Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Brolucizumab (rbe)

Proprietary Product Name: Beovu

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

April 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ADA	Antidrug antibodies
AE	Adverse event
AFL	Aflibercept
AMD	Age-related macular degeneration
ASA	Australian specific Annex
ATE	Arterial thromboembolic event(s)
$AUC_{0\text{-inf}}$	Area under the plasma concentration to time curve from time 0 extrapolated to infinity
BCVA	Best corrected visual acuity
CI	Confidence interval
CNV	Choroidal neovascularisation
CSFT	Central subfield thickness
DLP	Data lock point
ECG	Electrocardiogram
EMA	European medicines agency (EU)
EU	European Union
EU-RMP	European Union-risk management plan
FAS	Full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice
IOP	Intraocular pressure
IRF	Intraretinal fluid
IVT	Intravitreal
LCL	Lower confidence limit

Abbreviation	Meaning
LS	Least squares
nAb	Neutralising antibody
nAMD	Neovascular age-related macular degeneration
OCT	Optical coherence tomography
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PPS	Per-protocol analysis set
PSUR	Periodic safety update report
q12w	Every 12 weeks
q4w	Every 4 weeks
q8w	Every 8 weeks
rbe	Recombinant biological entity
RMP	Risk management plan
RPE	Retinal pigment epithelium
RTH/RTH258	Brolucizumab (drug development name)
SAE	Serious adverse event
SAF	Safety analysis set
scFv	Single-chain variable fragment
SD	Standard deviation
TEAE	Treatment emergent adverse event
T_{max}	Time to maximum plasma concentration
US(A)	United States (of America)
VEGF	Vascular endothelial growth factor
VEGF-A	Vascular endothelial growth factor A
VEGFR-1	Vascular endothelial growth factor receptor-1
VEGFR-2	Vascular endothelial growth factor receptor 2

Abbreviation	Meaning
VTE	Venous thromboembolic events

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	15 January 2020
Date of entry onto ARTG:	16 January 2020
ARTG numbers:	313680, 313681
, *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Active ingredient:	Brolucizumab (rbe)
Product name:	Beovu
Sponsor's name and address:	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road Macquarie Park NSW 2113
Dose form:	Solution for injection
Strength:	120 mg/mL
Containers:	Vial or prefilled syringe
Pack size:	1
Approved therapeutic use:	*Beovu is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD).*
Route of administration:	Intravitreal injection
Dosage:	Beovu must be administered by a qualified ophthalmologist experienced in administering intravitreal injections. The recommended dose is 6 mg brolucizumab (0.05 mL solution) administered by intravitreal injection every 4 weeks (monthly) for the first 3 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 with disease activity, treatment every 8 weeks (2 months) should be considered. In patients without disease activity, treatment up to every 12 weeks (3 months) should be considered. The physician may further individualise treatment intervals based on disease activity.

If visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment, Beovu should be discontinued.

For further information refer to the Product Information.

Product background

This AusPAR describes the application by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to register Beovu brolucizumab (rbe);[1] 120 mg/mL solution for injection for the following proposed indication:

> *Beovu is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD).*

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in people over the age of 65 affecting 10% to 13% of individuals in North America, Europe, and Australia.[2,3,4] Genetic, environmental and health factors play an important role in the pathogenesis of the disease. AMD is classified into 2 clinical subtypes: the non-neovascular (atrophic) or dry form and the neovascular (exudative) or wet form.[5,6,7] Neovascular AMD (nAMD) is characterised by the growth of abnormal new blood vessels (neovascularisation) under the retinal pigment epithelium (RPE) or subretinal space from the subjacent choroid, termed choroidal neovascularisation (CNV).[5] These newly formed vessels have an increased likelihood to leak blood and serum, damaging the retina by stimulating inflammation and scar tissue formation. This damage to the retina results in progressive, severe, and irreversible vision loss.[8,9] Without treatment, most affected eyes will have poor central vision (Snellen fraction 20/200);[10] within 12 months. Although the neovascular form of the disease is only present in about 10% of all AMD cases, it accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-vascular endothelial growth factor (VEGF) treatments.[11,12,13]

[1] Rbe = recombinant biological entity
[2] Kawasaki, R. et al. The Prevalence of Age-Related Macular Degeneration in Asians: A Systematic Review and Meta-Analysis, *Ophthalmology*, 2010; 117: 921–927.
[3] Rein, D. B. et al. Forecasting Age-Related Macular Degeneration Through the Year 2050: The Potential Impact of New Treatments, *Arch Ophthalmol*, 2009; 127 (4): 533-540.
[4] Smith, W. et al. Risk Factors for Age-related Macular Degeneration; Pooled Findings from Three Continents, *Ophthalmology*, 2011; 108 (4), 697-704.
[5] Ferris, F.L., Fine, S.L. and Hyman, L. Age-Related Macular Degeneration and Blindness due to Neovascular Maculopathy, *Arch Opthalmol*, 1984; 102: 1640-1642.
[6] Lim, L.S. et al. Age-related macular degeneration, *Lancet*, 2012; 379: 1728-1738.
[7] Miller, J.W. Age-Related Macular Degeneration Revisited – Piecing the Puzzle: The LXIX Edward Jackson Memorial Lecture, *Am J Ophthalmol*, 2013; 155: 1–35.
[8] Shah, A.R. and Lucian, V. Progressive Visual Loss in Subfoveal Exudation in Age-related Macular Degeneration: A Metaanalysis Using Lineweaver-Burke Plots, *Am J Ophthalmol*, 2007; 143: 83–89.
[9] Shah, A.R. and Lucian, V. Natural history of predominantly classic, minimally classic, and occult subgroups in exudative age-related macular degeneration, Ophthalmology, 2009; 116(10): 1901-1907.
[10] 20/200 is a visual acuity measurement using the Snellen chart. This notation means that a person needs to be at a distance of 20 feet from the chart, in order to read letters that a person with normal visual acuity could read at 200 feet. The metric equivalent for the notation 20/200 is 6/60, meaning that a person needs to be at a distance of 6 metres from the chart, in order to read letters that a person with normal visual acuity could read at 60 metres.
[11] Ferris, F.L. Senile macular degeneration: review of epidemiologic features. *Am J Epidemiol*. 1983; 118(2): 132-151.
[12] Sommer, A.S. Racial differences in the cause-specific prevalence of blindness in east Baltimore, *N Engl J Med*, 1991; 325(20): 1412-1417.
[13] Wong, T. The Natural History and Prognosis of Neovascular Age-Related Macular Degeneration: A Systematic Review of the Literature and Meta-analysis, *Opthalmology*, 2008; 115: 116-126.

VEGF has been shown to be elevated in patients with neovascular AMD and is thought to play a key role in the neovascularisation process.[14] The use of intravitreal pharmacotherapy targeting VEGF has significantly improved visual outcomes in patients with neovascular AMD.[15,16] Anti-VEGF treatments inhibit VEGF signalling pathways and have been shown to halt the growth of neovascular lesions and resolve retinal oedema.

The current recommended treatments for nAMD are:[17]

- Ranibizumab: the dosing regimen for nAMD is one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity, that is, no change in visual acuity and in other signs and symptoms of the disease under continued treatment. The injection volume is 50 µL.
- Aflibercept: the dosing regimen for nAMD is one injection per month for three consecutive months, followed by one injection every two months. The injection volume is 50 µL.

Photodynamic therapy should only be offered as an adjunct to anti-VEGF as second-line treatment for late AMD in the context of a randomised controlled trial.[17] Thermal laser therapy (for example, argon or diode) should not be offered for treating drusen in people with early AMD.

The currently available anti-VEGF treatments have improved the quality of life in patients with nAMD but the frequency of the intravitreal injections is a burden on patients and is resource intensive. In regions with fewer healthcare resources, specifically ophthalmologists and nurse practitioners, this can limit access to treatment. There is ongoing need for a treatment with equivalent or greater efficacy and extended dosing intervals.

Brolucizumab is a humanised monoclonal single-chain variable fragment (scFv) antibody fragment, produced in *Escherichia coli* cells by recombinant DNA technology. Brolucizumab binds with high affinity to vascular endothelial growth factor A (VEGF-A) isoforms (for example, the isoforms VEGF110, VEGF121, and VEGF165), thereby preventing binding of VEGF-A to its receptors vascular endothelial growth factor receptors-1 and 2 (VEGFR-1; andVEGFR-2). By inhibiting VEGF-A binding, brolucizumab suppresses endothelial cell proliferation, thereby reducing pathological neovascularisation and decreasing vascular permeability.

Regulatory status

Beovu brolucizumab (rbe) is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this application, a similar application had been approved in the United States (US), and was under consideration in the European Union (EU), Canada, Switzerland and Singapore (Table 1).

[14] Spilsbury, K. Overexpression of Vascular Endothelial Growth Factor (VEGF) in the Retinal Pigment Epithelium Leads to the Development of Choroidal Neovascularization, *Am J of Pathol*, 2000; 157: 135-144.
[15] Bloch, S.B., Larsen, M. and Munch, I.C. Incidence of Legal Blindness From Age-Related Macular Degeneration in Denmark: Year 2000 to 2010, *Am J Ophthalmol*, 2012; 153: 209–213.
[16] Campbell, J.P., Bressler, S.B., and Bressler, N.M. Impact of availability of anti-vascular endothelial growth factor therapy on visual impairment and blindness due to neovascular age-related macular degeneration, *Arch Ophthalmol*. 2012; 130(6): 794-795.
[17] National Institute for Health and Care Excellence (NICE, UK), Guidance on Age-related macular degeneration, NICE guideline NG82, published January 2018. Available from the NICE website.

Table 1: International regulatory status of Beovu brolucizumab as of November 2019

Region	Submission date	Status	Indications
US	7 February 2019	Approved 7 October 2019	*For the treatment of neovascular (wet) Aged-related Macular Degeneration (AMD)*
EU	6 February 2019	Under review	Under review
Canada	26 March 2019	Under review	Under review
Switzerland	23 February 2019	Under review	Under review
Singapore	29 March 2019	Under review	Under review

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 2 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2019-00106-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	6 March 2019
First round evaluation completed	12 August 2019
Sponsor provides responses on questions raised in first round evaluation	12 September 2019
Second round evaluation completed	10 October 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	5 November 2019
Sponsor's pre-Advisory Committee response	19 November 2019
Advisory Committee meeting	6 December 2019

Description	Date
Registration decision (Outcome)	15 January 2020
Completion of administrative activities and registration on the ARTG	16 January 2020
Number of working days from submission dossier acceptance to registration decision*	189

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

The following TGA-adopted regulatory guidance applies to the present application:

- European Medicines Agency (EMA), Guideline on development, production, characterisation and specification for monoclonal antibodies and related products, EMA/CHMP/BWP/532517/2008; 21 July 2016.

Quality

Brolucizumab is a humanised scFv with a molecular weight of approximately 26 kilodaltons (kDa). It is an inhibitor of VEGF-A, preventing binding to its receptors VEGFR1 and VEGFR2. Brolucizumab is produced in *Escherichia coli* cells by recombinant DNA technology. The drug product is a sterile, single-use, preservative-free, colourless to slightly brownish yellow solution for injection.

The biological evaluation has assessed the application and supporting data relating to the composition, development, manufacture, quality control and stability of Beovu brolucizumab. The following points were summarised:

- There are no objections from a microbiological perspective to approval for the application to register Beovu brolucizumab (rbe) 120 mg/mL solution for injection in vial and prefilled syringe.
- The evaluator recommends that Beovu brolucizumab (rbe) is acceptable for registration with respect to container safety.
- The evaluator has concluded that sufficient evidence has been provided to demonstrate that the risks related to adventitious agents in the manufacturing of brolucizumab have been managed to an acceptable level.
- Issues with Good Manufacturing Practice (GMP) clearance and drug product specification were satisfactorily resolved.

Following the resolution of the above issues following the second round of evaluation, there were no objections on quality grounds to the approval of Beovu brolucizumab (rbe).

Nonclinical

The following conclusions and recommendation were summarised in the nonclinical evaluation:

- The pharmacology studies support the proposed indication.
- The absence of secondary pharmacology studies is noted. Such studies should be submitted in a subsequent submission (the sponsor's response to this point was noted).[18]
- The repeat dose toxicity studies do not raise any clinically relevant safety concerns attributable to brolucizumab; however:
  - Systemic exposures were low and potential systemic toxicities have not been adequately assessed. Potential systemic effects are expected to be similar to those for other VEGF binding antibodies registered for the same indication.
  - Retinal degeneration observed with pilot batches of the drug substance indicate endotoxin levels should be controlled to as low as reasonably practicable. The currently proposed limit may not be sufficient to allay concerns of adverse effects associated with endotoxin.
- The draft PI should be amended as directed in the nonclinical evaluation report.
- Until the endotoxin limit in the drug product specification is reduced to the acceptable level based on safety data, registration of the product cannot be supported from a nonclinical perspective. The sponsor subsequently agreed to lower the limit for endotoxin in the drug product specifications as per the nonclinical evaluator's request.
- As this concern was satisfactorily addressed, there were now no objections on nonclinical grounds to the registration of Beovu brolucizumab (rbe) for the proposed indication.

Clinical

The clinical dossier consisted of:

- One pharmacokinetic study: Study RTH258-E003.
- Two Phase II, proof of concept and dose finding studies: Study RTH258-C-10-083 and Study RTH258-C12-005.
- Two Phase III, pivotal efficacy and safety studies: Study RTH258-C001 and Study RTH258-C002.
- One extension study, conducted over 24 weeks and designed to provide data on the formulation intended for marketing: Study RTH258-A2301E1.
- One Phase II study suitable for evaluating safety: Study TRH258-13-001.

Pharmacology

Pharmacokinetics

There were two studies providing pharmacokinetic (PK) data: Study RTH258-E003 and Study RTH-C-10-083. Plasma samples were collected during the pivotal studies but many

[18] The sponsor commented that secondary pharmacodynamic effects of brolucizumab, including wound healing, are described in the primary pharmacodynamic studies provided in the dossier, and justified that, therefore, there is no need to provide such studies in a subsequent submission.

of these were below the limit of quantification and no pharmacometric analyses were performed using these data.

Following intravitreal administration of brolucizumab, there was systemic exposure that was highly variable. In Study RTH258-003 following intravitreal administration, systemic exposure was not dose proportional: mean (standard deviation (SD)) area under the plasma concentration to time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$) was 3380 (6860) hr*ng/mL for the 3 mg dose and 9770 (12600) hr*ng/mL for the 6 mg dose. The systemic half-life of brolucizumab was 5 to 6 days. Time to maximum plasma concentration (T_{max}) was highly variable with a range of 5 to 75 hours. There was no indication of systemic accumulation with repeated dosing.

The PK data presented in the dossier is sufficient for the proposed indication.

Pharmacodynamics

There were no studies included in the dossier in support of pharmacodynamics (PD). The statements relating to PD in the PI are supported by the pivotal efficacy studies and refer to efficacy endpoints in those studies.

Primary pharmacodynamic effects

Study RTH258-C-10-083 examined the dose range for brolucizumab of 0.5 mg up to 6 mg. The decrease in central subfield thickness (CSFT) was greatest 2 months post dose and in the 6 mg group. There was a clear dose response relationship. For best corrected visual acuity (BCVA), there were greater gains in the 6.0 mg group compared to Lucentis (ranibizumab) and this was significant at Months 1.5, 2.5 and 3.

Study RTH258-C001 examined the 3 mg and 6 mg dose levels. There were similar effects on BCVA and CSFT for both dose levels. There was a rapid improvement in BCVA to Week 8 that stabilised to Week 48. There was a greater decrease in CSFT with both brolucizumab groups than the comparator, aflibercept 2 mg.

Secondary pharmacodynamic effects

Secondary PD effects were not reported. The concentration effect relationship would be difficult to describe because brolucizumab was administered locally, by intravitreal injection, and concentrations at site of effect could not be measured or estimated.

Efficacy

Study RTH258-C-10-083 examined the dose range 0.5 mg to 6 mg. There was no statistically significant difference between 3 mg, 4.5 mg and 6 mg, but overall the 6 mg dose appeared to offer greater efficacy without an increase in adverse effects (AEs). Study RTH258-C001 examined the 3 mg and 6 mg dose levels. There was greater efficacy for the 6 mg dose level compared to the 3 mg for both BCVA and CSFT.

There were two pivotal Phase III studies: Study RTH258-C001 (published as the HAWK trial) and Study RTH258-C002 (the HARRIER trial).[19] There were two Phase II proof of concept/dose finding studies: Study RTH-C-10-083 and Study RTH258-C-12-006. There was one continuation study (from Study RTH-C001) that used the formulation intended for marketing: Study RTH258-A2301E1.

[19] Dugel PU, Koh A, Ogura Y, Jaffe GJ, Schmidt-Erfurth U, Brown DM, Gomes AV, Warburton J, Weichselberger A, Holz FG; HAWK and HARRIER Study Investigators. HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration. *Ophthalmology*. 2020 Jan; 127(1): 72-84.

Study RTH258-C001 (HAWK trial)

Study RTH258-C001 (the HAWK trial) was a randomised, double masked, multicentre, three arm study comparing the efficacy and safety of two dose levels of brolucizumab (3 mg and 6mg / 50 µL) with aflibercept (2 mg/50 µL) in patients with nAMD.

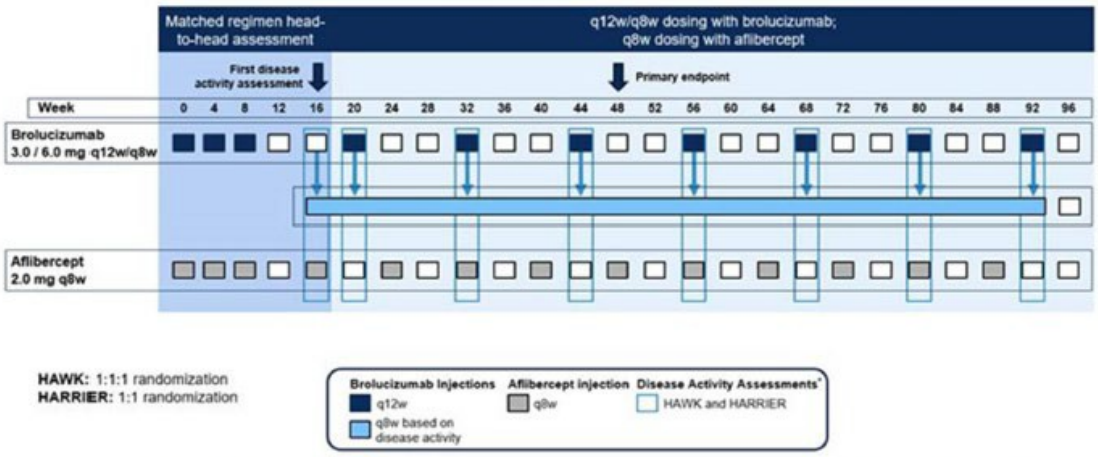
Study design and treatments

The brolucizumab injections were at Day 0, Week 4, Week 8, Week 16 or Week 20 and then 8 or 12 weekly until Week 88. The decision to shift to a regimen of 1 injection every 8 weeks (q8w) was based on clinical assessment and could occur at Week 16 or any subsequent 1 injection every 12 weeks (q12w) treatment. Once a patient switched to the q8w regimen they remained on this regimen for the duration of the study.

Subjects randomised to either the brolucizumab 3 mg arm (Study RTH258-C001 (HAWK trial) only) or brolucizumab 6 mg (Studies RTH258-C001 (HAWK trial) and RTH258-C002 (HARRIER trial)) were treated with adjustment to their individual treatment needs according 'q12w/q8w', that is, they were scheduled for q12w injections unless disease was identified, resulting in permanent adjustment to q8w. Disease activity in Study RTH258-C001 (HAWK trial) was assessed by masked investigators at Week 16 and at scheduled q12w treatment visits (Weeks 20, 32, 44, 56, 68, 80 and 92 (8 assessments). In Study RTH258-C002 (HARRIER trial), additional assessments were performed 8 weeks after every scheduled q12w brolucizumab injection based on health authority feedback, that is, assessments were made at Week 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92 (14 assessments).

Subjects randomised to the aflibercept 2 mg arm had active treatment administered q8w until Week 88.

Figure 1: Drug administration and disease activity assessment schedule in Studies RTH258-C001 (HAWK trial) and RTH258-C002 (HARRIER trial)



Note: Study RTH258-C002 had additional disease activity assessment at Weeks 28, 40, 52, 64, 76, and 88.
Source: [Study RTH258-C001-Figure 9-1] and [RTH258-C002-Figure 9-1]

The following criteria for disease activity were provided as guidance and the investigator should have considered the guidance while also applying their own expert judgment when making q12w/q8w treatment decisions.

Disease activity guidance criteria at 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 nAMD disease activity compared with Week 12.

- New or worse intraretinal fluid (IRF)/intraretinal cysts compared with Week 12.

Disease activity guidance criterion at Weeks 20, 32, and 44:

- Decrease in BCVA of ≥ 5 letters due to nAMD disease activity compared with Week 12.

Disease activity guidance criterion at Weeks 56, 68, 80, and 92:

- Decrease in BCVA of ≥ 5 letters due to nAMD disease activity compared with Week 48.

The aflibercept injections were at Day 0, Week 4, Week 8, Week 16 then 8 weekly until Week 88. From Week 16, patients who did not receive an active injection due to differences in treatment regimen received a sham injection.

Sample size and analysis populations

A sample size of 297 subjects 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%. The efficacy analysis was based on the full analysis set (FAS) which included all randomized patients who received at least one intravitreal injection of study treatment and the safety analysis was based on the safety analysis set (SAF) which included patients who received at least one intravitreal injection.

Participant flow and baseline characteristics

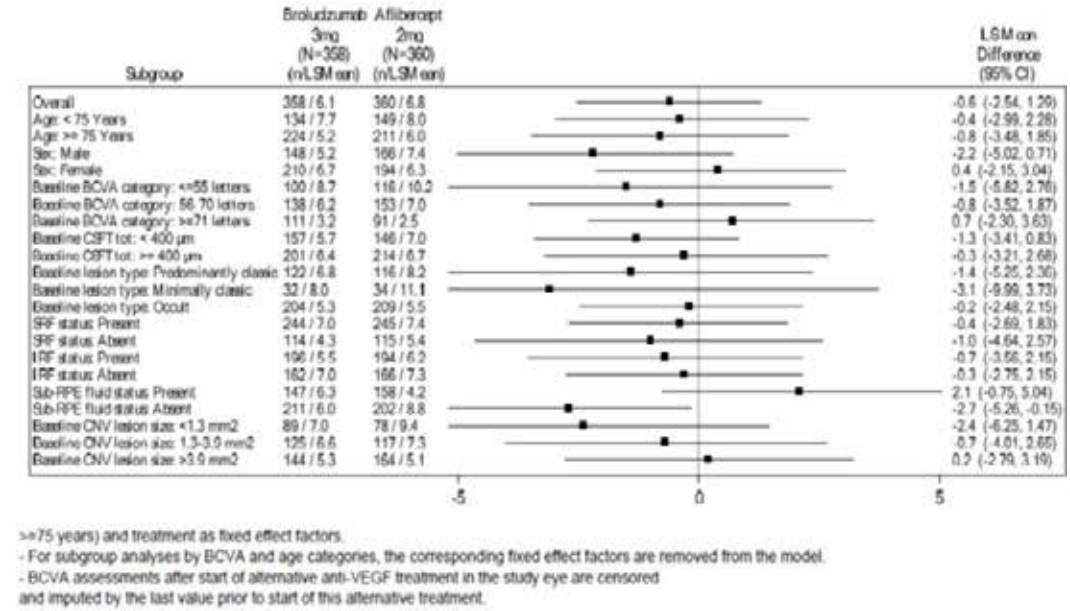
There were 1775 patients screened and 1082 randomised to treatment: 360 to brolucizumab 3 mg, 361 to brolucizumab 6 mg and 361 to aflibercept 2 mg. There were 1078 patients who received study treatment and 994 who completed to Week 48 (911 to Week 96). There were 114 (10.5%) patients who discontinued. Discontinuations due to AEs were recorded for eight (2.2%) patients in the brolucizumab 3 mg group, 11 (3.0%) in the brolucizumab 6 mg and eight (2.2%) in the aflibercept 2 mg.

There were 609 (56.5%) females, 469 (43.5%) males and the age range was 50 to 97 years. The treatment groups were similar in demographic characteristics and baseline ocular characteristics.

Efficacy outcomes

The primary efficacy outcome was the change in BCVA from Baseline to Week 48. Non-inferiority was demonstrated for both the 3 mg and 6 mg brolucizumab dose levels compared with aflibercept 2. The mean (SD) change from Baseline in BCVA, letters read, was 5.9 (13.49) for brolucizumab 3 mg, 6.4 (14.40) for brolucizumab 6 mg and 7.0 (13.6) for aflibercept; least squares (LS) mean difference (95% confidence interval (CI)) brolucizumab – aflibercept, for 3 mg was -0.6 (-2.5 to 1.3) letters read, and for 6 mg was -0.2 (-2.1 to 1.8) letters read. The per-protocol analysis set (PPS) analysis supported the FAS analysis.

Figure 2: Study RTH258-C001 (HAWK trial) best corrected visual acuity (letters), forest plot of analysis of variance estimates for change from Baseline at Week 48 by subgroups of interest (full analysis set, last observation carried forward)



>=75 years) and treatment as fixed effect factors.
- For subgroup analyses by BCVA and age categories, the corresponding fixed effect factors are removed from the model.
- BCVA 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.

Key secondary efficacy outcome measures:

- For the average change in BCVA from Baseline over the period Week 36 to Week 48, non-inferiority was also demonstrated for both the 3 mg and 6 mg brolucizumab dose levels compared with aflibercept 2 mg. The mean (SD) change from Baseline in BCVA, letters read, was 6.0 (13.37) for brolucizumab 3 mg, 6.5 (13.85) for brolucizumab 6 mg and 6.9 (12.61) for aflibercept; LS mean difference (95% CI) brolucizumab - aflibercept, for 3 mg was -0.5 (-2.4 to 1.3) letters read, and for 6 mg was 0.0 (-1.9 to 1.9) letters read.
- The probability (95% CI) of patients remaining on q12w treatment at Week 44 was 0.4939 (0.4939 to 0.5461) in the brolucizumab 3 mg group and 0.5563 (0.5016 to 0.6075) in the 6 mg.
- Among patients with no q8w need identified during the initial q12w cycle, the probability (95% CI) of patients remaining on q12w treatment at Week 44 was 0.8085 (0.7454 to 0.8574) in the brolucizumab 3 mg group and 0.8539 (0.7987 to 0.8950) in the 6 mg.

The study was designed as a non-inferiority study and the margin for non-inferiority appeared generous. The effect for aflibercept in the study was an improvement in 7 letters read from Baseline. The margin for non-inferiority was -4 letters read, which would allow brolucizumab to have less than half the efficacy of aflibercept. However, in the studies the actual lower confidence limit (LCL) for the difference between the 6 mg dose level and aflibercept was -2.1 letters read in Study RTH258-C001 and -2.4 letters read in Study RTH258-C002, which indicates the LCL is > 2/3 the efficacy of aflibercept, which is reassuring and hence the non-inferiority margin is considered acceptable.

Study RTH258-C002 (HARRIER trial)

Study RTH258-C002 (HARRIER trial) was a randomised, double-masked, multicentre, two arm study comparing the efficacy and safety of brolucizumab 6 mg with aflibercept in patients with neovascular age-related macular degeneration.

Study design and treatments

The study was similar in design to Study RTH258-C001 (HAWK trial), except there were only two treatment groups, and the brolucizumab 3 mg dose level was not tested (see Figure 1, above).

Participant flow and baseline characteristics

There were 1048 patients screened and 743 randomised to treatment: 372 to brolucizumab 6 mg and 371 to aflibercept 2 mg. There were 739 patients who received study treatment and 706 who completed to Week 48. There were 37 (5.0%) patients who discontinued the study to Week 48. Discontinuations of the study due to AE were recorded for five (1.3%) patients in the brolucizumab 6 mg group and one (0.3%) in the aflibercept 2 mg. There were 49 (6.6%) patients who discontinued treatment. Discontinuations of treatment due to AEs were recorded for 12 (3.2%) patients in the brolucizumab 6 mg group and four (1.1%) in the aflibercept 2 mg.

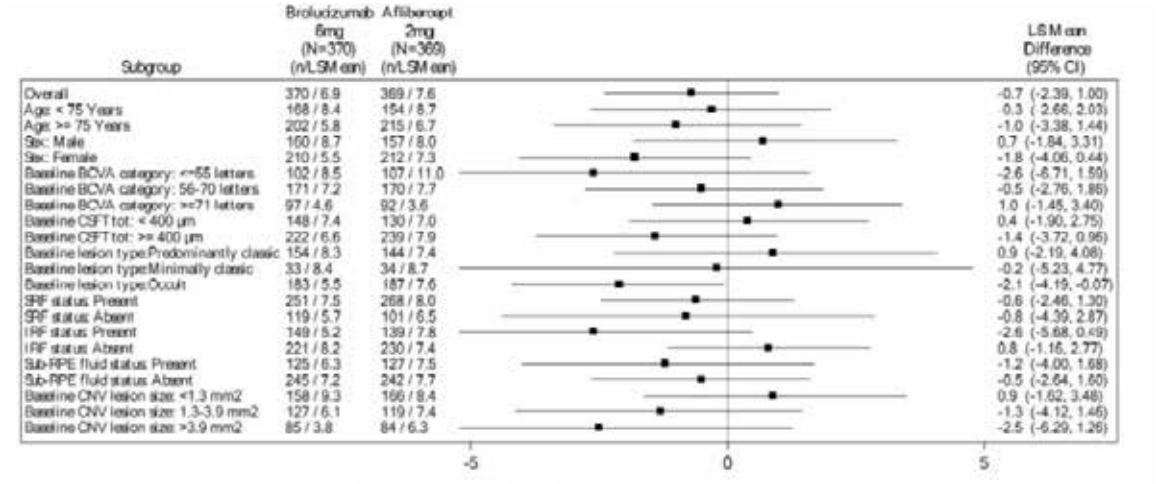
There were 422 (57.1%) females, 317 (42.9%) males and the age range was 50 to 95 years. There were 681 (92.2%) White patients and 45 (6.1%) Asian patients. The treatment groups were similar in demographic characteristics and baseline ocular characteristics.

Efficacy outcomes

Primary efficacy outcome: non-inferiority was demonstrated for brolucizumab 6 mg compared with aflibercept 2 mg. The mean (SD) change from Baseline in BCVA, letters read, was 6.9 (11.47) for brolucizumab 6 mg and 7.6 (12.47) for aflibercept; LS mean difference (95% CI) brolucizumab – aflibercept, was -0.7 (-2.4 to 1.0) letters read. The PPS analysis supported the FAS analysis.

In the subgroup analysis there was less efficacy for brolucizumab in patients with occult type baseline lesion, LS mean difference (95% CI) brolucizumab – aflibercept, was -2.1 (-4.19 to -0.07) letters read; and there was a trend to lesser efficacy with increasing CNV lesion size and decreasing baseline BCVA. This might probably indicate lesser efficacy in patients with greater disease severity.

Figure 3: Study RTH258-C002 (HARRIER trial) best-corrected visual acuity (letters) for change from Baseline at Week 48 by subgroups of interest (full analysis set, last observation carried forward)



Key secondary efficacy outcome measures included:

- For the average change in BCVA from Baseline over the period Week 36 to Week 48, non-inferiority was also demonstrated for brolucizumab 6 mg compared with aflibercept 2 mg. The mean (SD) change from baseline in BCVA, as letters read, was 6.6 (11.10) for brolucizumab and 7.7 (11.81) for aflibercept; LS mean difference (95% CI) brolucizumab – aflibercept, was -1.2 (-2.8 to 0.5) letters read.
- The probability (95% CI) of patients remaining on q12w treatment with brolucizumab at Week 44 was 0.5101 (0.4567 to 0.5610). The Kaplan Meier plot indicates that most of the patients requiring q8w treatment did so by Week 20.
- Among patients with no q8w need identified during the initial q12w cycle, the probability (95% CI) of patients remaining on q12w treatment with brolucizumab at Week 44 was 0.8170 (0.7582 to 0.8629).

Other efficacy (supportive) studies

Study RTH258-C-10-083

Study RTH258-C-10-083 was a prospective, multicentre, double masked, randomised, single dose, ascending, active controlled, parallel group Phase II study. It was a proof of concept and dose finding study. The criterion for non-inferiority was generous (a lower bound > -40 μm), and the hypothesis tests used 90% CI instead of 95% CI. The study found that the dose range 3 mg to 6 mg was non-inferior to ranibizumab 0.5 mg (approved dose in Australia).

Study RTH258-C-12-006

Study RTH258-C-12-006 was a prospective, randomised, double-masked, multicentre, two arm study comparing intravitreal brolucizumab with Eylea (aflibercept) in patients with exudative age-related macular degeneration. It explored the efficacy of the brolucizumab 6 mg dose level in comparison with the approved dose of aflibercept. After a loading phase of 3 monthly (q4w) injections, subjects were treated q8w up to Week 32. After Week 32, subjects randomised to aflibercept 2 mg continued on a q8w interval, (that is, received 2 injections at Weeks 40 and 48), while subjects randomized to brolucizumab were switched to a quarterly regimen (q12w) receiving only one additional injection at Week 44, thus allowing for head-to-head efficacy comparison up to Week 40.

The criterion for non-inferiority were extremely generous, with the lower limit of the two-sided 80% CI for treatment difference being > -5 letters, and the hypothesis test using the lower bound of the 80% CI. In regard to the primary objective, the LS estimate of the mean 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 mean difference between treatment arms in BCVA changes from Baseline to Week 12 was −1.13 letters, with the lower limit of the 80% CI being −4.19 letters. Thus, non-inferiority of brolucizumab 6 mg to aflibercept 2 mg at Week 12 was demonstrated for the specified non-inferiority margin of 5 letters. The study concluded that 6 mg was non-inferior to aflibercept.

Study CRTH258A2301E1

Study CRTH258A2301E1 was a 24 week, double masked, multicentre, two arm extension of Study RTH258-C001 (the HAWK trial). The study was conducted to obtain data for the formulation intended for marketing. The treatment duration was 24 weeks. This study provides some data for the formulation intended for marketing. These data indicate a preservation of treatment effect for a further 24 week treatment period. However, this study did not test for non-inferiority and therefore does not prove that the two formulations are identical in effect.

Additional analyses

In response to TGA questions (dated 25 October 2019) the sponsor has submitted an analyses for brolucizumab treated patients based on the dosing interval (q8w or q12w) status at Week 48 (time point of primary endpoint of pivotal studies). The subjects were grouped based on the dosing frequency status at Week 48 (6 mg q8w; 6 mg q12w).

Results

Limitations in the interpretation of the results: The subgroup analyses for the brolucizumab 6 mg arms suffer from significant selection biases, as the allocation of the patients into a given brolucizumab subgroup (q12w versus q8w treatment intervals) is not randomised but based on post-baseline disease statuses (absence versus presence of disease activity) resulting from an interaction between the patients' specific disease profiles and the treatment.

Table 3: Study RTH258-C001 (HAWK trial) descriptive statistics of best corrected visual acuity (letters) at Baseline by q12w/q8w status at Week 48 for brolucizumab-treated subjects (full analysis set)

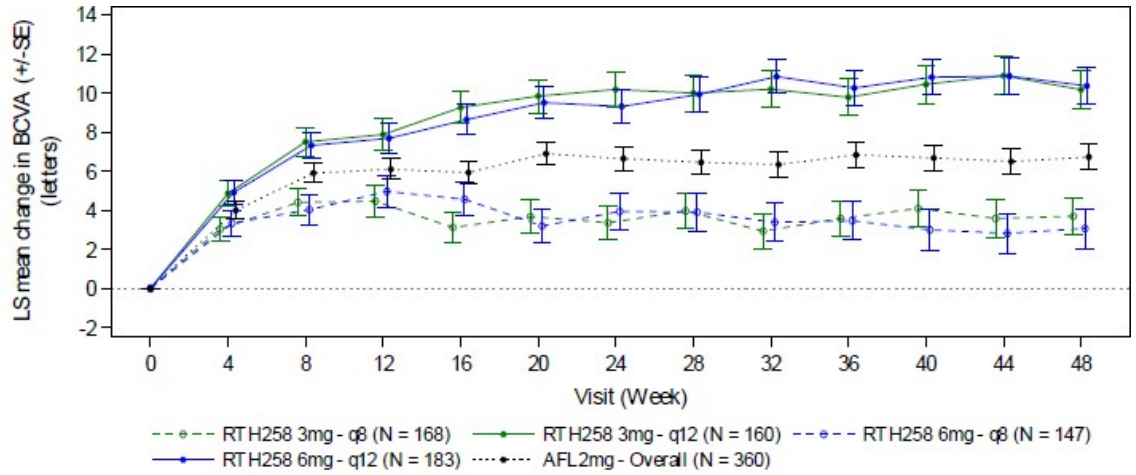
Descriptive Statistics	RTH6mg-q8w (N = 147)	RTH6mg-q12w (N = 183)	AFL2mg (N = 360)
n	147	183	360
Mean (95% CI)	59.0 (56.5, 61.5)	62.0 (60.2, 63.9)	60.0 (58.5, 61.4)
SE	1.25	0.94	0.73
Median	63	65	63
Min, Max	23, 79	23, 78	16, 83
1st, 3rd quartile	51.0, 71.0	56.0, 72.0	53.0, 71.0

AFL = aflibercept, RTH = brolucizumab.

Table 4: Study RTH258-C002 (HARRIER trial) descriptive statistics of best corrected visual acuity (letters) at Baseline by q12w/q8w status for brolucizumab-treated subjects at Week 48 (full analysis set)

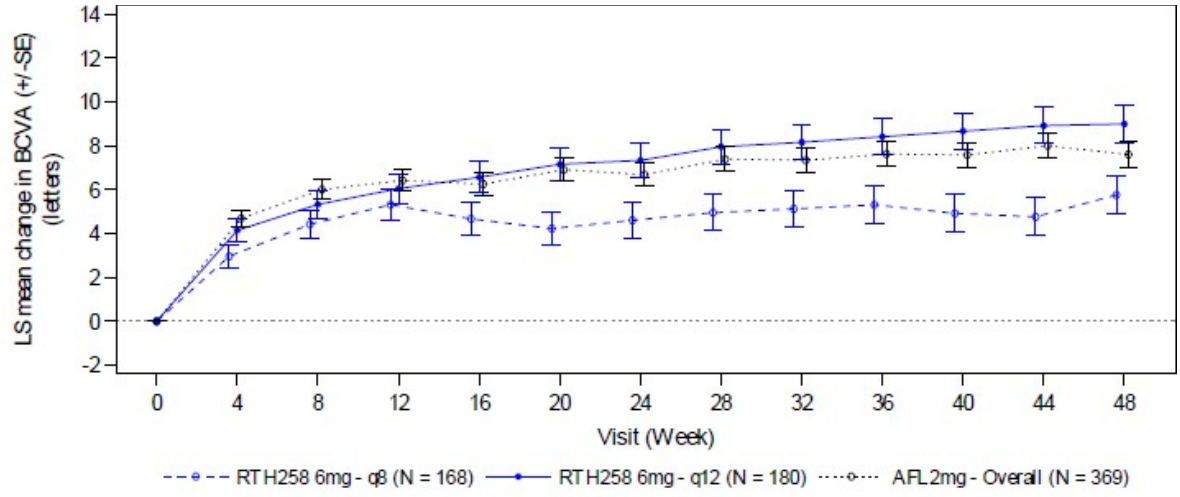
Descriptive Statistics	RTH6mg-q8w (N = 168)	RTH6mg-q12w (N = 180)	AFL2mg (N = 369)
n	168	180	369
Mean (95% CI)	60.4 (58.2, 62.5)	62.9 (61.3, 64.5)	60.8 (59.5, 62.1)
SE	1.1	0.82	0.67
Median	63.5	65	64
Min, Max	22, 78	31, 78	23, 79
1st, 3rd quartile	54.0, 72.0	56.0, 71.0	53.0, 70.0

Figure 4: Study RTH258-C001 (HAWK trial) least squares mean change (± standard error) from Baseline by visit and q12w/q8w Status at Week 48 for brolucizumab-treated subjects (full analysis set, last observation carried forward)



- LS mean and SE estimates are based on an ANOVA model with baseline BCVA categories (<=55, 56-70, >=71 letters), age categories (<75, >=75 years) and treatment as fixed effect factors.
- BCVA 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.

Figure 5: Study RTH258-C002 (HARRIER trial) best corrected visual acuity (letters), least squares mean change (± standard error) from Baseline by visit and q12w/q8w status at Week 48 for brolucizumab-treated subjects in the (full analysis set, last observation carried forward)



- LS mean and SE estimates are based on an ANOVA model with baseline BCVA categories (<=55, 56-70, >=71 letters), age categories (<75, >=75 years) and treatment as fixed effect factors.

Safety

There were no pivotal studies that assessed safety as the sole primary outcome in the dossier. It was evaluated from the efficacy studies discussed above and Study RTH258-13-001 (a Phase II proof of concept study). Study RTH258-13-001 was a prospective, single-masked study to evaluate the effects of volume reduction and reduced flow rates on the efficacy of brolucizumab in an adaptive two-stage study design with independent cohorts. This looked at 4 doses of brolucizumab: 1.2 mg, 0.6 mg in 10 µL and 1 mg, 0.5 mg in 8.3 µL. The outcome measures were CSFT and BCVA. A patient was coded as a responder if there was ≥ 4-letter gain in BCVA and ≥ 80 µm decrease in CSFT on

Days 14 and 28. The safety variables included AEs, slit-lamp bio-microscopy, intraocular pressure (IOP), dilated fundus examination and vital signs.

Overall exposure to brolucizumab in the development program is 1182 patients. There were 383 patients exposed to 3 mg and 799 exposed to 6 mg. All patients were aged ≥ 50 years, with 358 patients aged 65 to 74 years, 504 patients aged 75 to 84 years and 197 patients aged ≥ 85 years. There were 673 (56.9%) females and 509 (43.1%) males. In total, there have been 3772 injections of 3 mg and 7671 of 6 mg. There were 993 (84.0%) White patients and 154 (13.0%) Asian patients.

In the pivotal studies, both conducted over a 96 week period, the exposure to 6 mg/50 µL intravitreal was ten injections for 268 (36.7%) patients, 13 for 214 (29.3%) and 12 for 80 (11.0%). The median (range) number of injections was 10.0 (1 to 13) for the brolucizumab 6 mg/50 µL group compared to 13.0 (1 to 14) for the aflibercept 2 mg/50 µL group.

Overall the rate of treatment emergent adverse events (TEAEs) was higher with brolucizumab than with aflibercept, and the difference was primarily due to ocular TEAEs. The rate of ocular TEAEs was higher with the brolucizumab 3 mg dose than the 6 mg. In the pivotal studies, there were 115 (30.0%) patients with brolucizumab 3 mg/50 µL, 202 patients (25.3%) with brolucizumab 6 mg/50 µL and 161 patients (20.8%) with aflibercept 2 mg who reported ocular TEAEs. The most common were: conjunctival haemorrhage, vitreous floaters, eye pain, visual acuity reduced, vitreous detachment and retinal pigment epithelial tear. The proportion of patients with ocular infections and infestations was greater with brolucizumab: five (1.3%) patients with brolucizumab 3 mg/50 µL, ten (1.3%) patients with brolucizumab 6 mg/50 µL and five (0.6%) patients with aflibercept 2 mg.

Overall, the rate of treatment related TEAEs was higher with brolucizumab than with aflibercept, and the difference was primarily due to ocular TEAEs. Ocular TEAEs related to the study were reported in 61 (15.9%) patients with brolucizumab 3 mg/50 µL, 93 (11.6%) patients with brolucizumab 6 mg/50 µL and 66 (8.5%) patients with aflibercept 2 mg. Ocular TEAEs related to treatment administration were reported in 52 (13.6%) patients with brolucizumab 3 mg/50 µL, 73 (9.1%) patients with brolucizumab 6 mg/50 µL and 52 (6.7%) patients with aflibercept 2 mg. Ocular TEAEs related to study treatment were reported in 12 (3.1%) patients with brolucizumab 3 mg/50 µL, 27 (3.4%) patients with brolucizumab 6 mg/50 µL and 18 (2.3%) patients with aflibercept 2 mg.

The rate of non-ocular TEAEs was similar for brolucizumab and aflibercept. In the pivotal studies, non-ocular TEAEs related to the study were reported in one (0.3%) patient with brolucizumab 3 mg/50 µL, four (0.5%) with brolucizumab 6 mg/50 µL and no patients with aflibercept 2 mg.

Deaths were uncommon, and were mostly due to age-related conditions. In Study RTH258-C001 (HAWK trial(one death in the brolucizumab 3 mg group was considered by the investigator to be related to study treatment: cerebrovascular accident.

In the pivotal studies, serious adverse events (SAEs) in the study eye were more common with brolucizumab than aflibercept. In Study RTH258-C001 (HAWK trial), SAEs in the study eye were reported in seven (2.0%) patients in the brolucizumab 3 mg group, 12 (3.3%) in the brolucizumab 6 mg, and five (1.4%) in the aflibercept. The most common ocular SAE was endophthalmitis, occurring in three (0.8%) patients in the brolucizumab 3 mg group, three (0.8%) in the brolucizumab 6 mg, and none in the aflibercept group. In Study RTH258-C002 (HARRIER trial), SAEs in the study eye were reported in 13 (3.5%) patients in the brolucizumab 6 mg group and six (1.6%) in the aflibercept group. The most common ocular SAEs were uveitis, occurring in three (0.8%) patients in the brolucizumab 6 mg group and none in the aflibercept; and retinal pigment epithelial tear, occurring in

two (0.5%) patients in the brolucizumab 6 mg group and one (0.3%) in the aflibercept group.

In the pivotal studies, a higher proportion of patients treated with brolucizumab discontinued due to adverse events compared with aflibercept. Ocular TEAEs leading to discontinuation of study treatment were reported in four (1.0%) patients with brolucizumab 3 mg/50 µL, eight (1.0%) with brolucizumab 6 mg/50 µL and four (0.5%) with aflibercept 2 mg. The most common ocular AEs leading to discontinuation with brolucizumab were uveitis and endophthalmitis. In Study RTH258-C002 (HARRIER trial) two patients in the brolucizumab group discontinued because of ischaemic stroke.

Antidrug antibodies (ADA) were commonly detected in patients at baseline: 37.1% patients in Study RTH258-C001 (HAWK) and 52.3% in Study RTH258-C002 (HARRIER). Neutralising antibodies (nAb) were detected at Baseline in 8% patients in Study RTH258-C001 and 20.7% of patients in the brolucizumab group in Study RTH258-C002. Treatment induced or boosted ADA status was reported for 18.8% to 23% of the patients treated with brolucizumab at Week 48 and 23.1% to 27.5% at Week 88. The clinical significance of anti-brolucizumab antibodies on clinical efficacy and safety of Beovu brolucizumab is not known/unclear at this time.

In the pivotal studies, intraocular inflammation was reported in 32 (4.4%) patients with brolucizumab 6 mg/50 µL and six (0.8%) patients with aflibercept 2 mg/50 µL; the largest category being uveitis which was reported in 31 (4.2%) patients with brolucizumab 6 mg/50 µL and six (0.8%) with aflibercept 2 mg. The onset of ocular inflammation appeared to be evenly spread across the study duration. In Study RTH258-C002 (HARRIER trial), in the brolucizumab group four of these events were SAEs, all resolved, but two had sequelae. In Study RTH258-C001 (HAWK trial), intraocular inflammation appeared to be associated with ADA: 14 patients in the brolucizumab 3 mg group, 15 in the brolucizumab 6 mg had induced or boosted ADA. In Study RTH258-C002, in the brolucizumab 6 mg group, of patients with induced or boosted ADA: five (6.2%) reported ocular inflammation, compared with five (1.9%) in those without induced or boosted ADA status.

The sponsor has confirmed (response dated 25 October 2019) that the majority of these intraocular inflammation and endophthalmitis events were assessed by the investigator as mild or moderate (over 90%), were treated with topical corticosteroids.

Endophthalmitis: the majority (7 out of 9 subjects) of endophthalmitis cases in the brolucizumab arm resolved within 2 months from diagnosis. The causality of endophthalmitis was assessed by the investigator. The majority of endophthalmitis events (6 out of 9) in the brolucizumab-treated subjects were assessed as related to study treatment administration procedure; 1 event was assessed as related to study medication and study treatment administration procedure, 1 event as related to study medication, and 1 event as not related to either study medication or administration procedure. Overall, 2 events were culture positive and 3 events were culture negative; for the remaining 4 subjects culture was either not taken or the results were not interpretable.

Intraocular inflammation (uveitis): overall, 70 intraocular inflammation events were reported in 48 subjects treated with brolucizumab in Studies RTH258-C001 (HAWK trial) and RTH258-C002 (HARRIER trial);32 events resolved within approximately a month from onset, 16 events resolved approximately 1 to 3 months and 17 events resolved more than 3 months from onset (range 105 to 617 days).

In Study RTH258-C001 (HAWK trial), AEs of special interest occurred at similar rates in the three treatment groups. However, retinal detachments/tears occurred in three (0.8%) patients in the brolucizumab 3 mg group, nine (2.5%) in the brolucizumab 6 mg, and four (1.1%) in the aflibercept. Retinal pigment epithelial tears occurred in five (1.4%) patients in the brolucizumab 3 mg group, 14 (3.9%) in the brolucizumab 6 mg group, and four (1.1%) in the aflibercept group.

There was no significant difference between the treatment groups in IOP or adverse events of increased IOP. There were no between group differences or significant trends in laboratory tests. Electrocardiogram (ECG) findings were not reported in the studies. There were no apparent differences between the treatments in vital signs.

The formulations of brolucizumab used in development contained the same excipients as the formulation of brolucizumab proposed for marketing in Australia but in slightly different amounts. In the opinion of the clinical evaluator, these differences are unlikely to impact on either efficacy or safety, which the Delegate considers acceptable.

Clinical evaluator's recommendation

The clinical evaluator has recommended rejection of Beovu brolucizumab (rbe) for the proposed indication and dosage regimens.

The reason for recommending rejection is that the following dosing recommendations are not supported by the data presented in the dossier:

> 'The recommended dose is 6 mg (0.05 mL) administered by intravitreal injection (IVT) every 4 weeks (monthly) for the first three doses. Thereafter, brolucizumab is administered every 12 weeks (3 months). The physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. The treatment interval could be as frequent as every 8 weeks (2 months).'

The proposed dosing recommendations are rejected for the following reasons:

- The q12w dosing recommendation is not supported by the data presented in the dossier. The dosing used in the pivotal studies was a hybrid q8w/q12w dosing strategy. A separate analysis of the q12w dosing was not performed and therefore the efficacy of the q12w strategy has not been demonstrated.
- The proposed strategy of commencing with a q12w dosing regimen, then reducing the dosing interval to as frequently as q8w, based on treatment failure is novel, and does not reflect the dosing regimen used in the pivotal studies or the standard of care in Australia. The pivotal studies used either q8w or q12w dosing for brolucizumab. The standard of care in Australia is to commence with q8w dosing, and then to extend the dosing interval based on clinical response. The standard of care in Australia is not to commence with q12w and reduce the dosing interval based on treatment failure.
- The sponsor does not recommend adequate surveillance of disease activity. Both pivotal studies had an assessment of disease activity 8 weeks after the third dose (16 weeks after commencing treatment). In one of the pivotal studies there was an assessment of disease activity 8 weeks after each subsequent does (whether q8w or q12w). The long-term suitability of the q12w dosing regimen, whereby < 50% of patients were maintained on the q12w regimen for 2 years, indicates the need for assessments at 8 weeks post dose.
- The sponsor does not provide sufficient guidance on the parameters used to monitor disease activity. In the pivotal studies, the principal criteria used, in addition to the treating ophthalmologist's clinical judgement, was a decrease in BCVA of ≥ 5 letters compared with Baseline or, after Week 48, from the Week 48 assessment.

Risk management plan

- The sponsor has submitted European Union-risk management plan (EU-RMP) version 1.0 (10 January 2019; data lock point (DLP) 23 April 2018) and Australian specific Annex (ASA) version 1.0 (24 January 2019) in support of this application. Following

the second round evaluation, the sponsor submitted EU-RMP version 1.2 (31 October 2019; DLP 23 April 2018) and ASA version 2.0 (12 November 2019; DLP 23 April 2018) in support of this application.

- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 5.[20]

Table 5: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Intraocular inflammation	ü	ü	ü	ü‡
	Endophthalmitis*	ü	–	ü	ü‡
	Transient intraocular pressure increased*	ü	–	ü	–
	Retinal detachment/tear*	ü	–	ü	ü‡
Important potential risks	Non ocular events (ATE, VTE and non-ocular haemorrhage)*	ü	–	ü	–
Missing information	Safety beyond two years of treatment	ü	–	–	–
	Non-ocular safety after bilateral treatment*	ü	–	–	–

* The sponsor made these changes following the second round of evaluation in response to recommendations by the clinical evaluator and the Delegate. ‡ Patient education materials. ATE = arterial thromboembolic events, VTE = venous thromboembolic events.

- The summary of safety concerns is acceptable at this time. Following the second round of evaluation, the sponsor removed hypersensitivity as an important identified risk and added endophthalmitis, transient intraocular pressure increase and retinal detachment/tear. Non–ocular events (ATE, VTE and non-ocular haemorrhage) was added as an important potential risk and non-ocular safety after bilateral treatment was added as missing information.
- The sponsor has proposed routine pharmacovigilance activities for all safety concerns and an additional pharmacovigilance activity in the form of a specific adverse event follow up checklist to help characterise the important identified risk of 'intraocular inflammation'. This is acceptable.

[20] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- The sponsor has proposed routine risk minimisation activities for all safety concerns except missing information. An additional risk minimisation activity in the form of patient education materials is proposed for the important identified risks of endophthalmitis, intraocular inflammation and retinal detachment/tear. The sponsor will include the PI and IFU in the product package. Subject to Delegate consideration of wording in the PI regarding the risks added to the summary of safety concerns following the second round of evaluation, and wording of the Consumer Medicines Information (CMI) as outlined in the risk management plan (RMP) evaluation report, the risk minimisation plan is acceptable.

Risk-benefit analysis

Delegate's considerations

Discussion

Quality

Following the reduction of the endotoxin limit in the drug product specification to the acceptable level based on safety data, there are no objections on nonclinical grounds to the registration of Beovu brolucizumab for the proposed indication.

From the biological evaluation; GMP clearance and drug product specification issues were satisfactorily resolved following the second round of evaluation.

Efficacy

The pivotal studies, Study RTH258-C001 (HAWK trial) and Study RTH258-C002 (HARRIER trial), demonstrated efficacy in the primary endpoint defined as the change from Baseline in BCVA at Week 48. In both studies, Beovu (brolucizumab 6 mg/50 µL intravitreal) treated patients had a similar mean change from baseline in BCVA as the patients treated with aflibercept 2 mg (fixed q8w), demonstrating non-inferiority.

The dosing used in the pivotal studies was a hybrid q8w/q12w dosing strategy based on assessment of disease activity. This was different from the usual 'treat and extend' therapy. In the Phase III studies, after the loading phase of 3 doses administered q4w, subjects in the brolucizumab q12w/q8w treatment arms with an identified q8w need were switched from a q12w treatment interval to a q8w interval. They remained on this regimen for the remainder of the study and were not allowed to switch back to a q12w interval.

Further to the initially proposed dosing regimen (as discussed in the 'Clinical evaluator's recommendation' section, above), the sponsor's amended the proposed recommended dosing regimen in a post second round evaluation response (dated 25 October 2019) to:

> 'The recommended dose is 6 mg brolucizumab (0.05 ml solution) administered by intravitreal injection every 4 weeks (monthly) for the first 3 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 with disease activity, treatment every 8 weeks (2 months) should be considered. In patients without disease activity, treatment up to every 12 weeks (3 months) should be considered. The physician may further individualise treatment intervals based on disease activity.'

Safety

There is a higher risk of ocular adverse reactions occurring in brolucizumab patients, specifically intraocular inflammation (4%) and endophthalmitis (0.7%) compared to

aflibercept (1% and 0.1% respectively). The majority (7 out of 9 subjects) of endophthalmitis cases in the brolucizumab arm resolved within 2 months from diagnosis. Longer duration of endophthalmitis was reported in two subjects (167 days and 176 days). In some patients the duration of endophthalmitis/uveitis was prolonged (the duration of endophthalmitis was up to 176 days; and the duration of uveitis was up to 651 days). Sequelae occur in 33.3% (3 episodes) of cases of endophthalmitis and 8.3% of patients with uveitis following treatment with brolucizumab. When described, the sequelae appear to be decrease in BCVA ≥ 30 letters. The disability also appears to be predominantly visual loss. The risk mitigation strategies (in place and that proposed by the Delegate) are:

- intraocular inflammation has been included in the RMP as important identified risk and the Delegate has recommended endophthalmitis to be included as well. This was subsequently included by the sponsor; also
- endophthalmitis is included in the 'Special warnings and precautions for use' section of the PI and the Delegate has recommended to include uveitis/intraocular inflammation as well. This was subsequently included by the sponsor.

There was one death due to cerebrovascular accident attributed to brolucizumab, and two discontinuations due to ischaemic stroke. The Delegate has recommended that ATE should be included under 'Special warning and precaution for use' section as there is biological plausibility for an association. This was subsequently included by the sponsor.

Overall

Beovu (brolucizumab 6 mg/50 µL intravitreal) used in the pivotal studies as hybrid (q8w/q12w) dosing strategy (based on assessment of disease activity) demonstrated efficacy in the primary endpoint defined as the change from Baseline in BCVA at Week 48. There were higher risk of ocular adverse reactions occurring in brolucizumab patients, specifically intraocular inflammation (4%) and endophthalmitis (0.7%) compared to aflibercept (1% and 0.1% respectively). There are risk mitigation strategies in place and further proposed by the Delegate to deal with these. Considering the acceptance of the Delegate's recommended amendments to the PI, RMP and upon finalisation of the dosing regimen, overall the benefit risk profile of Beovu brolucizumab in the proposed indication for the treatment of nAMD appears favourable although advice is sought from the committee regarding the specific issues raised above.

Conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> 'The Brolucizumab EU-Risk Management Plan (RMP) (version 1.0, dated 10 January 2019, data lock point 23 April 2018), with Australian specific Annex (version 1.0, dated 24 January 2019), included with submission PM-2019-00106-1-5, to be revised to the satisfaction of the TGA, will be implemented in Australia.'

The following wording is recommended for the periodic safety update report (PSUR) requirement:

> 'An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

> Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.'

As brolucizumab is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> 'Beovu (brolucizumab) is to be included in the Black Triangle Scheme. The PI and CMI for Beovu must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TA of supply of the product.'

The Delegate considers that the benefit risk profile of Beovu (brolucizumab 6 mg/0.05 mL single use vials and pre-filled syringes) for the treatment of nAMD as favourable and approvable subject to sponsor's acceptance for below recommendations (alternative recommended posology), conditions of registration.

Summary of issues

The primary issues with this submission is as follows with further information in the Discussion section, above:

1. The dosing used in the pivotal studies was a hybrid q8w/q12w dosing strategy based on assessment of disease activity, however, different from the usual 'treat and extend' therapy.
2. There is a higher risk of ocular adverse reactions occurring in brolucizumab patients, specifically intraocular inflammation (4%) and endophthalmitis (0.7%) compared to aflibercept (1% and 0.1% respectively). Risk mitigation strategies are in place.
3. Establishing the cause of these ocular adverse events; disease, drug, inflammation or infection.

Questions for the sponsor

The sponsor was requested to address the following issues in the pre-ACM response. The sponsor's response to each question is shown below.

1. The increased rate of endophthalmitis compared to other agents is noted. Please comment on why? Was aseptic technique followed in the clinical trials?

Sponsor's response

In all clinical studies with brolucizumab, the sponsor required physicians to use aseptic techniques as per standard medical practice. The specific instructions for the Phase III studies were: 'The intravitreal injection should be carried out under controlled aseptic conditions per standard of care at the site, which include surgical hand disinfection and the use of povidone iodine (or other sterilising agent, per standard of care at the site). Adequate anaesthesia and a topical broad-spectrum microbiocide should be given prior to

the injection per standard of care at the site.' (Manual of Procedures, Section 11.2 Administration of study injection).

Additionally, endophthalmitis could not be linked to any specific clinical trial site. Hence, non-aseptic conditions are not likely to be the root cause of the numerically higher reported rate of endophthalmitis in the brolucizumab treatment group. There is no reason to believe that the cause of endophthalmitis in the brolucizumab group would be different than the one in the aflibercept group.

The number of patients with an endophthalmitis in the brolucizumab 2 year pivotal studies was low (brolucizumab 6 mg: 0.7% (n = 5), aflibercept 2 mg: 0.1% (n = 1). The risk difference between these two treatments was less than 1.0% (0.5% (95% CI: −0.27, 1.67)). It is worth noting, that the numerical difference in endophthalmitis cases between brolucizumab 6 mg and aflibercept 2 mg was only observed in one of the two pivotal studies (Study RTH258-C001/HAWK trial : n = 4 versus 1, Study RTH258- C002/HARRIER trial : n = 1 versus 0, respectively).

All 5 endophthalmitis cases reported on brolucizumab 6 mg were very likely related to the intravitreal injection procedure, as supported by the time to onset since the last active injection (all 5 events started within 5 days of the last injection) and the clinical management of the cases (all 5 events were treated with intravitreal antibiotics).

2. ***The clinical significance of anti-brolucizumab antibodies on clinical efficacy and safety of Beovu is not known. Why wasn't a formal analysis of the relationship between plasma concentrations and the development/boosting of ADA done?***

Sponsor's response

As mentioned in the Clinical Study Reports of our two pivotal Phase III studies (HAWK and HARRIER trials), serum samples for systemic concentrations of brolucizumab were collected together with samples for ADA analyses at predetermined visits and prior to the intravitreal administration of the study treatment (that is, at trough), to confirm that, at these time-points, the serum brolucizumab concentrations were below the drug tolerance limit for the ADA and neutralising antibody assays. Most of these serum samples were below the limit of quantification for free brolucizumab and accordingly, no pharmacokinetic analyses could be performed using these data. A formal analysis of the relationship between serum concentration and the development/boosting of ADA was therefore not possible for the HAWK and HARRIER trials.

PK analyses were performed in the Phase II PK (SHRIKE trial/Study RTH258-E003). In this study, the PK parameters were generated following the initial dose of brolucizumab and concurrently the ADA were assessed prior to dosing and at approximately Day 28. During the initial month of treatment when the PK samples were collected, no patients receiving brolucizumab 6 mg and only two patients receiving brolucizumab 3 mg had treatment-induced or treatment-boosted ADA. A formal analysis of the relationship between serum concentration and the development/boosting of ADA was therefore not possible in the SHRIKE trial.

In conclusion, the sponsor agrees with the Delegate that the clinical significance of ADA on clinical efficacy and safety of Beovu is not known. This information is included in the PI for completeness.

Proposed action

The Delegate has no reason to say, at this time, that the application for Beovu should not be approved for registration.

Request for Advisory Committee on Medicines advice

The committee is requested to provide advice on the following specific issues:

1. In clinical practice, how often are patients with nAMD evaluated during the course of treatment with VEGF agents? Do ophthalmologists use a fixed or variable dosing regimen?
2. Please comment on the AE and SAE in the clinical trials in relation to severity and likely relationship to drug or procedure or chance?
3. Is inflammation after intraocular injection transient? Is it related to procedure or drug?
4. Please comment on likely causes of endophthalmitis?
5. Please comment of pathophysiology of uveitis after VEGF? Is it disease, drug, inflammation, infection?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Advisory Committee Considerations[21]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

The ACM considered the referral for advice from the TGA Delegate in relation to the submission to register Beovu single use vials and pre-filled syringes, containing 6 mg/0.05 mL of brolucizumab.

The ACM considered this product to have an overall positive benefit-risk profile for the proposed indication:

> *Beovu is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD).*

The ACM agreed that Beovu had an overall positive benefit-risk profile for the proposed indication as the evidence submitted did satisfactorily establish the quality, safety and efficacy of the product.

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice.

1. In clinical practice, how often are patients with nAMD evaluated during the course of treatment with VEGF agents? Do ophthalmologists use a fixed or variable dosing regimen?

The ACM advised that good clinical practice necessitates that all patients are examined based on their injection schedule from 4 weekly to 12 weekly intervals. The ACM advised

[21] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

that the majority of ophthalmologists (especially retinal specialists) in Australia use a variable dosing regimen known as 'Treat and Extend'. Generally, the eye is injected every 4 weeks initially and examined each visit for haemorrhage, and an optical coherence tomography (OCT) scan taken to assess for fluid to indicate whether the CNV is active or not. If inactive, then the interval is extended to 6 weeks and so on up to 12 weeks. If there is fluid on OCT and/or haem, then the interval is reduced.

The ACM noted, however, that there is a lack of trial data for the 'Treat and Extend' approach, as this is difficult to mask in trials.

2. Please comment on the AE and SAE in the clinical trials in relation to severity and likely relationship to drug or procedure or chance?

The ACM noted that most TEAEs were minor and the variation in their incidence was likely determined by chance.

The ACM advised that ATEs are potentially related to VEGF inhibition. The ATE rate was 4.5% (33 out of 730) in brolucizimab treated eyes and 4.7% (34 out of 729) in aflibercept treated eyes. ATE are more common in patients with wet AMD than those without.

The ACM considered the rate of endophthalmitis to be very high in all treatment groups of both trials (0.6%, to 1.3%). The ACM commented that an acceptable rate with good evidence based clinical practice should be between 1/7000 to 1/10,000. This warrants further extensive comment, see Specific Question 4, below.

3. Is inflammation after intraocular injection transient? Is it related to procedure or drug?

The ACM was of the view that inflammation after intraocular injection with brolucizumab may be related to the drug rather than the procedure, as the rates of intraocular inflammation in both brolucizumab arms (3 and 6 mg) were higher than for other intravitreous anti-VEGF agents. However, the ACM advised that in general, most cases of intraocular inflammation are treatable with topical or systemic therapy (corticosteroids) and thus transient, and that clinically significant inflammation is rare.

4. Please comment on likely causes of endophthalmitis?

The ACM advised that endophthalmitis is caused by either ocular surface biological contamination or from either the patient or the surgeon's nose and mouth. The ACM also advised that in the past, endophthalmitis has also been caused by inadequate compounding in the manufacture of off-label bevacizumab. Contamination of a commercially manufactured intravitreous molecule had not occurred.

The ACM was of the view that the difference in endophthalmitis between brolucizumab and aflibercept appears to be due to chance alone, and has been noted in previous trials comparing aflibercept with ranibizumab and bevacizumb (CATT trial).[22]

5. Please comment of pathophysiology of uveitis after VEGF? Is it disease, drug, inflammation, infection?

The ACM was of the view that this is likely the result of the drug rather than disease, but the causes of this are unclear. The ACM noted however that this uveitis is rarely clinically significant and that in practice, the same anti-VEGF therapy can result in reactions in the same patient on some occasions, but not others.

[22] Forooghian F, Albiani DA, Kirker AW, Merkur AB. Comparison of endophthalmitis rates following intravitreal injection of compounded bevacizumab, ranibizumab, and aflibercept. *Canadian Journal of Ophthalmology*. Elsevier BV; 2017 Dec; 52(6): 616–619.

6. The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACM commented that there is an observation bias in clinical trials that results in higher rates of mild or trivial intraocular inflammation detected in trials that is not replicated in post marketing surveillance or clinical practice. This mild intraocular inflammation is not symptomatic, not associated with poorer outcomes and resolves generally within a few days post injection, and is therefore rarely noted.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Beovu brolucizumab (rbe) 120 mg/mL solution for injection, indicated for:

> *Beovu is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD).*

Specific conditions of registration applying to these goods

- Beovu brolucizumab (rbe) is to be included in the Black Triangle Scheme. The PI and CMI for Beovu must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the products.
- The brolucizumab EU-RMP, version 1.2, dated 31 October 2019 (data lock point 23 April 2018), with ASA, version 2.0, dated 12 November 2019, included with submission PM-2019-00106-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of PSURs.

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

- Batch release testing and compliance with Certified Product Details (CPD)
  - All batches of Beovu brolucizumab imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - Up to 5 initial batches of Beovu brolucizumab imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index.
  - The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product.

  More information on TGA testing of biological medicines is available at https://www.tga.gov.au/publication/testing-biological-medicines.

  This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until the sponsor is notified in writing of any variation.

Attachment 1. Product Information

The PI for Beovu approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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