Date: 3 August 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

BEOVU

International non-proprietary name: brolucizumab

Pharmaceutical form: solution for injection in pre-filled syringe
solution for injection in a vial

Dosage strength(s): 120 mg / 1 mL

Route(s) of administration: intravitreal

Marketing Authorisation Holder: Novartis Pharma Schweiz AG

Marketing Authorisation No.: 67244

Decision and Decision date: approved on 2 June 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Table of contents

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AMD	Age-related macular degeneration
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCVA	Best-corrected visual acuity
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DAA	Disease activity assessment
DDI	Drug-drug interaction
DME	Diabetic macular oedema
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
IOP	Intraocular pressure
IP	Investigational product
ITT	Intention-to-treat
IVT	Intravitreal
LoQ	List of Questions
LS	Least-square
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
nAMD	Neovascular (wet) age-related macular degeneration
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

2 Background Information on the Procedure

2.1 Applicant's Request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested to add or change the indication in accordance with Article 23 TPO.

2.2 Indication and Dosage

2.2.1 Requested Indication

Beovu is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) *and diabetic macular oedema (DME)*.

2.2.2 Approved Indication

Beovu is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) and diabetic macular oedema (DME).

2.2.3 Requested Dosage

Summary of the applied standard dosage:
The recommended dose for Beovu is 6 mg (0.05 ml) administered as an intravitreal injection, with the first five injections taking place at 6-week intervals. Thereafter, Beovu is administered every 12 weeks (3 months).The physician may individually define treatment intervals based on disease activity as measured by visual acuity and/or anatomical parameters. In patients with disease activity, treatment every 8 weeks (2 months) could be considered.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	30 August 2021
Formal control completed	6 September 2021
List of Questions (LoQ)	15 December 2021
Answers to LoQ	4 February 2022
Predecision	12 April 2022
Answers to Predecision	29 April 2022
Final Decision	2 June 2022
Decision	approval

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

3 Medical Context

Diabetic macular oedema (DME) is manifested as retinal thickening caused by the accumulation of intraretinal fluid, primarily in the inner and outer plexiform layers. It is believed to be a result of hyperpermeability of the retinal vasculature. DME can be present with any level of diabetic retinopathy. WHO estimates that there are more than 150 million patients with diabetes worldwide. However, the absolute prevalence of DME may be increasing due to the overall increased prevalence of diabetes in industrialised nations. It is expected that the incidence of DME will decrease as excellent metabolic control is increasingly embraced as a therapeutic goal by patients and healthcare workers. Macular oedema is strongly positively associated with diabetic retinopathy severity. Glycaemic control is a conclusively identified risk factor for retinopathy progression as well as for DME. Duration of diabetes is strongly correlated with prevalence and incidence of macular oedema, retinopathy progression and other diabetic complications. Diagnosis of type 2 diabetes occasionally occurs sometime after subclinical diabetes manifests, which yields a small proportion of patients who may present with macular oedema at the time of diagnosis, or even have decreased vision from macular oedema as the presenting sign. In contrast, persons with type 1 diabetes are very unlikely to experience advanced retinopathy and macular oedema before 5 years of duration. The most effective treatment strategies first aim at the underlying causes of macular oedema, such as diabetes or high blood pressure, and then directly treat the damage to the retina. Treatments for diabetic macular oedema and macular oedema caused by other conditions are often the same. However, some cases of macular oedema may need additional treatments to address associated conditions. The current standard of care for macular oedema is intravitreal injection. Anti-VEGF treatment blocks the activity of VEGF and slows the progress of macular oedema. Anti-VEGF drugs all work in similar ways to block vessel formation and prevent leakage in the retina. Brolucizumab is a humanised single-chain variable fragment that blocks VEGF-A from binding to its receptors, VEGFR-1 and VEGFR-2. It is administered by IVT injection.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

4 Nonclinical Aspects

The applicant submitted documentation for the line extension for Beovu (brolucizumab) to support the new indication diabetic macular oedema (DME) in adults. No nonclinical documentation was submitted to support the new indication. This is acceptable as there are no changes with regard to posology and method of administration. The pharmacological activity and the toxicological profile of brolucizumab were considered sufficiently characterised in the initial marketing authorization application for the approved indication (patients with neovascular (wet) age-related macular degeneration (nAMD)).

An enhanced pre- and postnatal developmental (ePPND) study in cynomolgus monkeys was conducted at the request of the FDA. Considering the low safety margin and the mode of action of brolucizumab, the study did not provide any valuable data to exclude a harmful effect of VGF-inhibition on pregnancy and embryofetal development. The recommendation that brolucizumab should not be used during pregnancy remains in the information for healthcare professionals.

Justification for the absence of ERA studies and an updated version of the RMP were submitted.

From the nonclinical point of view, there are no objections to approval of the proposed indication extension.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

No additional pharmacokinetic (PK) studies were conducted with brolucizumab to support this new indication.

5.2 Dose Finding and Dose Recommendation

The doses for brolucizumab are based on the Phase III brolucizumab studies in nAMD, wherein brolucizumab 6 mg and 3 mg doses showed comparable efficacy and safety profiles to existing anti-VEGFs, with numerical advantages related to efficacy for the higher dose. No new dose-finding studies were conducted.

5.3 Efficacy

The key clinical studies providing efficacy and safety data in subjects with DME are:

a) **Study B2301**
b) **Study B2302**.

Both pivotal studies differed slightly in design, Study B2301 having three and Study B2302 two arms.

In other respects, they were identical in terms of the inclusion/exclusion criteria and the primary/secondary endpoints.

Design:

Studies B2301 and B2302 were phase III, randomised, double-masked, multi-centre, active-controlled studies to evaluate the efficacy and safety of

a) brolucizumab 6 mg and 3 mg compared to the active control, aflibercept 2 mg
b) brolucizumab 6 mg compared to the active control, aflibercept 2 mg

in subjects with diabetic macular oedema (DME).

Both studies included a screening period of up to 2 weeks to assess eligibility, followed by a double-masked treatment period (Day 1 to Week 96). The baseline visit was defined as Day 1/Visit 1, and the end-of-treatment visit as Visit 27 (Week 96). After the last treatment visit, a post-treatment follow-up period was planned from Week 96 to Week 100.

Subjects were assigned to:

a) **B2301**

one of **three** treatment arms in a 1:1:1 ratio: brolucizumab 6 mg/0.05 mL administered 5 x every 6 weeks (q6w) during loading phase then q12w/every 8 weeks (q8w) during maintenance phase; brolucizumab 3 mg/0.05 mL administered 5 x every 6 weeks (q6w) during loading phase then q12w/q8w during maintenance phase; or aflibercept 2 mg/0.05 mL administered 5 x every 4 weeks (q4w) during loading phase then q8w during maintenance phase.

a) **B2302**

one of **two** treatment arms in a 1:1 ratio: brolucizumab 6 mg/0.05 mL administered 5 x every 6 weeks (q6w) during loading phase then q12w/q8w during maintenance phase or aflibercept 2 mg/0.05 mL administered 5 x every 4 weeks (q4w) during loading phase then q8w during maintenance phase.

For Study B2301, a total of 566 subjects were randomised in a 1:1:1 ratio to the brolucizumab 6 mg arm (n=189), the brolucizumab 3 mg arm (n=190) or the aflibercept 2 mg arm (n=187).

For Study, B2302 a total of, 360 subjects were randomised in a 1:1 ratio to the brolucizumab 6 mg arm (n=179) or the aflibercept 2 mg arm (n=181). Subjects who were eligible were aged >18 years,

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

with type 1 or type 2 diabetes mellitus and HbA1c of ≤10% at screening, whose medication for the management of diabetes had to be stable within 3 months prior to randomisation. Visual impairment due to DME consisted of a best-corrected visual acuity (BCVA) score between 78 and 23 letters in a visual acuity test and DME involving the centre of the macula, with central subfield retinal thickness of ≥320 µm.

The primary endpoint was defined as change from baseline in BCVA at Week 52 to demonstrate that brolucizumab is non-inferior to aflibercept with respect to the visual outcome after the first year of treatment. The first key secondary endpoint was defined as a change from baseline in BCVA averaged over a period Week 40 to Week 52 to demonstrate that brolucizumab is non-inferior to aflibercept with respect to visual outcome during the last 3 months of the first year of treatment. For both studies a non-inferiority margin of 4 letters was set. Both, the primary and the secondary endpoint were assessed to be acceptable and of clinical relevance

Population:

A majority of patients (over 90%) had type II diabetes. Overall, the study population had a mean age of 63 years, the majority was male (over 60%) and white (over 70%), consistent with the target population.

Approximately 50% of subjects had unilateral DME at baseline in one eye and 50% in the other eye, with over 60% being diagnosed ≤ 3 months prior to study entry. The mean baseline BCVA was 65 letters with 40% of subjects having a BCVA ≥ 71 letters. The baseline characteristics in terms of BCVA were comparable to previous studies with brolucizumab.

Efficacy results:

a) In study B2301, the non-inferiority margin of 4 letters was met for the primary endpoint for brolucizumab 6 mg (LS mean difference of -1.3 letters) with a lower limit of the 95% confidence interval of -2.9 letters. The mean change in BCVA for aflibercept was 10.5 letters and 9.3 letters for brolucizumab 6 mg. Meanwhile, non-inferiority of brolucizumab 3 mg to aflibercept 2 mg could not be demonstrated. The results were supported by those for the key secondary endpoint.
b) In study B2302, the non-inferiority margin of 4 letters was met for the primary endpoint for brolucizumab 6 mg (LS mean difference of 1.2 letters) with a lower limit of the 95% confidence interval of -0.6 letters. The mean change in BCVA for aflibercept was 9.4 letters and 10.6 letters for brolucizumab 6 mg. The results were supported by those for the key secondary endpoint.

For further details, please see the “Properties/effects” and “Clinical efficacy” sections of the information for healthcare professionals.

5.4 Safety

Over 70% of the patients who received brolucizumab had at least seven injections, approximately 30% of study participants received eight injections. In the aflibercept arm, most subjects received nine active IVT injections (80.1%) due to the fixed q8w dosing schedule (following 5×q4w loading phase regimen). This difference between the two treatment arms was driven by the different IVT injection schedules during the loading phase for each arm and the changes in IVT injection schedule based on DAA during the maintenance phase in the brolucizumab arm.

Over 80% of study participants completed the studies with no imbalances between study arms. Between 8% and 10% of subjects discontinued, mainly due to the subjects’ decision, followed by adverse events.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

In the pooled analysis, non-ocular adverse events occurred with a slightly higher frequency in the aflibercept treatment group as compared to brolucizumab. The most frequently reported non-ocular adverse events in the brolucizumab group were hypertension (n=30, 8.2% versus n=26, 7.1%, respectively), nasopharyngitis (n=27, 7.3% versus n=25, 6.8%, respectively) and urinary tract infection (n=15, 4.1% versus n=10, 2.7%, respectively).

The overall incidence of non-ocular serious AEs reported was numerically slightly lower in the brolucizumab 6 mg arm than in the aflibercept 2 mg arm (n=65, 17.7% vs. n=74, 20.1%).

Serious ocular adverse events occurred with similar frequency across treatment groups: n=6 (1.6%) in the brolicizumab 6 mg group vs n=7 (1.9%) in the aflibercept group.

In the pooled safety analysis, incidence of AEs of special interest was numerically higher in the broculizumab 6 mg group than in the aflibercept arm: n=12 (3.3%) vs. n=7 (1.9%) with most of these events being attributed to intraocular inflammation: n=10 (2.7%) in the broculizumab 6 mg group vs. n=4 (1.1%) in the aflibercept arm.

In the pooled analysis of ocular and non-ocular AEs of special interest, more events were reported in the broculizumab 6 mg group: n= 66 (17.9%) vs. n=52 (14%) in the afilbercept group.

Cases of retinal vascular occlusion were also reported more frequently in the brolucizumab arms:

n= 2 (0.5%) vs. n=1 (0.3%) in the afilbercept group. Warnings have been implemented in the information for healthcare professionals.

There were eight cases of death in the brolucizumab 6 mg group, four in the aflibercept group and one in the brolucizumab 3 mg group. A causal relation between deaths and the IP was assessed as unlikely.

As with other anti-VEGF drug products administered by intravitreal injection, uncertainties remain regarding the potential role of brolucizumab in systemic AE occurrence, for example arterial thromboembolic events, venous thromboembolic events, hypertension and non-ocular haemorrhage. However, similar rates were reported for brolucizumab comparing to aflibercept.

For further details, please see the “Undesirable effects” and “Warnings and precautions” sections of the information for healthcare professionals.

5.5 Final Clinical and Clinical Pharmacology Benefit-Risk Assessment

In two pivotal studies, statistically significant differences versus baseline in the primary endpoint BCVA at Week 52 were shown for brolucizumab 6 mg. These differences can be regarded as clinically relevant. In both studies, non-inferiority versus aflibercept could be demonstrated for brolucizumab 6 mg.

Regarding safety and tolerability, the findings from Studies B2301 and B2302 were consistent with the results from previous studies for brolucizumab and no new safety issues emerged.

Overall, the safety profile of brolucizumab 6 mg vs. aflibercept seemed comparable.

The benefit-risk ratio for brolucizumab 6mg for the treatment of DME was assessed to be positive.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

7 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Beovu was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.
is binding and legally valid.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

▼ This medicinal product is subject to additional monitoring. This allows quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse effects. See “Adverse effects” for information on reporting adverse effects.

Beovu®

Composition

Active substances

Brolucizumab is a humanised monoclonal single-chain Fv (scFv) antibody fragment with a molecular weight of approximately 26 kDa produced in *Escherichia coli* cells by recombinant DNA technology.

Excipients

2.58 mg/ml sodium citrate, 58 mg/ml sucrose, 0.2 mg/ml polysorbate 80, sodium hydroxide (for pH adjustment to approx. 7.2) and water for injections.

Pharmaceutical form and quantity of active substance per unit

Vial
Each vial contains 27.6 mg brolucizumab in 0.23 ml of solution. This amount is sufficient to administer a single dose of 0.05 ml, containing 6 mg brolucizumab. 1 ml of solution for intravitreal injection contains 120 mg brolucizumab.

Pre-filled syringe
Each pre-filled syringe contains 19.8 mg brolucizumab in 0.165 ml of solution. This amount is sufficient to administer a single dose of 0.05 ml, containing 6 mg brolucizumab. 1 ml of solution for intravitreal injection contains 120 mg brolucizumab.

Indications/Potential uses

Beovu is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) and diabetic macular oedema (DME).

Dosage/Administration

Single-use vial or single-use pre-filled syringe. For intravitreal use only. Each vial or pre-filled syringe may only be used for the treatment of a single eye.
Beovu must be administered by a qualified physician.

Usual dosage

Neovascular (wet) age-related macular degeneration (AMD)
The recommended dose for Beovu is 6 mg (0.05 ml) administered as an intravitreal injection, with the first three injections taking place at 4-week intervals (monthly). Thereafter, Beovu is administered every 12 weeks (3 months). The physician may individually define treatment intervals based on disease activity as measured by visual acuity and/or anatomical parameters. The treatment interval may be adjusted to every 8 weeks (2 months) (see “Properties/Actions”); however, it should not be less than every 8 weeks (2 months) (see “Warnings and precautions”).

Diabetic macular oedema (DME)
The recommended dose for Beovu is 6 mg (0.05 ml) administered by intravitreal injection, with the first five injections taking place at 6-week intervals. Thereafter, Beovu is administered every 12 weeks (3 months). The physician may individually define treatment intervals based on disease activity as measured by visual acuity and/or anatomical parameters. In patients with disease activity, treatment every 8 weeks (2 months) may be considered (see “Properties/Actions”); however, the treatment interval should not be less than every 8 weeks (2 months) (see “Warnings and precautions”).

To ensure traceability of medicinal products produced using biotechnology, it is recommended that the trade name and batch number be documented at every treatment.

Special dosage instructions

Patients with hepatic impairment

No studies have been performed in patients with hepatic impairment.

Patients with renal impairment

No dose adjustment is recommended in patients with renal impairment. There are only limited data available in patients with moderate renal impairment and no data in patients with severe renal impairment (see “Properties/Actions”).

Elderly patients

No dose adjustment is required in patients aged 65 years or above.

Children and adolescents

The safety and efficacy of Beovu in children and adolescents have not been established.

Method of administration

As with all medicinal products for intravitreal use, Beovu should be inspected visually prior to administration (see “Instructions for use and handling”).
The intravitreal injection must be carried out under aseptic conditions. This includes surgical hand disinfection, sterile surgical gloves, a sterile drape and a sterile eyelid speculum (or similar instrument). Sterile paracentesis equipment should be available as a precautionary measure. The patient’s medical history should be thoroughly evaluated for possible hypersensitivity reactions prior to the intravitreal injection (see “Contraindications”). Adequate anaesthesia and a broad-spectrum topical antiseptic to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.
For information on the preparation of Beovu, see Instructions for use and handling (see “Other information”).
The injection needle should be inserted 3.5 to 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 ml can then be injected slowly. Subsequent injections must be performed at different scleral sites.
The safety and efficacy of Beovu treatment in both eyes concurrently have not been studied.

Contraindications

- Hypersensitivity to the active substance or any of the excipients.
- Existing or suspected ocular or periocular infection.
- Existing intraocular inflammation.

Warnings and precautions

Intravitreal injection-related reactions
Endophthalmitis, intraocular inflammation, retinal detachment, retinal vasculitis and/or retinal vascular occlusion
Intravitreal injections, including those with Beovu, have been associated with endophthalmitis, intraocular inflammation and retinal detachment.

Cases of retinal vasculitis and/or retinal vascular occlusion have been reported in patients treated with Beovu. Treatment with Beovu must be discontinued in affected patients. The described cases of retinal vasculitis/retinal vascular occlusion are immune-mediated adverse events and may occur after the first intravitreal injection. These events are generally associated with intraocular inflammation (i.e. intraocular inflammation represents a possible risk factor for these adverse effects). To reduce the risk of retinal vasculitis and/or retinal vascular occlusion, patients who develop intraocular inflammation during treatment with Beovu must be carefully monitored. In addition, the incidence of intraocular inflammation was investigated based on anti-brolucizumab antibody (ADA) status before

and during treatment with Beovu. The corresponding analysis of data from the phase III studies (HAWK and HARRIER) showed that patients with an immune response to Beovu (induction or boost of ADAs) had a risk of developing intraocular inflammation that was multiple times higher than in patients without an immune response (see “Contraindications” and “Adverse effects”). Beovu must be always administered under aseptic injection conditions. Patients should be instructed to report possible symptoms of any of the above-mentioned events without delay.
In a phase IIIa clinical study (MERLIN) patients with nAMD who received Beovu every 4 weeks as a maintenance dose experienced a higher incidence of intraocular inflammation (including retinal vasculitis) and retinal vascular occlusion than patients who received Beovu every 8 or 12 weeks as a maintenance dose in the pivotal phase III clinical studies (HAWK and HARRIER). The interval between 2 Beovu doses during maintenance treatment should not be less than 8 weeks (see “Dosage/Administration”).

Intraocular pressure increases
Transient increases in intraocular pressure have been seen within the first 30 minutes of injection, similar to those observed with intravitreal administration of other VEGF inhibitors (see “Adverse effects”). Sustained intraocular pressure increases have also been reported. Particular caution is required in patients with poorly controlled glaucoma (do not inject Beovu while the intraocular pressure is ≥30 mmHg). Both intraocular pressure and perfusion of the optic nerve head must be monitored and managed as necessary.

Immunogenicity
As this is a therapeutic protein, there is a potential for immunogenicity with brolucizumab (see “Adverse effects”). Patients should be instructed to inform their physician if they develop symptoms such as eye pain or increased eye discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision or increased sensitivity to light (see “Adverse effects”).

Withholding treatment
In intravitreal anti-VEGF treatments, treatment should be withheld and not resumed earlier than the next scheduled treatment in the following cases:

- a decrease in best-corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity
- a retinal tear
- a subretinal haemorrhage involving the centre of the fovea or if the size of the haemorrhage is ≥50% of the total affected lesion
- performed or planned intraocular surgery within the previous or next 28 days.

Retinal pigment epithelial tear

Large-scale and/or severe pigment epithelial retinal detachment represent risk factors for the development of a retinal pigment epithelial tear after anti-VEGF therapy in patients with wet AMD. When initiating brolucizumab therapy, caution is required in patients with these risk factors for retinal pigment epithelial tears.

Rhegmatogenous retinal detachment or macular holes

Treatment should be discontinued in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.

Systemic effects following intravitreal use

Systemic adverse effects, including non-ocular haemorrhages and arterial thromboembolic events, have been reported following intravitreal injection of VEGF inhibitors. There is a theoretical risk that these may relate to VEGF inhibition. There are only limited safety data on the treatment of AMD and DME patients with a history of stroke, transient ischaemic attacks or myocardial infarction within the last 3 months. Caution should be exercised when treating such patients.

Interactions

No formal interaction studies have been performed.

Pregnancy/Breast-feeding

Women of childbearing potential

Women of childbearing potential must use a reliable method of contraception during treatment with Beovu and for at least one month after stopping treatment with Beovu.

Pregnancy

There are no adequate and well-controlled studies of Beovu administration in pregnant women. The potential risk of use of Beovu in pregnancy is unknown. Animal studies showed no evidence of reproductive toxicity (see “Preclinical data”).
However, based on the anti-VEGF mechanism of action brolucizumab must be regarded as potentially teratogenic and embryo-/fetotoxic. Therefore, Beovu must not be administered during pregnancy unless absolutely necessary.

Breast-feeding

It is unknown if brolucizumab is transferred into human milk after administration of Beovu. There are no data on the effects of Beovu on the breast-fed infant or milk production. Because of the potential

for adverse drug reactions in breast-fed infants breast-feeding is not recommended during treatment and for at least one month after stopping treatment with Beovu.

Fertility

No relevant data are available.

Effects on ability to drive and use machines

Patients may experience temporary visual impairment after an intravitreal injection with Beovu and the associated eye examination. Patients must therefore be advised not to drive or use machines until visual function has recovered sufficiently.

Adverse effects

Patients with wet AMD

A total of 1,088 patients treated with Beovu constituted the safety population in the two phase III studies HAWK and HARRIER. The cumulative exposure to Beovu was 96 weeks and 730 patients were treated with the recommended dose of 6 mg.

The most frequently reported adverse drug reactions (in over 5% of patients treated with 6 mg Beovu) were reduced visual acuity (7.3%), cataract (7.0%), conjunctival haemorrhage (6.3%) and vitreous floaters (5.1%).

Less common serious adverse drug reactions reported in less than 1% of patients treated with 6 mg Beovu were endophthalmitis, blindness, retinal artery occlusion and retinal detachment.

Patients with DME

The safety of Beovu was studied in two active-controlled phase III studies (KESTREL and KITE) each conducted in 368 patients with visual impairment due to DME treated with the recommended dose of 6 mg brolucizumab for 52 weeks.

The ocular and non-ocular events in the KESTREL and KITE studies were reported with a similar frequency and severity to those seen in the nAMD studies. Retinal vascular occlusion was reported in two patients (0.5%) treated with Beovu and one patient (0.3%) treated with 2 mg aflibercept. Retinal vasculitis was reported in one patient (0.3%) treated with Beovu and no patients treated with 2 mg aflibercept.

Adverse drug reactions from the HAWK and HARRIER clinical studies are listed by frequency, with the most frequent adverse drug reactions listed first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Immune system disorders
Common: Hypersensitivity[a]

Eye disorders
Common: Reduced visual acuity, cataract, conjunctival haemorrhage, vitreous floaters, eye pain, retinal haemorrhage, vitreous detachment, increased intraocular pressure, conjunctivitis, retinal pigment epithelial tear, blurred vision, uveitis, corneal abrasion, punctate keratitis, iritis, retinal tear.
Uncommon: Conjunctival hyperaemia, increased lacrimation, blindness, retinal artery occlusion, abnormal sensation in eye, endophthalmitis, retinal detachment, detachment of retinal pigment epithelium, vitritis, anterior chamber inflammation, iridocyclitis, anterior chamber flare, corneal oedema, vitreous haemorrhage.

a) Including urticaria, rash, pruritus, erythema.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)
The following adverse drug reactions are from spontaneous reports and literature cases associated with post-marketing experience with Beovu. Because these effects are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequencies. Therefore, these adverse drug reactions have been assigned the frequency category “not known”. Adverse drug reactions are listed by MedDRA system organ class. Within each system organ class adverse drug reactions are listed in order of decreasing seriousness.
Eye disorders
Not known: Retinal vascular occlusion, retinal vasculitis

Intraocular inflammation
In clinical studies intraocular inflammation-related adverse events, including retinal vasculitis and retinal vascular occlusion, were reported more frequently in female patients treated with Beovu than in male patients (e.g. 5.3% females vs 3.2% males in the HAWK and HARRIER studies).
Post-marketing safety data indicate a risk of intraocular inflammation, including retinal vasculitis and retinal vascular occlusion, during Beovu treatment. To identify potential risk factors, real-world data from nAMD patients treated for up to 6 months were analysed retrospectively. The results of this analysis indicate an increased risk of the above-mentioned events in patients who have experienced intraocular inflammation and/or retinal vascular occlusion in the year prior to the start of Beovu treatment.

Immunogenicity
As with all therapeutic proteins, there is also a potential risk of an immune response in patients treated with Beovu. The immunogenicity of Beovu was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for

antibodies to Beovu in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons comparison of the incidence of antibodies to Beovu with the incidence of antibodies to other products may be misleading. Antibodies, including single-chain antibodies, to a variety of therapeutic proteins produced using biotechnology have been detected in treatment-naïve patients before the start of treatment.

Wet AMD
The pre-treatment incidence of anti-brolucizumab antibodies was 35-52%. After administration of Beovu for a period of 88 weeks treatment-emergent anti-brolucizumab antibodies were detected in 23-25% of patients.

Diabetic macular oedema (DME)
The pre-treatment incidence of anti-brolucizumab antibodies was 64%. After dosing with Beovu for 52 weeks, treatment-emergent anti-brolucizumab antibodies were detected in 12 to 18% of patients.

In wet AMD and DME anti-brolucizumab antibodies were not associated with an impact on clinical efficacy. Among patients with treatment-emergent antibodies a higher number of intraocular inflammation events were observed. Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, are immune-mediated adverse events related to exposure to Beovu. This treatment-emergent antibody response may occur after the first intravitreal injection (see “Warnings and precautions”).

Product class-related adverse effects
There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. A low incidence rate of arterial thromboembolic events was observed in the brolucizumab clinical studies in patients with AMD. There were no major differences between the groups treated with brolucizumab and the comparator.

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via the online portal ElViS (Electronic Vigilance System). You can find further information at www.swissmedic.ch.

Overdose

An overdose with more than the recommended injection volume may increase intraocular pressure. Therefore, in case of overdose intraocular pressure should be monitored and, if deemed necessary by the treating physician, treated.

Properties/Actions

ATC code

S01LA06

Mechanism of action

Increased levels of signalling through the vascular endothelial growth factor A (VEGF-A) pathway are associated with pathological ocular angiogenesis and retinal oedema. Brolucizumab binds with high affinity to VEGF-A isoforms (e.g. $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{165}$), thereby preventing VEGF-A from binding to its receptors VEGFR-1 and VEGFR-2. By inhibiting binding to VEGF-A, brolucizumab suppresses endothelial cell proliferation, thereby reducing pathological neovascularisation and decreasing vascular permeability.

Pharmacodynamics

Wet AMD

In the HAWK and HARRIER studies related anatomical parameters were part of the disease activity assessments forming the basis of treatment decisions. Reductions in central subfield thickness (CST) and in the presence of intraretinal/subretinal fluid (IRF/SRF) or subretinal pigment epithelium (sub-RPE) fluid were observed in patients treated with Beovu as early as 4 weeks after treatment initiation and up to week 48 and week 96.

In these studies reductions in CNV lesion size in patients treated with Beovu were observed as early as 12 weeks and at weeks 48 and 96 after treatment initiation.

Diabetic macular oedema (DME)

In the KESTREL and KITE studies relevant anatomical parameters were part of the disease activity assessment guiding treatment decisions. Reductions in central subfield thickness (CST) and in presence of intraretinal/subretinal fluid (IRF/SRF) were observed in patients treated with Beovu as early as 4 weeks after treatment initiation and up to week 52.

Clinical efficacy

Treatment of wet AMD

The safety and efficacy of Beovu were assessed in two randomised, multicentre, double-blind, active-controlled phase III studies (HAWK and HARRIER) in patients with neovascular AMD. A total of 1,817 patients were treated in these studies for two years (1,088 with brolucizumab and 729 with aflibercept). Patient ages ranged from 50 to 97 years, with a mean age of 76 years.

In the HAWK study patients were randomised in a 1:1:1 ratio to the following dosing regimens:

1) 3 mg brolucizumab administered every 12 or 8 weeks (q12w/q8w) after the first 3 monthly doses.
2) 6 mg brolucizumab administered every 12 or 8 weeks (q12w/q8w) after the first 3 monthly doses.
3) 2 mg aflibercept administered every 8 weeks (q8w) after the first 3 monthly doses.

In the HARRIER study patients were randomised in a 1:1 ratio to the following dosing regimens:

1) 6 mg brolucizumab administered every 12 or 8 weeks (q12w/q8w) after the first 3 monthly doses.
2) 2 mg aflibercept administered every 8 weeks (q8w) after the first 3 monthly doses.

In both studies, after the first 3 monthly doses (week 0, 4 and 8), brolucizumab patients were treated every 12 weeks with the option of switching to an 8-week treatment interval based on disease activity. Disease activity was assessed by a physician during the first 12-week interval (at weeks 16 and 20) and at each subsequent scheduled 12-weekly treatment visit. Patients who showed disease activity (e.g. decreased visual acuity, increased central subfield thickness (CST) or presence of retinal fluids (IRF/SRF, sub-RPE)) at any of these visits were switched to an 8-week treatment interval.

Results

The primary efficacy endpoint for the studies was the change from baseline in best corrected visual acuity (BCVA) at week 48 as measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter charts, with the primary objective being to demonstrate non-inferiority of Beovu versus aflibercept. In both studies Beovu (administered in a 12-/8-week regimen) demonstrated non-inferior efficacy to 2 mg aflibercept administered every 8 weeks.

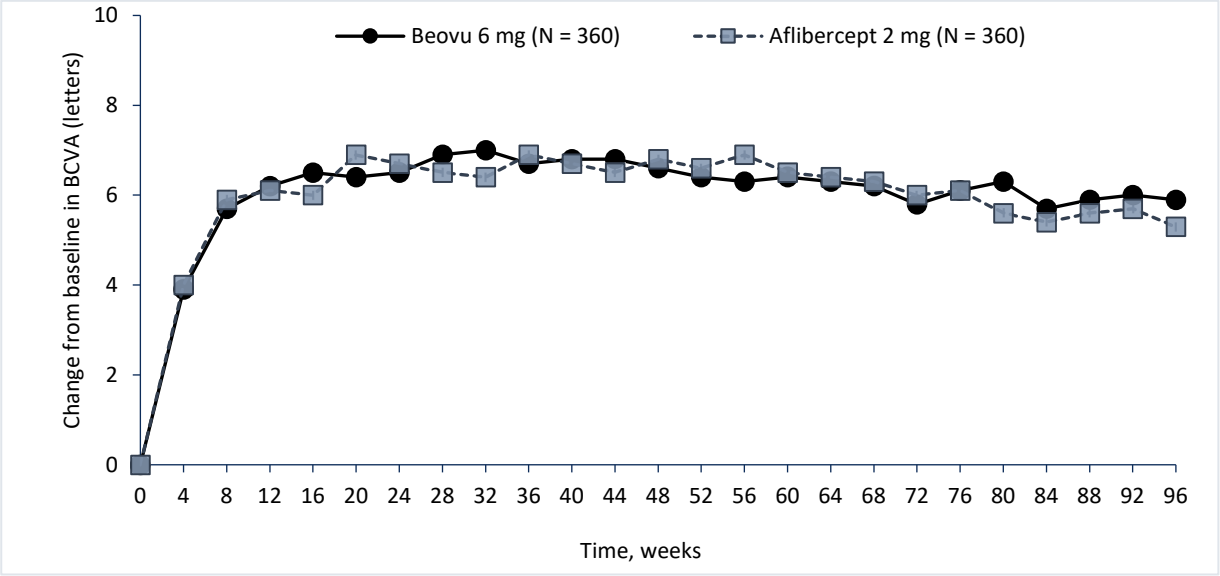
In the HAWK study, at week 48 patients achieved a mean change from baseline of +6.6 letters and +6.8 letters ($p<0.0001$) in the 6 mg Beovu and aflibercept groups, respectively. The mean change from baseline in the 3 mg Beovu group was +6.1 letters ($p=0.0003$). The proportion of patients who achieved a gain in visual acuity of at least 15 letters from baseline was 33.6% in the brolucizumab group versus 25.4% in the aflibercept group. The proportion of patients who lost 15 letters or more of visual acuity from baseline was 6.4% in the 6 mg brolucizumab group versus 5.5% in the aflibercept group.

In the HARRIER study, at week 48 patients achieved a mean change from baseline of +6.9 letters and +7.6 letters (p<0.0001) in the Beovu and aflibercept groups, respectively. The proportion of patients who achieved a gain in visual acuity of at least 15 letters from baseline was 29.3% in the brolucizumab group versus 29.9% in the aflibercept group. The proportion of patients who lost 15 letters or more of visual acuity from baseline was 3.8% in the 6 mg brolucizumab group versus 4.8% in the aflibercept group.

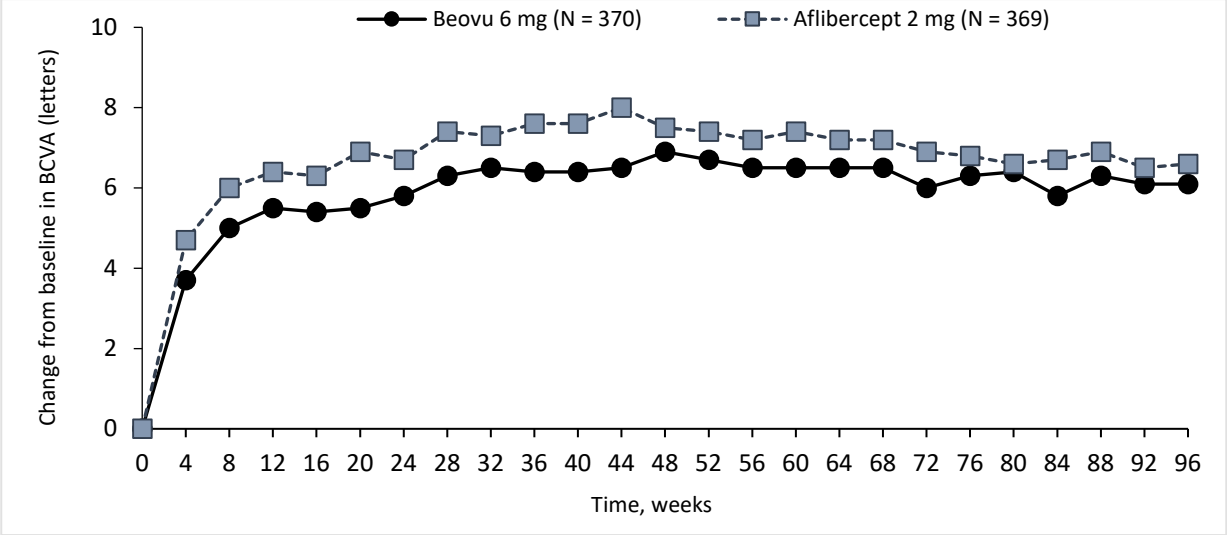
The visual acuity gains observed in the first year were maintained in the second year.

Figure 1 Mean change in visual acuity from baseline to week 96 in HAWK and HARRIER studies

HAWK



HARRIER



In the HAWK and HARRIER studies 56% and 51% of patients, respectively, treated with Beovu at a 12-week treatment interval achieved these visual acuity gains (mean change from baseline) at week 48 and 45% and 39% of patients, respectively, did so at week 96.
Among patients who, during the first 12-week treatment interval, had been identified as suitable for this treatment interval, the 12-week treatment interval was continued up to week 48 in 85% and 82% of patients, respectively. In 82% and 75% of patients, respectively, who had been treated on the basis of the 12-week treatment interval at week 48 the 12-week treatment interval was maintained from week 48 to week 96.

Treatment effects in evaluable subgroups (e.g. age, gender, ethnicity, baseline visual acuity, baseline retinal thickness, lesion type, lesion size, fluid status) in both studies were largely consistent with the results in the overall population.
Disease activity was assessed by changes in visual acuity and/or morphological criteria, including central subfield thickness (CST) and presence of retinal fluids (IRF/SRF, sub-RPE). At week 16, when disease activity was first assessed to determine the treatment interval, statistically fewer patients treated with Beovu showed disease activity compared to patients treated with 2 mg aflibercept (24% vs 35% in HAWK, p=0.0013; 23% vs 32% in HARRIER, p=0.0021). Disease activity was assessed throughout the studies. Morphological criteria of disease activity were decreased at week 48 and at week 96 in the Beovu group compared to aflibercept (Table 1).

Table 1 Disease activity evaluation in HAWK and HARRIER studies up to week 96

		HAWK			**HARRIER**		
Efficacy outcome (pre-specified secondary endpoints)	**At week**	**Beovu (N=360)**	**2 mg Aflibercept (N=360)**	**Difference (95% CI) brolucizumab and aflibercept**	**Beovu (N=360)**	**2 mg Afliberce pt (N=369)**	**Difference (95% CI) brolucizumab and afliber cept**
Mean change in CST from baseline (µm)	16 [c)]	-161.4 (SE=6.2)	-133.6 (SE=6.2)	-27.8 (-45.1, -10.5) p=0.0008 [a)]	-174.4 (SE=6.7)	-134.2 (SE=6.7)	-40.2 (-58.9, -21.6) p<0.0001 [a)]
	48	-172.8 (SE=6.7)	-143.7 (SE=6.7)	-29.0 (-47.6, -10.4) p=0.0012 [a)]	-193.8 (SE=6.8)	-143.9 (SE=6.8)	-49.9 (-68.9, -30.9) p<0.0001 [a)]
	96	-174.8 (SE=7.3)	-148.7 (SE=7.3)	-26.0 (-46.2, -5.9) p=0.0115 [b)]	-197.7 (SE=7.0)	-155.1 (SE=7.0)	-42.6 (-62.0, -23.3) p<0.0001 [b)]

CST: central subfield thickness; IRF/SRF: intraretinal/subretinal fluid; RPE: retinal pigment epithelium

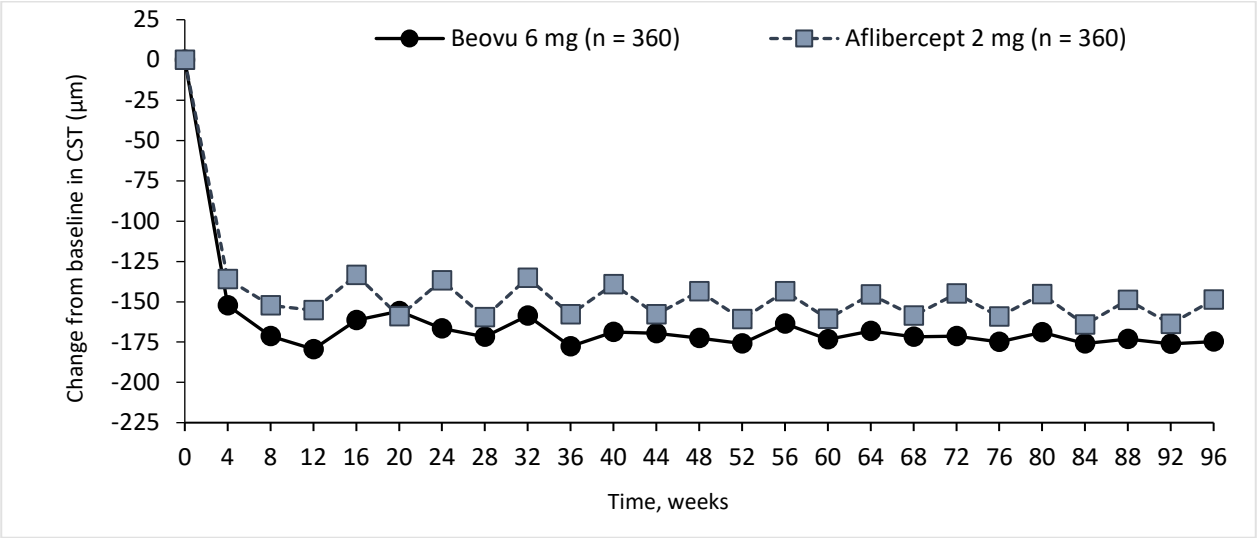
[a)] Secondary endpoint in HARRIER, confirmatory analysis in HAWK. 1-sided p-values for superiority of brolucizumab

[b)] Secondary endpoint in HAWK and HARRIER; 2-sided p-values.

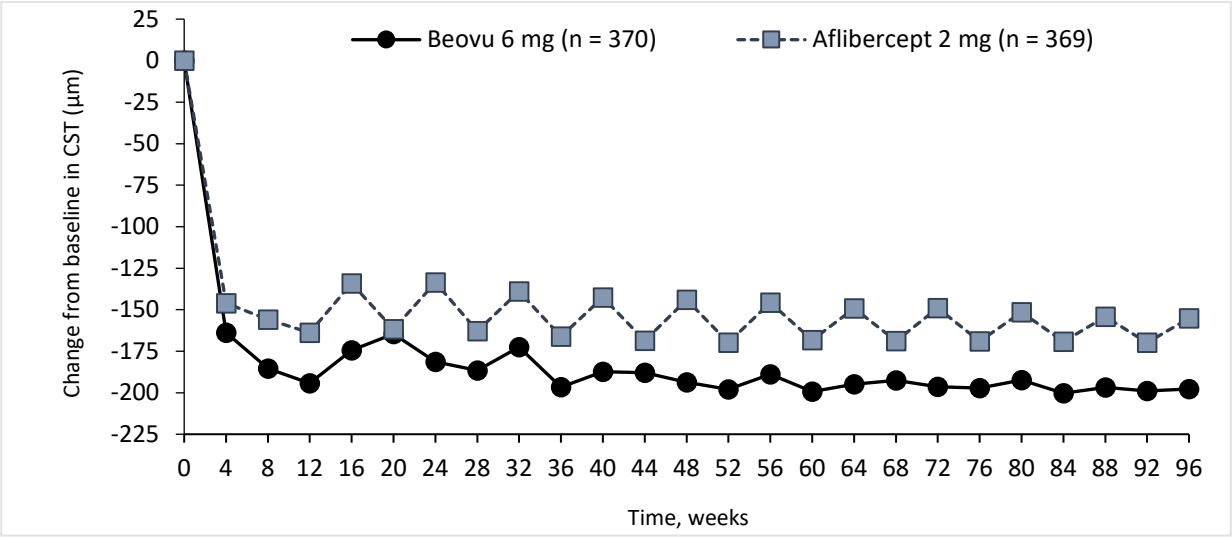
[c)] Up to week 16 treatment exposure was identical, allowing a matched comparison of Beovu and aflibercept.

Figure 2 Central subfield thickness change from baseline to week 96 in HAWK and HARRIER studies

HAWK



HARRIER



In both studies treatment with Beovu led to clinically meaningful changes from baseline in the pre-specified secondary efficacy endpoint of patient-reported outcomes, recorded using US National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, corresponding to a 15-letter gain in best corrected visual acuity (BCVA). Patient-reported outcome benefits were maintained in the second year.

No clinically meaningful differences were found between Beovu and aflibercept in changes from baseline to week 48 in NEI VFQ-25 total score and subscales (general vision, ocular pain, near vision, distance vision, social functioning, mental health, difficulties in performing social roles, dependency on others, driving, colour vision and peripheral vision).

Treatment of DME

The safety and efficacy of Beovu were assessed in two randomised, multicentre, double-blind, active-controlled phase III studies (KESTREL and KITE) in patients with diabetic macular oedema (DME). A total of 926 patients were treated in these studies for 1 year (558 with brolucizumab and 368 with 2 mg aflibercept). Patient ages ranged from 23 to 87 years, with a mean age of 63 years.

In the KESTREL study patients were randomised in a 1:1:1 ratio to the following dosing regimens:

- 6 mg brolucizumab administered once every 6 weeks (q6w) for the first 5 doses, followed by 6 mg brolucizumab every 12 or 8 weeks (q12w/q8w).
- 3 mg brolucizumab administered once every 6 weeks (q6w) for the first 5 doses, followed by 3 mg brolucizumab every 12 or 8 weeks (q12w/q8w).
- 2 mg aflibercept administered once every 4 weeks (q4w) for the first 5 doses, followed by 2 mg aflibercept every 8 weeks (q8w).

In the KITE study patients were randomised in a 1:1 ratio to the following dosing regimens:

- 6 mg brolucizumab administered once every 6 weeks (q6w) for the first 5 doses, followed by 6 mg brolucizumab every 12 or 8 weeks (q12w/q8w).
- 2 mg aflibercept administered once every 4 weeks (q4w) for the first 5 doses, followed by 2 mg aflibercept every 8 weeks (q8w).

In both studies, after the first five doses (at weeks 0, 6, 12, 18 and 24), patients were treated with brolucizumab every 12 weeks with the option of switching to an 8-week treatment interval based on disease activity. Disease activity was assessed by a physician during the first 12-week treatment interval (at weeks 32 and 36) and at each subsequent scheduled 12-weekly treatment visit. Patients who showed disease activity (e.g. decreased visual acuity, increased central subfield thickness (CST)) at any of these visits were switched to an 8-week treatment interval. The comparator aflibercept was administered every 8 weeks after the first 5 monthly doses.

Results

The primary efficacy endpoint for both studies was the change from baseline in best corrected visual acuity (BCVA) at week 52 as measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter charts, with the primary objective being to demonstrate non-inferiority of Beovu versus 2 mg aflibercept. In both studies Beovu (administered in a 12-/8-week regimen) demonstrated non-inferior efficacy to 2 mg aflibercept administered every 8 weeks.

The results of the KESTREL and KITE studies also demonstrated non-inferiority of Beovu versus 2 mg aflibercept for the key secondary endpoint (average change from baseline in visual acuity over the period from week 40 to week 52).

The median number of injections given over 12 months was 7 in patients treated with Beovu versus 9 in patients treated with 2 mg aflibercept.

Detailed results of both studies are shown in Table 2 and Figure 3 below.

Table 2 Efficacy outcomes at week 52 in the phase III KESTREL and KITE studies

		KESTREL			KITE		
Efficacy outcome	**At week**	**Beovu (n=189)**	**2 mg aflibercept (n=187)**	**Difference (95% CI) Beovu – aflibercept**	**Beovu (n=179)**	**2 mg aflibercept (n=181)**	**Difference (95% CI) Beovu – aflibercept**
Change from baseline in BCVA measured using ETDRS letter charts – LS mean (SE)	52	9.2 (0.57)	10.5 (0.57)	-1.3 (-2.9, 0.3) P <0.001[a]	10.6 (0.66)	9.4 (0.66)	1.2 (-0.6, 3.1) P <0.001[a]
	40-52	9.0 (0.53)	10.5 (0.53)	-1.5 (-3.0, 0.0) P <0.001[a]	10.3 (0.62)	9.4 (0.62)	0.9 (-0.9, 2.6) P < 0.001[a]
Gain of at least 15 letters in BCVA from baseline or BCVA of at least 84 letters (%)	52	36.0	40.1	-4.1 (-13.3, 5.9)	46.8	37.2	9.6 (-0.4, 20.2)
Mean change from baseline in CST (micrometres) – LS mean (SE)	40-52	-159.5 (5.88)	-158.1 (5.91)	-1.4 (-17.9, 15.0)	-187.1 (6.91)	-157.7 (6.89)	-29.4 (-48.6, -10.2) P =0.001[b]
Presence of IRF and/or SRF (%)	52	60.4	73.5	-13.2 (-23.2, -3.8)	54.5	72.9	-18.4 (-28.5, -8.3)

BCVA: Best corrected visual acuity; BCVA assessments after the start of alternative DME treatment in the study eye were censored and replaced by the last value prior to the start of this alternative treatment

CST: Central subfield thickness

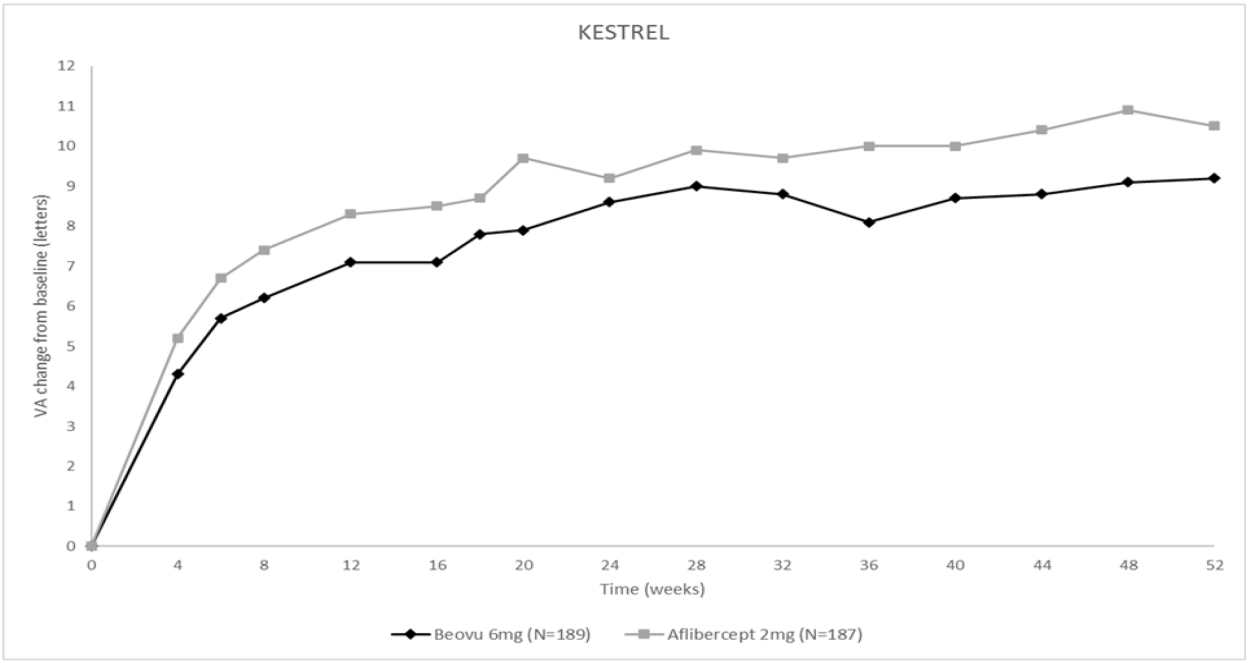
IRF: Intraretinal fluid; SRF: Subretinal fluid

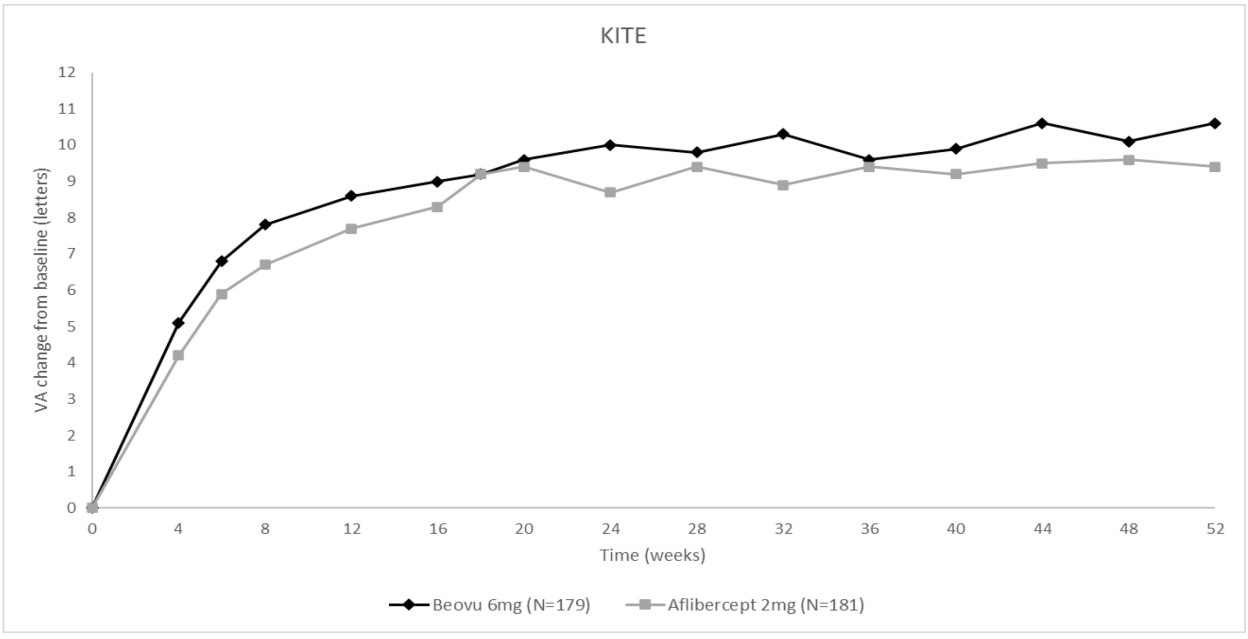
CST and fluid status assessments after the start of other DME treatment in the study eye were censored and replaced by the last value prior to the start of this other treatment

[a] *P-value referring to the non-inferiority hypothesis with a non-inferiority margin of 4 letters*

[b] *P-value referring to the superiority testing at one-sided type I error of 0.025*

Figure 3 Mean change in visual acuity from baseline to week 52 in KESTREL and KITE studies





In the KESTREL and KITE studies 55% and 50% of patients, respectively, treated with 6 mg Beovu at a 12-week treatment interval achieved these visual acuity gains at week 52. Among patients who, during the first 12-week treatment interval, had been identified as suitable for this treatment interval, the 12-week treatment interval was continued up to week 52 in 88% and 95% of patients, respectively.
Treatment effects in evaluable subgroups (e.g. age, gender, baseline HbA1c, baseline visual acuity, baseline retinal thickness, DME lesion type, duration of DME since diagnosis, retinal fluid status) in both studies were largely consistent with the results in the overall population.
In both studies treatment with Beovu led to improvements from baseline in the pre-specified secondary efficacy endpoint of patient-reported outcomes, recorded using the US National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, corresponding to a 15-letter gain in best corrected visual acuity (BCVA).
No treatment differences were found between Beovu and 2 mg aflibercept for other subscales of this questionnaire.
Diabetic Retinopathy Severity Score (DRSS) was determined in both the KESTREL and KITE studies. At baseline 98.1% of patients in both the KESTREL and KITE studies had a gradable Diabetic Retinopathy Severity Score. Based on the pooled analysis 28.9% of patients treated with Beovu experienced an at least 2-step improvement from baseline to week 52 in DRSS score compared to 24.9% of patients treated with 2 mg aflibercept. The estimated difference between Beovu and 2 mg aflibercept was 4.0% (95% CI: [-0.6, 8.6]).

Pharmacokinetics

Absorption

Beovu is administered directly into the vitreous body to exert local effects in the eye.

Distribution

After intravitreal administration of 6 mg brolucizumab per eye to nAMD patients the mean C_{max} of free brolucizumab in the serum was 49.0 ng/ml (range: 8.97 to 548 ng/ml) and was attained within one day. Mean AUC was 6000 h*ng/ml (range: 1420-60400 h*ng/ml).

Metabolism

Brolucizumab is a monoclonal antibody fragment and no drug metabolism studies have been conducted. As brolucizumab is a single-chain antibody fragment, free brolucizumab is expected to be eliminated through targeted disposition via binding to free endogenous VEGF, passive renal elimination and metabolism via proteolysis.

Elimination

After intravitreal injection brolucizumab was eliminated with an apparent systemic half-life of 4.4 days. Beovu did not accumulate in the serum when administered intravitreally every 4 weeks.

Pharmacokinetics in special populations

Hepatic impairment

Pharmacokinetics have not been studied in patients with hepatic impairment.

Renal impairment

The systemic pharmacokinetics of brolucizumab were evaluated in nAMD patients for whom both serum brolucizumab pharmacokinetic data and brolucizumab creatinine clearance data were available. The geometric mean ratio (90% CI) in patients with mild (60 to <90 ml/min (n=22)) and moderate (30 to <60 ml/min (n=3)) renal impairment compared to patients with normal renal function is 1.4 (0.7, 2.9) and 1.7 (1.0, 2.8), respectively, for brolucizumab C_{max} and the ratio for AUC_{inf} is 1.4 (0.7, 2.9) and 1.0 (0.5, 2.0), respectively. No patients with severe (<30 ml/min) renal impairment were studied.

Elderly patients

Data on the pharmacokinetics of brolucizumab in elderly patients are limited, so that it is not possible to draw conclusions regarding the effect of ageing on the pharmacokinetics of brolucizumab.

Genetic polymorphism

Ethnic groups

There were no ethnic differences in systemic pharmacokinetic characteristics following intravitreal injection in a study with 24 Caucasian and 26 Japanese patients.

Preclinical data

Long-term toxicity (repeated-dose toxicity)

Intravitreal injections of brolucizumab to cynomolgus monkeys at dosage strengths of up to 6 mg/eye every 4 weeks for 26 weeks resulted in no ocular or systemic effects and were well tolerated.

Mutagenicity/carcinogenicity

No studies have been conducted to assess the mutagenic or carcinogenic potential of Beovu.

Reproductive toxicity

In an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys brolucizumab was administered to all animals by intravitreal (IVT) injection to one eye at doses of 3 or 6 mg once every 4 weeks until delivery. One additional injection was administered to a subset of these animals 28 days post-partum, with blood and milk collected for toxicokinetic evaluations. The

intravitreal administration of brolucizumab had no impact on embryo-fetal development, pregnancy or parturition or on the survival, growth or postnatal development of offspring. The systemic exposure reached in this study corresponds to approximately 6 times therapeutic clinical exposure in humans (based on the maximum serum concentration, C_{max}) at the proposed clinical dose of 6 mg.
Brolucizumab was not detected in the maternal milk or infant serum of cynomolgus monkeys in the study.
However, VEGF inhibition has been shown to affect follicular development, corpus luteum function and fertility. Based on the mechanism of action of VEGF inhibitors there is a potential risk to female reproduction and embryo-fetal development.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use after the expiry date (= EXP) printed on the vial/pre-filled syringe.

Special precautions for storage
Keep out of the reach of children.

Vial: Store in the original carton to protect the contents from light. Store in a refrigerator (2-8°C). Do not freeze.
Prior to use the unopened vial can be stored at room temperature (25°C) for up to 24 hours.

Pre-filled syringe: Store in the sealed blister in the original pack to protect the contents from light. Store in a refrigerator (2-8°C). Do not freeze.
Prior to use the unopened blister can be stored at room temperature (25°C) for up to 24 hours.
For further information please see *"Instructions for use and handling"*.

Swissmedic number

67245, 67244

Pack sizes

One 0.23 ml vial, one filter needle. [B]
One 0.165 ml pre-filled syringe. [B]

Marketing authorisation holder

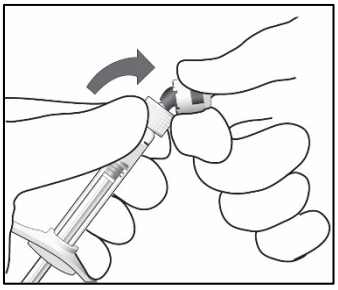
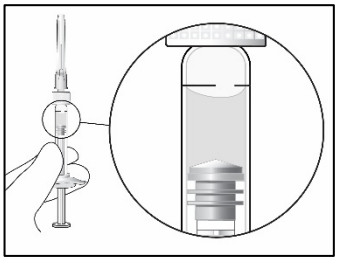
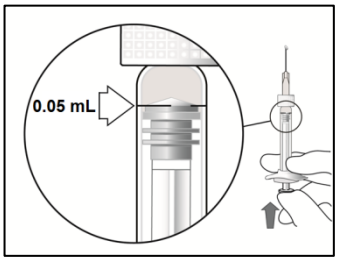
Novartis Pharma Schweiz AG, Risch, Switzerland; domicile: 6343 Rotkreuz, Switzerland

Information last revised

June 2022

Instructions for use and handling

To prepare Beovu for intravitreal administration, please follow the instructions for use:

1		Peel the foil off the blister and remove the syringe under aseptic conditions.
2		Snap off (do not turn or twist) the syringe cap.
3		Attach a **30 G x ½" injection needle to the syringe under aseptic conditions**.
4		To check the contents for air bubbles, hold the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top. Carefully remove the injection needle cap by pulling it straight off.
5		Hold the syringe at eye level and carefully push the plunger until the **edge below the dome of the rubber stopper** is aligned with the **0.05 ml** dose mark. The syringe is now ready for the injection.
6		Inject the solution slowly until the rubber stopper reaches the end of the syringe barrel to deliver the entire volume of 0.05 ml. **Confirm delivery of the**

		full dose by checking that the rubber stopper has reached the end of the syringe barrel. **Note:** Dispose of the used pre-filled syringe together with the needle in a sharps disposal container or in accordance with local requirements.