolucizumab (LP → Bro 6q12/q8w) had significantly greater odds of gaining at least 15 letters from Baseline to two years than sham IVT; none of the other results were significant based on the 95% credible intervals.

Figure 37: Forest plot of the NMA results comparing the odds of gaining at least 15 letters from Baseline to two years between LP → Bro 6q12/q8w and each comparator (fixed-effects)



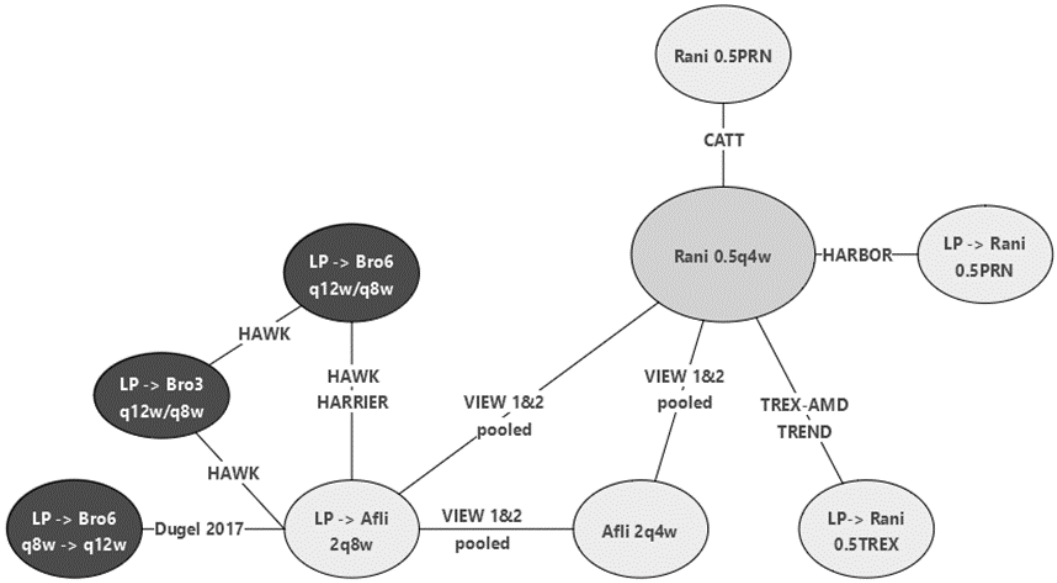
Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Mean change in central retinal thickness (Baseline to one year)

At one year, the base case NMA demonstrated brolucizumab (LP → Bro 6q12/q8w) to be statistically significantly superior to all aflibercept and ranibizumab regimens at decreasing central retinal thickness from Baseline

The network for mean change in retinal thickness from Baseline at one year is displayed in Figure 38. A total of eight studies were included in the analysis.

Figure 38: Network for mean change in central retinal thickness from Baseline to one year



Abbreviations: LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

The pairwise meta-analysis results are reported in Table 46. Each direct comparison included two trials. While significant heterogeneity was not present in any of the trials, four of the comparisons had an I-square value of at least 50%.

In addition, Schmidt-Erfurth 2014 reported the pooled results for VIEW 1&2.[98] These trials were therefore pooled in the NMA and considered one trial. This is the same approach that NICE used in their NMA in wAMD.[49]

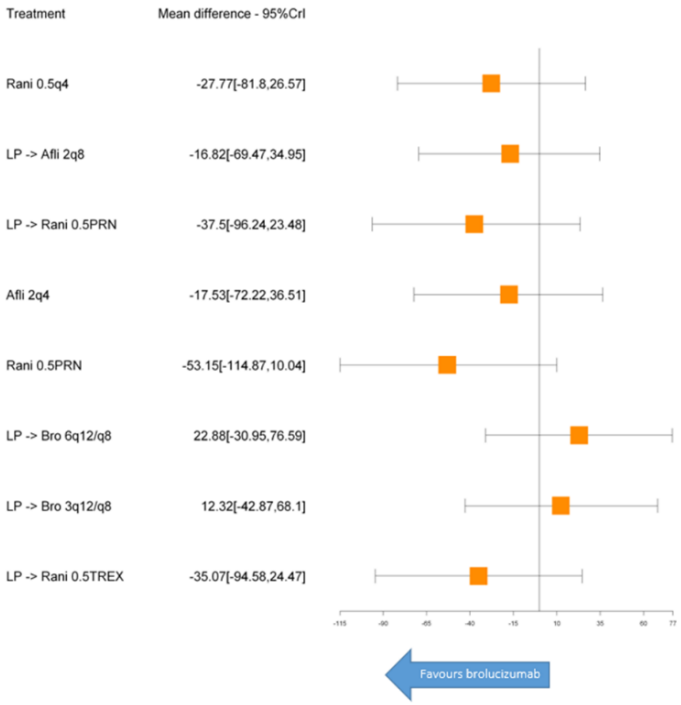
Table 46: Summary of direct comparison results for mean change in central retinal thickness from Baseline to one year

Comparison	Trials	Mean Difference [95% CI]		I-square	p-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP → Bro 6q12/q8w vs LP → Afli 2q8w	HARRIER HAWK	0.42 [-0.98;1.81]	0.42 [-0.98;1.81]	0.0%	0.625
LP → Rani 0.5TREX vs Rani 0.5q4w	TREND TREX-AMD	10.56 [-13.65;34.78]	28.45 [-36.82;93.72]	62.79%	0.10116
Rani 0.5q4w vs LP→ Afli 2q8w[a]	VIEW 1 VIEW 2	11.26 [-1.67; 24.18]	11.26 [-1.67; 24.18]	0.0%	0.940
Rani 0.5q4w vs Afli 2q4w[a]	VIEW 1 VIEW 2	7.41 [-5.22; 20.04]	8.21 [-9.95; 26.38]	50.6%	0.155
LP → Afli 2q8w vs Afli 2q4w[a]	VIEW 1 VIEW 2	-3.66 [-16.16; 8.85]	-2.83 [-22; 16.34]	56.7%	0.129
LP → Afli 2q8w vs LP → Bro 6q12/q8w	HARRIER HAWK	39.28 [26.02; 52.55]	39.41 [19.03; 59.79]	57.6%	0.125

[a]Direct comparisons come from VIEW 1&2, which were pooled in the NMA.
Abbreviations: CI: confidence interval; LP: loading phase; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

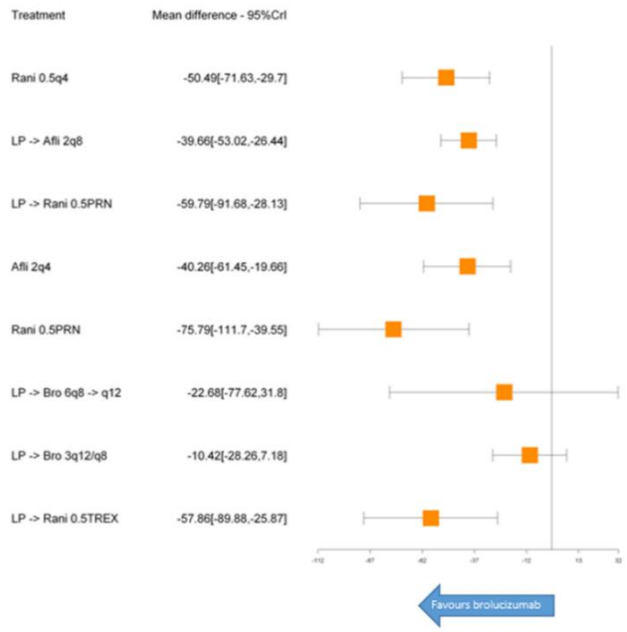
The DIC values were 152.2 and 151.8 for fixed and random-effects model, respectively. The fixed-effects model was chosen as the random-effects model encountered convergence issues. The indirect comparisons obtained through the NMA are reported in Figure 39 (LP → Bro 6q12/q8w versus each comparator) and Figure 40 (LP → Bro 6q12/q8w versus each comparator). The results for mean change in retinal thickness at one year indicated that brolucizumab (LP → Bro 6q12/q8w) is statistically significantly superior at decreasing retinal thickness than every comparator.

Figure 39: Forest plot of the NMA results comparing the difference in mean change in central retinal thickness from Baseline to one year between LP → Bro 6q8w → q12w and each comparator (fixed-effects)



Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Figure 40: Forest plot of the NMA results comparing the difference in mean change in central retinal thickness from Baseline to one year between LP → Bro 6q12/q8w and each comparator (fixed-effects)



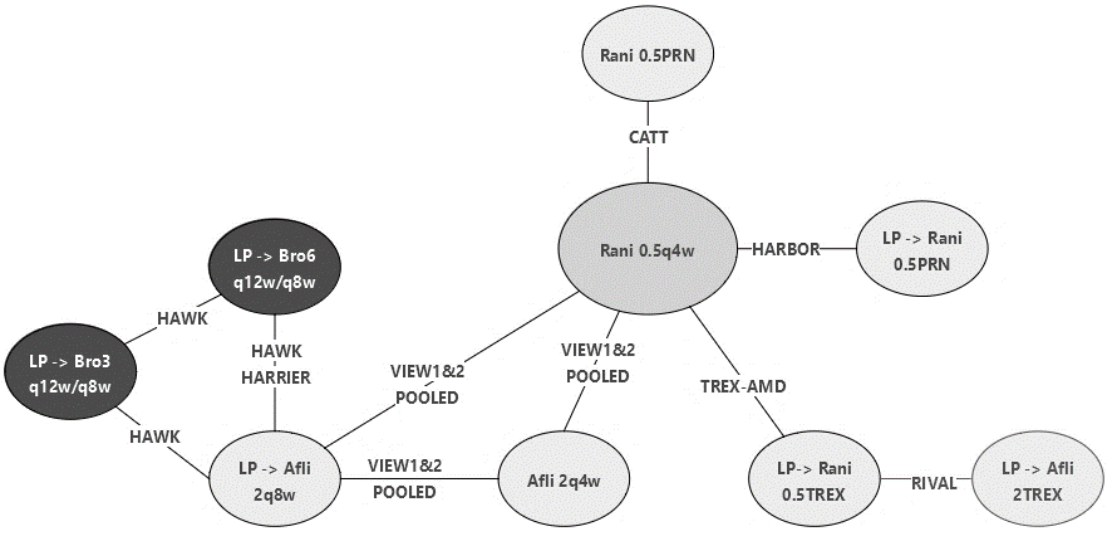
Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Mean change in central retinal thickness (Baseline to two years)

At two years, the base case NMA demonstrated brolucizumab to be statistically significantly superior to most aflibercept and ranibizumab regimens at decreasing retinal thickness from Baseline

The network for mean change in retinal thickness from Baseline to two years is displayed in Figure 41. Seven studies were included in the analysis.

Figure 41: Network for mean change in central retinal thickness from Baseline to two years



Abbreviations: LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

The pairwise meta-analysis results are reported in Table 47. One direct comparison needed to be evaluated for heterogeneity for the mean change in retinal thickness at two years. This was between LP → Afli 2q8w and LP → Bro 6q12/q8w, which was shared by HAWK and HARRIER. Low heterogeneity was present in the comparison, with an I-square value of 25% and Cochran test p-value of 0.25.

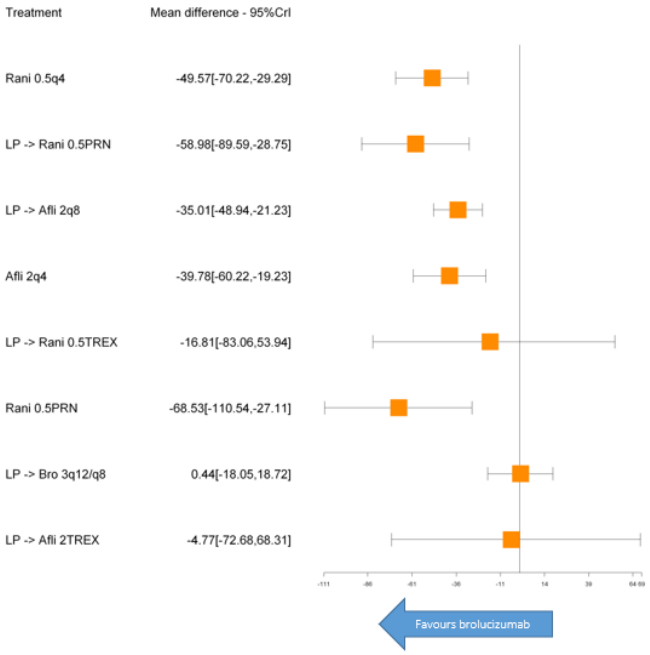
Table 47: Summary of direct comparison results for mean change in central retinal thickness from Baseline to two years

Comparison	Trials	Mean Difference [95% CI]		I-square	p-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP → Bro 6q12/q8w vs LP → Afli 2q8w	HARRIER HAWK	-34.69 [-48.64; -20.74]	-34.60 [-50.77; -18.44]	25.4%	0.247

Abbreviations: CI: confidence interval; LP: loading phase; qXw: one injection every X weeks.

This section presents the results from the fixed-effects model of the NMA, as the DIC values were 129.4 and 129.2 for fixed and random-effects model respectively. The indirect comparisons obtained through the NMA are reported in Figure 42 (LP → Bro 6q12/q8w versus each comparator). The results for mean change in retinal thickness at two years indicated that brolucizumab (LP → Bro 6q12/q8w) is statistically significantly superior at decreasing retinal thickness than every comparator other than LP → Rani 0.5TREX and LP → Afli 2TREX, which were not significant at a 95% credibility level.

Figure 42: Forest plot of the NMA results comparing the difference in mean change in central retinal thickness from Baseline to two years between LP → Bro 6q12/q8w and each comparator (fixed-effects)



Abbreviations: CrI: credibility interval; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Injection frequency (Baseline to one year)

Arm-based pooling demonstrated brolucizumab to have one of the lowest injection frequencies from Baseline to one year, when compared to aflibercept and ranibizumab regimens

The frequency of injections from Baseline to one year was assessed through arm-based pooling only. The absolute treatment effects for injection frequency at one year are presented in Table 48. Among the included treatments, Afli 2q4w had the highest injection frequency, with a mean number of 11.9 injections. LP → Rani 0.5PRNX had the lowest injection frequency, with an average of 5.5 injections during the first year of follow-up.

Table 48: Absolute treatment effects for injection frequency from Baseline to one year, where baseline pooling is conducted for treatments with more than one trial

Intervention	Number of Trials[a]	Fixed-effects		Random-effects		Pooled SD	Cochran Q Statistic	p-value Cochran Q	Between-trial variance
		Mean	SE	Mean	SE				
Afli 2q4w	1	11.90	0.13	11.90	0.13	3.13	0.00	-	0.00
LP → Afli 2TREX	1	9.70	0.22	9.70	0.22	2.55	0.00	-	0.00
LP → Afli 2q8w	3	7.23	0.04	7.14	0.15	1.90	26.72	0.00	0.06
LP → Bro 3q12/q8w	1	6.60	0.05	6.60	0.05	0.96	0.00	-	0.00
LP → Bro 6q12/q8w	2	6.66	0.04	6.66	0.05	1.03	1.64	0.20	0.00
LP → Rani 0.5PRN	2	7.52	0.12	7.08	0.65	2.17	14.17	0.00	0.79
LP → Rani 0.5PRNX	1	5.50	0.31	5.50	0.31	2.17	0.00	-	0.00
LP → Rani 0.5TREX	4	9.49	0.09	9.54	0.12	2.59	4.85	0.18	0.02
Rani 0.5PRN	1	6.90	0.18	6.90	0.18	3.00	0.00	-	0.00
Rani 0.5q4w	6	11.71	0.06	11.78	0.13	2.69	21.40	0.00	0.07

[a]When the treatment regimen included only one trial, the results are presented directly from that clinical trial. For treatments with more than one trial, baseline pooling was conducted to obtain an absolute treatment effect estimate.
Abbreviations: LP: loading phase; PRN: pro re nata dosing regimen; PRN: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SD: standard deviation; SE: standard error; TREX: treat-and-extend.

Injection frequency (Baseline to two years)

Arm-based pooling demonstrated brolucizumab to have the lowest injection frequency from Baseline to two years, when compared to aflibercept and ranibizumab regimens

The frequency of injections from Baseline to two years were assessed through arm-based pooling only. The absolute treatment effects for injection frequency at two years are presented in Table 49. Among the included treatments, Rani 0.5q4w had the highest annualised injection frequency, with a mean number of 11.4 injections per year for the random-effects model. The two brolucizumab regimens had the lowest annualised injection frequency, with an average of 5.7 injections for LP → Bro 6q12/q8w (random-effects model).

Table 49: Absolute treatment effects for injection frequency from Baseline to two years, where baseline pooling is conducted for treatments with more than one trial

Intervention	Number of Trials[a]	Fixed-effects		Random-effects		Pooled SD	Cochran Q Statistic	p-value Cochran Q	Between-trial variance
		Mean	SE	Mean	SE				
Afli 2q4w → PRN	1	8.70	0.07	8.70	0.07	1.73	0.00	-	0.0000
LP → Afli 2TREX	1	8.50	0.27	8.50	0.27	3.15	0.00	-	0.0000

LP → Afli 2q8w	2	6.41	0.06	6.35	0.25	1.50	19.23	0.0000	0.1185
LP → Afli 2q8w → PRN	1	6.10	0.06	6.10	0.06	1.57	0.00	-	0.0000
LP → Bro 3q12/q8w	1	5.70	0.07	5.70	0.07	1.38	0.00	-	0.0000
LP → Bro 6q12/q8w	2	5.73	0.05	5.70	0.20	1.38	14.16	0.0002	0.0744
LP → Rani 0.5PRN	1	6.70	0.12	6.70	0.12	2.00	0.00	-	0.0000
LP → Rani 0.5TREX	2	9.07	0.21	9.07	0.21	2.93	0.91	0.3394	0.0000
Rani 0.5PRN	2	6.85	0.12	6.76	0.45	2.80	12.35	0.0004	0.3722
Rani 0.5q4w	3	10.95	0.10	11.43	0.40	1.98	23.40	0.0000	0.3999

[a]When the treatment regimen included only one trial, the results are presented directly from that clinical trial. For treatments with more than one trial, baseline pooling was conducted to obtain an absolute treatment effect estimate.
Abbreviations: LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SD: standard deviation; SE: standard error; TREX: treat-and-extend.

3. State the effects of the technology versus the comparator(s) on the following aspects of quality of life (QOL):

- **generic health-related quality of life (HRQOL)**
- **disease-specific HRQOL**
- **work productivity**
- **activities of daily living.**

Not applicable. HRQoL outcomes were not assessed as part of the NMA.

4. State the effects of the technology versus the comparator(s) on aspects of patient satisfaction.

Not applicable. Patient satisfaction outcomes were not assessed in the HAWK and HARRIER trials or as part of the NMA.

5. Highlight the difference in the risks and any differences in the severity of adverse events of the technology and the comparator(s).

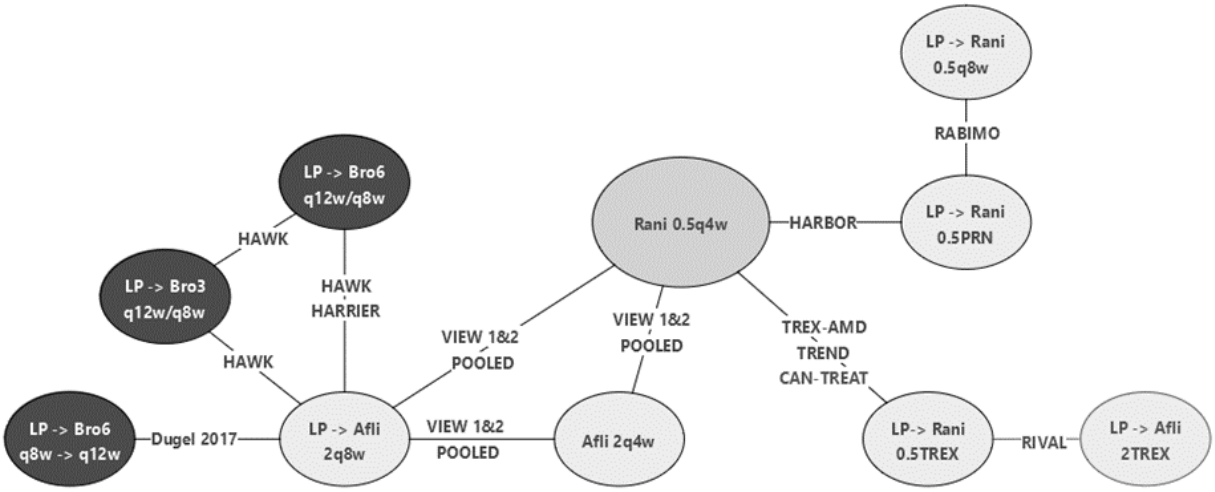
The results of the NMA for overall discontinuation and frequency of adverse events are presented in this section.

Overall rate of treatment discontinuation (Baseline to one year)

The base case NMA demonstrated brolucizumab to be associated with comparable odds of discontinuation to aflibercept and ranibizumab, from Baseline to one year

The network for overall discontinuation between Baseline and one year is displayed in Figure 43. A total of ten studies were included in the analysis.

Figure 43: Network for overall discontinuation from Baseline to one year



Abbreviations: LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

The pairwise meta-analysis results are reported in Table 50. Each direct comparison included two or three trials, and heterogeneity was present in one of the direct comparisons between trials VIEW 1 and VIEW 2 (Afli 2q4w versus LP → Afli 2q8w). However, as these trials were pooled in the NMA, they were considered as one trial.

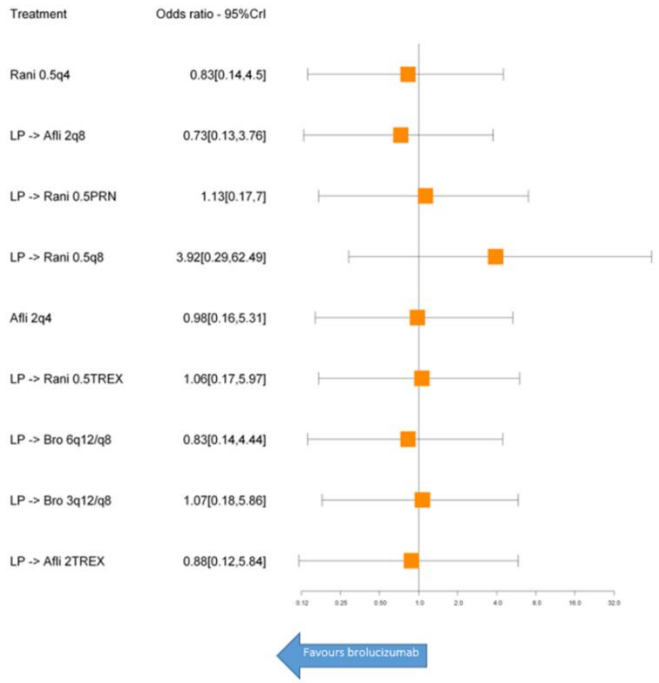
Table 50: Summary of direct comparison results for overall treatment discontinuation from Baseline to one year

Comparison	Trials	Mean Difference [95% CI]		I-square	p-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP → Rani 0.5TREX vs Rani 0.5q4w	TREND TREX-AMD CAN-TREAT	0.79 [0.54;1.14]	0.84 [0.39;1.81]	64.48%	0.060
LP → Afli 2q8w vs Rani 0.5q4w[a]	VIEW 1 VIEW 2	1.04 [0.72; 1.51]	1.04 [0.72; 1.51]	0.00%	0.668
Afli 2q4w vs Rani 0.5q4w[a]	VIEW 1 VIEW 2	0.86 [0.58; 1.27]	0.82 [0.44; 1.54]	59.14%	0.118
Afli 2q4w vs LP → Afli 2q8w[a]	VIEW 1 VIEW 2	0.83 [0.56; 1.23]	0.78 [0.35; 1.72]	74.53%	0.048+
LP → Bro 6q12/q8w vs LP → Afli 2q8w	HARRIER HAWK	0.87 [0.61; 1.25]	0.87 [0.61; 1.25]	0.00%	0.448

[a]Direct comparisons come from VIEW 1&2, which were pooled in the NMA.
Abbreviations: CI: confidence interval; LP: loading phase; TREX: treat-and-extend dosing regimen.

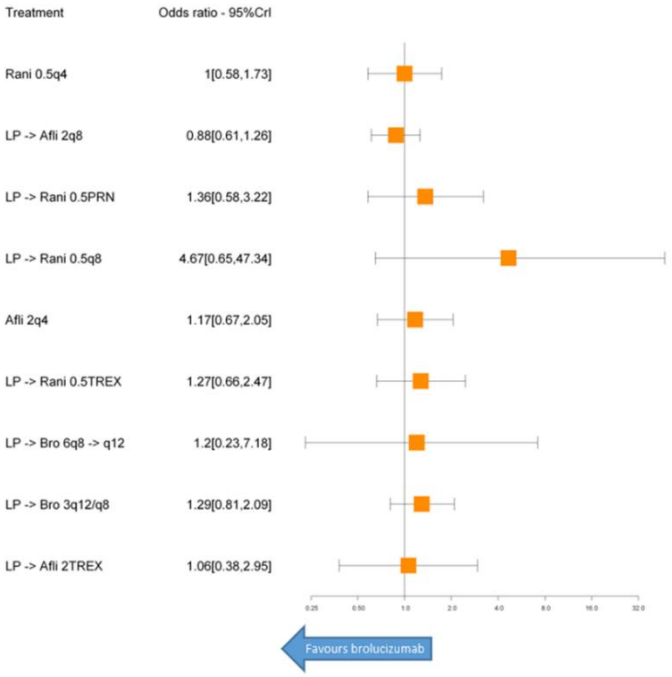
This section presents the results from the fixed-effects model of the NMA. The DIC values were 144.0 and 143.1 for fixed and random-effects model, respectively. The indirect comparisons obtained through the NMA are reported in Figure 44 (LP → Bro 6q8w → q12w versus each comparator) and Figure 45 (LP → Bro 6q12/q8w versus each comparator). Brolucizumab showed comparable efficacy to ranibizumab and aflibercept for the odds of discontinuation from Baseline to one year, with none of the treatment effects for this endpoint significant at a 95% credibility level.

Figure 44: Forest plot of the NMA results comparing the odds of treatment discontinuation from Baseline to one year between LP → Bro 6q8w → q12w and each comparator (fixed-effects)



Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Figure 45: Forest plot of the NMA results comparing the odds of treatment discontinuation from Baseline to one year between LP → Bro 6q12/q8w and each comparator (fixed-effects)



Abbreviations: CrI: credibility interval; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Molecule-based baseline pooling was conducted for treatment discontinuation, as discontinuation was not found to be statistically significantly affected by regimen characteristics in the NICE Guidelines in wAMD.[89] The results for aflibercept 2 mg, brolucizumab 6 mg, ranibizumab 0.5 mg and sham IVT are reported below in Table 51.

Table 51: Baseline pooling results for treatment discontinuation at one year

Intervention	Number of Trials	Fixed-effects		Random-effects		Pooled SD	Cochran Q Statistic	p-value Cochran Q	Between-trial variance
		Mean	SE	Mean	SE				
Aflibercept	8	0.088	0.006	0.094	0.011	0.291	20.984	0.004	0.001
Brolucizumab	3	0.080	0.010	0.081	0.013	0.275	3.054	0.217	0.000
Ranibizumab	14	0.085	0.005	0.087	0.008	0.285	21.978	0.056	0.000
Sham IVT	1	0.170	0.047	0.170	0.047	0.376	0.000	-	0.000

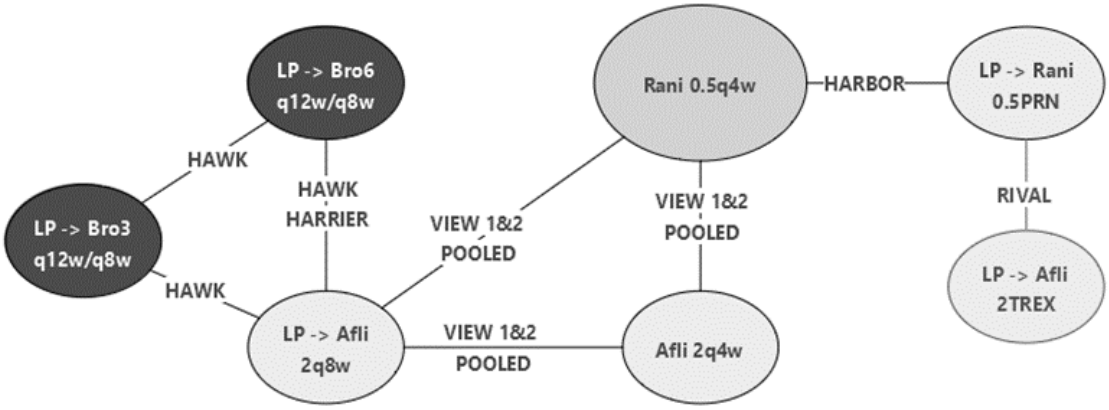
Abbreviations: IVT: intravitreal; SD: standard deviation; SE: standard error.

Overall rate of treatment discontinuation (Baseline to two years)

The base case NMA demonstrated brolucizumab to be associated with comparable odds of discontinuation to aflibercept and ranibizumab, from Baseline to two years

The network for mean change in retinal thickness from Baseline to two years is displayed in Figure 46. Five studies were included in the analysis.

Figure 46: Network for overall treatment discontinuation from Baseline to two years



Abbreviations: LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

The pairwise meta-analysis results are reported in Table 52. Only one direct comparison needed to be evaluated for heterogeneity for overall discontinuation at two years. This was between LP → Bro 6q12/q8w and LP → Afli 2q8w, which was shared by HAWK and HARRIER. No heterogeneity was present, with an I-square value of 0% and Cochran test p-value of 0.95.

Table 52: Summary of direct comparison results for overall treatment discontinuation from Baseline to two years

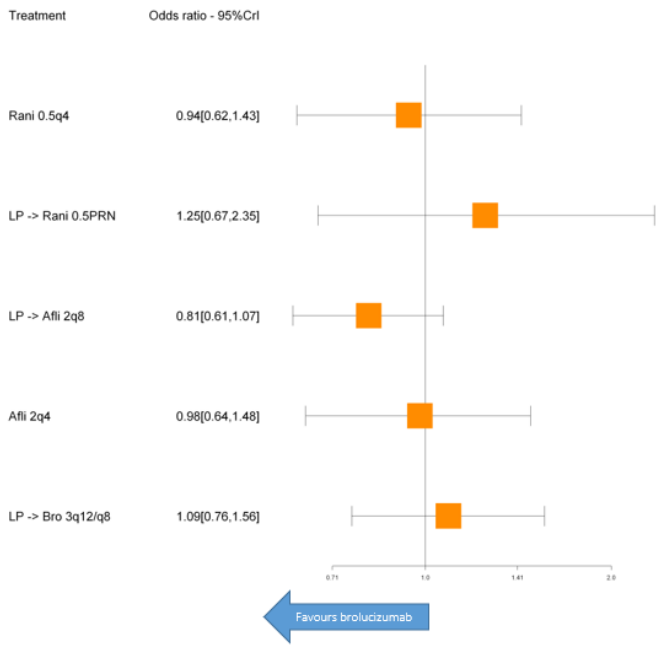
Comparison	Trials	Mean Difference [95% CI]		I-square	p-value of the Cochran test
		Fixed-effects model	Random-effects model		
LP → Bro 6q12/q8w	HARRIER HAWK	0.81 [0.61; 1.07]	0.81 [0.61; 1.07]	0.0%	0.950

vs LP → Afli 2q8w					

Abbreviations: CI: confidence interval; LP: loading phase; qXw: one injection every X weeks.

This section presents the results from the fixed-effects model of the NMA because the DIC was lower than that of the random-effects model (76.3 versus 77.5). The indirect comparisons obtained through the NMA are reported in Figure 47 (LP → Bro 6q12/q8w versus each comparator). Brolucizumab showed comparable efficacy to ranibizumab and aflibercept for the odds of treatment discontinuation from Baseline to two years, with none of the treatment effects for this endpoint significant at a 95% credibility level.

Figure 47: Forest plot of the NMA results comparing the odds of discontinuation from Baseline to two years between LP → Bro 6q12/q8w and each comparator (fixed-effects)



Abbreviations: CrI: credibility interval; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; qXw: one injection every X weeks.

Molecule-based baseline pooling was conducted for treatment discontinuation, as discontinuation was not found to be statistically significantly affected by regimen characteristics in the NICE Guidelines in wAMD.[89] The results for aflibercept 2 mg, brolucizumab 6 mg, and ranibizumab 0.5 mg are reported below in Table 53.

Table 53: Baseline pooling results for treatment discontinuation at two years

Intervention	Number of Trials	Fixed-effects		Random-effects		Pooled SD	Cochran Q Statistic	p-value Cochran Q	Between-trial variance
		Mean	SE	Mean	SE				
Aflibercept	5	0.164	0.008	0.171	0.015	0.371	12.954	0.012	0.001
Brolucizumab	2	0.144	0.013	0.151	0.036	0.355	7.421	0.006	0.002
Ranibizumab	6	0.152	0.010	0.152	0.010	0.359	1.780	0.619	0.000

Abbreviations: SD: standard deviation; SE: standard error.

Baseline pooling for adverse events

Molecule-based pooling and regimen-based pooling were conducted for serious adverse events. The results of the molecule-based pooling are reported in Table 54 to Table 61 results of the regimen-based pooling are reported in Table 63 to Table 69.

Molecule-based

Table 54: Frequency of cataracts (molecule-based pooling)

Molecule	Number of Trials	Mean (Fixed-effects)	SE (Fixed-effects)	Mean (Random-effects)	SE (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	p-value of Cochran Q	Between-trial variance
1 year									
Aflibercept	6	0.0030	0.0001	0.0030	0.0001	0.0274	2.0600	0.8408	0.0000
Brolucizumab	2	0.0030	0.0001	0.0030	0.0001	0.0030	0.0000	1.0000	0.0000
Ranibizumab	6	0.0036	0.0002	0.0038	0.0015	0.0273	85.8176	0.0000	0.0000
2 years									
Aflibercept	4	0.0069	0.0002	0.0060	0.0007	0.0182	16.5145	0.0009	0.0000
Brolucizumab	2	0.0030	0.0001	0.0030	0.0001	0.0030	0.0000	1.0000	0.0000
Ranibizumab	1	0.002	0.0000818	0.002	0.0000818	0.001996	0.0000	0.0000	0.0000

Abbreviations: SE: standard error.

Table 55: Frequency of endophthalmitis (molecule-based pooling)

Molecule	Number of Trials	Mean (Fixed-effects)	SE (Fixed-effects)	Mean (Random-effects)	SE (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	p-value of Cochran Q	Between-trial variance
1 year									
Aflibercept	6	0.0078	0.0005	0.0031	0.0023	0.0344	58.4628	0.0000	0.0000
Brolucizumab	2	0.0036	0.0001	0.0045	0.0015	0.0045	73.1813	0.0000	0.0000
Ranibizumab	15	0.0043	0.0001	0.0050	0.0012	0.0323	255.7260	0.0000	0.0000
Sham	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
2 years									
Aflibercept	4	0.0039	0.0001	0.0033	0.0015	0.0186	164.0280	0.0000	0.0000

Brolucizumab	2	0.0036	0.0001	0.0055	0.0025	0.0054	125.5503	0.0000	0.0000
Ranibizumab	6	0.0092	0.0003	0.0100	0.0021	0.0215	85.2762	0.0000	0.0000
Sham	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000

Abbreviations: SE: standard error.

Table 56: Frequency of intraocular inflammation (molecule-based pooling)

Molecule	Number of Trials	Mean (Fixed-effects)	SE (Fixed-effects)	Mean (Random-effects)	SE (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	p-value of Cochran Q	Between-trial variance
1 year									
Ranibizumab	5	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000
Sham	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
2 years									
Aflibercept	2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Brolucizumab	2	0.0091	0.0003	0.0095	0.0015	0.0094	18.1886	0.0000	0.0000
Ranibizumab	2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Abbreviations: SE: standard error.

Table 57: Frequency of retinal detachment (molecule-based pooling)

Molecule	Number of Trials	Mean (Fixed-effects)	SE (Fixed-effects)	Mean (Random-effects)	SE (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	p-value of Cochran Q	Between-trial variance
1 year									
Aflibercept	10	0.0030	0.0002	0.0030	0.0002	0.0327	2.0201	0.8464	0.0000
Brolucizumab	2	0.0030	0.0002	0.0030	0.0002	0.0201	0.7402	0.3896	0.0000
Ranibizumab	9	0.0030	0.0001	0.0030	0.0001	0.0325	2.4175	0.9655	0.0000
Sham	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
2 years									
Aflibercept	4	0.0023	0.0001	0.0025	0.0004	0.0107	55.0041	0.0000	0.0000
Brolucizumab	2	0.0030	0.0001	0.0030	0.0001	0.0030	0.0000	1.0000	0.0000
Ranibizumab	4	0.0049	0.0002	0.0041	0.0009	0.0270	3.9504	0.2669	0.0049
Sham	1	0.0040	0.0003	0.0040	0.0003	0.0040	0.0000	-	0.0000

Abbreviations: SE: standard error.

Table 58: Frequency of retinal pigment epithelial tear (molecule-based pooling)

Molecule	Number of Trials	Mean (Fixed-effects)	SE (Fixed-effects)	Mean (Random-effects)	SE (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	p-value of Cochran Q	Between-trial variance
1 year									
Aflibercept	6	0.0030	0.0001	0.0030	0.0001	0.0274	2.0893	0.8367	0.0000
Brolucizumab	2	0.0035	0.0001	0.0040	0.0010	0.0040	43.5997	0.0000	0.0000
Ranibizumab	6	0.0030	0.0002	0.0110	0.0048	0.0341	35.9310	0.0000	0.0001
2 years									
Aflibercept	4	0.0048	0.0002	0.0024	0.0015	0.0243	19.1822	0.0003	0.0000
Brolucizumab	2	0.0035	0.0001	0.0040	0.0010	0.0040	43.5997	0.0000	0.0000
Ranibizumab	1	0.0020	0.0001	0.0020	0.0001	0.0020	0.0000	-	0.0000

Abbreviations: SE: standard error.

Table 59: Frequency of retinal tear (molecule-based pooling)

Molecule	Number of Trials	Mean (Fixed-effects)	SE (Fixed-effects)	Mean (Random-effects)	SE (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	p-value of Cochran Q	Between-trial variance
1 year									
Aflibercept	2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000
Ranibizumab	7	0.0030	0.0001	0.0030	0.0001	0.0287	1.6657	0.9477	0.0000
2 years									
Aflibercept	1	0.0030	0.0002	0.0030	0.0002	0.0030	0.0000	-	0.0000
Brolucizumab	1	0.0050	0.0003	0.0050	0.0003	0.0050	0.0000	-	0.0000
Ranibizumab	3	0.0040	0.0003	0.0040	0.0003	0.0309	1.4049	0.4954	0.0000
Sham	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000

Abbreviations: SE: standard error.

Table 60: Frequency of gastrointestinal tear (molecule-based pooling)

Molecule	Number of Trials	Mean (Fixed-effects)	SE (Fixed-effects)	Mean (Random-effects)	SE (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	P-value of Cochran Q	Between-trial variance
1 year									
Ranibizumab	2	0.0080	0.0003	0.0085	0.0015	0.0084	18.4521	0.0000	0.0000
2 years									
Ranibizumab	2	0.0060	0.0005	0.0060	0.0005	0.0304	0.4877	0.4849	0.0000

Abbreviations: SE: standard error.

Table 61: Frequency of stroke (molecule-based pooling)

Molecule	Number of Trials	Mean (Fixed-effects)	SE (Fixed-effects)	Mean (Random-effects)	SE (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	p-value of Cochran Q	Between-trial variance
1 year									
Aflibercept	6	0.0037	0.0001	0.0050	0.0007	0.0051	281.1996	0.0000	0.0000
Brolucizumab	2	0.0102	0.0005	0.0063	0.0048	0.0240	23.4139	0.0000	0.0000
Ranibizumab	13	0.0045	0.0001	0.0058	0.0009	0.0213	288.3556	0.0000	0.0000
Sham	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
2 years									
Aflibercept	4	0.0084	0.0002	0.0094	0.0009	0.0090	64.7270	0.0000	0.0000
Brolucizumab	2	0.0102	0.0005	0.0063	0.0048	0.0240	23.4139	0.0000	0.0000
Ranibizumab	4	0.0059	0.0002	0.0104	0.0018	0.0098	257.7988	0.0000	0.0000
Sham	1	0.0080	0.0005	0.0080	0.0005	0.0079	0.0000	-	0.0000

Abbreviations: SE: standard error.

The table below shows the definitions that were used for pooling the proportion of patients with stroke. Both overall and serious adverse events were considered, as these events are generally severe in nature. In addition, this is consistent with the approach done in the NICE NG82 guideline, which incorporated multiple definitions of stroke in their analyses.[89]

Table 62: Definitions used for pooling patients with stroke

Trial name	Molecules included	Definition
CATT	Ranibizumab	Nonfatal stroke, serious
HARBOR	Ranibizumab	Nonfatal stroke
HARRIER	Aflibercept + brolucizumab	Cerebrovascular accident, overall
HAWK	Aflibercept + brolucizumab	Cerebrovascular accident, overall
MARINA	Ranibizumab + sham IVT	Nonfatal stroke
PIER	Ranibizumab + sham IVT	Nonfatal stroke
RABIMO	Ranibizumab	Stroke, serious
SALUTE	Ranibizumab	Stroke, overall/serious
TREND	Ranibizumab	Cerebrovascular accident, serious
VIEW 1&2	Aflibercept + ranibizumab	Nonfatal stroke

Abbreviations: IVT: intravitreal.

For gastrointestinal events, the only one trial with data available was CATT. For this reason, there was no need to run baseline pooling for this adverse event.

Regimen-based

The baseline pooling results for each treatment regimen are reported below.

Table 63: Frequency of cataracts (regimen-based pooling)

Treatment regimen	Number of Trials	Mean (Fixed-effects)	SE (Fixed-effects)	Mean (Random-effects)	SE (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	p-value of Cochran Q	Between-trial variance
1 year									
Afli 2q4w	2	0.0030	0.0002	0.0030	0.0002	0.0216	0.3382	0.5609	0.0000
LP → Afli 2q8w	4	0.0030	0.0002	0.0030	0.0002	0.0300	1.7113	0.6344	0.0000
LP → Bro 3q12/q8w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Bro 6q12/q8w	2	0.0030	0.0001	0.0030	0.0001	0.0030	0.0000	1.0000	0.0000
LP → Rani 0.5PRN	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Rani 0.5q8w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
Rani 0.5PRN	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
Rani 0.5q4w	3	0.0036	0.0002	0.0042	0.0017	0.0171	84.3905	0.0000	0.0000
2 years									
Afli 2q4w	1	0.0070	0.0003	0.0070	0.0003	0.0070	0.0000	-	0.0000
LP → Afli 2q8w	3	0.0068	0.0003	0.0036	0.0023	0.0233	16.1796	0.0003	0.0000
LP → Bro 3q12/q8w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Bro 6q12/q8w	2	0.0030	0.0001	0.0030	0.0001	0.0030	0.0000	1.0000	0.0000
Rani 0.5q4w	1	0.002	0.0001	0.0020	0.0001	0.0020	0.0000	-	0.0000

Abbreviations: LP: loading phase; PRN: *pro re nata* dosing regimen; qXw: one injection every X weeks; SE: standard error.

Table 64: Frequency of endophthalmitis (regimen-based pooling)

Treatment regimen	Number of Trials	Mean (Fixed-effects)	SE (Fixed-effects)	Mean (Random-effects)	SE (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	p-value of Cochran Q	Between-trial variance
1 year									
Afli 2q4w	2	0.0095	0.0006	0.0061	0.0042	0.0252	12.6574	0.0004	0.0000

LP → Afli 2q8w	4	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
LP → Bro 3q12/q8w	1	0.0080	0.0004	0.0080	0.0004	0.0079	0.0000	-	0.0000
LP → Bro 6q12/q8w	2	0.0036	0.0001	0.0045	0.0015	0.0045	73.1813	0.0000	0.0000
LP → Rani 0.5PRN	3	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
LP → Rani 0.5PRNX	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Rani 0.5q12w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Rani 0.5q8w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
Rani 0.5PRN	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
Rani 0.5TREX	2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Rani 0.5q4w	6	0.0043	0.0001	0.0061	0.0015	0.0153	250.5193	0.0000	0.0000
Sham IVT	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
2 years									
Afli 2q4w	1	0.0070	0.0003	0.0070	0.0003	0.0070	0.0000	-	0.0000
LP → Afli 2q8w	3	0.0030	0.0002	0.0022	0.0008	0.0239	4.1157	0.1277	0.0000
LP → Bro 3q12/q8w	1	0.0080	0.0004	0.0080	0.0004	0.0079	0.0000	-	0.0000
LP → Bro 6q12/q8w	2	0.0036	0.0001	0.0055	0.0025	0.0054	125.5503	0.0000	0.0000
LP → 0.5PRN	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
Rani 0.5TREX	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
Rani 0.5q4w	4	0.0093	0.0003	0.0120	0.0024	0.0133	76.817	0.0000	0.0000
Sham IVT	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000

Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SE: standard error; TREX: treat-and-extend dosing regimen.

Table 65: Frequency of intraocular inflammation (regimen-based pooling)

Treatment regimen	Number of Trials	Mean (Fixed-effects)	SE (Fixed-effects)	Mean (Random-effects)	SE (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	p-value of Cochran Q	Between-trial variance
1 year									
LP → Rani 0.5PRN	1	0.000	0.000	0.000	0.000	0.000	0	-	0

LP → Rani 0.5q12w	1	0.000	0.000	0.000	0.000	0.000	0	-	0
LP → Rani 0.5q8w	1	0.000	0.000	0.000	0.000	0.000	0	-	0
LP → Rani 0.5TREX	1	0.000	0.000	0.000	0.000	0.000	0	-	0
Rani 0.5q4w	1	0.000	0.000	0.000	0.000	0.000	0	-	0
Sham IVT	1	0.000	0.000	0.000	0.000	0.000	0	-	0
2 years									
LP → Afli 2q8w	2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000
LP → Bro 3q12/q8w	1	0.0030	0.0002	0.0030	0.0002	0.0030	0.0000	-	0.0000
LP → Bro 6q12/q8w	2	0.0091	0.0003	0.0095	0.0015	0.0094	18.1886	0.0000	0.0000
LP → Rani 0.5TREX	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
Rani 0.5q4w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000

Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SE: standard error; TREX: treat-and-extend dosing regimen.

Table 66: Frequency of retinal detachment (regimen-based pooling)

Treatment regimen	Number of Trials	Mean (Fixed-effects)	SE (Fixed-effects)	Mean (Random-effects)	SE (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	p-value of Cochran Q	Between-trial variance
1 year									
Afli 2q4w	2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000
LP → Afli 2q8w	4	0.0030	0.0002	0.0030	0.0002	0.0293	1.3435	0.7188	0.0000
LP → Bro 3q12/q8w	1	0.0030	0.0002	0.0030	0.0002	0.0030	0.0000	-	0.0000
LP → Bro 6q12/q8w	2	0.0030	0.0002	0.0030	0.0002	0.0201	0.7402	0.3896	0.0000
LP → Rani 0.5PRN	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Rani 0.5TREX	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Rani 0.5q12w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Rani 0.5q8w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
Rani 0.5PRN	1	0.0030	0.0002	0.0030	0.0002	0.0030	0.0000	-	0.0000
Rani 0.5q4w	4	0.0030	0.0002	0.0030	0.0002	0.0313	1.1035	0.7762	0.0000

Sham IVT	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
2 years									
Afli 2q4w	1	0.0020	0.0001	0.0020	0.0001	0.0020	0.0000	-	0.0000
LP → Afli 2q8w	3	0.0030	0.0001	0.0030	0.0002	0.0147	3.5086	0.1730	0.0000
LP → Bro 3q12/q8w	1	0.0030	0.0002	0.0030	0.0002	0.0030	0.0000	-	0.0000
LP → Bro 6q12/q8w	2	0.0030	0.0001	0.0030	0.0001	0.0030	0.0000	1.0000	0.0000
LP → Rani 0.5PRN	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
Rani 0.5PRN	1	0.0030	0.0043	0.0030	0.0043	0.0548	0.0000	-	0.0000
Rani 0.5q4w	3	0.0050	0.0002	0.0045	0.0009	0.0231	2.4576	0.2926	0.0000
Sham IVT	1	0.0040	0.0003	0.0040	0.0003	0.0040	0.0000	-	0.0000

Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SE: standard error; TREX: treat-and-extend dosing regimen.

Table 67: Frequency of retinal pigment epithelial tear (regimen-based pooling)

Treatment regimen	Number of Trials	Mean (Fixed-effects)	SE (Fixed-effects)	Mean (Random-effects)	SE (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	p-value of Cochran Q	Between-trial variance
1 year									
Afli 2q4w	2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
LP → Afli 2q8w	4	0.0030	0.0001	0.0030	0.0001	0.0215	1.4007	0.7054	0.0000
LP → Bro 3q12/q8w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Bro 6q12/q8w	2	0.0035	0.0001	0.0040	0.0010	0.0040	43.5997	0.0000	0.0000
LP → Rani 0.5PRN	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Rani 0.5q8w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Rani 0.5TREX	1	0.0300	0.0046	0.0300	0.0046	0.0291	0.0000	-	0.0000
Rani 0.5q4w	3	0.0030	0.0002	0.0030	0.0002	0.0265	0.7355	0.6923	0.0000
2 years									
Afli 2q4w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Afli 2q8w	3	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

LP → Bro 3q12/q8w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Bro 6q12/q8w	2	0.0035	0.0001	0.0040	0.0010	0.0040	43.5997	0.0000	0.0000
Rani 0.5q4w	1	0.0020	0.0001	0.0020	0.0001	0.0020	0.0000	-	0.0000

Abbreviations: LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SE: standard error; TREX: treat-and-extend dosing regimen.

Table 68: Frequency of retinal tear (regimen-based pooling)

Treatment regimen	Number of Trials	Mean (Fixed-effects)	SE (Fixed-effects)	Mean (Random-effects)	SE (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	p-value of Cochran Q	Between-trial variance
1 year									
Afli 2q4w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Afli 2q8w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Rani 0.5PRN	2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000
LP → Rani 0.5q8w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Rani 0.5TREX	1	0.0030	0.0002	0.0030	0.0002	0.0030	0.0000	-	0.0000
Rani 0.5q4w	3	0.0030	0.0002	0.0030	0.0002	0.0281	0.6585	0.7195	0.0000
2 years									
LP → Afli 2q8w	1	0.0030	0.0002	0.0030	0.0002	0.0030	0.0000	-	0.0000
LP → Bro 6q12/q8w	1	0.0050	0.0003	0.0050	0.0003	0.0050	0.0000	-	0.0000
LP → Rani 0.5PRN	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
Rani 0.5q4w	2	0.0040	0.0003	0.0040	0.0003	0.0247	0.7047	0.4012	0.0000
Sham IVT	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000

Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SE: standard error; TREX: treat-and-extend dosing regimen.

Overall adverse events

Regimen-based pooling was performed for the overall frequency of endophthalmitis, with the results reported in Table 69.

Table 69: Frequency of endophthalmitis (regimen-based pooling)

Molecule	Number of Trials	Mean (Fixed-effects)	Standard error (Fixed-effects)	Mean (Random-effects)	Standard Error (Random-effects)	Pooled Standard Deviation	Cochran Q Statistic	p-value of Cochran Q	Between-trial variance
1 year									
LP → Afli 2q8w	2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000
LP → Bro 3q12/q8w	1	0.0110	0.0006	0.0110	0.0006	0.0109	0.0000	-	0.0000
LP → Bro 6q12/q8w	2	0.0036	0.0001	0.0045	0.0015	0.0045	73.1813	0.0000	0.0000
LP → Rani 0.5PRN	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Rani 0.5PRNX	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Rani 0.5TREX	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
LP → Rani 0.5q12w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
Rani 0.5PRN	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
Rani 0.5q4w	2	0.0070	0.0004	0.0070	0.0004	0.0162	0.2658	0.6062	0.0000
Sham IVT	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
2 years									
LP → Afli 2q8w	2	0.0030	0.0002	0.0030	0.0002	0.0199	0.6695	0.4132	0.0000
LP → Bro 3q12/q8w	1	0.0110	0.0006	0.0110	0.0006	0.0109	0.0000	-	0.0000
LP → Bro 6q12/q8w	2	0.0035	0.0002	0.0070	0.0040	0.0069	181.3360	0.0000	0.0000
LP → Rani 0.5TREX	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
Rani 0.5PRN	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000
Rani 0.5q4w	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-	0.0000

Abbreviations: IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SE: standard error; TREX: treat-and-extend dosing regimen.

5.9 Conclusions

1. **Provide a general interpretation of the evidence base considering the benefits associated with the technology relative to those of the comparators.**

Evidence from the brolucizumab clinical trials

Evidence for the efficacy and safety of brolucizumab in wAMD derives from two pivotal phase III, head-to-head clinical trials versus aflibercept: HAWK and HARRIER.[19, 27, 104] Results from OSPREY, the phase II trial of brolucizumab in wAMD, also support the key primary and secondary outcomes from HAWK and HARRIER (see Appendix 7.4).[50, 105]

Brolucizumab achieved clinically meaningful and consistent visual gains in the HAWK and HARRIER trials, demonstrating non-inferiority in terms of BCVA to aflibercept, with a majority of patients treated with brolucizumab maintained on a q12w dosing regimen. The hypothesis of non-inferiority of brolucizumab 6 mg to aflibercept 2 mg was confirmed for the primary endpoint of mean change in BCVA from Baseline to Week 48 in HAWK and HARRIER with highly significant p- values. At Week 48, the least squares (LS)-mean change in BCVA from Baseline was 6.6 versus 6.8 letters, and 6.9 versus 7.6 letters, for brolucizumab 6 mg versus aflibercept 2 mg in HAWK and HARRIER respectively ($p<0.0001$ for both comparisons, non-inferior 4-letter margin). The key secondary endpoint of non-inferiority to aflibercept in mean change in BCVA over the period of Week 36–48 was also met with highly significant p-values in both HAWK ($p\leq0.0001$, non-inferior 4-letter margin) and HARRIER ($p<0.0003$, non-inferior 4-letter margin). These results are supported by results from the phase II OSPREY trial, where brolucizumab met the key primary and secondary endpoints of non-inferiority to aflibercept for mean change in BCVA from Baseline to Weeks 12 and 16.

The visual outcomes for the key endpoints in HAWK and HARRIER were achieved with a majority of patients maintained on a q12w dosing interval immediately following the loading dose phase. More than 50% (56% in HAWK and 51% in HARRIER) of brolucizumab 6 mg patients were exclusively maintained on a q12w regimen immediately following the loading dose phase through to Week 48. Patients treated with brolucizumab therefore received fewer injections on average from Baseline through to Week 96 than patients treated with aflibercept. Over 96 weeks, the mean number of active injections administered to patients on the brolucizumab treatment arms was between 1 and 1.5 fewer injections than the number administered on the aflibercept arms. Brolucizumab therefore achieved comparable visual outcomes to aflibercept, at a lower injection frequency. The high-frequency dosing schedules of currently available licensed anti-VEGF therapies represent a significant burden on patients, their carers, and ophthalmology clinics. This can result in patient under-treatment,[16, 19] due to the impact on patient adherence and clinic capacity constraints, risking symptom exacerbation and visual decline, and in some cases, vision loss. Brolucizumab therefore meets an unmet clinical need for a therapy which enables the administration of less frequent injections due to superior fluid reduction and better disease control, without reducing visual outcomes, with treatment and monitoring intervals based on an individual's anti-VEGF therapy need.

To enable the administration of less frequent injections, a treatment must control disease activity for longer than currently available licensed anti-VEGF therapies, with retinal specialists determining the need for patient retreatment based on visual and anatomical parameters of disease activity.[104] The control of fluid accumulation is essential to the effective management of

wAMD and high-quality European and international clinical guidelines (from EURETINA, AAO, HAS and NICE) recommend that treatment decisions are based around the presence of fluid.[8, 10, 38, 39] Results from HAWK and HARRIER show that brolucizumab was superior to aflibercept in terms of reductions in retinal fluid (IRF and/or SRF) and CSFT. An increase in retinal fluid or CSFT is an important indicator of disease activity, as fluid accumulation and oedema may result in vision deterioration and, in some cases, vision loss. Significantly fewer patients receiving brolucizumab had IRF and/or SRF at Week 16 and Week 48 compared with aflibercept, with differences maintained to Week 96.

At Week 16, the proportion of patients with IRF and/or SRF was 33.9% for brolucizumab 6 mg versus 52.2% for aflibercept 2 mg in HAWK (p<0.0001), and 29.4% versus 45.1% in HARRIER (p<0.0001). At Week 48, the proportion of patients with IRF and/or SRF was 31.2% for brolucizumab 6 mg versus 44.7% for aflibercept 2 mg in HAWK (p=0.0002), and 25.8% versus 43.9% in HARRIER (p<0.0001).[27] Brolucizumab 6 mg showed a superior reduction in CSFT compared with aflibercept 2 mg at Week 16 and Week 48 in HAWK (p=0.0008 and p=0.0012 respectively) and HARRIER (p<0.0001 for both time points). These differences were maintained at Week 96 (HAWK [p=0.0057] and HARRIER [p<0.0001]). Overall, brolucizumab was significantly superior to aflibercept in terms of anatomical outcomes and disease activity parameters; 30% fewer patients receiving brolucizumab had disease activity compared to those receiving aflibercept, at Week 16.

In addition, brolucizumab achieved a similar improvement in HRQoL compared with aflibercept. A comparable change from Baseline to Week 24 in VFQ-25 was observed for brolucizumab 6 mg and aflibercept 2 mg in both HAWK and HARRIER. The VFQ-25 analysis showed no relevant differences between treatment arms in the composite or any of the individual subscale scores.

Indirect comparative evidence of brolucizumab versus the relevant comparators

In order to address the lack of head-to-head comparative evidence for brolucizumab versus ranibizumab, an NMA was performed comparing brolucizumab to aflibercept and ranibizumab. Results from the NMA demonstrated brolucizumab to be associated with comparable efficacy to aflibercept and ranibizumab in terms of change in BCVA from Baseline to one and two years. Additionally, in line with results from the phase II and III clinical trials, the NMA also demonstrated brolucizumab to be statistically significantly superior than most aflibercept and ranibizumab regimens at decreasing retinal thickness from Baseline to one year. Visual and anatomical results were comparable for both LP → Bro 6q8w → q12w and LP → Bro 6q12/q8w regimens, where the latter regimen included over 50% of patients on a q12w brolucizumab dosing interval until Week 48. Results of the arm-based baseline pooling for injection frequency also demonstrated brolucizumab to be associated with one of the lowest injection frequencies across year one and the lowest injection frequency across year two versus most aflibercept and ranibizumab regimens. Brolucizumab therefore displays comparative visual gains in terms of BCVA and superior anatomical outcomes with a lower injection frequency than current standard of care.

2. Provide a general interpretation of the evidence base considering the harms associated with the technology relative to those of the comparators.

Results of the HAWK and HARRIER trials demonstrated the overall safety profile of brolucizumab to be comparable to aflibercept. The overall incidence of ocular and non-ocular AEs was balanced across all treatment groups in both HAWK and HARRIER trials. Overall, no new, previously unreported types of safety events were identified compared with other licensed anti-VEGF therapies.

Over 96 weeks, the proportion of patients experiencing ≥1 ocular AE was 218 (60.9%), 220 (61.1%) and 201 (55.8%) patients in the brolucizumab 3 mg, brolucizumab 6 mg and aflibercept 2 mg arms, respectively in HAWK, and 174 (47.0%) and 176 (47.7%) patients in the brolucizumab 6 mg and aflibercept 2 mg arms, respectively in HARRIER. In HAWK, conjunctival haemorrhage was the most frequently reported ocular AE, occurring in 39 (10.9%), 29 (8.1%), and 32 (8.9%) patients in the brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept 2 mg arms, respectively. In HARRIER, the most frequently reported ocular AE in the brolucizumab 6 mg arm was reduced VA, occurring in 32 (8.6%) patients; in the aflibercept 2 mg arm, cataract was the most frequently reported AE. Non-ocular AEs were predominantly mild or moderate in severity.

The most frequent non-ocular AEs were typical of those reported in a wAMD population and there were no notable differences between arms. In HAWK up to Week 96, 60 patients (16.8%) in the brolucizumab 3 mg arm, 48 patients (13.3%) in the brolucizumab 6 mg arm, and 72 patients (20.0%) in the aflibercept 2 mg arm experienced at least 1 severe non-ocular AE. In HARRIER, up to Week 96, 37 patients (10.0%) in the brolucizumab 6 mg arm and 44 subjects (11.9%) in the aflibercept 2 mg arm experienced at least 1 severe non-ocular AE.

Finally, results of the baseline pooling for serious AEs within the NMA demonstrated brolucizumab to be associated with a comparable safety profile to both aflibercept and ranibizumab.

5.10 Strengths and limitations

3. Summarise the internal validity of the evidence base, taking into account the study quality, the validity of the endpoints used as well as the overall level of evidence. Include a statement about the consistency of the results in the evidence base.

Strengths and limitations of the clinical evidence base

The clinical evidence base presented within this submission has been primarily derived from two phase III, international, multicentre, randomised, double-masked, head-to-head trials, and one phase II multicentre, randomised, double-masked, two-arm trial. HAWK and HARRIER enrolled more than 1,800 patients, with OSPREY enrolling a further 89. As large, blinded and randomised trials, these studies present robust clinical evidence for the efficacy and safety of brolucizumab. Comparable results for BCVA efficacy between aflibercept 2 mg arms in the VIEW studies and OSPREY further support the reliability of the results from the pivotal brolucizumab trials presented as part of this submission.[50]

Results of the HAWK and HARRIER trials demonstrate brolucizumab to be statistically superior to aflibercept in terms of reductions in CSFT and IRF and/or SRF accumulation, alongside non-inferior differences in BCVA. These differences may be explained by the fact that the trials were designed to show the ability of brolucizumab to deliver comparable visual gains in terms of BCVA with less injections, and were not designed to show a correlation between fluid accumulation and BCVA.

A limitation of the evidence base presented is that no head-to-head comparison is available between brolucizumab and ranibizumab. In order to overcome this limitation, an indirect treatment comparison was performed between aflibercept, ranibizumab and brolucizumab. The NMA was based on data from RCTs, which can be considered the gold standard in terms of evidence quality. The process for conducting the SLR and NMA was conducted in line with NICE guidelines,[88] conducted in a Bayesian framework and the best model (fixed-effects versus random-effects) was chosen based on the deviance information criterion (DIC). The results from

the NMA were similar to the results of the NMA in wAMD conducted by NICE in their clinical guideline (NG82)[10] and, in the few cases where there were differences, the source of the difference was found to be due to the decisions made on which studies to include. The study populations of the trials included in the NMA were similar, with no heterogeneity identified in direct comparisons. Furthermore, the results of the NMA were supported by several sensitivity analyses conducted to assess the robustness of the base case results.

In addition, appropriate methods were used to impute missing data for the SD/SE in order to include as much relevant evidence as possible. Among the trials included in the NMA, the study populations were similar, as shown by the characteristics reported at baseline. Whilst heterogeneity was identified in the direct comparison between TREND, TREX-AMD and CAN-TREAT for mean change in BCVA at one year, this was likely due to the inherent variability of the follow-up treatment intervals in the TREX regimen. Furthermore, no inconsistency was identified in the closed loop containing the HAWK and HARRIER trials. The results from this NMA therefore provide a robust, up-to-date comparison of brolucizumab versus the relevant comparators to this appraisal: aflibercept and ranibizumab.

It is acknowledged that there are some limitations associated with the NMA. It was not possible to obtain meta-regression results adjusted on relevant covariates such as Baseline BCVA and treatment regimen. This was because the networks did not provide enough information to allow the models to converge.

Another limitation of the NMA was that time equivalence was assumed for one-year and two-year outcomes. In order to include all available evidence for treatments of interest, equivalence was assumed between 48 and 52 weeks for one-year outcomes and between 96 and 104 weeks for two-year outcomes. No publication was found to validate this hypothesis, but the results for HAWK and HARRIER at Week 52 were similar to those at Week 48. In addition, the results from sensitivity analyses that extrapolated endpoints that were published at 48 weeks and 104 weeks were similar to the base case. This demonstrated that there was no impact on the results with the equivalence assumption used.

In order to connect the networks, an assumption was made for VIEW 1&2. Whilst patients in VIEW 1&2 began a PRN treatment regimen at 52 weeks, these patients were still considered as remaining on continuous treatment arms (i.e. LP → Afli 2q8w, Afli 2q4w, and Rani 0.5q4w) in order to connect to the brolucizumab treatments. To assess the impact of this assumption, heterogeneity for Rani 0.5q4w was assessed for each endpoint at two years and was only found for injection frequency. Since only baseline pooling was conducted for injection frequency, this switch to a PRN regimen was considered in these analyses. Furthermore, CNV lesion size was considered as a treatment effect modifier in wAMD following feedback from a leading clinical expert who indicated that VIEW 1&2 seemed to be the biggest outlier. However, as described above, this trial was needed to connect the network and therefore this represents a limitation of the analysis.

A final limitation of the NMA was that Rani 0.5q4w versus LP → Rani 0.5TREX and LP → Bro 6q12/q8w versus LP → Afli 2q8w were the only comparisons for which multiple studies were included (as VIEW 1&2 were pooled in the analyses). The other comparisons were all connected by one trial only, making these arms of the network less robust.

Despite the above limitations the results of the NMA are still considered to be robust and represent the most recent analysis of comparative efficacy between brolucizumab and the relevant comparators aflibercept and ranibizumab. Overall, the clinical evidence presented in this submission supports the non-inferiority of brolucizumab versus aflibercept, and the comparative efficacy of brolucizumab to ranibizumab, for visual outcomes in terms of BCVA. The evidence

also supports the clinical superiority of brolucizumab at improving anatomical outcomes, with increase in retinal fluid a key marker of disease activity. With the majority of brolucizumab-treated patients in the key phase III trials treated at a 12-week dosing interval immediately following the loading dose phase (56% in HAWK and 51% in HARRIER), it can be concluded that brolucizumab offers equivalent visual outcomes to current standard of care, at a reduced treatment and monitoring frequency. Brolucizumab therefore offers a solution to the current patient and healthcare system burdens associated with currently licensed anti-VEGF therapies.

4. Provide a brief statement of the relevance of the evidence base to the scope of the assessment.

The clinical evidence base presented within this submission has been primarily derived from two phase III, international, multicentre, randomised, double-masked, head-to-head trials, and one phase II multicentre, randomised, double-masked, two-arm trial. Across both HAWK and HARRIER, a total of 359 trial sites enrolled over 1,800 patients. Therefore, the results presented here are considered to reflect standard European clinical practice.

The patient populations enrolled across both the HAWK and HARRIER trials included patients aged over 50 years with a baseline BCVA between 23 and 78 letters. This represents a wider BCVA inclusion range than previous pivotal studies (ANCHOR, MARINA and VIEW I/II) and provides evidence for the efficacy of brolucizumab in patients with particularly good vision, including those still legally able to drive. Whilst differences can be seen in the magnitude of BCVA change seen in HAWK and HARRIER in comparison to previous trials (i.e. smaller BCVA gains in HAWK and HARRIER), this can be explained by the higher baseline BCVA value for HAWK and HARRIER with VA gain restricted due to the presence of a clinical expert defined "ceiling effect".[20, 27]

The comparator included within the HAWK and HARRIER trials was aflibercept, one of the gold standard licensed anti-VEGF therapies currently used for the first-line treatment of wAMD across Europe. As such, the HAWK and HARRIER trials provide robust, direct head-to-head evidence of the efficacy and safety of brolucizumab versus a relevant comparator to European clinical practice. The NMA further provides evidence of the comparative effectiveness of brolucizumab versus aflibercept, in addition to the comparative effectiveness of brolucizumab versus ranibizumab, which also comprises the gold standard of care for wAMD patients in Europe.

The outcomes assessed within the HAWK and HARRIER trials represent the gold standard in ophthalmology trials and the primary endpoint of mean change in BCVA aligns with the primary endpoint of the pivotal trials for the comparator therapies. Furthermore, the HAWK and HARRIER trials provide robust evidence for the benefits of brolucizumab in terms of reduction of retinal fluid (IRF and/or SRF) and CSFT, which is critical to the effective management of wAMD and improving and maintaining vision.

Summary

Brolucizumab provides improved vision gains, comparable in terms of change in BCVA versus ranibizumab and aflibercept, whilst providing statistically significantly superior anatomical outcomes in terms of greater reductions in CSFT. This was achieved with 56% (HAWK) and 51% (HARRIER) of brolucizumab 6 mg-treated patients maintained on a q12w dosing interval immediately after loading up to Week 48. Compared with aflibercept, treatment with brolucizumab also led to significantly fewer patients with disease activity, and significantly fewer patients with IRF and/or SRF. Brolucizumab is therefore able to provide equivalent visual gains in terms of BCVA to current standard of care, at a reduced injection frequency, offering a solution to the current patient and healthcare system burdens contributed to by ranibizumab and aflibercept.

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7 Appendices

7.1 International Classification of Diseases (ICD) coding

Table 70: ICD-9 codes for wAMD

ICD-9 Code	Description
362.52	Exudative senile macular degeneration

wAMD, wet age-related macular degeneration; ICD, International Classification of Diseases.
Source: ICD-9-CM Online.[106]

Table 71: ICD-10 codes for wAMD

ICD-10 Code	Description
H35.32	Exudative AMD
H35.321	Exudative AMD, right eye
H35.3210	Exudative AMD, right eye: stage unspecified
H35.3211	Exudative AMD, right eye: with active CNV
H35.3212	Exudative AMD, right eye: with inactive CNV
H35.3213	Exudative AMD, right eye: with inactive scar
H35.322	Exudative AMD, left eye
H35.3220	Exudative AMD, left eye: stage unspecified
H35.3221	Exudative AMD, left eye: with active CNV
H35.3222	Exudative AMD, left eye: with inactive CNV
H35.3223	Exudative AMD, left eye: with inactive scar
H35.323	Exudative AMD, bilateral
H35.3230	Exudative AMD, bilateral: stage unspecified
H35.3231	Exudative AMD, bilateral: with active CNV
H35.3232	Exudative AMD, bilateral: with inactive CNV
H35.3233	Exudative AMD, bilateral: with inactive scar
H35.329	Exudative AMD, unspecified eye
H35.3290	Exudative AMD, unspecified eye: stage unspecified
H35.3291	Exudative AMD, unspecified eye: with active CNV
H35.3292	Exudative AMD, unspecified eye: with inactive CNV
H35.3293	Exudative AMD, unspecified eye: with inactive scar

AMD, age-related macular degeneration; CNV, choroidal neovascularisation; wAMD, wet age-related macular degeneration; ICD, International Classification of Disease.
Source: ICD-10-CM.[107]

7.2 Identification and selection of relevant studies

A systematic literature (SLR) review was conducted to identify relevant evidence of the efficacy and safety of brolucizumab versus comparator therapies for the treatment of wet age-related macular degeneration (wAMD).

Search strategy

A PICOS framework was developed to conduct the SLR, as detailed in Table 72.

Table 72: PICOS framework

Topic	Criteria
Population	Adult patients (age ≥ 18 years old) with wAMD (also known as neovascular AMD)
Intervention	Brolucizumab
Comparators	• Ranibizumab (Lucentis®) • Aflibercept (Eylea®) • Pegaptanib® (Macugen®) • Photodynamic therapy with verteporfin (Visudyne) • Laser photocoagulation therapy • Macular surgeries
Outcomes	• Visual acuity (VA) (ETDRS letters or logMAR or Snellen equivalent) • Other measures of VA (blindness and ≥15 letter gain/loss) • Central retinal thickness • HRQoL • Severe ocular and systemic adverse events • Treatment discontinuation • Injection and monitoring frequencies
Study Type	• Randomised controlled trials (RCTs) of 44 weeks or longer, cross-over RCTs (if data presented at the time of cross-over) • Open-label extension studies of RCTs

Abbreviations: ETDRS: Early Treatment Diabetic Retinopathy Study; HRQoL: health related quality of life; logMAR: logarithm of the minimum angle of resolution; wAMD: wet age-related macular degeneration; RCT: randomised controlled trial; VA: visual acuity.

Electronic database searches

The electronic databases searched were EMBASE, Medline, Medline-in-Process and the Cochrane Library. In addition to the PICOS framework, the search terms used for EMBASE, Medline, and Medline-in-Process were developed according to methods NICE used in their SLR and NMA in wAMD.[49, 89, 90] Search terms used for Cochrane Library were adapted from a previously conducted SLR and NMA for ranibizumab in wAMD.[91] The search terms for each database are presented in Table 73 to Table 75.

An original search was conducted on 10th September 2018, with an update conducted on 13th June 2019. The searches were designed to be broad to capture all potentially relevant treatments and connections to support an NMA to ascertain the relative effectiveness of brolucizumab versus the relevant comparators aflibercept and ranibizumab.

Bevacizumab was therefore included in the broader searches run. However, off-license bevacizumab is not considered a relevant treatment. Bevacizumab is only licensed by the EMA for applications in oncology and is manufactured for intravenous administration; bevacizumab is therefore not licensed or formulated for intraocular use.[82] The purpose of EU marketing authorisation from the EMA is “To protect public health and ensure the availability of high quality, safe and effective medicines”.[83] While licensed treatments have been assessed to be clinically and cost effective, unlicensed medicines have not undergone rigorous regulatory scrutiny to enable a favourable analysis to be made. Publications that included only bevacizumab treatment arms were therefore excluded during the full-text review stage.

Table 73: Search terms for EMBASE via www.embase.com
(Date of the search: 13/06/2019)

PICOS component	#	Search Terms	# of Hits
Disease: wAMD	#1	'macular degeneration'/exp OR 'macular degeneration':ti,ab	35,215
	#2	'retinal degeneration'/exp OR 'retinal degeneration':ti,ab	56,164
	#3	'choroidal neovascular*'	8,666
	#4	'macula lutea'/exp	10,822
	#5	'retinal drusen'/exp	2,869
	#6	(neovascular OR exudative) AND degener*	8,165
	#7	(macul* OR retina* OR choroid* OR wet) AND degener*	61,622
	#8	(macul* OR retina* OR choroid*) AND neovasc*	25,061
	#9	maculopath* OR drusen*	12,664
	#10	macul* AND (lutea* OR syndrome)	20,684
	#11	macul* AND dystroph*	4,129
	#12	(macul* OR 'geography') AND atroph*	6,988
	#13	choroid* AND polyp*	2,004
	#14	amd OR armd OR wAMD	20,349
	#15	retina* AND angiomat* AND prolif*	461
	#16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	116,624
	#17	'acid mine drainage'	1,987
	#18	#16 NOT #17	115,844
Interventions and Comparators	#19	'brolucizumab'/exp OR brolucizumab:ti,ab,tn OR esba1008 OR dlx1008	45
	#20	'ranibizumab'/exp OR ranibizumab:ti,ab,tn OR lucentris:ti,ab,tn OR rg3645:ti,ab,tn	8,632
	#21	'bevacizumab'/exp OR bevacizumab:ti,ab,tn OR avastin:ti,ab,tn OR 'rhumbab-vegf':ti,ab,tn	54,197
	#22	'aflibercept'/exp OR aflibercept:ti,ab,tn OR eylae:ti,ab,tn OR 'bay865321':ti,ab,tn OR pegaptanib:ti,ab,tn OR macugen:ti,ab,tn	6,328
	#23	trapeye*:ti,ab,tn OR 'trap eye*':ti,ab,tn	92
	#24	'photochemotherapy'/exp OR photochemotherapy:ti,ab OR 'photodynamic therapy'/exp OR 'photodynamic therapy':ti,ab	42,121
	#25	'macul* surger*'	231
	#26	verteporfin:ti,ab,tn OR visudyne:ti,ab,tn	2,259
	#27	#19 OR #20 OR #21 OR #22 OR #23 OR #24 or #25 or #26	101,291
Outcomes	#28	'clinical trial'/exp	1,403,198
	#29	'randomized controlled trial'/exp	551,507

PICOS component	#	Search Terms	# of Hits
	#30	'randomization'/exp	82,418
	#31	'single blind procedure'/exp	35,1127
	#32	'double blind procedure'/exp	161,024
	#33	'crossover procedure'/exp	59,177
	#34	'multicenter study'/exp	215,751
	#35	'comparative study'/exp	1,344,774
	#36	'placebo'/exp	340,677
	#37	'randomi*ed controlled trial*':ti,ab,kw	208,811
	#38	rct:ti,ab,kw	34,420
	#39	'random* allocat*':ti,ab,kw	35,433
	#40	'allocated randomly':ti,ab,kw	2,439
	#41	(allocated NEXT/2 random):ti,ab,kw	855
	#42	'single blind*':ti,ab,kw	22,967
	#43	'double blind*':ti,ab,kw	199,736
	#44	((treble OR triple) NEXT/1 blind*):ti,ab,kw	980
	#45	'placebo*':ti,ab,kw	290,311
	#46	'prospective study'/exp	522,919
	#47	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46	3,308,700
	#48	'case study'/exp	60,839
	#49	'case report':ti,ab	396,799
	#50	'abstract report'/exp OR 'letter'/exp	1,098,667
	#51	'conference proceeding':it	0
	#52	'conference abstract':it	3,402,105
	#53	'editorial':it	609,238
	#54	'letter':it	1,058,816
	#55	'note':it	745,752
	#56	#48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55	6,255,687
	#57	#47 NOT #56	2,677,032
Disease, Treatments, Study Type	#58	#18 AND #27 AND #57	2,844
Remove Animal Studies	#59	'animal'/exp	26,006,413
	#60	'human'/exp	20,746,970
	#61	#59 NOT #60	5,259,443
	#62	#58 NOT #61	2,822
Limit to English	#63	#62 AND [english]/lim AND [10-9-2018]/sd NOT [13-6-2019]/sd	154

Abbreviations: wAMD: wet age-related macular degeneration.

Table 74: Search terms for MEDLINE and MEDLINE-IN-PROCESS via www.pubmed.com
(Date of the search: 13/06/2019)

PICOS Component	#	Search Terms	# of Hits
Disease: wAMD	#1	“macular degeneration”[TIAB] OR “macular degeneration”[MH]	29,734
	#2	“retinal degeneration”[TIAB] OR “retinal degeneration”[MH]	42,330
	#3	"Choroidal Neovascular*"[MH] OR "Macula lutea"[MH] OR "Retinal drusen"[MH]	13,427
	#4	(neovascular[TIAB] OR exudative[TIAB]) AND degener*[TIAB]	5,926
	#5	(macul*[TIAB] OR retina*[TIAB] OR choroid*[TIAB] OR wet[TIAB]) AND (degener*[TIAB])	34,081
	#6	(macul*[TIAB] OR retina*[TIAB] OR choroid*[TIAB]) AND (neovasc*[TIAB])	15,245
	#7	maculopath*[TIAB] OR drusen*[TIAB]	6,757
	#8	macul*[TIAB] AND (lutea*[TIAB] OR syndrome[TIAB])	3,904
	#9	macul*[TIAB] AND dystroph*[TIAB]	2,523
	#10	((macul*[TIAB] OR geographic*[TIAB]) AND atroph*[TIAB])	4,318
	#11	choroid*[TIAB] AND polyp*[TIAB]	293
	#12	AMD[TIAB] OR ARMD[TIAB] OR wAMD[TIAB]	12,755
	#13	retina*[TIAB] AND angiomat*[TIAB] AND prolif*[TIAB]	345
	#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	81,069
	#15	acid mine drainage	1,371
	#16	#14 NOT #15	80,409
Interventions and Comparators	#17	Brolucizumab[TIAB] OR Brolucizumab[MH] OR esba1008[TIAB] OR dlx1008[TIAB]	10
	#18	Ranibizumab[TIAB] OR ranibizumab[MH] OR lucentis[TIAB] OR lucentis[MH] OR RG3645[TIAB]	4,367
	#19	bevacizumab[TIAB] OR bevacizumab[MH] OR Avastin[TIAB] OR Avastin[MH] OR "rhuMAb-VEGF"[TIAB]	16,798
	#20	Aflibercept[TIAB] OR aflibercept[MH] OR Eylea[TIAB] OR "BAY86-5321"[TIAB] OR pegaptanib[TIAB] OR pegaptanib[MH] OR macugen[TIAB] OR macugen[MH]	2,081
	#21	"Trap Eye*"[TIAB] OR Trap-Eye*[TIAB]	48
	#22	photochemotherapy[TIAB] OR photochemotherapy[MH] OR "photodynamic therapy"[TIAB] OR "photodynamic therap"[MH]	24,954
	#23	macul*[TIAB] AND surger*[TIAB]	6,892
	#24	verteporfin[TIAB] OR visudyne[TIAB]	1,394
	#25	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	51,294

PICOS Component	#	Search Terms	# of Hits
Study Type (modified SIGN Filters)	#26	Randomized Controlled Trials as Topic[MH]	126,879
	#27	randomized controlled trial[MH]	126,879
	#28	random allocation[MH]	99,279
	#29	single blind method[MH]	26,867
	#30	double blind method[MH]	151,662
	#31	Clinical trial[MH]	326,708
	#32	“clinical trial, phase I”[PT]	19,002
	#33	“clinical trial, phase II”[PT]	30,673
	#34	“clinical trial, phase III”[PT]	15,114
	#35	“clinical trial, phase IV”[PT]	1,713
	#36	“controlled clinical trial”[PT]	572,296
	#37	“randomized controlled trial”[PT]	484,042
	#38	“multicenter study”[PT]	251,487
	#39	“clinical trial”[PT]	828,093
	#40	Clinical trials as topic[MeSH Terms]	326,708
	#41	#26 OR #27 OR #28 OR # 29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	2,179,732
	#42	“clinical trial*”[TW]	682,313
	#43	“single blind*”[TW] OR “double blind*”[TW] OR “treble blind*”[TW] OR “triple blind*”[TW]	218,871
	#44	Placebos[MeSH]	34,368
	#45	Placebo*[TW]	218,975
	#46	“allocated random*”[TW]	0
	#47	#42 OR #43 OR #44 OR #45 OR #46	845,243
	#48	#41 OR #47	2,287,139
	#49	“case report”[TW]	290,698
	#50	Letter/	1,094,569
	#51	Historical article/	388,650
	#52	#49 OR #50 OR #51	1,757,151
	#53	#48 NOT #52	2,222,952
Disease, Treatments, Study Type	#54	#16 AND #25 AND #53	2,525
Remove Animal Studies	#55	animal/	6,590,420
	#56	human/	18,449,092
	#57	#55 NOT #56	4,350,511
	#58	#54 NOT #57	2,519
Limit to English	#59	English[Language]	25,121,063
	#60	#58 AND #59	2,288

Abbreviations: wAMD: wet age-related macular degeneration; SIGN: Scottish Intercollegiate Guidelines Network.

Table 75: Search terms for Cochrane Library via www.cochranelibrary.com
(Date of the search: 12/06/2019)

PICOS Component	#	Search Terms	# of Hits
Disease: wAMD	#1	MeSH descriptor: [Retinal Degeneration] this term only	25
	#2	MeSH descriptor: [Macular Degeneration] explode all trees	2,167
	#3	MeSH descriptor: [Retinal Neovascularization] this term only	76
	#4	MeSH descriptor: [Choroidal Neovascularization] this term only	374
	#5	MeSH descriptor: [Macula Lutea] explode all trees	405
	#6	maculopath*:ti,ab,kw	379
	#7	((macula* or retina* or "sub-retina*" or choroid*) adj3 (degener* or neovascula* or "neo-vascula*"))	110
	#8	(macula* adj3 lutea)	27
	#9	AMD OR wAMD OR wAMD	2,218
	#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	4,233
Interventions and Comparators	#11	MeSH descriptor: [Vascular Endothelial Growth Factor A] this term only and with qualifier(s): [antagonists & inhibitors - AI]	485
	#12	MeSH descriptor: [Angiogenesis Inhibitors] this term only	1021
	#13	MeSH descriptor: [Antibodies, Monoclonal, Humanized] this term only	2,715
	#14	MeSH descriptor: [Photosensitizing Agents] this term only	634
	#15	MeSH descriptor: [Phototherapy] this term only	764
	#16	MeSH descriptor: [Photochemotherapy] explode all trees	789
	#17	(brolucizumab OR esba1008 OR dlx1008):ti,ab,kw	26
	#18	(ranibizumab OR lucentris OR rg3645):ti,ab,kw	1,661
	#19	(bevacizumab OR avastin OR rhumab-vegf):ti,ab,kw	5,402
	#20	(afilbercept OR eylea OR "bay86-5321" OR pegaptanib):ti,ab,kw	250
	#21	(photochemotherapy OR "photodynamic therapy"):ti,ab,kw	2,235
	#22	(verteporfin OR visudyne):ti,ab,kw	425
	#23	(macul* adj2 surger*)	53
	#24	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	12,068
Disease, Treatments, Study Type	#25	#10 AND #24 with Cochrane Library publication date from Sep 2018 to Jun 2019, in Trials	246

Abbreviations: AI: antagonist & inhibitors; wAMD: wet age-related macular degeneration.

Hand searches

Details of the hand searches conducted are presented in Table 76.

Table 76: Hand searches

Hand Searches	URLs	Search Terms	Years
Congress proceedings			
American Society of Retina Specialist	https://www.asrs.org/	"Age-related macular degeneration" OR Brolucizumab OR bevacizumab, ranibizumab OR aflibercept OR macular surgery	2015-2019
The American Macular Degeneration Foundation	https://www.macular.org/	brolucizumab; bevacizumab; ranibizumab; aflibercept; macular surgery	2015-2019
European Society of Retina Specialists	http://www.euretina.org/	"Age-related macular degeneration"; brolucizumab; bevacizumab; ranibizumab; aflibercept; macular surgery	2015-2019
The Retina International World Congress of Ophthalmology	http://www.retina-international.org/	"age related macular degeneration" OR Brolucizumab OR bevacizumab OR ranibizumab OR aflibercept OR macular surgery	2015-2019
The Association for Research and Vision in Ophthalmology	https://www.arvo.org/	"Age-related macular degeneration" OR brolucizumab OR bevacizumab, ranibizumab OR aflibercept OR macular surgery	2015-2019
American Academy of Ophthalmology	https://www.aao.org/	"Age-related macular degeneration" OR brolucizumab OR bevacizumab, ranibizumab OR aflibercept OR macular surgery	2015-2019
The Royal Australian and New Zealand College of Ophthalmologists	https://ranzco.edu/	"Age-related macular degeneration"; brolucizumab; bevacizumab; ranibizumab; aflibercept; macular surgery	2015-2019
Asia-Australia Controversies in Ophthalmology	http://www.comtecmed.com/cophy/aa/2019/	"Age-related macular degeneration"; brolucizumab; bevacizumab; ranibizumab; aflibercept; macular surgery	2015-2019
The Royal College of Ophthalmologists	https://www.rcophth.ac.uk/	"Age-related macular degeneration" OR Brolucizumab OR bevacizumab, ranibizumab OR aflibercept OR macular surgery	2015-2019

Clinical Trial Registries			
U.S. National Library of Medicine	https://clinicaltrials.gov	Disease: "Age-related macular degeneration" Other terms: Brolucizumab OR bevacizumab, ranibizumab OR aflibercept OR macular surgery	2015-2019
EU Clinical Trials Register	https://www.clinicaltrialsregister.eu/		

Abbreviations: EU: European Union; URL: Uniform Resource Locator; U.S.: United States.

Data extraction

Once the screening of titles and abstracts and the full-text review of articles was completed, data extraction was undertaken. Tabular summary templates were prepared based on the research questions, and the following fields were extracted:

- Publication details including: title, authors, date of publication, journal, volume and reference page
- Study characteristics including: objective, interventions (i.e. dose and regimen), blinding, sample size, length of follow-up, treatment duration, allowed concomitant therapies, primary and secondary endpoints, country/location, statistical methods of data analysis, relevant biases
- Patients' characteristics including: age, sex, race, smoking status, details of the intervention/comparator arms (i.e. including drug name and dose), medical history, treatment history and average disease duration
- Details of the results of interest (e.g. visual acuity outcomes, structural changes and any anatomical outcomes, etc.)

The risk of bias was also assessed in the included fields, using the Cochrane Risk of Bias Tool. The tabular summary was developed in Microsoft Excel®. An independent reviewer undertook the quality check of the data extraction by reviewing 20% of the extracted articles.

Quality assessment

In order to assess the quality of clinical trials, the list of assessment questions provided by Cochrane was used.[88]

Included studies

An overview of the trials included in the SLR is provided in Table 77. A total of 48 publications reporting on 38 RCTs were extracted for four treatments: ranibizumab, aflibercept, brolucizumab, and PDT.

Forty-five unique therapeutic regimens were identified, and the most commonly included treatment was ranibizumab 0.5 mg (monthly injections). All trials were head-to-head trials, except two trials that compared active treatments to sham IVT. Most of the trials (22/38) were double blind and eight included patients for open-label analysis. Results at one year were evaluated at either 48, 52 or 54 weeks. At two years, most studies (13/18) reported results at 104 weeks and four reported results at 96 weeks. In addition, one study had a time of assessment of nine months.

Table 77: Overview of the trials included in the SLR

Trial ID	Author, year	Time of assessment (months)	Trial name	Sample size (ITT)	Phase	Blinding status	Intervention	Comparator
1	**Dugel 2017**	12	OSPREY	90	2	Double-blind	LP → Bro 6q8w → q12w	LP → Afli 2q8w
2	**Dugel 2019**	96 weeks	HARRIER	743	3	Double-blind	LP → Bro 6q12/q8w	LP → Afli 2q8w
3	**Dugel 2019**	96 weeks	HAWK	1078	3	Double-blind	LP → Bro 3q12/q8w LP → Bro 6q12/q8w	LP → Afli 2q8w
4	**Martin 2011 / Martin 2012**	12/24	CATT	1143	NR	Single-blind	Rani 0.5q4w Rani 0.5PRN	Bev 1.25q4w Bev 1.25 PRN
5	**Eldem 2015**	12	SALUTE	77	4	Open-label	LP→ Rani 0.5mg PRNX	LP→ Rani 0.5mg PRN
6	**Feltgen 2017**	12	RABIMO	40	4	Open-label	LP → Rani 0.5q8w	LP → Rani 0.5PRN
7-8	**Heier 2012**	12	VIEW 1/VIEW 2	2412	3	Double-blind	Afli 0.5q4w Afli 2q4w LP → Afli 2q8w	Rani 0.5q4w
7-8	**Yuzawa 2015**	12	VIEW 1/VIEW 2	1202	3	Double-blind	LP → Afli 2q8w	Rani 0.5q4w
7-8	**Schmidt-Erfurth 2014**	96 weeks	VIEW 1/VIEW 2 (Combined)	1217	3	Double-blind	Afli 0.5q4w→PRN Afli 2q4w→PRN LP → Afli 2q8w→PRN	Rani 0.5q4w→PRN
9	**Ho 2014**	24	HARBOR	1089	3	Double-blind	Rani 0.5q4w Rani 2q4w	LP → Rani 0.5PRN LP → Rani 2PRN
10	**Gillies 2019/Hunyor 2018**	12/24	RIVAL	278	3	Double-blind	LP → Rani 0.5TREX	LP → Afli 2TREX
11	**Kertes 2019**	24	CAN-TREAT	580	NR	Open-label	LP → Rani 0.5TREX	Rani 0.5q4w
12	**Regillo 2008**	12	PIER	184	3b	Double-blind	LP → Rani 0.5q12w LP → Rani 0.3q12w	Sham IVT

Trial ID	Author, year	Time of assessment (months)	Trial name	Sample size (ITT)	Phase	Blinding status	Intervention	Comparator
13	**Rosenfeld 2006/ Chang 2007**	24	MARINA	716	3	Double-blind	Rani 0.5q4w Rani 0.3q4w	Sham IVT
14	**Silva 2017**	12	TREND	650	3b	Single-blind	LP → Rani 0.5TREX	Rani 0.5q4w
15	**Wykoff 2015 / Wykoff 2017**	12/24	TREX-AMD	60	3b	Open-label	LP → Rani 0.5TREX	Rani 0.5q4w
16	**Antoszyk 2007**	24	FOCUS	162	1/2	Single-blind	Vert PDT monthly	Rani 0.5q4w
17	**Berg 2015 / Berg 2016**	12/24	LUCAS	441	NR	Double-blind	Bev 1.25TREX	LP → Rani 0.5TREX
18	**Boyer 2009**	12	SAILOR	2378	3b	Single-blind	LP → Rani 0.3 PRN	LP → Rani 0.5 PRN
19	**Brown 2009/ Bressler 2009/2013**	24	ANCHOR	423	3	Double-blind	Vert PDT PRN	Rani 0.3q4w Rani 0.5q4w
20	**Campochiaro 2019**	9	Ladder	220	2	Open-label	PDS + Rani 10PRN, 40PRN, 100PRN	Rani 0.5q4w
21	**Guymer 2019**	24	FLUID	349	4	Single-blind	LP → Rani 0.5TREX (relaxed)	LP → Rani 0.5TREX (intensive)
22	**Hatz 2015**	12	NR	40	3	Double-blind	Vert PDT + Rani 0.3PRN	LP → Rani 0.3PRN
23	**Heier 2011**	12	CLEAR-IT 2	157	2	Double-blind	LP (w0-12) → Afli 0.5PRN LP (w0-12) → Afli 2PRN	LP (q12, w0-12) → Afli 0.5PRN LP (q12, w0-12) → Afli 2PRN LP (q12, w0-12) → Afli 4PRN
24	**Kaiser 2012**	12	DENALI	286	3b	Double-blind	Vert PDT + Rani 0.5q4w	Rani 0.5q4w

Trial ID	Author, year	Time of assessment (months)	Trial name	Sample size (ITT)	Phase	Blinding status	Intervention	Comparator
25	**Kodjikian 2013**	12	GEFAL	501	NR	Double-blind	LP → Bev 1.25PRN	LP → Rani 0.5PRN
26	**Krebs 2013 (1)**	12	NR	44	NR	Single-blind	Vert PDT + Rani 0.5q4w	Rani 0.5q4w
27	**Krebs 2013 (2)**	12	NR	317	NR	Double-blind	LP → Bev 1.25PRN	LP → Rani 0.5PRN
28	**Larsen 2012**	12	MONT BLANC	255	2	Double-blind	Vert PDT + Rani 0.5q4w	Rani 0.5q4w
29	**Li 2017**	12	SIGHT	304	3	Double-blind	LP → Afli 2q8w	Vert PDT PRN
30	**Mori 2017**	12	NR	58	NR	NR	LP → Afli PRN	LP → Afli q8w
31	**Nunes 2019**	12	NR	45	NR	Open-label	LP → Bev 1.25PRN LP (q2w) → Bev 1.25PRN	LP → Rani 0.5PRN
32	**Schauwvliegh e 2016**	12	BRAMD	327	NR	Double-blind	Bev 1.25q4w	Rani 0.5q4w
33	**Schmidt-Erfurth 2011**	12	EXCITE	233	3b	Double-blind	LP → Rani 0.3q12w	LP → Rani 0.5q12w Rani 0.3q4w
34	**Scholler 2014**	12	NR	55	NR	Open-label	LP → Rani 0.5PRN	LP → Bev 1.25PRN
35	**Subramanian 2010**	24	NR	22	NR	Double-blind	Bev 1.25q4w	Rani
36	**Söderberg 2012**	24	NR	92	NR	Double-blind	LP → Rani 0.5PRN	TTT + Rani 0.5PRN
37	**Tano 2010/2011**	12/24	EXTEND-I	76	1/2	Open-label	Rani 0.3q4w	Rani 0.5q4w
38	**Weingessel 2015**	12	NR	34	NR	NR	Vert PDT + Rani 0.5PRN	LP → Rani 0.5PRN

Abbreviations: Afli: aflibercept; Bev: bevacizumab; Bro: brolucizumab; IVT: intravitreal; LP: loading phase of three initial monthly injections; NR: not reported; Vert PDT: verteporfin photodynamic therapy; PRN: pro re nata dosing regimen; PRNX: PRN and extend dosing interval; qXw: one injection every X weeks; Rani: ranibizumab; TREX: treat-and-extend dosing interval; TTT: transpupillary thermotherapy.

Excluded publications

Table 78: Publications excluded from the narrative review, with reasons for exclusion

Publication	Author, year	Reason for exclusion
1	Bressler, 1999	Ineligible study design
2	Bressler, 2001	Ineligible study design
3	Verteporfin in Photodynamic Therapy Study Group, 2001	Ineligible study design
4	Mellish, 2001	Ineligible study design
5	Bressler, 2002	Ineligible outcomes
6	Rubin, 2002	Ineligible study design
7	Blumenkranz, 2002	Ineligible study design
8	Gragoudas, 2004	Ineligible intervention
9	Sivaprasad, 2004	Ineligible study design
10	Hawkins, 2004	Ineligible study design
11	Boyer, 2005	Ineligible intervention
12	Frennesson, 2005	Ineligible study design
13	Mieler, 2005	Ineligible intervention
14	D'Amico, 2005	Ineligible intervention
15	Heier, 2006	Duplicate
16	Brown, 2006	Duplicate
17	Chang, 2006	Duplicate
18	Suner, 2006	Ineligible outcome
19	Zlateva, 2006	Ineligible intervention
20	Chakravarthy, 2006	Ineligible study design
21	Gelisken, 2007	Ineligible study design
22	Lüke, 2007	Ineligible study design
23	Lanzetta, 2007	Duplicate
24	Ciulla, 2007	Duplicate
25	Modarres, 2007	Ineligible intervention
26	Chang, 2007	Duplicate
27	Suner, 2007	Duplicate
28	Odergren, 2008	Ineligible intervention
29	Singermen, 2008	Ineligible outcome
30	Jabbour, 2008	Not found
31	Tano, 2008	Ineligible intervention
32	Ho, 2008	Ineligible outcome
33	Regillo, 2008	Not found
34	Marcus, 2008	Ineligible intervention
35	Michels, 2008	Ineligible outcome
36	Win, 2008	Duplicate
37	Tano, 2008	Duplicate
38	Stifter, 2008	Ineligible intervention
39	Lüke, 2009	Ineligible study design
40	Kaiser, 2009	Ineligible intervention
41	Costagliola, 2010	Ineligible intervention
42	Odergren, 2010	Ineligible intervention

Publication	Author, year	Reason for exclusion
43	Sadda, 2010	Ineligible outcome
44	Vallance, 2010	Ineligible study design
45	Barbazetto, 2010	Ineligible study design
46	Tufail, 2010	Ineligible intervention
47	Abraham, 2010	Ineligible study design
48	Han, 2010	Ineligible study design
49	Lim, 2012	Ineligible population
50	Chakravarthy, 2012	Ineligible intervention
51	El-Mollayess, 2012	Ineligible outcomes
52	Singer, 2012	Ineligible study design
53	Li, 2012	Ineligible intervention
54	Menon, 2013	Ineligible intervention
55	Datseris, 2013	Ineligible intervention
56	Bressler, 2013	Ineligible study design
57	Chakravarthy, 2013	Ineligible outcomes
58	Busbee, 2013	Duplicate
59	Wykoff, 2013	Ineligible study design
60	Mayr-Spooner, 2013	Ineligible outcome
61	Lushchyk, 2013	Ineligible intervention
62	Ying, 2014	Ineligible outcome
63	Marcus, 2014	Duplicate
64	Schauwvlieghe, 2014	Duplicate
65	Waldstein, 2014	Ineligible outcome
66	Feltgen, 2014	Duplicate
67	Mahmood, 2015	Ineligible intervention
68	Barikian, 2015	Ineligible study design
69	Ogura, 2015	Ineligible outcome
70	Wykoff, 2015	Duplicate
71	Saviano, 2016	Ineligible study design
72	Maguire, 2016	Ineligible study design
73	Moshfeghi, 2016	Duplicate
74	Kertes, 2016	Duplicate
75	Ng, 2016	Ineligible study design
76	Yannuzzi, 2017	Duplicate
77	Silva, 2017	Duplicate
78	Kolar, 2017	Ineligible outcome
79	Gillies, 2017	Duplicate
80	Mones, 2017	Duplicate
81	Silva, 2017	Duplicate
82	Ohnaka, 2017	Ineligible population
83	Martin, 2017	Ineligible outcome
84	Wykoff, 2017	Duplicate
85	Haga, 2018	Ineligible population
86	Wykoff, 2018	Ineligible outcome
87	Figurska, 2018	Ineligible intervention
88	Rogers, 2018	Ineligible outcome

Publication	Author, year	Reason for exclusion
89	Kodjikian, 2018	Ineligible intervention
90	Gillies, 2018	Duplicate
91	Ho, 2018	Ineligible outcome
92	Euctr, 2018	Ineligible intervention
93	Hunyor, 2018	Duplicate
94	Am, 2018	Duplicate
95	Trivedi, 2018	Ineligible outcome
96	Daniel, 2019	Ineligible outcome
97	Semeraro, 2019	Ineligible intervention
98	Jaffe, 2019	Ineligible outcome
99	Amarakoon, 2019	Ineligible intervention

7.3 HAWK and HARRIER trials

Safety outcomes (Baseline to Week 48)

Further adverse event data from Baseline to Week 48 from the HAWK and HARRIER trials are presented in this section.

Table 79: Extent of exposure to study treatment: number of active injections from Baseline to Week 48 (SAF)

Trial name	HAWK			HARRIER	
Extent of exposure	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Number of injections – n (%)					
Total	358	360	360	370	369
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	3 (0.8)	8 (2.2)	1 (0.3)	2 (0.5)
2	3 (0.8)	4 (1.1)	3 (0.8)	2 (0.5)	3 (0.8)
3	8 (2.2)	9 (2.5)	6 (1.7)	11 (3.0)	6 (1.6)
4	7 (2.0)	8 (2.2)	14 (3.9)	2 (0.5)	2 (0.5)
5	21 (5.9)	12 (3.3)	7 (1.9)	6 (1.6)	5 (1.4)
6	195 (54.5)	215 (59.7)	29 (8.1)	203 (54.9)	17 (4.6)
7	124 (34.6)	109 (30.3)	293 (81.4)	145 (39.2)	333 (90.2)
8	-	-	-	0 (0.0)	1 (0.3)
Descriptive statistics					
N	358	360	360	370	369
Mean (SD)	6.1 (0.89)	6.1 (1.02)	6.5 (1.25)	6.2 (0.89)	6.8 (0.87)
Median	6.0	6.0	7.0	6.0	7.0
Min, Max	2, 7	1, 7	1, 7	1, 7	1, 8

Abbreviations: SAF: safety analysis set; SD: standard deviation.
Source: HAWK CSR;[24] HARRIER CSR.[25]

Table 80: Ocular adverse events up to Week 48 (greater than or equal to 2% in any treatment group) by preferred term for the study eye (SAF)

Trial name	HAWK			HARRIER	
Preferred term	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Number of patients with at least one event	175 (48.9)	179 (49.7)	170 (47.2)	122 (33.0)	119 (32.2)
Conjunctival haemorrhage	30 (8.4)	23 (6.4)	20 (5.6)	7 (1.9)	12 (3.3)
VA reduced	23 (6.4)	19 (5.3)	24 (6.7)	20 (5.4)	20 (5.4)
Vitreous floaters	24 (6.7)	18 (5.0)	11 (3.1)	11 (3.0)	3 (0.8)
Eye pain	21 (5.9)	16 (4.4)	15 (4.2)	10 (2.7)	12 (3.3)
Dry eye	11 (3.1)	14 (3.9)	15 (4.2)	8 (2.2)	6 (1.6)
Retinal haemorrhage	10 (2.8)	13 (3.6)	16 (4.4)	5 (1.4)	2 (0.5)
Retinal pigment epithelial tear	5 (1.4)	12 (3.3)	4 (1.1)	6 (1.6)	4 (1.1)
Vitreous detachment	16 (4.5)	10 (2.8)	13 (3.6)	7 (1.9)	5 (1.4)
Eye irritation	8 (2.2)	10 (2.8)	8 (2.2)	3 (0.8)	1 (0.3)
Intraocular pressure increased	11 (3.1)	9 (2.5)	8 (2.2)	12 (3.2)	9 (2.4)
Posterior capsule opacification	5 (1.4)	9 (2.5)	7 (1.9)	5 (1.4)	1 (0.3)
Uveitis	5 (1.4)	8 (2.2)	1 (0.3)	3 (0.8)	0 (0.0)
Blepharitis	4 (1.1)	8 (2.2)	7 (1.9)	8 (2.2)	3 (0.8)
Iritis	1 (0.3)	8 (2.2)	0 (0.0)	0 (0.0)	1 (0.3)
Cataract	10 (2.8)	7 (1.9)	8 (2.2)	4 (1.1)	12 (3.3)
Visual field defect	7 (2.0)	7 (1.9)	3 (0.8)	1 (0.3)	0 (0.0)
Vision blurred	11 (3.1)	6 (1.7)	5 (1.4)	1 (0.3)	2 (0.5)
Visual impairment	10 (2.8)	6 (1.7)	10 (2.8)	0 (0.0)	2 (0.5)

Punctate keratitis	5 (1.4)	6 (1.7)	8 (2.2)	1 (0.3)	3 (0.8)
Corneal abrasion	5 (1.4)	5 (1.4)	8 (2.2)	0 (0.0)	1 (0.3)
Conjunctivitis	2 (0.6)	7 (1.9)	3 (0.8)	10 (2.7)	3 (0.8)
Lenticular opacities	6 (1.7)	0 (0.0)	3 (0.8)	8 (2.2)	7 (1.9)

Abbreviations: SAF: safety analysis set.
Source: Dugel et al. 2019.[27]

Table 81: Non-ocular adverse events up to Week 48 (≥2% in any treatment group) by preferred term for the study eye (SAF)

Trial name	HAWK			HARRIER	
Preferred term	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Number of patients with at least one event	242 (67.6)	232 (64.4)	258 (71.7)	219 (59.2)	211 (57.2)
Nasopharyngitis	30 (8.4)	25 (6.9)	33 (9.2)	25 (6.8)	16 (4.3)
Urinary tract infection	26 (7.3)	19 (5.3)	25 (6.9)	10 (2.7)	9 (2.4)
Pneumonia	5 (1.4)	14 (3.9)	13 (3.6)	-	-
Influenza	8 (2.2)	13 (3.6)	8 (2.2)	10 (2.7)	15 (4.1)
Hypertension	24 (6.7)	12 (3.3)	14 (3.9)	17 (4.6)	13 (3.5)
Cough	10 (2.8)	9 (2.5)	6 (1.7)	-	-
Bronchitis	9 (2.5)	9 (2.5)	8 (2.2)	19 (5.1)	15 (4.1)
Upper respiratory tract infection	8 (2.2)	9 (2.5)	7 (1.9)	3 (0.8)	11 (3.0)
Arthralgia	7 (2.0)	9 (2.5)	10 (2.8)	10 (2.7)	8 (2.2)
Nausea	7 (2.0)	9 (2.5)	9 (2.5)	-	-
Diarrhoea	5 (1.4)	9 (2.5)	8 (2.2)	8 (2.2)	3 (0.8)
Sinusitis	10 (2.8)	8 (2.2)	7 (1.9)	-	-
Pain in extremity	7 (2.0)	8 (2.2)	6 (1.7)	-	-
Arthritis	2 (0.6)	8 (2.2)	10 (2.8)	-	-

Chronic obstructive pulmonary disease	2 (0.6)	8 (2.2)	8 (2.2)	-	-
Back pain	14 (3.9)	7 (1.9)	10 (2.8)	8 (2.2)	13 (3.5)
Headache	7 (2.0)	7 (1.9)	11 (3.1)	-	-
Constipation	4 (1.1)	7 (1.9)	8 (2.2)	-	-
Atrial fibrillation	7 (2.0)	6 (1.7)	10 (2.8)	-	-
Anaemia	7 (2.0)	5 (1.4)	8 (2.2)	-	-
Anxiety	9 (2.5)	4 (1.1)	6 (1.7)	-	-
Osteoarthritis	7 (2.0)	4 (1.1)	5 (1.4)	-	-
Gastroesophageal reflux disease	7 (2.0)	4 (1.1)	1 (0.3)	-	-
Fall	8 (2.2)	3 (0.8)	4 (1.1)	-	-
Blood urea increased	7 (2.0)	1 (0.3)	4 (1.1)	-	-
Cystitis	-	-	-	12 (3.2)	4 (1.1)
Hypercholesterolaemia	-	-	-	8 (2.2)	3 (0.8)

Abbreviations: SAF: safety analysis set.
Source: HAWK CSR;[24] HARRIER CSR;[25] Dugel et al. 2019.[27]

Table 82: Serious ocular adverse events up to Week 48 by preferred term for the study eye (SAF)

Trial name	**HAWK**			**HARRIER**	
Preferred term	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Number of patients with at least one event	5 (1.4)	11 (3.1)	3 (0.8)	9 (2.4)	4 (1.1)
Endophthalmitis	3 (0.8)	2 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)
Uveitis	1 (0.3)	2 (0.6)	0 (0.0)	3 (0.8)	0 (0.0)
Retinal detachment	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
VA reduced	0 (0.0)	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)
Macular hole	0 (0.0)	1 (0.3)	1 (0.3)	-	-
Cataract	0 (0.0)	1 (0.3)	0 (0.0)	-	-

Retinal artery thrombosis	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Retinal depigmentation	0 (0.0)	1 (0.3)	0 (0.0)	-	-
Retinopathy proliferative	0 (0.0)	1 (0.3)	0 (0.0)	-	-
Virtutis	0 (0.0)	1 (0.3)	0 (0.0)	-	-
Retinal artery occlusion	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Retinal pigment epithelial tear	-	-	-	2 (0.5)	0 (0.0)
Anterior chamber inflammation	-	-	-	1 (0.3)	0 (0.0)
Cataract traumatic	-	-	-	1 (0.3)	0 (0.0)
Retinal artery embolism	-	-	-	1 (0.3)	0 (0.0)
Dry age-related macular degeneration	-	-	-	0 (0.0)	1 (0.3)

Abbreviations: SAF: safety analysis set.
Source: Dugel et al. 2019.[27]

Table 83: Serious non-ocular adverse events up to Week 48 (≥3 patients in any treatment group) by preferred term (SAF)

Trial name	HAWK			HARRIER	
Preferred term	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Number of patients with at least one event	47 (13.1)	47 (13.1)	68 (18.9)	35 (9.5)	43 (11.7)
Pneumonia	3 (0.8)	4 (1.1)	5 (1.4)	0 (0.0)	3 (0.8)
Cerebrovascular accident	2 (0.6)	4 (1.1)	2 (0.6)	0 (0.0)	2 (0.5)
Atrial fibrillation	2 (0.6)	3 (0.8)	2 (0.6)	-	-
Sepsis	0 (0.0)	3 (0.8)	0 (0.0)	-	-
Chronic obstructive pulmonary disease	0 (0.0)	2 (0.6)	3 (0.8)	-	-
Coronary artery disease	3 (0.8)	1 (0.3)	2 (0.6)	-	-

Subdural haematoma	0 (0.0)	0 (0.0)	3 (0.8)	-	-
Cholecystitis acute	-	-	-	2 (0.5)	0 (0.0)
Gastroenteritis	-	-	-	2 (0.5)	0 (0.0)
Pulmonary oedema	-	-	-	2 (0.5)	0 (0.0)
Rectal haemorrhage	-	-	-	2 (0.5)	0 (0.0)
Cardiac failure	-	-	-	1 (0.3)	2 (0.5)
Syncope	-	-	-	1 (0.3)	2 (0.5)

Abbreviations: SAF: safety analysis set.
Source: HAWK CSR;[24] HARRIER CSR;[25] Dugel et al. 2019.[27]

Table 84: Deaths, SAE or AE leading to permanent study treatment discontinuation up to Week 48 (SAF)

Trial name	HAWK			HARRIER	
Patients with serious or significant AE	**Brolucizumab 3 mg, (N=358) n (%)**	**Brolucizumab 6 mg, (N=360) n (%)**	**Aflibercept 2 mg, (N=360) n (%)**	**Brolucizumab 6 mg, (N=370) n (%)**	**Aflibercept 2 mg, (N=369) n (%)**
Death	4 (1.1)	4 (1.1)	6 (1.7)	3 (0.8)	4 (1.1)
SAE	52 (14.5)	59 (16.4)	72 (20.0)	44 (11.9)	46 (12.5)
Study eye	5 (1.4)	11 (3.1)	3 (0.8)	9 (2.4)	4 (1.1)
Fellow eye	0 (0.0)	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)
Non-ocular	47 (13.1)	47 (13.1)	68 (18.9)	35 (9.5)	43 (11.7)
AE leading to permanent study treatment discontinuation	11 (3.1)	12 (3.3)	17 (4.7)	12 (3.2)	4 (1.1)
Study eye	10 (2.8)	9 (2.5)	10 (2.8)	8 (2.2)	4 (1.1)
Fellow eye	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-ocular	1 (0.3)	3 (0.8)	7 (1.9)	4 (1.1)	0 (0.0)

Abbreviations: AE: adverse event; SAE: serious adverse event**;** SAF: safety analysis set.
Source: HAWK CSR;[24] HARRIER CSR;[25] Dugel et al. 2019.[27]

7.4 OSPREY Trial

The phase II OSPREY trial also compared brolucizumab 6 mg with aflibercept 2 mg and provides supportive evidence of the efficacy and safety of brolucizumab in this indication.

Baseline demographics and characteristics

Baseline demographics and disease characteristics of the patients included in the OSPREY trial are presented in Table 85.

The demographic and disease characteristics of patients were similar between treatment arms. The mean age of patients included in OSPREY was 78.0 (brolucizumab 6 mg: 78.8; aflibercept 2 mg: 77.3), with majority being ≥75 years old (68.6%) at the time of study entry. A greater percentage of the patients were female than male (59.6%), and the patients were predominantly white (96.6%). The majority of the patients had unilateral wAMD (78.7) with occult CNV lesions (28.1%) at Baseline.

Table 85: Baseline characteristics of patients in the OSPREY trial (FAS)

Trial name	OSPREY	
Characteristic	**Brolucizumab 6 mg (n=44)**	**Aflibercept 2 mg (n=45)**
Age (years)		
Mean (SD)	78.8 (9.7)	77.3 (9.1)
Median (range)	80.0	79.0
Min–Max	(58, 96)	(55, 92)
Age category (years) – n (%)		
<65	6 (13.6)	6 (13.3)
65-74	6 (13.6)	10 (22.2)
75-84	19 (43.2)	18 (40.0)
≥85	13 (29.5)	11 (24.4)
Gender – n (%)		
Male	16 (36.4)	20 (44.4)
Female	28 (63.6)	25 (55.6)
Race – n (%)		
White	42 (95.5)	44 (97.8)
Black or African American	1 (2.3)	0 (0.0)
Asian	1 (2.3)	1 (2.2)
Ethnicity – n (%)		
Hispanic/Latino	0 (0.0)	1 (2.2)
Not Hispanic or Latino	44 (100.0)	44 (97.8)
Laterality – n (%)		
Unilateral AMD	32 (72.7)	38 (84.4)
Bilateral AMD	12 (27.3)	7 (15.6)
Study Eye – n (%)		
Right eye	18 (40.9)	16 (35.6)
Left eye	26 (59.1)	29 (64.4)

Time since diagnosis (Days)		
Mean (SD)	14.0 (9.3)	16.9 (10.7)
Median	12.0	14.0
(Min, Max)	(4, 48)	(3, 61)
Time since diagnosis categories – n (%)		
≤30 days	42 (95.5)	42 (93.3)
>30 days	2 (4.5)	3 (6.7)
BCVA (Letters)		
Mean (SD)	54.1 (13.9)	55.6 (12.3)
Median	59.0	56.0
(Min, Max)	(25, 72)	(24, 72)
BCVA categories – n (%)		
<55 letters	16 (36.4)	15 (33.3)
≥55 letters	28 (63.6)	30 (66.7)
OCT type – n (%)		
Cirrus	13 (29.5)	19 (42.2)
Spectralis	31 (70.5)	26 (57.8)
CSFT (µm)		
Mean (SD)	490.1 (149.2)	495.7 (144.6)
Median	472.0	476.0
(Min, Max)	(241, 926)	(231, 907)
CSFT categories, n (%)		
<400µm	12 (27.3)	14 (31.1)
≥400µm	32 (72.7)	31 (68.9)
Presence of intraocular haemorrhage – n (%)		
Yes	14 (31.8)	18 (40.0)
No	30 (68.2)	27 (60.0)
Lesion type – n (%)		
Predominantly classic	21 (47.7)	23 (51.1)
Minimally classic	12 (27.3)	8 (17.8)
Occult	11 (25.0)	14 (31.1)
Foveal Involvement – n (%)		
Subfoveal CNV	44 (100)	45 (100)
Hyperreflective Material – n (%)		
Yes	37 (84.1)	38 (84.4)
No	7 (15.9)	7 (15.6)
SRF, n (%)		
Yes	40 (90.9)	40 (88.9)
No	4 (9.1)	5 (11.1)
IRF - Cystoid Oedema, n (%)		
Yes	38 (86.4)	38 (84.4)

No	6 (13.6)	7 (15.6)

Abbreviations: BCVA: best-corrected visual acuity; CSFT: central subfield thickness; CNV: choroidal neovascularisation; FAS: full analysis set; IRF: intraretinal fluid; OCT: optical coherence tomography; SD: standard deviation; SRF: subretinal fluid.
Source: OSPREY CSR;[105] Dugel et al. 2017.[50]

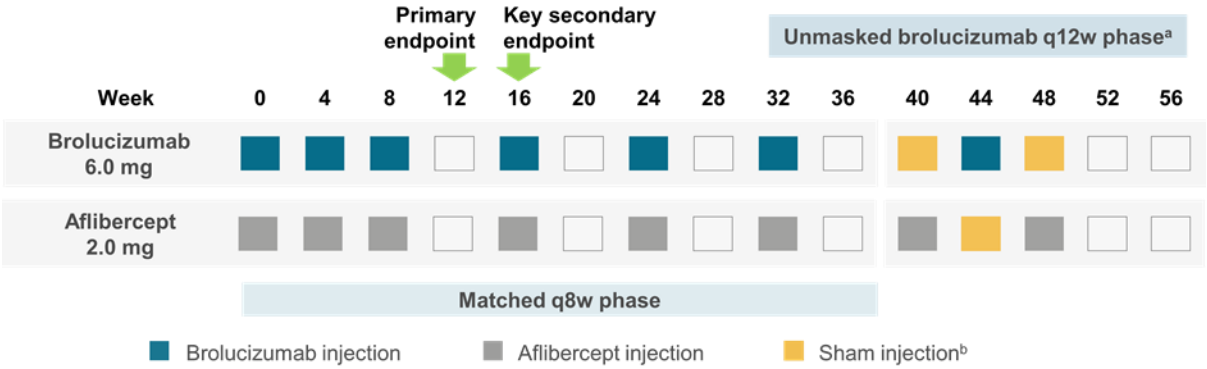
Trial design and methodology

The OSPREY trial (NCT01796964) was a prospective, randomised, double-masked, multicentre, two-arm, phase II study comparing the efficacy and safety of brolucizumab versus aflibercept in patients with wAMD.

Enrolled participants were randomised in 1:1 ratio using a web-based interactive response technology system to receive either brolucizumab 6 mg or aflibercept 2 mg via intravitreal injection. For masking purposes, sham treatment was administered when necessary, as described below.

A schematic of the study design of the OSPREY trial is presented in Figure 48.

Figure 48: OSPREY trial design



[a]Only the assessing physicians were unmasked from Week 40 onwards; the BCVA and photographic technicians remained masked; [b]Investigators were allowed to administer the injection from Week 40 onwards, so masking may have been incomplete.
Abbreviations: IVT: intravitreal; qXw: one injection every X weeks.
Source: Dugel *et al.* (2017);[50] OSPREY CSR.[105]

The trial consisted of three treatment periods. In the first period, loading doses of the study drug were administered at Baseline and at Weeks 4 and 8, with a corresponding efficacy assessment at Week 12. The second period included three matching q8w dosing cycles (at Weeks 16, 24, and 32) for both treatment groups, with a corresponding assessment period up to Week 40 (8 weeks after the last q8w dose administration in both treatment arms). During the third period up to Week 56, participants in the brolucizumab group received only one additional treatment at Week 44, extending the final q8w dosing cycle to a q12w dosing cycle, and a second q12w cycle was completed at Week 56; participants on aflibercept continued on a q8w cycle, with treatments at Weeks 40 and 48. To preserve masking during Weeks 40 through 48, both groups had appropriately timed sham injections. At study visits when no active treatment was scheduled, the masked Investigator could provide an unscheduled treatment with the participant's assigned treatment if the Investigator determined it was medically necessary and after confirmation with the sponsor. At visits with potential sham injections, the Investigator also had the option to apply an active treatment instead of a scheduled sham treatment based on medical need.

An overview of the methodology of the OSPREY trial is presented in Table 86.

Table 86: Summary of the trial methodology of the OSPREY trial

Trial name	**OSPREY**

Locations	41 investigational centres across USA
Trial design	A prospective, randomised, double-masked, multicentre, two-arm, phase II study comparing the efficacy and safety of brolucizumab versus aflibercept in patients with wAMD
Eligibility criteria for participants	A summary of the key inclusion and exclusion criteria is provided below: **Key inclusion criteria** • Patients 50 years of age or older at time of screening • Untreated and active CNV lesion due to AMD in the study eye • Confirmed evidence of leakage on FA and subretinal, intraretinal, or subretinal pigment epithelium fluid as assessed by SD-OCT in the study eye • Total area of CNV (including both classic and occult components) must have comprised >50% of the total lesion area in the study eye • Subretinal blood, if present, must have spared the fovea and must have been ≤ 50% of the lesion in the study eye • A BCVA, using ETDRS testing, between 73 and 23 letters, inclusive in the study eye • Patient's fellow eye must have had a BCVA of 20 letters **Key exclusion criteria** • Any active intraocular or periocular infection or active intraocular inflammation in either eye at Baseline • Any approved or investigational treatment for exudative AMD in the study eye • Any current or history of macular or retinal disease other than exudative AMD in the study eye • Any serous pigment epithelial detachment under the foveal centre or RPE tear/rip in the study eye • Current vitreous haemorrhage or a history of rhegmatogenous retinal detachment Full details of the inclusion and exclusion criteria are listed in the OSPREY CSR
Method of study drug administration	Brolucizumab and aflibercept were administered as intravitreal injection **Dosing and number of patients** • Brolucizumab 6 mg (n=44) • Aflibercept 2 mg (n=45) **Loading dose (3 monthly doses)** • Brolucizumab 6 mg (Day 0, Week 4, and Week 8) • Aflibercept 2 mg (Day 0, Week 4, and Week 8) **Maintenance regimen** • Brolucizumab 6 mg q8w/q12w (q8w doses Week 16, Week 24 and Week 32, q12w dose Week 44) • Aflibercept 2 mg q8w
Permitted and disallowed concomitant medication	• Study eye: use of intra or periocular within 90 days of screening or at any time during the study • Study eye: use of topical ocular corticosteroids for 30, or more, consecutive days within 90 days prior to screening

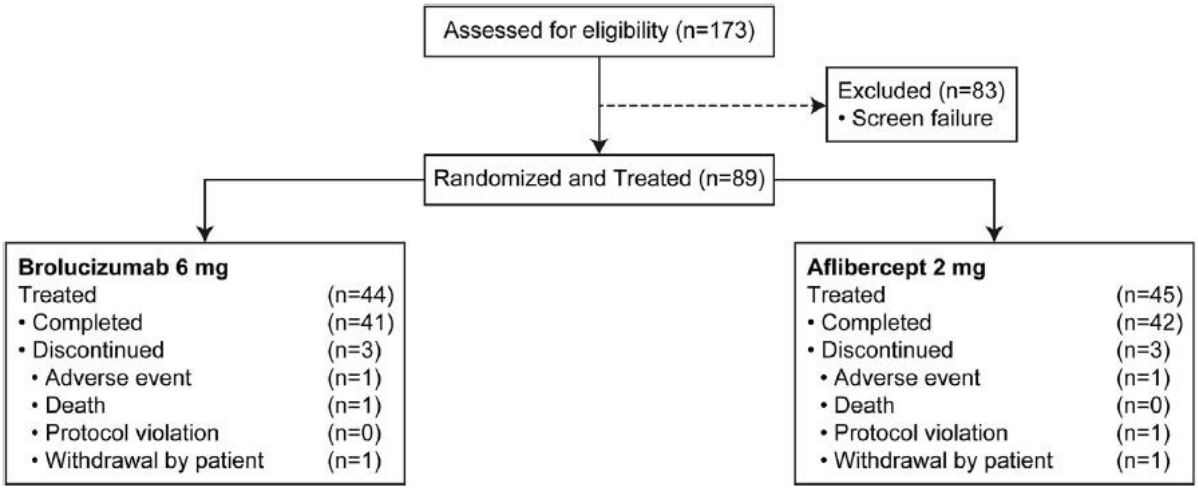
	• Study eye: previous therapeutic radiation in the region of the study eye • Fellow eye: treatment with unapproved or investigational VEGF medication within four weeks of screening • Systemic: use of systemic corticosteroids for 30 or more consecutive days within 90 days prior to screening visit
Primary outcome	• The primary objective was to demonstrate that brolucizumab is non-inferior to aflibercept with respect to the BCVA change from Baseline at Week 12
Secondary and other outcomes	**Key secondary objectives** • To demonstrate that brolucizumab is non-inferior to aflibercept with respect to the BCVA change from Baseline at Week 16 **Other secondary objectives** • BCVA change from Baseline by visit • Average BCVA change from Baseline over the periods of Week 4 to Week 16, Week 4 to Week 24, Week 4 to Week 40, and Week 4 to Week 56 • Average BCVA change from Week 12 over the periods of Week 16 to Week 24, Week 16 Week 40, and Week 16 to Week 56 • One-month BCVA changes following no treatment for 1-month • One-month BCVA changes following treatment by visit • Two-months BCVA changes following no treatment for 1 month in brolucizumab treatment group • CSFT change from Baseline by visit
Pre-planned subgroups	• Age category (<75 years and ≥75 years) • Sex (male and female) • Baseline BCVA categories (≤55 and ≥55) • Baseline CSFT category (<400 and ≥400 µm) • Baseline lesion type (predominantly classic, minimally classic/occult) • Baseline foveal involvement (subfoveal CNV and extrafoveal CNV)
Duration of study and follow-up	• 56 weeks • The study was initiated on 11th March 2013 • The study was completed on 18th August 2014

Abbreviations: AMD: age-related macular degeneration; BCVA: best-corrected visual acuity; CNV: choroidal neovascularisation; CRC: Central Reading Center; CSFT: central subfield thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; FA: fluorescein angiography; qXw: one injection every X weeks; RPE: retinal pigment epithelium; SD-OCT: spectral-domain optical coherence tomography; VEGF: vascular endothelial growth factor; wAMD: wet age-related macular degeneration.
Source: OSPREY CSR.[105]

Patient disposition

A flow diagram of participant disposition in the OSPREY trial is presented in Figure 49.

Figure 49: Participant disposition in the OSPREY trial



Source: Dugel et al 2017.[50]

A total of 173 patients were screened, of which there were 83 screen failures. Overall, 90 patients were randomised to a treatment arm, including 45 patients in each treatment group. Of the 90 patients who were randomised, seven discontinued early from the study (three in the brolucizumab 6 mg arm and four in the aflibercept 2 mg arm). The reasons for discontinuation were AE (one patient in each treatment group), withdrawal by patient (one patient in each treatment group), protocol violation (two patients in the aflibercept 2 mg arm, including one patient who received no treatment), and death (one patient in the brolucizumab 6 mg arm). Of the 89 randomised patients who received treatment, one patient who should have received brolucizumab 6 mg received aflibercept 2 mg at Baseline. The treatment misallocation was not considered to have been the result of systemic error and the patient continued to receive aflibercept 2 mg for the duration of the study.

Definitions of the study populations analysed in OSPREY are presented in Table 87.

Table 87: Trial populations used for the analysis of outcomes in OSPREY

Analysis set	Description
Full analysis set (FAS) as randomised/treated	• All patients who were randomised, received at least one treatment, had a Baseline value, and had at least one post-Baseline measurement of the primary efficacy variable, BCVA
Safety analysis set	• All patients who were randomised and received at least one IVT injection. Patients were analysed according to the first treatment received
Per protocol analysis set (PPS)	• Was defined in relation to Week 12 and included all patients in the FAS who received all three initial IVT injections, had no critical protocol deviations during the study period up to Week 12, and had a valid assessment of the primary efficacy variable (BCVA) at Week 12 (primary endpoint)

Abbreviations: BCVA: best-corrected visual acuity; FAS: full analysis set; IVT: intravitreal; PPS: per protocol.
Source: OSPREY CSR.[105]

Methods of analysis

A summary of the number of patients included in each analysis set by treatment arm is presented in Table 88.

Table 88: Analysis sets (all enrolled patients)

Trial name	OSPREY	
Analysis set	**Brolucizumab 6 mg, n (%)**	**Aflibercept 2 mg, n (%)**
FAS (as randomised)	45 (100)	44 (100)
FAS (as treated)	44 (97.8)	45 (102.3)
PPS	43 (95.6)	41 (93.2)
Safety set	44 (97.8)	45 (102.3)

Abbreviations: FAS: full analysis set; PPS: per protocol analysis set.
Source: OSPREY CSR;[105] Dugel et al. 2017.[50]

The statistical analyses used in the OSPREY trial for the primary and secondary endpoints, alongside sample size calculations and methods for handling missing data are presented in Table 89.

Table 89: Statistical methods for primary analyses of the OSPREY trial

Trial name	OSPREY
Hypothesis objective	• The primary efficacy endpoint was the change in BCVA from Baseline to Week 12 • The first key secondary efficacy endpoint was the change in BCVA from Baseline to Week 16 • The statistical hypotheses for the primary and first key secondary efficacy endpoints were intended to demonstrate the non-inferiority of brolucizumab to aflibercept
Statistical analysis	• Non-inferiority was concluded at a 1-sided alpha level of 0.1 if the lower limit of the corresponding 2-sided, 80% confidence CI for the treatment group difference (brolucizumab [6 mg or 3 mg] − aflibercept 2 mg) was greater than −5 letters
Sample size, power calculation	• A sample size of 40 patients per treatment arm was considered sufficient to demonstrate non-inferiority (margin = 5 letters) of brolucizumab 6 mg versus aflibercept 2 mg with respect to the change in BCVA from Baseline to Week 12 and Week 16 at a 1-sided alpha level of 0.1 with a power of 80%, assuming equal efficacy and a common SD of 10 letters • To account for a dropout rate of 5% up to Week 16, a total of 84 patients were planned for randomisation
Data management, patient withdrawals	• Discontinuation was defined as patient withdrawal from the study, regardless of reason, after Baseline visit. For patients who discontinued from the study, all attempts were made to complete the exit procedures and exit form, within the eCRF, documenting the reason for discontinuation • Patients were discontinued from the study at any time if, in the opinion of the Investigator or medical monitor, their continued participation posed a health risk. Additionally, at any time during the study, and for any reason, patients may have withdrawn their consent to continue participation • Patients who discontinued study treatment were encouraged to continue with the study visits and procedures as long as such procedures did not pose a risk to their well-being. Patients who exhibited any clinically relevant signs, symptoms, or other clinical observations that possibly could have been associated with suspected sensitivity or intolerance to one of the study treatments had the relevant sign, symptom, or

	observation recorded as an AE. If the patient discontinued the study with an ongoing AE, relevant follow-up procedures were performed and documented • If the patient discontinued the study between visits, the Investigator attempted to contact the patient and request their return for the exit procedures. If the patient was unable or unwilling to return for the exit procedures, they were considered lost to follow-up. In this case, the "date of exit" from the study was recoded as the date the patient was last seen in the investigational centre or was last contacted by other communication. In all cases, patients who discontinued from the study were not replaced. When appropriate, the Investigator advised the patient of subsequent therapy and/or procedures necessary for their health

Abbreviations: AE: adverse event; BCVA: best-corrected visual acuity; CI: confidence interval; eCRF: electronic case report form; SD: standard deviation.
Source: OSPREY CSR.[105]

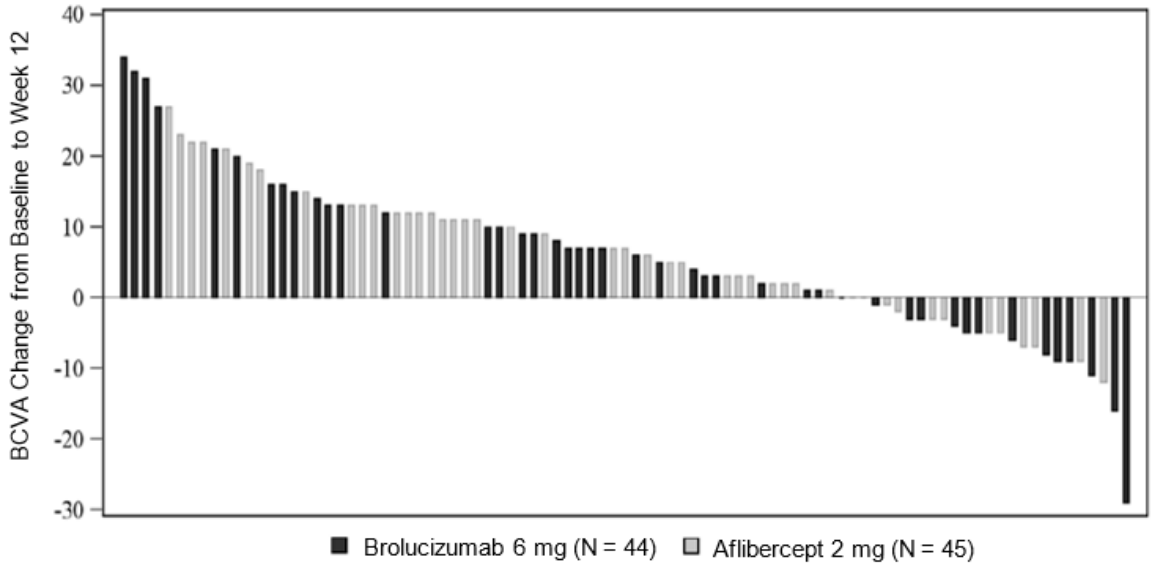
Clinical outcomes

Primary endpoint: BCVA change from Baseline to Week 12

Brolucizumab met the key primary endpoint of non-inferiority to aflibercept for mean change in BCVA from Baseline to Week 12, supporting the results of the primary endpoint presented in HAWK and HARRIER

The LS-mean estimate of the BCVA change from Baseline to Week 12 was 5.75 letters in the brolucizumab 6 mg arm and 6.89 letters in the aflibercept 2 mg arm. The LS estimate of the difference between treatment groups was -1.13 letters (80% CI: -4.19–1.93). The distribution of BCVA changes from Baseline to Week 12 is presented as a waterfall plot in Figure 50. The greatest changes from Baseline were seen in the brolucizumab 6 mg arm. These results demonstrate the non-inferiority of brolucizumab 6 mg compared with aflibercept 2 mg at Week 12 at a 1-sided alpha level of 0.1 and a non-inferiority margin of 5 letters.

Figure 50: BCVA change from Baseline to Week 12 (FAS-LOCF)



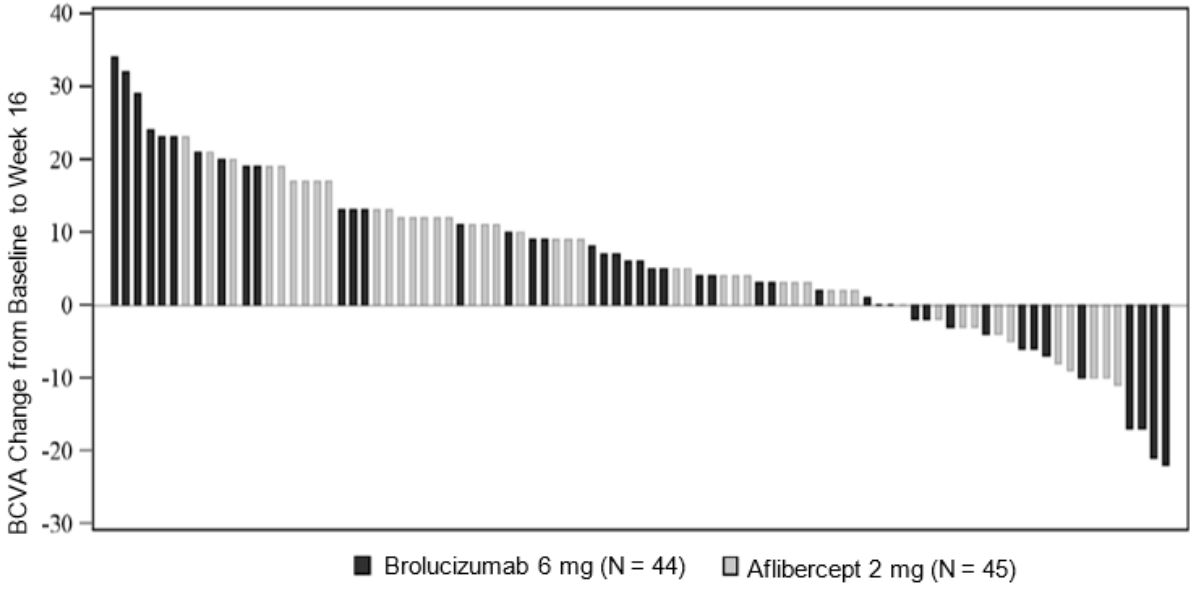
Abbreviations: BCVA: best-corrected visual acuity; FAS: full analysis set; LOCF: last observation carried forward.
Source: OSPREY CSR.[105]

Key secondary endpoint: BCVA change from Baseline to Week 16

Brolucizumab met the key secondary endpoint of non-inferiority to aflibercept for mean change in BCVA change from Baseline to Week 16, which supports the results of the primary endpoint presented in HAWK and HARRIER

The LS-mean estimate of the BCVA change from Baseline to Week 16 was 6.04 letters in the brolucizumab 6 mg arm and 6.62 letters in the aflibercept 2 mg arm. The LS estimate of the difference between treatment groups was -0.58 letters (80% CI: -3.72–2.56). The distribution of BCVA changes from Baseline to Week 12 is presented as a waterfall plot in Figure 51, where a higher variability was observed in the brolucizumab 6 mg arm. These results demonstrate the non-inferiority of brolucizumab 6 mg compared with aflibercept 2 mg at Week 16 at a 1-sided alpha level of 0.1 and a non-inferiority margin of 5 letters.

Figure 51: BCVA change from Baseline to Week 16 (FAS-LOCF)



Abbreviations: BCVA: best-corrected visual acuity; FAS: full analysis set; LOCF: last observation carried forward.
Source: OSPREY CSR.[105]

Additional secondary endpoints: functional outcomes

BCVA change from Baseline by visit

At the end of the matching q8w treatment cycles, the results for mean change in BCVA from Baseline were comparable for the brolucizumab 6 mg and aflibercept 2 mg arms

Across visits, the LS-mean BCVA change from Baseline ranged from 4.78 letters at Week 4 to 8.27 letters at Week 28 in the brolucizumab 6 mg arm and from 4.37 letters at Week 4 to 8.21 letters at Week 24 in the aflibercept 2 mg arm (Table 90). During the loading phase and the period of matching q8w treatment cycles, there were no meaningful differences between treatment arms. At the end of the matching q8w treatment cycles, the LS-mean BCVA change from Baseline was 6.25 letters and 5.75 letters in the brolucizumab 6 mg arm and aflibercept 2 mg arm, respectively, and a treatment difference of 0.50 letters (80% CI, -3.39 to 4.39).

Table 90: BCVA change from Baseline by visit (FAS-LOCF)

Trial name	OSPREY	
Timepoint	Brolucizumab 6 mg (n=44)	Aflibercept 2 mg (n=45)

Week 4		
LSM (SE)	4.78 (1.24)	4.37 (1.23)
LSMD (80% CI)	0.41 (-1.85, 2.67)	
p-value	0.8145	
Week 8		
LSM (SE)	6.00 (1.52)	6.55 (1.51)
LSMD (80% CI)	-0.55 (-3.32, 2.22)	
p-value	0.7973	
Week 12		
LSM (SE)	5.75 (1.68)	6.89 (1.67)
LSMD (80% CI)	-1.13 (-4.19, 1.93)	
p-value	0.6335	
Week 16		
LSM (SE)	6.04 (1.73)	6.62 (1.71)
LSMD (80% CI)	-0.58 (-3.72, 2.56)	
p-value	0.8117	
Week 20		
LSM (SE)	7.49 (1.84)	7.30 (1.82)
LSMD (80% CI)	0.19 (-3.15, 3.53)	
p-value	0.9415	
Week 24		
LSM (SE)	7.03 (1.82)	8.21 (1.80)
LSMD (80% CI)	-1.18 (-4.49, 2.12)	
p-value	0.6457	
Week 28		
LSM (SE)	8.27 (1.85)	6.65 (1.83)
LSMD (80% CI)	1.63 (-1.73, 4.98)	
p-value	0.5330	
Week 32		
LSM (SE)	6.61 (1.99)	6.58 (1.97)
LSMD (80% CI)	0.03 (-3.59, 3.66)	
p-value	0.9901	
Week 36		
LSM (SE)	6.10 (2.20)	6.45 (2.18)
LSMD (80% CI)	-0.35 (-4.35, 3.65)	
p-value	0.9100	
Week 40		
LSM (SE)	6.25 (2.14)	5.75 (2.12)
LSMD (80% CI)	0.50 (-3.39, 4.39)	
p-value	0.8685	
Week 44		
LSM (SE)	6.94 (2.09)	6.59 (2.07)

LSMD (80% CI)	0.35 (-3.46, 4.15)	
p-value	0.9069	
Week 48		
LSM (SE)	6.10 (2.25)	6.84 (2.23)
LSMD (80% CI)	-0.74 (-4.84, 3.35)	
p-value	0.8157	
Week 52		
LSM (SE)	5.96 (2.23)	7.30 (2.21)
LSMD (80% CI)	-1.34 (-5.40, 2.71)	
p-value	0.6701	
Week 56		
LSM (SE)	4.84 (2.37)	7.33 (2.34)
LSMD (80% CI)	-2.49 (-6.80, 1.82)	
p-value	0.4579	

Abbreviations: BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; LOCF: last observation carrier forward; LSM: least squares mean; LSMD: least squares mean difference; SE: standard error.
Source: OSPREY CSR;[105] Dugel et al. 2017.[50]

BCVA change from Week 36 by visit

An analysis of BCVA change from Week 36 was carried out to investigate the influence of 12-week treatment cycles on patients receiving brolucizumab 6 mg. For the first q12w treatment cycle in the brolucizumab 6 mg arm, the mean BCVA change from Week 36 to Week 44 was 0.8 letters (80% CI -0.6 to 2.2, median change: 0 letters), suggesting stability. For the second q12w treatment cycle, the mean BCVA change from Week 48 to Week 56 was -1.3 letters (80% CI -2.2 to -0.3, median change: 0 letters). This suggests that for a proportion of patients, there was as a trend toward decreased vision during the second 12-week treatment cycle, however, that proportion must have been <50% since the median change remained 0.

12-week treatment potential for brolucizumab 6 mg

The q12w treatment phase showed the potential for long-lasting efficacy with brolucizumab, supporting secondary endpoints presented in HAWK and HARRIER

Overall, 39 patients in the brolucizumab 6 mg arm had completed two 12-week treatment cycles (patients who had assessment of BCVA at Week 32 and Week 44 with injections, and Week 56). Of these, 25 had no additional or unscheduled injections during the period of Week 36 to Week 52. 18 patients who had completed two valid 12-week treatment cycles had stable BCVA and seven had unstable BCVA. The other 19 patients either did not complete two 12-week treatment cycles (5 patients) or at least one of their complete 12-week treatment cycles was not valid due to additional injections (14 patients).

1-month changes in BCVA following no treatment for 1 month

The LS estimates for one-month changes in BCVA following no treatment for one month is presented in Table 91 for Week 16, Week 24, Week 32 and Week 40. The results suggest neither systematic changes over time within treatment arms, nor relevant treatment differences regarding the behaviour of BCVA during the second month after an injection.

Table 91**: One-month BCVA changes following no treatment for 1 month (FAS-LOCF)**

Trial name	**OSPREY**	
Timepoint	**Brolucizumab 6 mg (n= 44)**	**Aflibercept 2 mg (n= 45)**

Week 16		
LSM (SE)	0.29 (0.81)	-0.26 (0.81)
LSMD (80% CI)	0.55 (-0.93, 2.03)	
p-value	0.6307	
Week 24		
LSM (SE)	-0.46 (0.77)	0.91 (0.77)
LSMD (80% CI)	-1.37 (-2.78, 0.04)	
p-value	0.2115	
Week 32		
LSM (SE)	-1.66 (0.63)	-0.07 (0.62)
LSMD (80% CI)	-1.59 (-2.73, -0.45)	
p-value	0.0756	
Week 40		
LSM (SE)	0.15 (0.89)	-0.70 (0.88)
LSMD (80% CI)	0.85 (-0.77, 2.47)	
p-value	0.4986	

Abbreviations: BCVA: best-corrected visual acuity; CI: confidence interval; FAS: full analysis set; LOCF: last observation carrier forward; LSM: least squares mean; LSMD: least squares mean difference; SE: standard error.
Source: OSPREY CSR.[105]

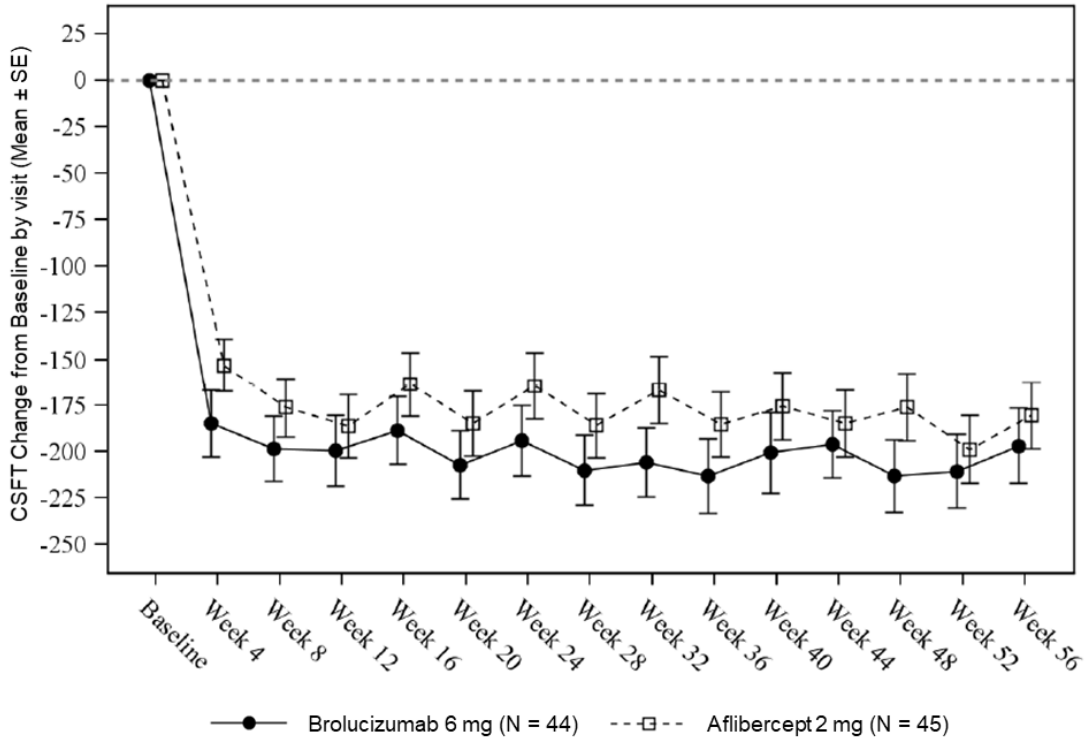
Additional secondary endpoints: anatomical outcomes

CSFT change from Baseline by visit

Treatment with brolucizumab was associated with more stable reductions in CSFT from Baseline to Week 56 versus aflibercept, with a pronounced statistically significant difference at Week 4 and Week 32

The LS mean CSFT change from Baseline ranged in the brolucizumab 6 mg arm from −209.90 to −182.25 µm and in the aflibercept 2 mg arm from −201.95 to −155.34 µm. During the 8-week treatment cycle period from Week 16 to Week 40, greater reductions were consistently observed for the brolucizumab 6 mg arm relative to the aflibercept 2 mg arm. These treatment differences, as assessed by LS mean estimates, ranged from −16.09 to −33.63 µm and showed a pattern of being more pronounced at the end of the 8-week treatment cycles (with the exception of Week 40), resulting in less fluctuation in response to the 8-week treatment cycles for the brolucizumab 6 mg arm. Overall, up to Week 40, the most pronounced statistical differences between treatment groups were seen at Week 4 and Week 32 (both in favour of brolucizumab 6 mg). A graphical display of the mean change from Baseline are presented in Figure 52.

Figure 52: CSFT change from Baseline (µm) by visit (FAS-LOCF)



Abbreviations: CSFT: central subfield thickness; FAS: full analysis set; LOCF: last observation carried forward; SE: standard error.
Source: OSPREY CSR.[105]

Presence of SRF and/or IRF by visit

The percentage of patients with SRF from Week 12 to Week 40 was significantly lower in the brolucizumab arm compared to the aflibercept arm, supporting the results of the HAWK and HARRIER trial

At Baseline, 90.9% and 88.9% of patients in the brolucizumab 6 mg arm and aflibercept 2 mg arm, respectively, had SRF present and 86.4% and 84.4% of patients in the respective arms had IRF present (Table 92). The percentage of patients with SRF present during the period of Week 12 to Week 40 ranged from 7.0% to 16.7% in the brolucizumab 6 mg arm and from 20.9% to 40.5% in the aflibercept 2 mg arm. The difference between treatment arms over this period ranged from −10.2% to −25.5%; the statistical relevance of the difference can be seen in the 80% CIs, which excluded 0 for all related time points with the exception of Week 36. The percentage of patients with IRF present during the same period ranged from 19.0% to 55.8% in the brolucizumab 6 mg arm and from 35.9% to 54.5% in the aflibercept 2 mg arm. The difference between treatment groups over this period ranged from 11.5% to −16.8%.

Table 92: Presence of SRF and/or IRF by visit (FAS-LOCF)

Trial name	OSPREY		
Timepoint	**Brolucizumab 6 mg (n=44), n (%)**	**Aflibercept 2 mg (n=45), n (%)**	**Difference, % (80% CI)**
Baseline			
SRF	40 (90.9)	40 (88.9)	2.0 (-6.2, 10.2)
IRF	38 (86.4)	38 (84.4)	1.9 (-7.7, 11.5)
Week 4			
SRF	14 (31.8)	26 (57.8)	-26.0 (-39.0, -12.9)

IRF	25 (56.8)	27 (60.0)	-3.2 (-16.6, 10.2)
Week 8			
SRF	7 (15.9)	15 (34.9)	-19 (-30.7, -7.3)
IRF	27 (61.4)	22 (51.2)	10.2 (-3.4, 23.8)
Week 12			
SRF	4 (9.3)	9 (20.9)	-11.6 (-21.4, -1.9)
IRF	21 (48.8)	21 (48.8)	0 (-13.8, 13.8)
Week 16			
SRF	7 (16.3)	16 (36.4)	-20.1 (-31.9, -8.3)
IRF	24 (55.8)	24 (54.5)	1.3 (-12.4, 14.9)
Week 20			
SRF	3 (7.0)	11 (25.6)	-18.6 (-28.5, -8.7)
IRF	16 (37.2)	16 (37.2)	0 (-13.4, 13.4)
Week 24			
SRF	7 (16.7)	17 (38.6)	-22 (-33.9, -10.0)
IRF	22 (52.4)	18 (40.9)	11.5 (-2.2, 25.2)
Week 28			
SRF	5 (11.9)	11 (27.5)	-15.6 (-26.7, -4.5)
IRF	8 (19.0)	14 (35.9)	-16.8 (-29.4, -4.3)
Week 32			
SRF	6 (15.0)	17 (40.5)	-25.5 (-37.6, -13.4)
IRF	16 (40.0)	22 (52.4)	-12.4 (-26.4, 1.6)
Week 36			
SRF	6 (15.4)	11 (25.6)	-10.2 (-21.5, 1.1)
IRF	11 (28.2)	19 (44.2)	-16.0 (-29.4, -2.6)
Week 40			
SRF	6 (14.6)	13 (32.5)	-17.9 (-29.7, -6.0)
IRF	15 (36.6)	16 (40.0)	-3.4 (-17.3, 10.4)
Week 44			
SRF	10 (23.8)	6 (14.3)	9.5 (-1.4, 20.4)
IRF	21 (50.0)	16 (38.1)	11.9 (-1.9, 25.7)
Week 48			
SRF	6 (14.3)	12 (29.3)	-15 (-26.4, -3.5)
IRF	13 (31.0)	18 (43.9)	-13 (-26.4, 0.5)
Week 52			
SRF	7 (17.5)	7 (17.5)	0 (-10.9, 10.9)
IRF	16 (40.0)	15 (37.5)	2.5 (-11.5, 16.5)
Week 56			
SRF	9 (22.0)	10 (24.4)	-2.4 (-14.4, 9.5)
IRF	23 (57.5)	19 (46.3)	11.2 (-3.0, 25.3)

Abbreviations: FAS: full analysis set; IRF: intraretinal fluid; LOCF: last observation carrier forward; SRF: subretinal fluid.
Source: OSPREY CSR;[105] Dugel et al. 2017.[50]

Safety outcomes

Treatment exposure

The frequency and percentage of patients receiving treatment by visit are presented in Table 93. At each scheduled treatment visit more than 90% of patients were treated in each arm.

Table 93: Frequency and percentage of patients receiving treatment by visit (FAS)

Trial name	OSPREY	
Timepoint	**Brolucizumab 6 mg (n= 44), n (%)**	**Aflibercept 2 mg (n= 45), n (%)**
Baseline	44 (100.0)	45 (100.0)
Week 4	44 (100.0)	44 (97.8)
Week 8	44 (100.0)	44 (97.8)
Week 12	3 (6.8)	5 (11.1)
Week 16	43 (97.7)	44 (97.8)
Week 20	1 (2.3)	4 (8.9)
Week 24	43 (97.7)	44 (97.8)
Week 28	0 (0.0)	3 (6.7)
Week 32	40 (90.9)	42 (93.3)
Week 36	2 (4.5)	3 (6.7)
Week 40	11 (25.0)	41 (91.1)
Week 44	42 (95.5)	8 (17.8)
Week 48	5 (11.4)	41 (91.1)
Week 52	2 (4.5)	4 (8.9)
Week 56	0 (0.0)	0 (0.0)

Abbreviations: FAS: full analysis set.
Source: OSPREY CSR;[105] Dugel et al. 2017.[50]

Adverse events

Ocular and non-ocular treatment emergent adverse events

The frequencies of study eye ocular and non-ocular TEAEs (treatment-emergent adverse events) are presented in Table 94. Overall, the most commonly occurring AE in the study eye was conjunctival haemorrhage, which was reported by five patients in the brolucizumab 6 mg (11.4%) arm and seven patients in the aflibercept 2 mg arm (15.6). Other commonly reported study-eye ocular AEs included vitreous floaters, reduced visual acuity, and vitreous detachment, and commonly reported non-ocular AEs were upper respiratory tract infection and urinary tract infection.

Table 94: Ocular and non-ocular treatment emergent adverse events (≥3 patients in any treatment group) by preferred term (safety set)

Trial name	OSPREY	
Adverse event	**Brolucizumab 6 mg (n= 44)**	**Aflibercept 2 mg (n= 45)**
Ocular* – n (%)		
Conjunctival haemorrhage	5 (11.4)	7 (15.6)
Visual acuity reduced	4 (9.1)	4 (8.9)

Vitreous floaters	5 (11.4)	4 (8.9)
Age-related macular degeneration	3 (6.8)	1 (2.2)
Vitreous detachment	3 (6.8)	3 (6.7)
Punctate keratitis	1 (2.3)	3 (6.7)
Vision blurred	1 (2.3)	3 (6.7)
Retinal haemorrhage	1 (2.3)	2 (4.4)
Cataract	1 (2.3)	3 (6.7)
Macular fibrosis	3 (6.8)	1 (2.2)
Foreign body sensation in eyes	0 (0.0)	3 (6.7)
Non-ocular – n (%)		
Upper respiratory tract infection	5 (11.4)	3 (6.7)
Urinary tract infection	2 (4.5)	4 (8.9)
Nausea	3 (6.8)	1 (2.2)
Chronic obstructive pulmonary	3 (6.8)	0 (0.0)

*Ocular adverse events related to study eye
Source: Dugel et al. 2017.[50]

Deaths and serious adverse events

The frequencies of deaths and serious adverse events reported during the course of the study are presented in Table 95. One 80-year-old patient in the brolucizumab 6 mg arm, with a medical history of hypertension, died of myocardial ischemia. The event was reported as being related to brolucizumab, as a causal relationship could not be ruled out.

A total of 19 patients experienced nonfatal SAEs (10 in the brolucizumab 6 mg arm and 9 in the aflibercept 2 mg arm) with only one patient in the aflibercept 2 mg arm experiencing a treatment-related SAE. One patient discontinued due to an SAE of pancreatic carcinoma and another patient discontinued due to an SAE of retinal detachment in the study eye, in the brolucizumab 6 mg and aflibercept 2 mg arms respectively; neither event was considered to be treatment-related. No other nonfatal events led to study discontinuation.

Table 95: Deaths and serious adverse events (safety set)

Trial name	**OSPREY**	
Adverse event	**Brolucizumab 6 mg (n= 44), n (%)**	**Aflibercept 2 mg (n= 45), n (%)**
Serious AEs	11 (25.0)	9 (20.0)
Deaths	1 (2.3)	0 (0.0)
Nonfatal serious AEs	10 (22.7)	9 (20.0)
AEs leading to study discontinuation	2 (4.5)	1 (2.2)
Related to study drug	1 (2.3)	0 (0.0)

Abbreviations: AE: adverse event
Source: Dugel et al. 2017.[50]

7.5 Overview of studies included in the base case NMA

An overview of the baseline demographics, baseline disease characteristics and efficacy and safety results for the studies included in the base case NMA is presented in the following tables and figures.

Table 96: Baseline demographic characteristics of the studies included in the base case NMA

Trial ID	Author	Trial name	Treatment	Age			Gender (male)	
				Mean	SD	Range	n	%
1	**Dugel 2017**	OSPREY	LP → Bro 6q8w → q12w LP → Afli 2q8w	78.8 77.3	9.7 9.1	NR	16 20	36.4 44.4
2	**Dugel 2019**	HARRIER	LP → Bro 6q12/q8w LP → Afli 2q8	74.8 75.5	8.6 7.9	NR	160 157	43.2 42.5
3	**Dugel 2019**	HAWK	LP → Bro 3q12/q8w LP → Bro 6q12/q8w LP → Afli 2q8w	76.7 76.7 76.2	8.3 9 8.8	NR	148 155 166	41.3 43.1 46.1
4	**Martin 2011**	CATT – 1 year[a]	Rani 0.5q4w Rani 0.5PRN Bev 1.25q4w Bev 1.25 PRN	79.2 78.4 80.1 79.3	7.4 7.8 7.3 7.6	NR	118 113 106 116	39.2 37.9 37.1 38.7
4	**Martin 2012**	CATT – 2 years[a]	Rani 0.5q4w Rani 0.5PRN Bev 1.25q4w Bev 1.25 PRN	79.5 78.3 79.7 78.9	7.4 7.8 7.5 7.4	NR	56 108 53 104	38.4 37.6 39.3 38.5
5	**Eldem 2015**	SALUTE	LP→ Rani 0.5PRNX LP→ Rani 0.5PRN	70.4[b] 70.3[b]	NR	53.6–86.8 52.7–83.8	25 25	52 56
6	**Feltgen 2017**	RABIMO	LP → Rani 0.5q8w LP → Rani 0.5PRN	79 81	NR	NR	6 8	30 40
7-8	**Heier 2012**	VIEW 1	Afli 0.5q4w Afli 2q4w LP → Afli 2q8w Rani 0.5q4w	78.4 77.7 77.9 78.2	8.1 7.9 8.4 7.6	NR	134 110 123 132	44.5 36.2 40.9 43.4
7-8	**Heier 2012**	VIEW 2	Afli 0.5q4w Afli 2q4w LP → Afli 2q8w	74.7 74.1 73.8	8.6 8.5 8.6	NR	149 133 131	50.3 43 42.8

Trial ID	Author	Trial name	Treatment	Age			Gender (male)	
				Mean	SD	Range	n	%
			Rani 0.5q4w	73	9		122	41.9
7-8	**Schmidt-Erfurth 2014**	VIEW 1&2 pooled	Afli 0.5q4w Afli 2q4w LP → Afli 2q8w Rani 0.5q4w	75.6 76.5 75.9 75.8	8.7 8.5 8.4 8.8	NR	254 283 243 254	42.7 47.4 39.6 41.8
9	**Ho 2014**	HARBOR	Rani 0.5q4w Rani 2q4w LP → Rani 0.5PRN LP → Rani 2PRN	78.8 79.3 78.5 78.3	8.4 8.3 8.3 8.3	53-97 50-96 53-97 54-98	113 104 112 117	41.1 38 40.7 42.9
10	**Gillies 2019**	RIVAL	LP → Rani 0.5TREX LP → Afli 2TREX	76.6 78.7	8.5 7.45	NR	70 63	49.3 45.3
10	**Hunyor 2018**	RIVAL	LP → Rani 0.5TREX LP → Afli 2TREX	NR	NR	NR	NR	NR
11	**Kertes 2019**	CAN-TREAT	LP → Rani 0.5TREX Rani 0.5q4w	78.9 78.7	7.7 8	NR	113 117	39.4 39.9
12	**Regiollo 2008**	PIER	LP → Rani 0.5q12w LP → Rani 0.3q12w Sham IVT	78.8 78.7 77.9	7.9 6.3 7.1	NR	28 26 20	45.9 43.3 31.7
13	**Rosenfeld 2006**	MARINA	Rani 0.5q4w Rani 0.3q4w Sham IVT	77 77 77	8 8 7	52-93 52-95 56-94	88 85 79	36.7 35.7 33.2
14	**Silva 2017**	TREND	LP → Rani 0.5TREX Rani 0.5q4w	75.3 75.2	8.6 8.1	NR	144 146	44.6 44.6
15	**Wykoff 2015/2017**	TREX-AMD	LP → Rani 0.5TREX Rani 0.5q4w	65 79	NR	59-91 60-96	14 8	35 40

[a]In CATT –Year 2, switchers groups were not considered. [b]Trial reported the median age only.
Abbreviations: ID: identification; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; NR: Not Reported; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SD: standard deviation; TREX: treat-and-extend dosing regimen.

Table 97: Baseline disease characteristics of the studies included in the base case NMA

Trial ID	Author	Trial Name	Treatment	Lesion composition			BCVA		CRT		CFT		Other anatomical measure		
				Predom-inantly classic (%)	Minim-ally classic (%)	Occult (%)	Mean	SD	Mean	SD	Mean	SD	Type	Mean	SD
1	Dugel 2017	OSPREY	LP → Bro 6q8w → q12w LP → Afli 2q8w	47.7 51.1	27.3 17.8	25.0 31.1	54.1 55.6	13.9 12.3	NR	NR	NR	NR	CSFT	490.1 495.7	149.2 144.6
2	Dugel 2019	HARRIER	LP → Bro 6q12/q8w LP → Afli 2q8w	41.6 39.5	8.9 9.3	49.5 51.2	61.5 60.8	12.6 12.9	NR	NR	NR	NR	CSFT	473.6 465.3	171.4 151.2
3	Dugel 2019	HAWK	LP → Bro 3q12/q8w LP → Bro 6q12/q8w LP → Afli 2q8w	34.1 31.4 32.3	8.9 10.8 9.5	57.0 57.8 58.2	61.0 60.8 60.0	13.6 13.7 13.9	NR	NR	NR	NR	CSFT	466.6 463.1 457.9	167.42 166.62 146.37
4	Martin 2011/ 2012	CATT	Rani 0.5q4w Rani 0.5PRN Bev 1.25q4w Bev 1.25PRN	NR	NR	NR	59.9 60.2 61.6 60.6	14.2 13.6 13.1 13.0	254.0 248.0 249.0 251.0	127.0 124.0 117.0 116.0	460 459 462 462	190 195 205 173	NR	NR	NR
5	Eldem 2015	SALUTE	LP→ Rani 0.5PRNX LP→ Rani 0.5PRN	NR	NR	NR	55.0[a] 56.0[a]	NR	325.0[a] 327.0[a]	NR	NR	NR	NR	NR	NR
6	Feltgen 2017	RABIMO	LP → Rani 0.5q8 LP → Rani 0.5PRN	NR	NR	NR	60.5 60.5	NR	370.0 428.0	NR	NR	NR	NR	NR	NR
7-8	Heier 2012	VIEW 1	Afli 0.5q4w Afli 2q4w LP → Afli 2q8w Rani 0.5q4w	26.9 28.6 23.6 27.0	32.2 34.5 36.5 33.3	40.2 36.2 39.2 37.8	55.6 55.2 55.7 54.0	13.1 13.2 12.8 13.4	313.2 313.6 324.4 325.9	106.0 103.4 111.2 110.9	NR	NR	NR	NR	NR
7-8	Heier 2012	VIEW 2	Afli 0.5q4w Afli 2q4w LP → Afli 2q8w Rani 0.5q4w	27.0 23.3 28.8 24.1	34.8 36.2 34.6 35.7	38.2 39.8 35.9 39.9	51.6 52.8 51.6 53.8	14.2 13.9 13.9 13.5	326.5 334.6 342.6 325.9	116.5 119.8 124.0 110.9	NR	NR	NR	NR	NR
7-8	Schmidt-Erfurth 2014	VIEW 1&2 Pooled	Afli 0.5q4w Afli 2q4w LP → Afli 2q8w Rani 0.5q4w	34.5 33.5 35.4 35.6	25.5 27.0 25.9 26.2	38.8 39.2 30.0 37.6	53.9 53.6 54.0 53.6	13.4 13.8 13.6 13.5	296.0 296.0 299.0 306.0	123.0 132.0 126.0 134.0	NR	NR	NR	NR	NR
9	Ho 2014	HARBOR	Rani 0.5q4w Rani 2q4w LP → Rani 0.5PRN LP → Rani 2PRN	15.3 14.6 17.1 15.0	46.2 46.0 46.5 46.9	38.5 39.4 36.4 38.1	54.2 53.5 54.5 53.5	13.3 13.1 11.7 13.2	NR	NR	348.3 332.9 347.8 347.9	146.3 138.7 143.8 142.9	NR	NR	NR
10	Gillies 2019	RIVAL	LP → Rani 0.5TREX LP → Afli 2TREX	NR	NR	NR	65.3 65.1	15.1 12.53	NR	NR	NR	NR	NR	NR	NR
10	Hunyor 2018	RIVAL	LP → Rani 0.5TREX LP → Afli 2TREX	NR	NR	NR	65.3 65.1	15.1 12.5	NR	NR	NR	NR	CSFT	468 484	151 168
11	Kertes 2019	CAN-TREAT	LP → Rani 0.5TREX Rani 0.5q4w	NR	NR	NR	58.9 59.5	NR	382.5 374.2	113.2 111.9	NR	NR	NR	NR	NR
12	Regillo 2008	PIER	LP → Rani 0.5q12w	21.3	29.5	49.2	53.7	15.5	NR	NR	NR	NR	NR	NR	NR

Trial ID	Author	Trial Name	Treatment	Lesion composition			BCVA		CRT		CFT		Other anatomical measure		
				Predom-inantly classic (%)	Minim-ally classic (%)	Occult (%)	Mean	SD	Mean	SD	Mean	SD	Type	Mean	SD
			LP → Rani 0.3q12 w Sham IVT	13.3 22.2	36.7 46.0	48.3 31.7	55.8 55.1	12.2 13.9							
13	**Rosenfeld 2006**	MARINA	Rani 0.5q4w Rani 0.3q4w Sham IVT	0.0 0.4 0.0	37.9 36.1 36.6	62.1 63.4 63.4	53.7 53.1 53.6	12.8 12.9 14.1	NR	NR	NR	NR	NR	NR	NR
14	**Silva 2017**	TREND	LP → Rani 0.5TREX Rani 0.5q4w	8.4 7.0	10.2 3.4	42.7 52.3	59.5 60.6	13.2 13.9	369.0[a] 369.0[a]	NR	NR	NR	CMT	394.7 394.7	109.7 109.7
15	**Wykoff 2015 / 2017**	TREX-AMD	LP → Rani 0.5TREX Rani 0.5q4w	NR	NR	NR	59.9 60.3	NR	489.0 533.0	NR	NR	NR	NR	NR	NR

*Median.
Abbreviations: BCVA: best corrected visual acuity; CFT: central field thickness; CRT: central retinal thickness; CMT: central macular thickness; CSFT: central subfield thickness; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; NR: not reported; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SD: standard deviation; TREX: treat-and-extend dosing regimen.

Table 98: Efficacy results of the studies included in the base case NMA

Trial ID	Author	Trial name	Treatment	Change in BCVA				Change in CRT				Patients gaining ≥15 letters		Patients losing ≥15 letters	
				1 year		2 years		1 year		2 years		1 year	2 years	1 year	2 years
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	%	%	%	%
1	**Dugel 2017**	OSPREY	LP → Bro 6q8 → q12w LP → Afli 2q8w	6 7.2	NR 13.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2	**Dugel 2019**	HARRIER	LP → Bro 6q12/q8w LP → Afli 2q8w	6.9 7.5	11.7 11.7	6.1 6.6	NR	-193.8 -143.9	131.6 131.4	197.7 155.1	134.1 134.1	29.3 29.9	29.1 31.5	3.8 4.8	7.1 7.5
3	**Dugel 2019**	HAWK	LP → Bro 3q12/q8w LP → Bro 6q12/q8w LP → Afli 2q8w	6.1 6.6 6.8	13.1 13.5 13.5	5.6 5.9 5.3	14.9 14.8 14.8	-167.5 -172.6 -143.5	131.1 127.1 127.1	179.7 174.8 148.7	134.0 137.9 137.9	25.2 33.6 25.5	32.6 34.2 27.1	5.9 6.4 5.6	8.6 8.1 7.5
4	**Martin 2011/ 2012**	CATT	Rani 0.5q4w Rani 0.5PRN Bev 1.25q4w Bev 1.25PRN	8.5/9.1[a] 6.8/6.9[a] 8/8.66[a] 5.9/5.89[a]	14.1/NR[a] 13.1/NR[a] 15.8/NR[a] 15.7/NR[a]	8.8 6.7 7.8 5.0	15.9 14.6 15.5 17.9	-100.0 -81.0 -79.0 -79.0	130 134 132 123	-91.0 -78.0 -84.0 -84.0	152.0 131.0 133.0 145.0	34.2 24.9 31.3 28.0	32.8 30.7 31.8 28.3	5.6 4.6 6.0 8.5	6.7 7.2 7.8 11.6
5	**Eldem 2015**	SALUTE	LP→ Rani0.5PRNX LP→ Rani 0.5PRN	9.0 6.0	NR	NR	NR	88.5 61.0	NR	NR	NR	34.2 23.1	NR	10.5 10.3	NR
6	**Feltgen 2017**	RABIMO	LP → Rani 0.5q8w LP → Rani 0.5PRN	8.5 6.5	NR	NR	NR	-123 -198	80 69	NR	NR	30.0 40.0	NR	10.0 5.0	NR

Trial ID	Author	Trial name	Treatment	Change in BCVA				Change in CRT				Patients gaining ≥15 letters		Patients losing ≥15 letters	
				1 year		2 years		1 year		2 years		1 year	2 years	1 year	2 years
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	%	%	%	%
7-8	**Heier 2012**	VIEW 1	Afli 0.5q4w Afli 2q4w LP → Afli 2q8w Rani 0.5q4w	6.9 10.9 7.9 8.1	13.4 13.8 15 15.3	NR	NR	-115.6 -116.5 -128.5 -116.8	104.1 98.4 108.5 109	NR	NR	24.9 37.5 30.6 30.9	NR	5 4.9 5.6 6.2	NR
7-8	**Heier 2012**	VIEW 2	Afli 0.5q4w Afli 2q4w LP → Afli 2q8w Rani 0.5q4w	9.7 7.6 8.9 9.4	14.1 12.6 14.4 13.5	NR	NR	-129.8 -156.8 -149.2 -138.5	114.8 122.8 119.7 122.2	NR	NR	34.8 29.4 31.4 34.0	NR	4.7 5.5 4.6 5.2	NR
7-8	**Schmidt-Erfurth 2014**	VIEW 1&2 Pooled	Afli 0.5q4w Afli 2q4w LP → Afli 2q8w Rani 0.5q4w	8.4 9.3 8.7 8.3	NR	6.6 7.6 7.6 7.9	NR	-139.0 -138.0 -128.0 -123.0	NR	-133.0 -128.0 -118.0 -113.0	NR	30.9 33.4 32.4 29.8	33.4 31.2 31.6 28.1	4.7 5.7 5.6 3.9	7.6 7.8 8.4 8.5
9	**Ho 2014**	HARBOR	Rani 0.5q4w Rani 2q4w LP → Rani 0.5PRN LP → Rani 2PRN	10.1 9.2 8.2 8.6	13.3 14.6 13.3 13.8	9.1 8 7.9 7.6	14.9 17.4 14.7 15.3	NR	NR	NR	NR	34.5 36.1 30.2 33.0	34.5 37.6 33.1 34.8	2.2 6.6 5.5 5.1	5.8 9.9 9.1 8.4
10	**Gillies 2019**	RIVAL	LP → Rani 0.5TREX LP → Afli 2TREX LP → Rani 0.5TREX LP → Afli 2TREX	7.16 4.85 6.9 5.2	NR NR 12.25 12.83	NR	NR	NR	NR	NR	NR	22.0 20.7 NR NR	NR	3.1 5.0	NR
10	**Hunyor 2018**	RIVAL	LP → Rani 0.5TREX LP → Afli 2TREX	NR	NR	6.6 4.6	NR	NR	NR	NR	NR	NR	NR	NR	NR
11	**Kertes 2019**	CAN-TREAT	LP → Rani 0.5TREX Rani 0.5q4w	8.4 6	11.9 11.9	NR	NR	NR	NR	NR	NR	25.5 20.1	NR	3.0 4.8	NR
12	**Regillo 2008**	PIER	LP → Rani 0.5q12w LP → Rani 0.3q12w Sham IVT	-0.2 -1.6 -16.3	NR	NR	NR	NR	NR	NR	NR	13.1 11.7 9.5	NR	NR	NR
13	**Rosenfeld 2006**	MARINA	Rani 0.5q4w Rani 0.3q4w Sham IVT	7.2 6.5 -10.4	NR	6.5 5.4 -14.9	NR	NR	NR	NR	NR	33.8 24.8 5.0	33.3 26.1 3.8	NR	NR
14	**Silva 2017**	TREND	LP → Rani 0.5TREX Rani 0.5q4w	6.6 7.9	NR	NR	NR	NR	NR	NR	NR	25.8 26.4	NR	6.2 3.7	NR
15	**Wykoff 2015 / 2017**	TREX-AMD	LP → Rani 0.5TREX Rani 0.5q4w	9.9 9.2	NR	6.8 10.5	NR	-172 -256	NR	-199 -170	NR	25.0 15.0	30 20	NR	13 0

[a]In CATT –Year 2, switchers groups were not considered.

Abbreviations: BCVA: best corrected visual acuity; CRT: central retinal thickness; ID: identification; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; NR: not reported; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SD: standard deviation; TREX: treat-and-extend dosing regimen.

Table 99: Imputed data for the base case NMA – mean change in BCVA

Trial	Treatment	1 year			2 years		
		SD	SE	Method	SD	SE	Method
CATT	Rani 0.5PRN	13.1	0.80	SD provided in publication	14.6	0.90	SD provided in publication
	Rani 0.5q4w	14.1	0.80	SD provided in publication	15.9	1.37	SD provided in publication
OSPREY	LP → Afli 2q8w	13.2	1.97	SD provided in publication	NR	NR	Endpoint not reported
	LP → Bro 6q8w → q12w	16.6	2.50	SE digitised from graph	NR	NR	Endpoint not reported
HARBOR	LP → Rani 0.5PRN	13.3	0.80	SD provided in publication	14.7	0.89	SD provided in publication
	Rani 0.5q4w	13.3	0.80	SD provided in publication	14.9	0.90	SD provided in publication
HARRIER	LP → Afli 2q8w	11.7	0.61	SE provided in CSR	14.0	0.73	SE provided in CSR
	LP → Bro 6q12/q8w	11.7	0.61	SE provided in CSR	14.0	0.73	SE provided in CSR
HAWK	LP → Afli 2q8w	13.5	0.71	SE provided in CSR	14.8	0.78	SE provided in CSR
	LP → Bro 3q12/q8w	13.1	0.69	SE provided in CSR	15.0	0.79	SE provided in CSR
	LP → Bro 6q12/q8w	13.5	0.71	SE provided in CSR	14.8	0.78	SE provided in CSR
MARINA	Rani 0.5q4w	15.0	0.97	SE digitised from graph	16.4	1.06	SE digitised from graph
	Sham IVT	17.4	1.13	SE digitised from graph	18.1	1.17	SE digitised from graph
PIER	LP → Rani 0.5q12w	13.9	1.78	SE calculated from digitised CI	NR	NR	Endpoint not reported
	Sham IVT	22.5	2.84	SE calculated from digitised CI	NR	NR	Endpoint not reported
RABIMO	LP → Rani 0.5q8 w	10.4	2.32	SD calculated as IQR/1.35	NR	NR	Endpoint not reported
	LP → Rani 0.5PRN	11.9	2.65	SD calculated as IQR/1.35	NR	NR	Endpoint not reported
SALUTE	LP → Rani 0.5PRN	20.9	3.35	SD provided in publication	NR	NR	Endpoint not reported
	LP → Rani 0.5PRNX	15.9	2.58	SD provided in publication	NR	NR	Endpoint not reported
TREND	Rani 0.5q4w	12.6	0.70	SE digitised from graph	NR	NR	Endpoint not reported
	Rani 0.5TREX	12.5	0.70	SE digitised from graph	NR	NR	Endpoint not reported
TREX-AMD	Rani 0.5q4w	13.0	2.98	Imputed SD from mean of other trials[a]	13.9	3.19	Imputed SD from mean of other trials*
	Rani 0.5TREX	13.0	2.14	Imputed SD from mean of other trials[a]	13.9	2.29	Imputed SD from mean of other trials*
VIEW 1&2	Afli 2q4w	13.0	0.53	Imputed SD from mean of other trials[a]	13.9	0.56	Imputed SD from mean of other trials*
	LP → Afli 2q8w	13.0	0.53	Imputed SD from mean of other trials[a]	13.9	0.57	Imputed SD from mean of other trials*
	Rani 0.5q4w	13.0	0.53	Imputed SD from mean of other trials[a]	13.9	0.56	Imputed SD from mean of other trials*
RIVAL	LP → Rani 0.5TREX	10.2	0.86	SE calculated from CI reported in the publication	10.5	0.97	SE calculated from CI reported in the publication

Trial	Treatment	1 year			2 years		
		SD	SE	Method	SD	SE	Method
	LP → Afli 2TREX	10.2	0.87	SE calculated from CI reported in the publication	10.6	1.02	SE calculated from CI reported in the publication
CAN-TREAT	LP → Rani 0.5TREX	11.9	0.73	SD provided in publication	NR	NR	Endpoint not reported
	Rani 0.5q4	11.9	0.74	SD provided in publication	NR	NR	Endpoint not reported

*Imputed from the mean SD of all trials where either the SD or SE was provided in the publication.
Abbreviations: BCVA: best-corrected visual acuity; CI: confidence interval; CSR: clinical study report; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; NR: not reported; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SD: standard deviation; SE: standard error; TREX: treat-and-extend dosing regimen.

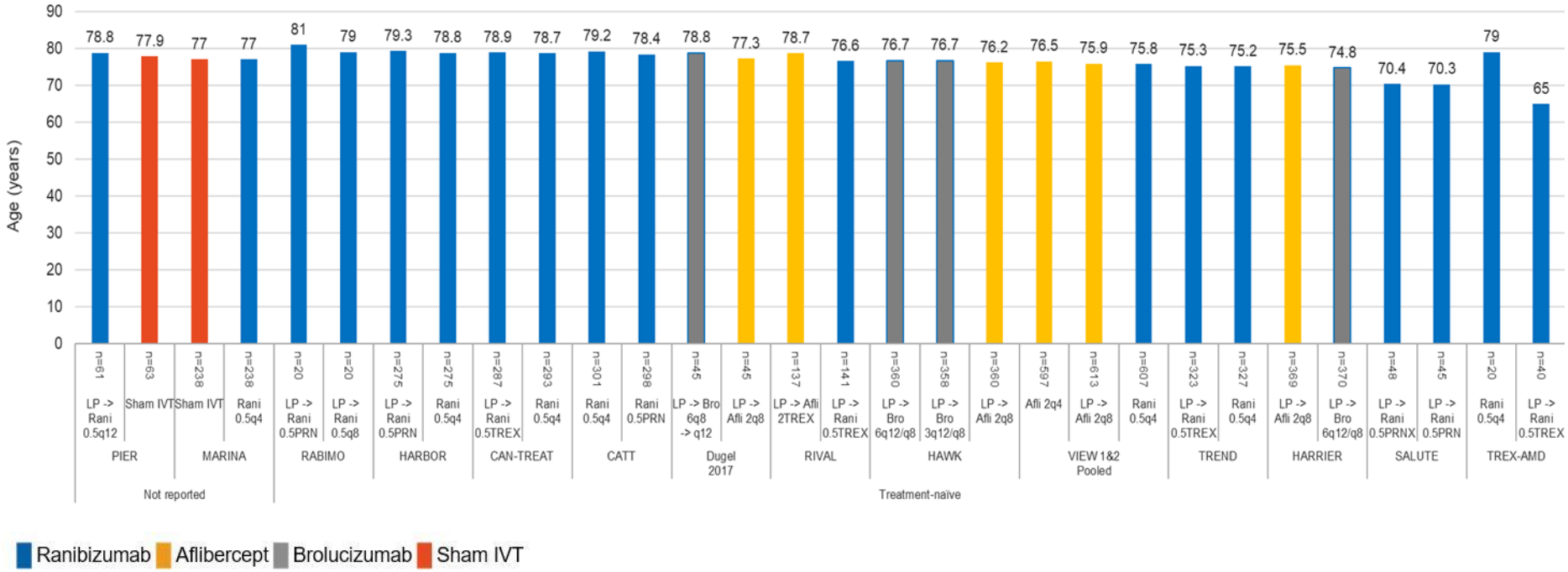
Table 100: Safety results of the studies included in the base case NMA

Trial ID	Author	Trial name	Treatment	Serious adverse events				Discontinuation				Injection frequency			
				1 year		2 years		1 year		2 years		1 year		2 years	
				N	%	N	%	N	%	N	%	Mean	SD	Mean	SD
1	**Dugel 2017**	OSPREY	LP → Bro 6q8w → q12w LP → Afli 2q8w	NR	NR	NR	NR	3 4	6.8 8.9	NR	NR	NR	NR	NR	NR
2	**Dugel 2019**	HARRIER	LP → Bro 6q12/q8w LP → Afli 2q8w	NR	NR	174 176	47.0 47.7	25 24	6.7 6.5	43 52	11.6 14.0	6.2 6.8	0.9 0.9	10.9 12.1	2.4 2.3
3	**Dugel 2019**	HAWK	LP → Bro 3q12/q8w LP → Bro 6q12/q8w LP → Afli 2q8w	NR	NR	218 220 201	60.9 61.1 55.8	31 37 46	8.6 10.2 12.7	63 68 80	17.5 18.8 22.2	6.1 6.1 6.5	0.9 1.0 1.3	10.5 10.2 11.3	2.6 2.7 3.2
4	**Martin 2011/ 2012**	CATT	Rani 0.5q4w Rani 0.5PRN Bev 1.25q4w Bev 1.25PRN	NR	NR	NR	NR	NR	NR	NR	NR	11.7 6.9 11.9 7.7	1.5 3.0 1.2 3.5	22.4 12.6 23.4 14.1	3.9 6.6 2.8 7.0
5	**Eldem 2015**	SALUTE	LP→ Rani 0.5PRNX LP→ Rani 0.5PRN	24 25	50.0 55.6	NR	NR	2 1	4.2 2.2	NR	NR	6.0 6.6	NR	NR	NR
6	**Feltgen 2017**	RABIMO	LP → Rani 0.5q8w LP → Rani 0.5PRN	15 13	75 65	NR	NR	2 5	10.0 25.0	NR	NR	8.0 4.0	NR	NR	NR
7-8	**Heier 2012**	VIEW 1	Afli 0.5q4w Afli 2q4w LP → Afli 2q8w Rani 0.5q4w	NR	NR	NR	NR	30 16 30 27	9.9 5.3 9.9 8.8	NR	NR	NR	NR	NR	NR

Trial ID	Author	Trial name	Treatment	Serious adverse events				Discontinuation				Injection frequency			
				1 year		2 years		1 year		2 years		1 year		2 years	
				N	%	N	%	N	%	N	%	Mean	SD	Mean	SD
7-8	**Heier 2012**	VIEW 2	Afli 0.5q4w Afli 2q4w LP → Afli 2q8w Rani 0.5q4w	NR	NR	NR	NR	45 37 33 33	14.5 11.8 10.5 10.9	NR	NR	NR	NR	NR	NR
7-8	**Schmidt-Erfurth 2014**	VIEW 1&2 Pooled	Afli 0.5q4w Afli 2q4w LP → Afli 2q8w Rani 0.5q4w	NR	NR	NR	NR	64 43 56 49	10.4 7.0 9.1 8.0	113 88 103 90	18.4 14.3 16.7 14.8	NR	NR	11.2 16.0 16.5 16.2	NR
9	**Ho 2014**	HARBOR	Rani 0.5q4w Rani 2q4w LP → Rani 0.5PRN LP → Rani 2PRN	NR	NR	NR	NR	17 16 12 15	6.2 5.8 4.4 5.5	28 19 26 21	10.2 6.9 9.5 7.7	11.3 11.2 7.7 6.9	NR	21.4 21.6 13.3 NR	NR
10	**Gillies 2019**	RIVAL	LP → Rani 0.5TREX LP → Afli 2TREX LP → Rani 0.5TREX LP → Afli 2TREX	NR	NR	NR	NR	14 16	10.1 11.5	NR	NR	9.7 9.7	2.77 2.55	NR	NR
10	**Hunyor 2018**	RIVAL	LP → Rani 0.5TREX LP → Afli 2TREX	NR	NR	NR	NR	NR	NR	24 29	17.0 21.2	NR	NR	17.7 17.0	6.4 6.3
11	**Kertes 2019**	CAN-TREAT	LP → Rani 0.5TREX Rani 0.5q4w	NR	NR	NR	NR	18 36	16.3 12.3	NR	NR	9.4 11.8	NR	NR	NR
12	**Regillo 2008**	PIER	LP → Rani 0.5q12w LP → Rani 0.3q12w Sham IVT	NR	NR	NR	NR	NR	NR NR 27.0	NR	NR	NR	NR	NR	NR
13	**Rosenfeld 2006**	MARINA	Rani 0.5q4w Rani 0.3q4w Sham IVT	NR	NR	21 22 13	8.8 9.2 5.5	NR	NR	NR	NR	NR	NR	NR	NR
14	**Silva 2017**	TREND	LP → Rani 0.5TREX Rani 0.5q4w	NR	NR	NR	NR	33 32	10.2 9.8	NR	NR	8.7 11.1	2.68 2.43	NR	NR
15	**Wykoff 2015 / 2017**	TREX-AMD	LP → Rani 0.5TREX Rani 0.5q4w	NR	NR	NR	NR	NR	NR	NR	NR	10.1 13	NR	18.6 25.5	NR

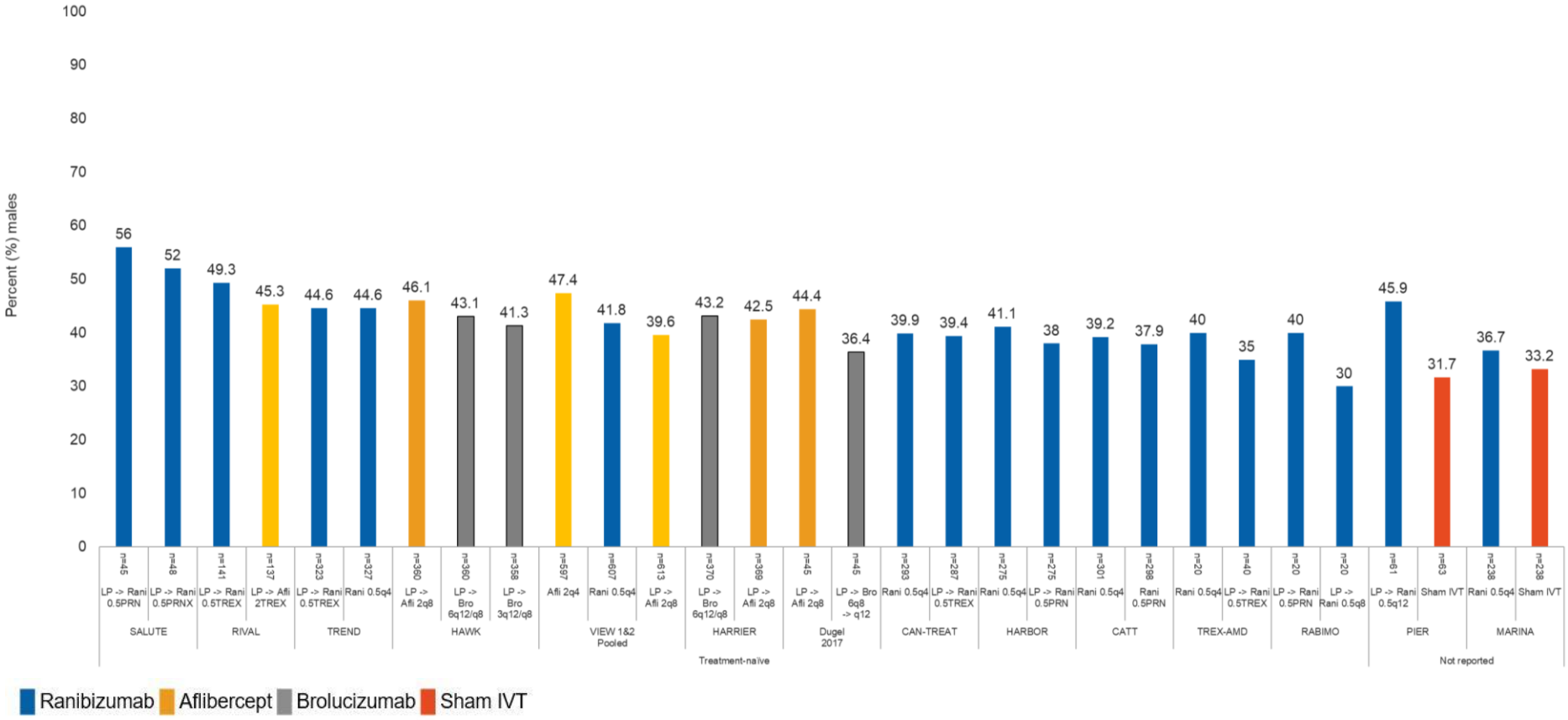
[a]Number of re-injections reported rather than number of injections.
Abbreviations: ID: identification; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; NR: not reported; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SD: standard deviation; TREX: treat-and-extend dosing regimen.

Figure 53: Baseline age of participants for studies included in the NMA



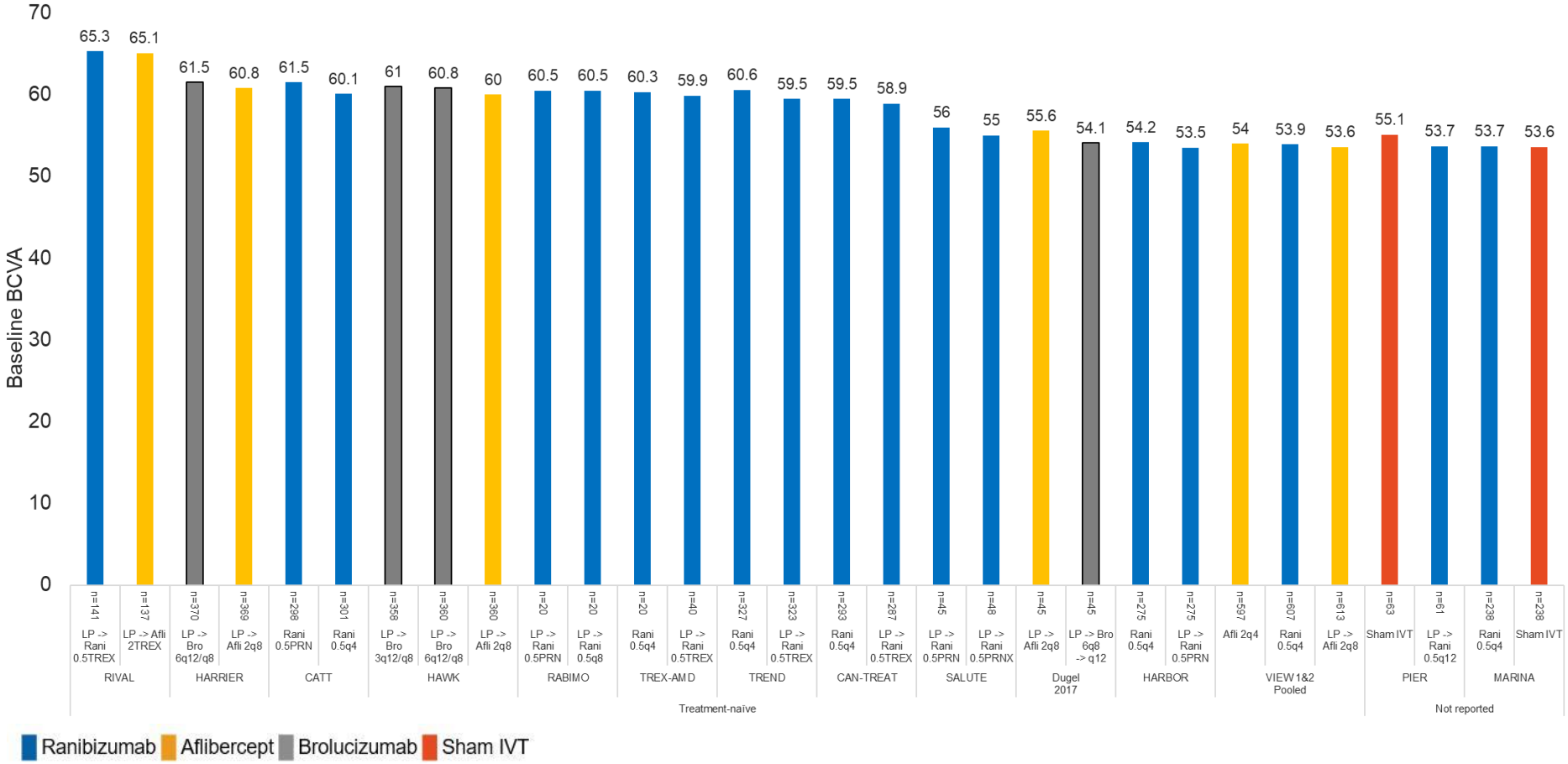
Abbreviations: IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qX: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Figure 54: Baseline sex (proportion of males) of participants for studies included in the NMA



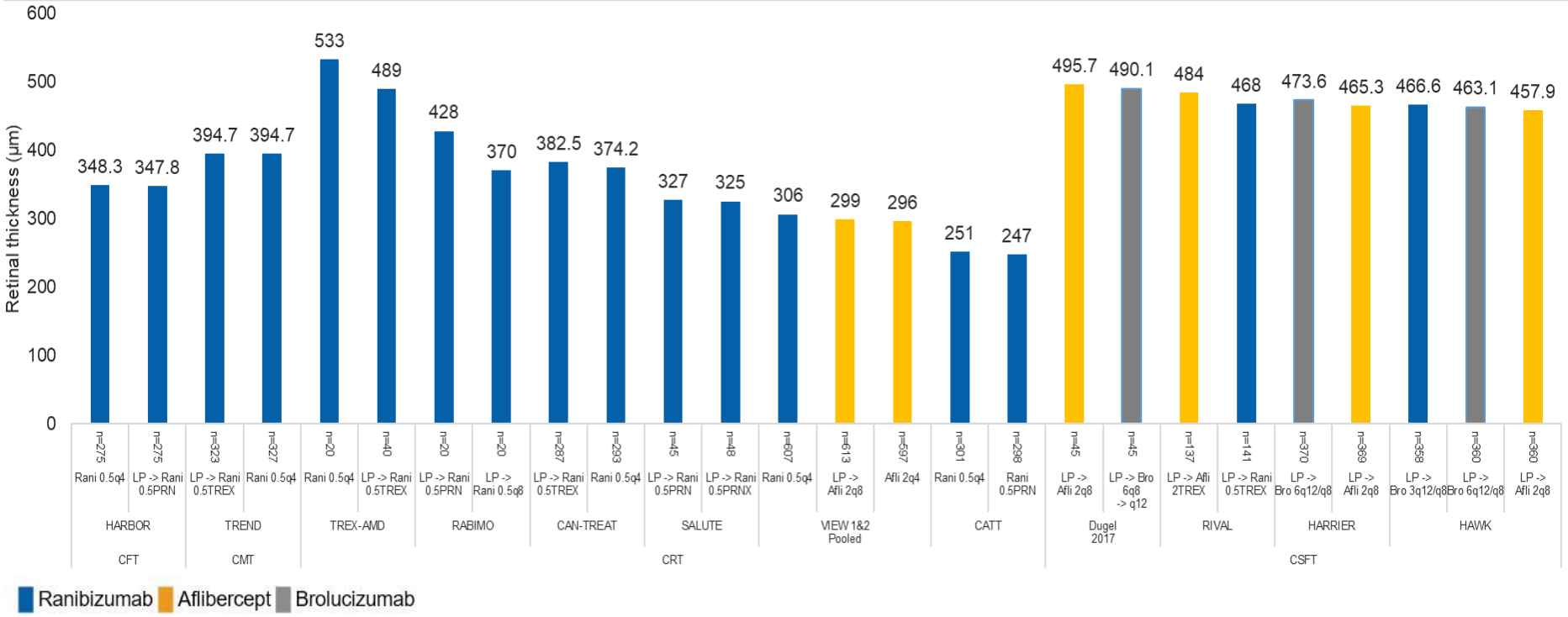
Abbreviations: IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qX: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Figure 55: Baseline visual acuity (ETDRS) of participants for studies included in the NMA



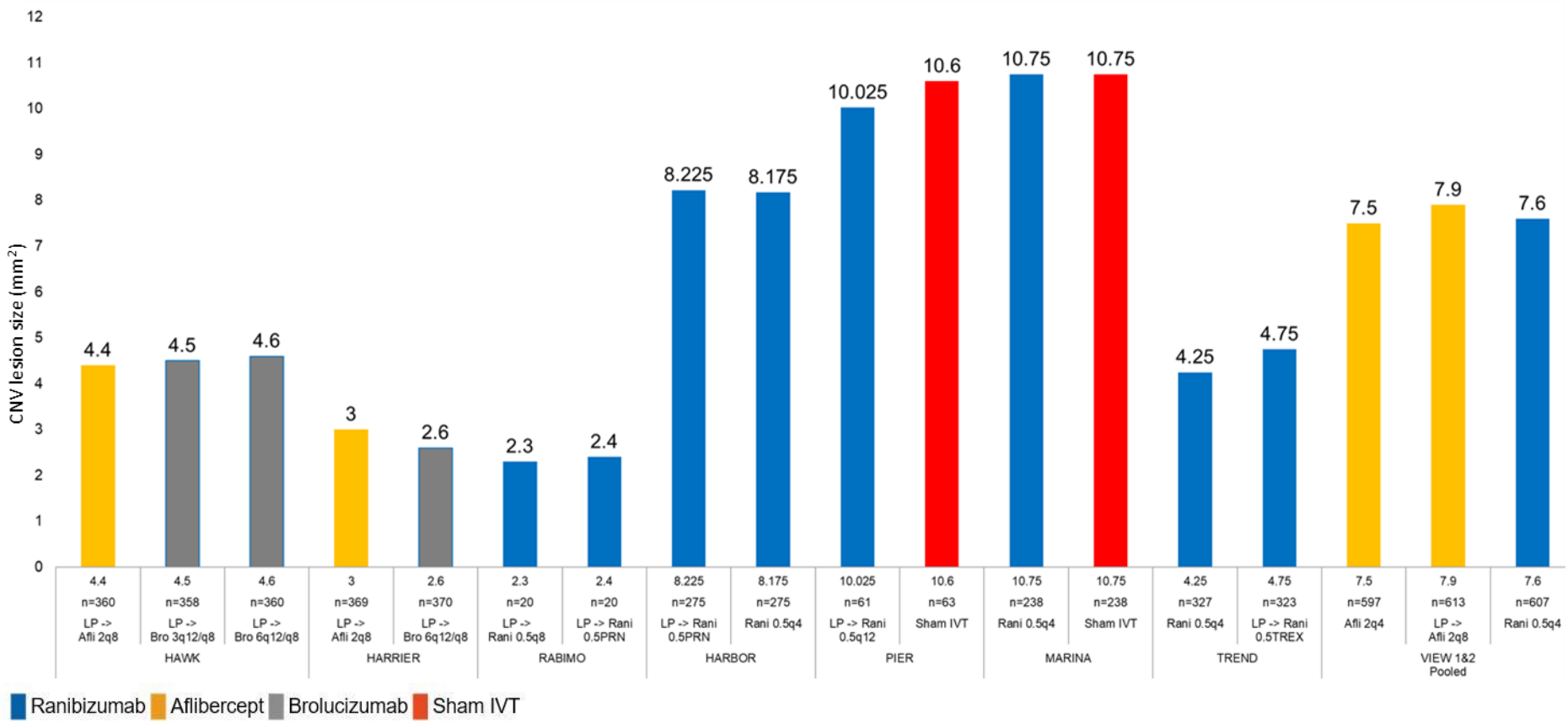
Abbreviations: BCVA: best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qX: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Figure 56: Baseline retinal thickness (CRT, CMT, CSFT, CFT) of participants for studies included in the NMA



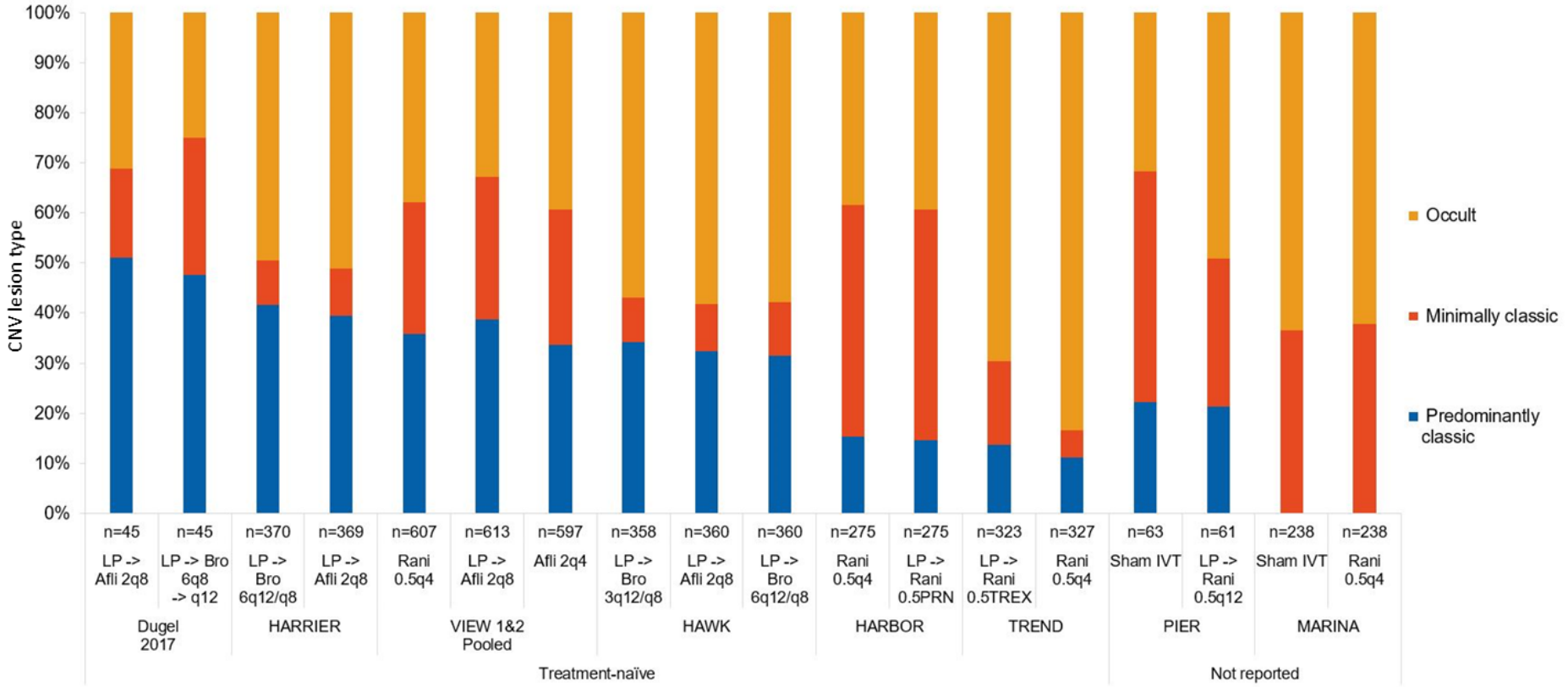
Abbreviations: CFT: central field thickness; CMT: central macular thickness; CRT: central retinal thickness; CSFT: central subfield thickness; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qX: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Figure 57: Baseline CNV lesion size (mm^2) of participants for studies included in the NMA



For the HARBOR, PIER, MARINA and TREND studies, disc area measurement was converted to mm^2.
Abbreviations: CNV: choroidal neovascularisation; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; qX: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Figure 58: Baseline CNV lesion types (predominantly classic, minimally classic, and occult) of participants for studies included in the NMA



Abbreviations: CNV: choroidal neovascularisation; IVT: intravitreal; LP: loading phase; NMA: network meta-analysis; PRN: pro re nata dosing regimen; qX: one injection every X weeks; TREX: treat-and-extend dosing regimen.

7.6 Methods of evidence synthesis

Baseline pooling methodology

Baseline pooling was conducted to estimate the absolute treatment effect for treatment regimens with more than one trial. The following outcomes were considered:

- Mean change in BCVA
- Proportion of patients gaining at least 15 ETDRS letters
- Proportion of patients losing at least 15 ETDRS letters
- Overall discontinuation
- Injection frequency
- Adverse events (intraocular inflammation, endophthalmitis, retinal detachment, retinal tear, retinal pigment epithelial tear, and cataract)

Regimen-based pooling was conducted for the mean change in BCVA, patients gaining at least 15 letters, patients losing at least 15 letters, injection frequency, and adverse events. Molecule-based pooling was conducted for discontinuation as well as adverse events.

An NMA for injection numbers using a regimen-based approach was not conducted as the number of injections was directly related to the type of regimen. The assumption made for VIEW1&2 in all other networks at year 2 (patients that began a PRN treatment regimen at 52 weeks were still considered as continuous treatment arms in order to connect to the brolucizumab treatments) could also not be applied in this case. This is because number of injections is highly correlated with treatment regimen.

While an NMA would have been a superior method to study relative effects for adverse events, it was not feasible due to a general lack of data on individual adverse events. In addition, multiple zero events in the analysis could cause problems in running NMAs. For these reasons, a baseline pooling method was chosen.

Inverse-variance weighting was used to obtain the weighted average absolute treatment effects.[108] Both fixed and random-effects models were tested using the following equations:

Fixed-effects:

$\hat{\theta}_{fixed} = \frac{\sum_{i=1}^{N} w_i \theta_i}{\sum_{i=1}^{N} w_i}$ where $w_i = \frac{1}{Var(\theta_i)}$

$Var(\hat{\theta}_{fixed}) = \frac{1}{\sum_{i=1}^{N} w_i}$

Random-effects:

$\hat{\theta}_{random} = \frac{\sum_{i=1}^{N} w_i^* \theta_i}{\sum_{i=1}^{N} w_i^*}$ where $w_i^* = \frac{1}{Var(\theta_i)+\tau^2}$ and $\hat{\tau} = \frac{Q-(N-1)}{\sum_{i=1}^{N} w_i - \frac{\sum_{i=1}^{N} w_i^2}{\sum_{i=1}^{N} w_i}}$

$$Var(\hat{\theta}_{random}) = \frac{1}{\sum_{i=1}^{N} w_i^*}$$

Q is the Cochran's Q value, which is calculated as $Q = \sum_{i=1}^{N} w_i(\theta_i - \hat{\theta}_{fixed})^2$ where $\hat{\theta}$=mean, N= number of studies and w= weight for each study.

Pooled standard deviations

In addition to pooling mean treatment effects, pooled standard deviations for each outcome were obtained using a weighted average. The following equation was used to obtain these estimates [108]:

$$\hat{\theta} = \sum_{i=1}^{n} w_i \theta_i \text{ where } w_i = \frac{N_i}{\sum_{i=1}^{n} N_i}$$

θ_i is the standard deviation of the ith study for the treatment of interest and N_i is the number of patients in the treatment arm of interest for the ith study.

Methods of indirect treatment comparison

Statistical model selection

The relative goodness of fit of the models were assessed using the DIC (Deviance Information Criterion). The fixed-effects and random-effects models were developed and the one associated with the lowest DIC was selected. If the absolute difference between the DICs values of the two models is less than three points, the fixed-effect model will be chosen.[109] The model with the smallest DIC is the model with the best compromise between adequacy and complexity:[109]

$$DIC = \overline{D} + P_D$$

where $\overline{D}$ is the posterior mean residual deviance and PD is the effective number of parameters.

The posterior mean residual deviance $\overline{D}$ was also used to assess the absolute goodness of fit of the model. For a model that fits well, $\overline{D}$ approximates the number of unconstrained data points.[110]

Multi-arm trials

When trials compared more than two treatments of interest, an adjustment was made in order to include all arms assessing a treatment of interest in the analysis. The approach adjusted for the correlation between treatment effects from the same trials. In doing so, multi-arm trials estimate a vector of random-effects rather than only one value. This vector is calculated using a conditional distribution in which one of the random-effects will be estimated given another one from the same multi-arm trial. This allows the between-arm correlation to be taken into account. This approach is based on a conditional distribution formulation of the multivariate normal distribution.

Meta-regression

Meta-regressions were considered in accordance with published recommendations from the NICE Decision Support Unit.[111] Of three types of meta-regression models, the first model assumes independent and unrelated interactions for each treatment. In the second model, the interaction terms are assumed exchangeable, and the third model assumes a single interaction effect for all treatments. The first model requires a large amount of data to converge. In addition, the assumption of exchangeable interactions terms cannot be validated in this context. Therefore, the model with a single interaction term for all treatments was considered. The interaction between treatment effect and effect-modifying covariates was assumed the same across trials. The meta-regression conducted by NICE in their clinical guidelines for wAMD followed the same approach of assuming the same effect modification for all covariates.[49]

The following covariates were considered in the meta-regression: Baseline BCVA value and type of treatment regimen (e.g. treatment as needed, routing monthly schedule, etc.). Baseline BCVA was chosen as it has been identified as a potential treatment effect modifier and the values do not appear homogenous across trials. In addition, treatment regimen was included as a covariate in the meta-regression conducted by NICE in their clinical guidelines for wAMD as there are

shared features among the different treatment regimens[49]. In the case of non-convergence of the meta-regression models, a standard NMA was used.

Meta-regression convergence was tested using both attribute-based characteristics and Baseline BCVA using two separate models. Baseline BCVA was chosen because it was identified as a potential treatment effect modifier and the values did not appear homogenous across trials. In addition, treatment regimens were included as covariates given that there are shared features among the different regimens (this was the approach used in the NICE NMA in wAMD[49]). When adjusting on only Baseline BCVA in one model, and on PRN regimen in another model, neither the fixed nor random-effects model converged. Multiple methods were used to attempt to reach convergence, including increasing the number of iterations and burn-in to 100,000 in the fixed-effects model and 200,000 in the random-effects model, testing different prior distributions, and changing the initial values. Finally, models converged due to the larger number of trials included to inform the analysis since unlicensed doses and treatments were considered in their analyses. The present study contained more restrictions, including only licensed doses and treatments, in order to reduce heterogeneity and provide relevant comparisons. Given the lack of convergence of the meta-regression models, standard NMA models were considered most appropriate for the analyses.

Outputs

The outputs included mean, standard deviation (of the posterior distribution for the parameter), median and credible interval at 95% for brolucizumab versus comparators and for all treatments versus each other.

Implementation

Non-informative prior distributions were used for unknown parameters in order to obtain results driven by the data. The following priors were used for the base case analysis[112]:

- Normal distributions with a mean of 0 and a variance of 10,000 for treatments effects
- For random-effects models, a uniform distribution for the between-trial standard deviation, with a range of [0,2]

The NMA was performed with WinBUGS V1.4 using MCMC (Markov Chain Monte Carlo) simulation method. Three chains[111] were simulated and their convergence was assessed by examining the history, trace and Gelman-Rubin plots.[113] Starting values were arbitrarily selected for all fixed-effect nodes for each chain. Initial values were generated automatically by WinBUGS for random-effects nodes. A total of 20,000 iterations were used as burn-in followed by 20,000 iterations to monitor the parameters for fixed-effects model, and 100,000 iterations as burn-in and 100,000 to monitor the parameters for random-effects models.[112]

Injection frequency

For injection frequency, the annualised rate was calculated for trials reporting results at 48 weeks and 96 weeks. For results at one year, the following formula was used:

$$\overline{Inj}_{52} = \frac{\overline{Inj}_{48}}{48/52}$$

where $\overline{Inj}_{52}$ is the average number of injections from Week 0-52 and $\overline{Inj}_{48}$ is the average number of injections from Week 0-48. Similarly, the annualised rate for results at two years was calculated using the following formula when results were reported at 96 weeks:

$$\overline{Inj}_{104} = \frac{1}{2}\left(\frac{\overline{Inj}_{96}}{96/104}\right)$$

When results were reported at 104 weeks, the annualised rate was taken by dividing the mean number of injections between Baseline and two years by two.

The annualised rate from Week 52-104 was taken by subtracting $\overline{Inj}_{52}$ from $\overline{Inj}_{104}$:

$$\overline{Inj}_{52-104} = \left(\frac{\overline{Inj}_{96}}{96/104}\right) - \overline{Inj}_{52}$$

Mean difference and variance between one and two years

For the injection frequency and mean change in BCVA between one and two years, the mean difference between one and two years was calculated. The variance of this value was calculated using the following equation:

$$\sigma_{change}{}^2 = \sigma_{final}{}^2 + \sigma_{baseline}{}^2 - 2\rho\sqrt{\sigma_{final}{}^2 * \sigma_{baseline}{}^2}$$

where σ2 is the variance reported for the outcome. A correlation of ρ = 0.5 was assumed.

Assumptions adopted in the NMA

An assumption has been made involving LP → Afli 2q8w and Rani 0.5q4w for results at two years. In VIEW 1&2, patients began a PRN treatment schedule from Weeks 56–96, with patients switching from LP → Afli 2q8w, Rani 0.5q4w, and Afli 2q4w to PRN. This resulted in the HAWK and HARRIER studies for brolucizumab being disconnected from the network. In order to connect the networks for two-year outcomes, equivalence was assumed between:

- LP → Afli 2q8w and LP → Afli 2q8w (year 1) → PRN (year 2)
- Rani 0.5q4w and Rani 0.5q4w (year 1) → PRN (year 2)

During the PRN phase of VIEW 1&2 (Weeks 56–96), patients received on average 4.2 injections in the LP → Afli 2q8w group. In HAWK and HARRIER, patients in the aflibercept group received five injections between Weeks 56 and 96. Given the similar number of injections during the second year of follow-up, any differences between these trials may not be due to the reduced number of injections during the PRN phase of VIEW 1&2. In addition, in order to be consistent with the assumptions made, the same assumption was made for the Rani 0.5q4w arm.

To assess the impact of the assumption made for VIEW1&2, the outcomes were synthesised and a test for heterogeneity was conducted to see if there was evidence of a heterogeneity between trials for Rani 0.5q4w at two years. There was no significant heterogeneity identified for mean change in BCVA, or for the proportion of patients gaining or losing at least 15 letters, when including VIEW 1&2. However, significant heterogeneity was identified for injection frequency, which reflect the switch to a PRN regiment at 2 year in VIEW 1&2. The other main assumptions made in the analysis are as follows:

- CRT, CFT, CSFT, and CMT were considered as the same measure, as validated by Novartis's medical expert
- Equivalence was assumed for assessment times between 48 and 52 Weeks for 12-month outcomes, and between 96 and 104 Weeks for 24-month outcomes
- Treatment-naïve patients were considered comparable to mixed patients/trials not reporting previous anti-VEGF treatment use

Programming language for the indirect treatment comparison

NMA – Fixed-effects

```
model{ # *** PROGRAM STARTS
	for(i in 1:ns){ # LOOP THROUGH STUDIES
		mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
		for (k in 1:na[i]) { # LOOP THROUGH ARMS
			var[i,k] <- pow(se[i,k],2) # calculate variances
			prec[i,k] <- 1/var[i,k] # set precisions
			y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # normal likelihood
			theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]] # model for linear predictor
			dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k] #Deviance contribution	}

		resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial	}


	totresdev <- sum(resdev[]) #Total Residual Deviance
	d[1]<-0 # treatment effect is zero for reference treatment
	for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects

##Estimate
 #Rank
	for (k in 1:nt){
		rk[k]<- (nt+1)-rank(d[],k)
		best[k]<-equals(rk[k],1)		}

 #Differences
	for(i in 1:nt){
		for  (k in 1:nt){
			diff[i,k]<-d[i]-d[k]
			prob.diff[i,k]<-step(d[i]-d[k])		}		}		} # *** PROGRAM
ENDS
```

NMA – Random-effects

```
model{ # *** PROGRAM STARTS
	for(i in 1:ns){ # LOOP THROUGH STUDIES

		w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm

		delta[i,1] <- 0 # treatment effect is zero for control arm

		mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines

		 for (k in 1:na[i]) { # LOOP THROUGH ARMS

			var[i,k] <- pow(se[i,k],2) # calculate variances

			prec[i,k] <- 1/var[i,k] # set precisions
			y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # normal likelihood

			theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor

			dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k] #Deviance contribution }

	resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial

 for (k in 2:na[i]) { # LOOP THROUGH ARMS

	delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions

	md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of treat effects distributions (with multi-arm trial correction)

	taud[i,k] <- tau *2*(k-1)/k # precision of treat effects distributions (with multi-arm trial correction)
```

```
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-arm RCTs

        sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials}                    }

totresdev <- sum(resdev[]) #Total Residual Deviance

d[1]<-0 # treatment effect is zero for reference treatment

for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects

sd ~ dunif(0,5) # vague prior for between-trial SD.

tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)


for (k in 1:nt) {
        #   rk[k] <- nt+1-rank(d[],k) # assumes events are “good”
        rk[k] <- rank(d[],k) # assumes events are “bad”

        best[k] <- equals(rk[k],1) #calculate probability that treat k is best

        for (j in 1:nt){hist[k,j]<-equals(rk[k],j)}                    }

for(i in 1:nt){
                for  (k in 1:nt){
                        diff[i,k]<-d[i]-d[k]
                        prob.diff[i,k]<-step(d[i]-d[k])
                        CumRank[i,k]<-sum(hist[i,1:k])}
        SUCRA[i]<- sum(CumRank[i,1:(nt-1)]) /(nt-1)                    }} # *** PROGRAM ENDS
```

Binary Outcomes

NMA – Fixed-effects

```
model{ # *** PROGRAM STARTS
        for(i in 1:ns){ # LOOP THROUGH STUDIES
                 mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
                for (k in 1:na[i]) { # LOOP THROUGH ARMS
                          r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
                        logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]] # model for linear predictor
                        rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
                        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance contribution
                                                                + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
                }
         resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
        }

        totresdev <- sum(resdev[]) #Total Residual Deviance
        d[1]<-0 # treatment effect is zero for reference treatment
        for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:nt) {
                #or[1,(c+1)] <- exp(d[c+1])
                for (k in 1:nt) {
                        or[k,c] <- exp(d[c] - d[k])
                        lor[k,c] <- (d[c]-d[k])
                        prob.lor[k,c]<-step(d[c] - d[k])
                }
        }

# ranking on relative scale
for (k in 1:nt) {
#   rk[k] <- nt+1-rank(d[],k) # assumes events are “good”
        rk[k] <- rank(d[],k) # assumes events are “bad”
```

```
        best[k] <- equals(rk[k],1)
        for (j in 1:nt){hist[j,k]<-equals(rk[k],j)}
}

} # *** PROGRAM ENDS
```

NMA – Random-effects

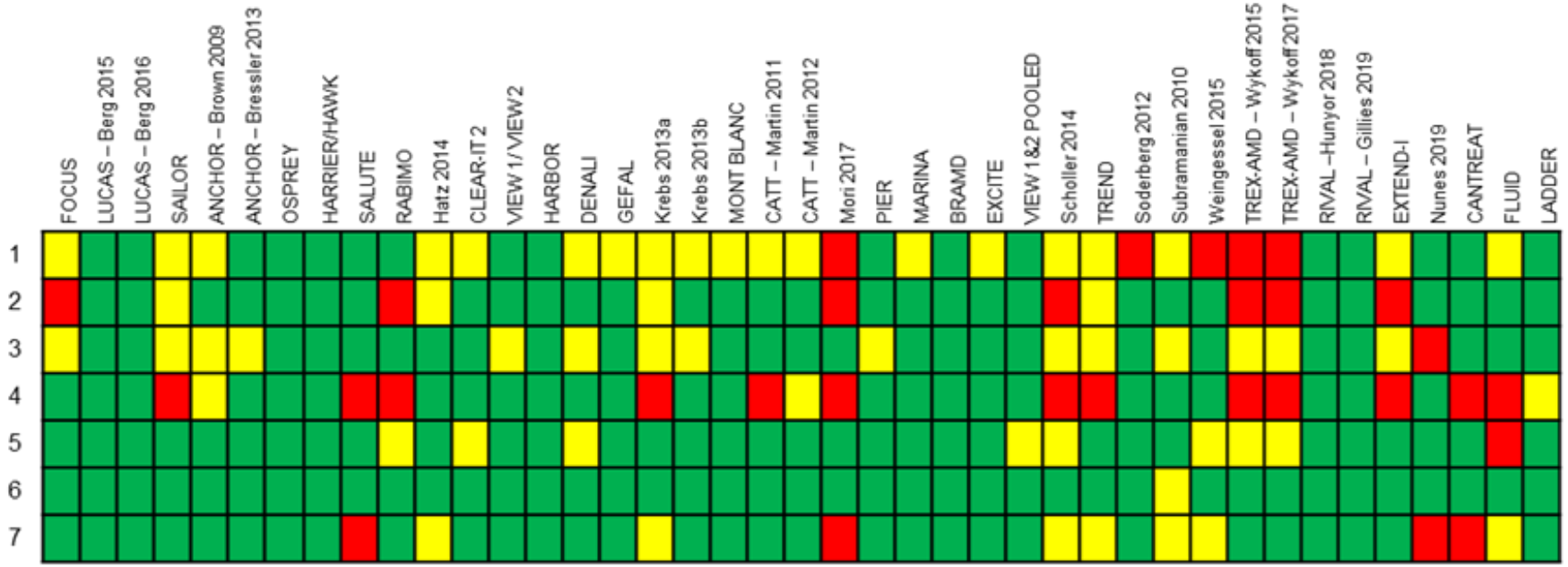
```
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
   w[i,1] <- 0                   # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0            # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {            # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {            # LOOP THROUGH ARMS
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
      taud[i,k] <- tau *2*(k-1)/k
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }  }
totresdev <- sum(resdev[])          # Total Residual Deviance
d[1]<-0      # treatment effect is zero for reference treatment
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,2)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
for (c in 1:nt) {
        for (k in 1:nt) {
                or[k,c] <- exp(d[c] - d[k])
                lor[k,c] <- (d[c]-d[k])
                prob.lor[k,c]<-step(d[c] - d[k])
        } }

# ranking on relative scale
for (k in 1:nt) {
#   rk[k] <- nt+1-rank(d[],k) # assumes events are “good”
        rk[k] <- rank(d[],k) # assumes events are “bad”
        best[k] <- equals(rk[k],1)
        for (j in 1:nt){hist[k,j]<-equals(rk[k],j)}}
for(k in 1:nt) {
                for(j in 1:nt) {
                        cumeffectiveness[k,j]<- sum(hist[k,1:j])        } }

for(k in 1:nt){
        for(j in 1:nt){
        CumRank[k,j]<-sum(hist[k,1:j])
        }}
        #SUCRAS#
        for(k in 1:nt) {
                SUCRA[k]<- sum(CumRank[k,1:(nt-1)]) /(nt-1) }}                  # *** PROGRAM ENDS
```

7.7 Quality assessment of trials included in the NMA

Table 101: Quality assessment of trials included in the NMA



1. Was randomisation carried out appropriately?
2. Was the concealment of treatment allocation adequate?
3. Where the groups similar at the outset of the study in terms of prognostic factors?
4. Were the care providers, participants, and outcome assessors blind to treatment allocation?
5. Were there any unexpected imbalances in drop-outs between groups?
6. Is there any evidence to suggest the authors measured more outcomes than they reported?
7. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

7.8 Results of the sensitivity analyses for the NMA

The results of the sensitivity analyses performed are provided here – please see Section 5.7 for the rationale behind the sensitivity analyses performed.

Inclusion of median change

A sensitivity analysis was conducted including trials that reported only the median change in BCVA and retinal thickness and the results are presented in Table 102 and Table 103 below.

Table 102: Sensitivity analysis for inclusion of median change, for mean change in BCVA from Baseline to one year

Treatment	LP → Bro 6q8w → q12w		LP → Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-1.51 [-7.94, 4.88]	32.4%	-0.74 [-2.74, 1.24]	23.2%
LP → Afli 2q8w	-1.21 [-7.43, 4.99]	35.3%	-0.44 [-1.72, 0.85]	25.4%
LP → Rani 0.5q12w	-0.02 [-9.61, 9.67]	49.9%	0.76 [-6.68, 8.28]	57.9%
LP → Rani 0.5q8w	-1.6 [-11.26, 8.02]	37.4%	-0.84 [-8.4, 6.67]	41.4%
LP → Rani 0.5PRN	0.39 [-6.39, 7.12]	54.4%	1.13 [-1.86, 4.13]	77.4%
Afli 2q4w	-2.1 [-8.52, 4.28]	26.1%	-1.34 [-3.31, 0.63]	9.1%
LP → Rani 0.5TREX	-1.67 [-8.22, 4.89]	31.0%	-0.9 [-3.3, 1.51]	23.2%
Rani 0.5PRN	0.2 [-6.65, 6.97]	52.3%	0.95 [-2.07, 3.94]	73.2%
LP → Bro 6q12/q8w	-0.77 [-7.14, 5.56]	40.6%	-	-
LP → Bro 6q8w → q12w	-	-	0.77 [-5.56, 7.14]	59.4%
LP → Bro 3q12/q8w	-0.36 [-6.86, 6.07]	45.6%	0.4 [-1.39, 2.19]	66.9%
Sham IVT	16.09 [8.97, 23.14]	100.0%	16.85 [13.3, 20.4]	100.0%
LP → Rani 0.5PRNX	-4.05 [-14.72, 6.56]	22.6%	-3.3 [-12.12, 5.48]	22.8%
LP → Afli 2TREX	0.75 [-6.23, 7.74]	58.3%	1.52 [-1.87, 4.9]	80.9%

Abbreviations: BCVA: best-corrected visual acuity; CrI: credibility interval; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 103: Sensitivity analysis for inclusion of median change, for mean change in retinal thickness from Baseline to one year

Treatment	LP → Bro 6q8w → q12w		LP → Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-27.72 [-82.62, 27.64]	83.8%	-50.24 [-70.82, -29.61]	100.0%
LP → Afli 2q8w	-17.13 [-70.1, 36.2]	73.5%	-39.62 [-52.83, -26.33]	100.0%
LP → Rani 0.5q8w	-110.74 [-179.41, -41.27]	99.9%	-133.38 [-179.07, -87.8]	100.0%
LP → Rani 0.5PRN	-36.19 [-96.24, 23.62]	88.1%	-58.88 [-90.08, -27.24]	100.0%
Afli 2q4w	-17.76 [-73.44, 38.27]	73.4%	-40.22 [-61.13, -19.76]	100.0%
Rani 0.5PRN	-52.83 [-116, 10.06]	95.1%	-75.48 [-111.38, -39.35]	100.0%
LP → Bro 6q12/q8w	22.45 [-31.81, 77.36]	20.8%	-	-
LP → Bro 6q8w → q12w	-	-	-22.45 [-77.36, 31.81]	79.2%
LP → Bro 3q12/q8w	12.07 [-43.78, 68.42]	33.6%	-10.4 [-28.01, 7.3]	87.7%
LP → Rani 0.5PRNX	-8.13 [-80.84, 63.74]	58.7%	-30.84 [-82.4, 20.76]	87.9%
LP → Afli 0.5TREX	-34.9 [-95.29, 25.06]	87.3%	-57.5 [-89.34, -26.15]	100.0%

Abbreviations: CrI: credibility interval; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Time extrapolation

An additional sensitivity analysis was considered that extrapolates results prior to 52 Weeks and 104 Weeks. Given that time equivalence was assumed between 48 and 52 Weeks for one-year results and between 96 and 104 Weeks for two-year results, this analysis made it possible to identify if the results are highly influenced by this assumption.

The results of this analysis are presented in Table 104 to Table 107 below.

Mean change in BCVA from Baseline to one year

Table 104: Direct comparison and heterogeneity assessment

Comparison	Trial names	Mean Difference (95% CI)		I-square	p-value for the Cochran test
		Fixed-effects model	Random-effects model		
LP → Bro 6q12/q8w vs LP → Afli 2q8w	HARRIER HAWK	0.49 [-0.86; 1.83]	0.49 [-0.86; 1.83]	0%	0.718
LP → Rani 0.5TREX vs Rani 0.5q4w	TREND TREX-AMD CAN-TREAT	0.16 [-1.22; 1.54]	0.31 [-3.2; 3.81]	77.76%	0.01114

Abbreviations: CI: confidence interval; LP: loading phase; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Table 105: Network meta-analysis results

Treatment	LP → Bro 6q12/q8w		LP → Bro 6q8w → q12w	
	Difference [95% CrI]	Prob. superior	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-0.78 [-2.81, 1.24]	22.7%	-1.53 [-7.89, 4.9]	32.1%
LP → Afli 2q8w	-0.48 [-1.83, 0.86]	24.0%	-1.22 [-7.38, 5.01]	34.9%
LP → Rani 0.5q12w	0.73 [-6.73, 8.25]	57.7%	-0.02 [-9.63, 9.55]	49.9%
LP → Rani 0.5PRN	1.12 [-1.89, 4.14]	76.6%	0.37 [-6.4, 7.18]	54.3%
Afli 2q4w	-1.38 [-3.39, 0.63]	8.8%	-2.13 [-8.48, 4.25]	25.7%
LP → Rani 0.5TREX	-0.94 [-3.41, 1.53]	22.9%	-1.66 [-8.19, 4.88]	30.6%
Rani 0.5PRN	0.91 [-2.1, 3.94]	72.3%	0.18 [-6.6, 6.99]	51.9%
LP → Bro 6q8w → q12w	0.74 [-5.59, 7.04]	59.1%	-	-
LP → Bro 6q12/q8w	-	-	-0.74 [-7.04, 5.59]	40.9%
LP → Bro 3q12/q8w	-0.15 [-2.04, 1.74]	43.9%	-0.89[-7.37, 5.62]	39.3%
Sham IVT	16.81 [13.26, 20.39]	100.0%	16.06[9.1, 23.1]	100.0%
LP → Rani 0.5PRNX	-3.37 [-12.17, 5.48]	22.5%	-4.13[-14.83, 6.54]	22.5%
LP → Afli 2TREX	1.47 [-1.98, 4.89]	79.7%	0.71[-6.23, 7.72]	58.0%

Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Mean change in BCVA from Baseline to two years

Table 106: Direct comparison and heterogeneity assessment

Comparison	Trial names	Mean Difference (95% CI)		I-square	P-value for the Cochran test
		Fixed-effects model	Random-effects model		
LP → Bro 6q12/q8w vs LP → Afli 2q8w	HARRIER HAWK	0.07 [-1.53; 1.67]	0.07 [-1.53; 1.67]	0.0%	0.429

Abbreviations: CI: confidence interval; LP: loading phase; qXw: one injection every X weeks.

Table 107: Network meta-analysis results

Treatment	LP→Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-0.25 [-2.58, 2.05]	41.3%
LP → Afli 2q8w	0.06 [-1.53, 1.67]	53.2%
Afli 2q4w	0.26 [-2.04, 2.55]	58.8%
LP → Rani 0.5TREX	3.29 [-5.2, 11.93]	77.6%
LP → Rani 0.5PRN	0.96 [-2.42, 4.34]	70.9%
Rani 0.5PRN	1.84 [-2.16, 5.8]	81.9%
LP → Bro 3q12/q8w	-0.56 [-2.77, 1.66]	31.0%
LP → Bro 6q12/q8w	-	-
Sham IVT	21.25 [17.35, 25.11]	100%
LP → Afli 2TREX	5.28 [-3.61, 14.32]	87.9%

Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Minimum/Maximum for imputed SD

Two sensitivity analyses were conducted regarding trials with imputed standard error from the mean standard deviation of the other trials, including:

- The minimum standard deviation instead of the mean
- The maximum standard deviation instead of the mean

The results of the analyses using the minimum standard deviation are presented in Table 108 to Table 113, and the results of the analyses using the maximum standard deviation are presented in Table 114 to Table 119 below.

Minimum SD

Mean change in BCVA from Baseline to one year

Table 108: Direct comparison and heterogeneity assessment

Comparison	Included trials	Mean Difference (95% CI)		I-square	P-value for the Cochran test
		Fixed-effects model	Random-effects model		
LP → Rani 0.5TREX vs Rani 0.5q4w	TREND TREX-AMD	0.18 [-1.19; 1.54]	0.33 [-2.99; 3.65]	77.8%	0.01106
Rani 0.5q4w vs LP → Afli 2q8w[a]	VIEW 1 VIEW 2	0.36 [-1.28; 2.00]	0.36 [-1.28; 2.00]	0.0%	0.858
Rani 0.5q4w vs Afli 2q4w[a]	VIEW 1 VIEW 2	-0.26 [-1.81; 1.29]	-0.47 [-4.98; 4.04]	88.0%	0.004
LP → Afli 2q8w vs Afli 2q4w[a]	VIEW 1 VIEW 2	-0.70 [-2.26; 0.87]	-0.83 [-5.04; 3.39]	86.1%	0.007
LP → Afli 2q8w vs LP → Bro 6q12/q8w	HARRIER HAWK	0.43 [-0.85; 1.71]	0.43 [-0.85; 1.71]	0.0%	0.763

[a]Direct comparisons come from VIEW 1&2; which were pooled in the NMA.
Abbreviations: CI: confidence interval; IVT: intravitreal; LP: loading phase; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Table 109: Network meta-analysis results

Treatment	LP → Bro 6q8w → q12w		LP → Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-1.53 [-7.81, 4.81]	31.9%	-0.72 [-2.46, 1.00]	20.6%
LP → Afli 2q8w	-1.22 [-7.38, 5.01]	34.9%	-0.43 [-1.71, 0.86]	25.6%
LP → Rani 0.5q12w	-0.03 [-9.57, 9.51]	49.8%	0.79 [-6.6, 8.22]	58.4%
LP → Rani 0.5PRN	0.38 [-6.33, 7.09]	54.2%	1.17 [-1.65, 4.00]	79.2%
Afli 2q4w	-2.13 [-8.39, 4.20]	25.5%	-1.33 [-3.04, 0.39]	6.4%
LP → Rani 0.5TREX	-1.69 [-8.12, 4.80]	30.3%	-0.9 [-3.11, 1.31]	21.3%
Rani 0.5PRN	0.17 [-6.52, 6.91]	52.0%	0.96 [-1.84, 3.80]	74.9%
LP → Bro 6q8w → q12w	-	-	0.79 [-5.53, 7.08]	59.8%
LP → Bro 3q12/q8w	-0.42 [-6.87, 6.06]	44.9%	0.38 [-1.41, 2.17]	66.1%
LP → Bro 6q12/q8w	-0.79 [-7.08, 5.53]	40.2%	-	100.0%

Sham IVT	16.05 [9.16, 23.03]	100.0%	16.87 [13.46, 20.27]	22.7%
LP → Rani 0.5PRNX	-4.12 [-14.76, 6.52]	22.4%	-3.32 [-12.03, 5.48]	81.6%
LP → Afli 2TREX	0.69 [-6.17, 7.63]	57.9%	1.51 [-1.75, 4.75]	20.6%

Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Mean change in BCVA from Baseline to two years

Table 110: Network meta-analysis results

Treatment	LP → Bro 6q12/q8	
	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-0.3 [-2.2; 1.58]	37.9%
LP → Afli 2q8w	0.01 [-1.49; 1.49]	50.5%
Afli 2q4w	0.01 [-1.88; 1.89]	50.6%
LP → Rani 0.5TREX	3.36 [-2.65; 9.42]	86.2%
LP → Rani 0.5PRN	0.89 [-2.21; 4]	71.1%
Rani 0.5PRN	1.76 [-1.22; 4.69]	87.8%
LP → Bro 3q12/q8w	0.01 [-2.03; 2.04]	50.5%
LP → Bro 6q12/q8w	-	-
Sham IVT	21.19 [17.54; 24.81]	100%
LP → Afli 2TREX	5.33 [-1.24; 12.02]	94.5%

Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Mean change in retinal thickness from Baseline to one year

Table 111: Direct comparison and heterogeneity assessment

Comparison	Number of studies	Mean Difference (95% CI)		I-square	p-value for the Cochran test
		Fixed-effects model	Random-effects model		
LP → Rani 0.5TREX vs Rani 0.5q4w	TREND TREX-AMD	12.18 [-11.73; 36.08]	31.05 [-35.63; 97.73]	70.2%	0.0669
Rani 0.5q4w vs LP → Afli 2q8w[a]	VIEW 1 VIEW 2	11.26 (-1.67; 24.18)	11.26 (-1.67; 24.18)	0.0%	0.940

Rani 0.5q4w vs Afli 2q4w[a]	VIEW 1 VIEW 2	7.41 (-5.22; 20.04)	8.21 (-9.95; 26.38)	50.6%	0.155
LP → Afli 2q8w vs Afli 2q4w[a]	VIEW 1 VIEW 2	-3.66 (-16.16; 8.85)	-2.83 (-22; 16.34)	56.7%	0.129
LP → Bro 6q12/q8w vs LP → Afli 2q8w	HARRIER HAWK	-39.28 [-52.55; -26.02]	-39.41 [-59.79; -19.03]	57.6%	0.125

[a]Direct comparisons come from VIEW 1&2; which were pooled in the NMA.
Abbreviations: CI: confidence interval; LP: loading phase; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Table 112: Network meta-analysis results

Treatment	LP → Bro 6q8w → q12w		LP → Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-27.84 [-82.29, 26.74]	83.9%	-50.54 [-70.13, -31.11]	100%
LP → Afli 2q8w	-16.88 [-70.15, 35.82]	73.4%	-39.66 [-53.01, -26.45]	100%
Afli 2q4w	-17.65 [-72.53, 37.02]	73.7%	-40.41 [-60.04, -21.04]	100%
LP → Rani 0.5PRN	-37.35 [-95.78, 21.43]	89.5%	-60.09 [-89.04, -31.41]	100%
Rani 0.5PRN	-53.07 [-115.26, 8.81]	95.3%	-75.8 [-111.12, -40.37]	100%
LP → Bro 6q8w → q12w	-	-	-22.65 [-76.76, 32.33]	79.1%
LP → Bro 3q12/q8w	12.33 [-43.47, 67.71]	33.4%	-10.41 [-28.22, 7.14]	87.4%
LP → Bro 6q12/q8w	22.65 [-32.33, 76.76]	20.9%	-	-
LP → Rani 0.5TREX	-36.9 [-96.22, 22.94]	88.7%	-59.52 [-90.4, -28.88]	100%

Abbreviations: CrI: credibility interval; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Mean change in retinal thickness from Baseline to two years

Table 113: Network meta-analysis results

Treatment	LP → Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-49.89 [-65.97, -34.14]	100%
LP → Afli 2q8w	-35.04 [-48.95, -21.1]	100%
Afli 2q4w	-39.92 [-55.84, -24.24]	100%
LP → Rani 0.5TREX	-20.3 [-59.96, 19.03]	84.5%
LP → Rani 0.5PRN	-59.99 [-79.84, -40.41]	100%

Rani 0.5PRN	-69.4 [-109.05, -29.64]	100%
LP → Bro 3q12/q8w	0.41 [-18.17, 18.9]	48.2%
LP → Bro 6q12/q8w	-	-
LP → Afli 2TREX	-8.07 [-51.55, 34.89]	64.2%

Abbreviations: CrI: credibility interval; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Maximum SD

Mean change in BCVA from Baseline to one year

Table 114: Direct comparison and heterogeneity assessment

Comparison	Included trials	Mean Difference (95% CI)		I-square	p-value for the Cochran test
		Fixed-effects model	Random-effects model		
LP → Rani 0.5TREX vs Rani 0.5q4w	TREND TREX-AMD CAN-TREAT	0.15 [-1.24; 1.55]	0.28 [-3.45; 4]	77.73%	0.01121
Rani 0.5q4w vs LP → Afli 2q8w[a]	VIEW 1 VIEW 2	0.36 [-1.28; 2.00]	0.36 [-1.28; 2.00]	0.0%	0.858
Rani 0.5q4w vs Afli 2q4w[a]	VIEW 1 VIEW 2	-0.26 [-1.81; 1.29]	-0.47 [-4.98; 4.04]	88.0%	0.004
LP → Afli 2q8w vs Afli 2q4w[a]	VIEW 1 VIEW 2	-0.70 [-2.26; 0.87]	-0.83 [-5.04; 3.39]	86.1%	0.007
LP → Bro 6q12/q8w vs LP → Afli 2q8w	HARRIER HAWK	-0.43 [-1.71;0.85]	-0.43 [-1.71;0.85]	0.0%	0.763

[a]Direct comparisons come from VIEW 1&2; which were pooled in the NMA.
Abbreviations: CI: confidence interval; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Table 115: Network meta-analysis results

Treatment	LP → Bro 6q12/q8w		LP → Bro 6q8w → q12w	
	Difference [95% CrI]	Prob. superior	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-0.71 [-3.42, 2.00]	30.5%	-1.49 [-8.12, 5.17]	32.8%
LP → Afli 2q8w	-0.43 [-1.72, 0.86]	25.7%	-1.22 [-7.38, 5.01]	34.9%

LP → Rani 0.5q12w	0.8 [-6.92, 8.49]	58.0%	0.01 [-9.79, 9.76]	50.1%
LP → Rani 0.5PRN	1.18 [-2.33, 4.71]	74.5%	0.39 [-6.63, 7.43]	54.4%
Afli 2q4w	-1.32 [-4, 1.35]	16.5%	-2.13 [-8.73, 4.53]	26.4%
LP → Rani 0.5TREX	-0.87 [-3.95, 2.16]	29.3%	-1.64 [-8.46, 5.15]	31.6%
Rani 0.5PRN	0.99 [-2.57, 4.47]	70.7%	0.18 [-6.83, 7.24]	52.0%
LP → Bro 6q8w → q12w	0.79 [-5.52, 7.08]	59.7%	-	-
LP → Bro 3q12/q8w	0.38 [-1.42, 2.17]	66.2%	-0.42 [-6.88, 6.07]	44.9%
LP → Bro 6q12/q8w	-	-	-0.79 [-7.08, 5.52]	40.3%
Sham IVT	16.87 [12.89, 20.89]	100%	16.07 [8.88, 23.32]	100%
LP → Rani 0.5PRNX	-3.32 [-12.36, 5.72]	23.5%	-4.13 [-14.96, 6.71]	22.9%
LP → Afli 2TREX	1.55 [-2.37, 5.37]	78.2%	0.74 [-6.45, 7.96]	58.0%

Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Mean change in BCVA from Baseline to two years

Table 116: Network meta-analysis results

Treatment	LP → Bro 6q12/q8w	
	Difference [95% CrI]	**Prob. superior**
Rani 0.5q4w	-0.31 [-2.68, 2.02]	39.4%
LP → Afli 2q8w	0.01 [-1.46, 1.49]	50.4%
Afli 2q4w	0.00 [-2.34, 2.32]	50.1%
LP → Rani 0.5TREX	3.19 [-6.05, 12.61]	75.1%
LP → Rani 0.5PRN	0.89 [-2.52, 4.31]	69.7%
Rani 0.5PRN	1.78 [-2.25, 5.76]	80.9%
LP → Bro 6q12/q8w	-	-
LP → Bro 3q12/q8w	0.01 [-2.00, 2.04]	50.4%
Sham IVT	21.19 [17.28, 25.08]	100.0%
LP → Afli 2TREX	5.19 [-4.42, 14.98]	85.7%

Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Mean change in retinal thickness from Baseline to one year

Table 117: Direct comparison and heterogeneity assessment

Comparison	Trial names	Mean Difference (95% CI)		I-square	p-value for the Cochran test
		Fixed-effects model	Random-effects model		
LP → Rani 0.5TREX vs Rani 0.5q4w	TREND TREX-AMD	8.12 [-16.55; 32.79]	20.54 [-37.56; 78.64]	40.16%	0.19613
Rani 0.5q4w vs LP → Afli 2q8w[a]	VIEW 1 VIEW 2	11.26 [-1.67; 24.18]	11.26 [-1.67; 24.18]	0.0%	0.940
Rani 0.5q4w vs Afli 2q4w[a]	VIEW 1 VIEW 2	7.41 [-5.22; 20.04]	8.21 [-9.95; 26.38]	50.6%	0.155
LP → Afli 2q8w vs Afli 2q4w[a]	VIEW 1 VIEW 2	-3.66 [-16.16; 8.85]	-2.83 [-22.00; 16.34]	56.7%	0.129
LP → Bro 6q12/q8w vs LP → Afli 2q8w	HARRIER HAWK	-39.28 [-52.55; -26.02]	-39.41 [-59.79; -19.03]	57.6%	0.125

[a]Direct comparisons come from VIEW 1&2; which were pooled in the NMA.
Abbreviations: CI: confidence interval; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; TREX: treat-and-extend dosing regimen.

Table 118: Network meta-analysis results

Treatment	LP → Bro 6q12/q8w		LP → Bro 6q8w → q12w	
	Difference [95% CrI]	Prob. superior	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-50.33 [-74.99, -25.88]	100%	-27.73 [-83.67, 28.98]	83.1%
LP → Afli 2q8w	-39.67 [-53.02, -26.45]	100%	-16.92 [-70.17, 35.80]	73.5%
Afli 2q4w	-40.18 [-64.94, -15.75]	100%	-17.40 [-74.25, 39.30]	72.6%
LP → Rani 0.5PRN	-58.69 [-98, -19.37]	99.9%	-36.05 [-99.97, 28.49]	86.5%
Rani 0.5PRN	-75.60 [-114.13, -37.1]	100%	-52.90 [-116.48, 10.70]	94.8%
LP → Bro 6q8w → q12w	-22.57 [-76.71, 32.38]	79.1%	-	
LP → Bro 3q12/q8w	-10.41 [-28.24, 7.18]	87.4%	12.29 [-43.45, 67.72]	33.4%
LP → Bro 6q12/q8w	-	-	22.57 [-32.38, 76.71]	20.9%
LP → Rani 0.5TREX	-55.29 [-90.08, -20.56]	99.9%	-32.56 [-94.04, 29.27]	85.0%

Abbreviations: CrI: credibility interval; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Mean change in retinal thickness from Baseline to two years

Table 119: Network meta-analysis results

Treatment	LP→Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-49.29 [-74.51, -24.25]	100%
LP → Afli 2q8w	-35.05 [-49.01, -21.15]	100%
Afli 2q4w	-39.36 [-64.66, -14.28]	99.9%
LP → Rani 0.5TREX	-17.78 [-101.69, 65.14]	64.4%
LP → Rani 0.5PRN	-56.93 [-97.52, -16.77]	99.7%
Rani 0.5PRN	-68.68 [-112.52, -24.09]	99.9%
LP → Bro 6q12/q8w	-	-
LP → Bro 3q12/q8w	0.39 [-18.11, 18.93]	48.3%
LP → Afli 2TREX	-5.77 [-90.39, 78.55]	52.2%

Abbreviations: BCVA: best-corrected visual acuity; CrI: credibility interval; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Exclusion of RIVAL

A sensitivity analysis was performed, where the RIVAL study was excluded from visual acuity outcomes (mean change in BCVA, and patients gaining and losing at least 15 letters), as patients in RIVAL had the highest mean BCVA at Baseline and the results from this study appeared to be outlying values.

The results of this analysis are reported in Table 120 to Table 123 below.

Table 120: Mean change in BCVA from Baseline to one year

Treatment	LP → Bro 6q12/q8w		LP → Bro 6q8w → q12w	
	Difference [95% CrI]	Prob. superior	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-0.74 [-2.69, 1.22]	23.0%	-1.5 [-7.93, 4.89]	32.3%
LP → Afli 2q8w	-0.43 [-1.72, 0.86]	25.5%	-1.19 [-7.47, 4.98]	35.3%
LP → Rani 0.5PRN	1.15 [-1.78, 4.11]	77.9%	0.41 [-6.44, 7.18]	54.7%
LP → Rani 0.5q12w	0.76 [-6.69, 8.08]	58.0%	-0.01 [-9.59, 9.49]	49.9%
Afli 2q4w	-1.33 [-3.3, 0.61]	8.9%	-2.08 [-8.53, 4.26]	25.9%
LP → Rani 0.5TREX	-0.90 [-3.29, 1.49]	23.0%	-1.66 [-8.25, 4.87]	30.8%
Rani 0.5PRN	0.95 [-2.01, 3.92]	73.5%	0.19 [-6.66, 6.96]	52.2%
LP → Bro 6q8w → q12w	0.76 [-5.62, 7.18]	59.4%	-	-
LP → Bro 6q12/q8w	-	-	-0.76 [-7.18, 5.62]	40.6%
LP → Bro 3q12/q8w	0.39 [-1.41, 2.18]	66.8%	-0.38 [-6.91, 6.13]	45.4%
Sham IVT	16.86 [13.35, 20.34]	100%	16.09 [9.05, 23.1]	100.0%
LP → Rani 0.5PRNX	-3.28 [-12.03, 5.47]	23.3%	-4.02 [-14.8, 6.64]	23.0%

Abbreviations: BCVA: best-corrected visual acuity; CrI: credibility interval; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 121: Mean change in BCVA from Baseline to two years

Treatment	LP → Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-0.27 [-2.46, 1.88]	40.30%
LP → Rani 0.5PRN	0.90 [-2.41, 4.18]	70.40%
LP → Afli 2q8w	0.02 [-1.46, 1.49]	51.10%
Afli 2q4w	0.01 [-2.14, 2.17]	50.40%
LP → Rani 0.5TREX	3.46 [-4.57, 11.49]	80.00%
Rani 0.5PRN	1.83 [-2.03, 5.68]	82.40%
LP → Bro 6q12/q8w	-	-
LP → Bro 3q12/q8w	0.01 [-2.02, 2.02]	50.30%
Sham IVT	21.21 [17.45, 24.96]	100.00%

Abbreviations: BCVA: best-corrected visual acuity; CrI: credibility interval; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 122: Patients gaining at least 15 letters from Baseline to one year

Treatment	LP → Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	1.12 [0.80, 1.55]	74.6%
LP → Rani 0.5PRN	1.37 [0.84, 2.22]	89.4%
LP → Afli 2q8w	1.19 [0.95, 1.50]	94.0%
LP → Rani 0.5q12w	7.56 [1.90, 29.75]	99.7%
LP → Rani 0.5q8w	2.18 [0.52, 9.42]	85.8%
Afli 2q4w	1.07 [0.77, 1.48]	65.2%
LP → Rani 0.5TREX	0.95 [0.62, 1.45]	40.0%
Rani 0.5PRN	1.75 [1.07, 2.86]	98.7%
LP → Bro 6q12/q8w	-	-
LP → Bro 3q12/q8w	1.36 [1.00, 1.86]	97.6%
Sham IVT	11.03 [5.48, 23.67]	100.0%
LP → Rani 0.5PRNX	0.78 [0.24, 2.39]	33.1%

Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 123: Patients losing at least 15 letters from Baseline to one year

Treatment	LP → Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	0.81 [0.39, 1.66]	72.1%
LP → Rani 0.5PRN	0.30 [0.08, 0.98]	97.7%
LP → Afli 2q8w	0.97 [0.61, 1.55]	54.9%
LP → Rani 0.5q12w	0.74 [0.19, 3.07]	66.6%
LP → Rani 0.5q8w	0.11 [0.00, 2.19]	92.8%
Afli 2q4w	0.98 [0.47, 2.05]	52.6%
LP → Rani 0.5TREX	0.72 [0.29, 1.81]	75.6%
Rani 0.5PRN	1.01 [0.35, 2.9]	49.3%
LP → Bro 6q12/q8w	-	-

LP → Bro 3q12/q8w	1.01 [0.57, 1.85]	48.6%
Sham IVT	0.07 [0.03, 0.19]	100.0%
LP → Rani 0.5PRNX	0.29 [0.04, 2.10]	89.1%

Abbreviations: CrI: credibility interval; IVT: intravitreal; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Exclusion of PIER and MARINA

A sensitivity analysis was conducted where the PIER and MARINA studies were excluded, as these two trials compared an active treatment to sham IVT, which could have introduced bias into the relative efficacy results versus results from studies comparing anti-VEGF treatments.

The results of this analysis are reported in Table 124 to Table 130 below.

Table 124: Mean chance in BCVA from Baseline to one year

Treatment	LP → Bro 6q12/q8w		LP → Bro 6q8w → q12w	
	Difference [95% CrI]	Prob. superior	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-0.74 [-2.68, 1.21]	23.0%	-1.49 [-7.93, 4.88]	32.3%
LP → Afli 2q8w	-0.43 [-1.71, 0.86]	25.8%	-1.19 [-7.42, 5.03]	35.5%
LP → Rani 0.5PRN	1.16 [-1.78, 4.08]	78.0%	0.40 [-6.36, 7.19]	54.6%
Afli 2q4w	-1.34 [-3.3, 0.59]	9.0%	-2.10 [-8.54, 4.29]	26.3%
LP → Rani 0.5TREX	-0.91 [-3.31, 1.47]	23.0%	-1.68 [-8.25, 4.89]	30.8%
Rani 0.5PRN	0.95 [-1.99, 3.9]	73.5%	0.19 [-6.6, 6.97]	52.2%
LP → Bro 6q8w → q12w	0.77 [-5.57, 7.12]	59.2%	-	-
LP → Bro 6q12/q8w	-	-	-0.77 [-7.12, 5.57]	40.8%
LP → Bro 3q12/q8w	0.38 [-1.4, 2.16]	66.2%	-0.38 [-6.88, 6.09]	45.5%
LP → Rani 0.5PRNX	-3.34 [-12.15, 5.37]	22.9%	-4.09 [-14.76, 6.62]	22.5%
LP → Afli 2TREX	1.48 [-1.96, 4.84]	80.1%	0.73 [-6.3, 7.69]	57.9%

Abbreviations: BCVA: best-corrected visual acuity; CrI: credibility interval; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 125: Mean change in BCVA from Baseline to two years

Treatment	LP → Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	-0.27 [-2.46, 1.88]	40.3%
LP → Rani 0.5PRN	0.90 [-2.41, 4.18]	70.4%
LP → Afli 2q8w	0.02 [-1.46, 1.49]	51.1%
Afli 2q4w	0.01 [-2.14, 2.17]	50.4%
LP → Rani 0.5TREX	3.36 [-4.45, 11.67]	79.3%
Rani 0.5PRN	1.83 [-2.03, 5.68]	82.4%
LP → Bro 6q12/q8w	-	-
LP → Bro 3q12/q8w	0.01 [-2.02, 2.02]	50.3%
LP → Afli 2TREX	5.33 [-2.93, 14.1]	89.3%

Abbreviations: BCVA: best-corrected visual acuity; CrI: credibility interval; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 126: Mean change in BCVA from one to two years

Treatment	LP → Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior
LP → Rani 0.5PRN	-0.27 [-3.48, 2.93]	43.5%
LP → Afli 2q8w	0.42 [-0.97, 1.80]	72.1%
Rani 0.5q4w	0.43 [-1.63, 2.48]	65.5%
Afli 2q4w	1.31 [-0.73, 3.37]	89.6%
LP → Bro 6q12/q8w	-	-
LP → Bro 3q12/q8w	-0.39 [-2.31, 1.53]	34.6%
LP → Rani 0.5TREX	4.87 [-2.89, 12.57]	88.9%

Abbreviations: BCVA: best-corrected visual acuity; CrI: credibility interval; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 127: Patients gaining at least 15 letters from Baseline to one year

Treatment	LP → Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	1.11 [0.80, 1.55]	73.4%
LP → Rani 0.5PRN	1.36 [0.84, 2.22]	89.2%
LP → Afli 2q8w	1.19 [0.95, 1.49]	93.8%
LP → Rani 0.5q8w	2.18 [0.53, 9.45]	85.9%
Afli 2q4w	1.06 [0.76, 1.48]	64.3%
LP → Rani 0.5TREX	0.95 [0.62, 1.45]	39.9%
Rani 0.5PRN	1.74 [1.06, 2.86]	98.6%
LP → Bro 6q12/q8w	-	-
LP → Bro 3q12/q8w	1.37 [1.01, 1.86]	97.7%
LP → Rani 0.5PRNX	0.77 [0.24, 2.39]	32.8%
LP → Afli 2TREX	1.03 [0.49, 2.17]	53.1%

Abbreviations: CrI: credibility interval; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend treatment regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 128: Patients gaining at least 15 letters from Baseline to two years

Treatment	LP → Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	1.22 [0.88, 1.70]	88.3%
LP → Rani 0.5PRN	1.30 [0.81, 2.12]	86.1%
LP → Afli 2q8w	1.12 [0.89, 1.40]	82.8%
Afli 2q4w	1.25 [0.9, 1.73]	90.6%
Rani 0.5PRN	1.35 [0.77, 2.36]	85.4%
LP → Bro 6q12/q8w	-	-
LP → Bro 3q12/q8w	0.96 [0.72, 1.29]	39.8%
LP → Rani 0.5TREX	0.68 [0.15, 2.49]	28.5%

Abbreviations: CrI: credibility interval; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 129: Patients losing at least 15 letters from Baseline to one year

Treatment	LP → Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	0.80 [0.39, 1.64]	72.7%
LP → Rani 0.5PRN	0.30 [0.09, 0.97]	97.8%
LP → Afli 2q8w	0.97 [0.61, 1.55]	54.8%
LP → Rani 0.5q8w	0.12 [0.00, 2.10]	92.6%
Afli 2q4w	0.98 [0.47, 2.04]	52.4%
LP → Rani 0.5TREX	0.71 [0.29, 1.79]	76.3%
Rani 0.5PRN	1.01 [0.35, 2.88]	49.3%
LP → Bro 6q12/q8w	-	-
LP → Bro 3q12/q8w	1.01 [0.56, 1.85]	49.1%
LP → Rani 0.5PRNX	0.29 [0.04, 2.05]	89.6%
LP → Afli 2TREX	0.43 [0.08, 2.19]	84.6%

Abbreviations: CrI: credibility interval; LP: loading phase; PRN: pro re nata dosing regimen; PRNX: pro re nata and extend treatment regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.

Table 130: Patients losing at least 15 letters from Baseline to two years

Treatment	LP → Bro 6q12/q8w	
	Difference [95% CrI]	Prob. superior
Rani 0.5q4w	0.89 [0.50, 1.56]	66.3%
LP → Rani 0.5PRN	0.54 [0.23, 1.26]	91.9%
LP → Afli 2q8w	1.00 [0.67, 1.47]	50.7%
Afli 2q4w	0.96 [0.54, 1.70]	55.6%
Rani 0.5PRN	0.81 [0.29, 2.18]	66.3%
LP → Bro 6q12/q8w	-	-
LP → Bro 3q12/q8w	0.89 [0.54, 1.47]	68.0%
LP → Rani 0.5TREX	0.08 [0.00, 1.26]	96.1%

Abbreviations: CrI: credibility interval; LP: loading phase; PRN: pro re nata dosing regimen; qXw: one injection every X weeks; SUCRA: surface under the cumulative ranking curve; TREX: treat-and-extend dosing regimen.