Date: 5 March 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Beovu

International non-proprietary name: brolucizumabum
Pharmaceutical form: solution for injection in a vial or pre-filled syringe
Dosage strength: 120 mg/1 mL, solution for injection
Route(s) of administration: intravitreal use
Marketing Authorisation Holder: Novartis Pharma Schweiz AG
Marketing Authorisation Nos.: 67244 (vial) and 67245 (pre-filled syringe)
Decision and Decision date: approved on 16 January 2020

Note:

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

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- 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.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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Table of contents

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
AMD	Age-related macular degeneration
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24 h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCVA	Best-corrected visual acuity
CI	Confidence interval
Cmax	Maximum observed plasma/serum concentration of drug
CSR	Clinical study report
CYP	Cytochrome P450
DDI	Drug-drug-interaction
EC_{50}	Half maximal effective concentration
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
HPLC	High Performance Liquid Chromatography
hVEGF	Human vascular endothelial growth factor
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
IVT	intravitreal
LoQ	List of Questions
Max	Maximum
MAH	Marketing Authorisation Holder
Min	Minimum
N/A	Not applicable
nAB	neutralising antibody
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PFS	Prefilled syringe
Ph. Eur	Pharmacopoe Europaea
PSP	Pediatric Study Plan (US-FDA)
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
RMP	Risk Management Plan
RPE	Retinal pigment epithelium
scFv	Single-chain fragment variable
SE-HPLC	Size-exclusion high-performance liquid chromatography
SwissPAR	Swiss Public Assessment Report
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)
USP	United States Pharmacopeia
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance (INN) of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

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

2.2.2 Approved Indication

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

2.2.3 Requested Dosage

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

Usual dosage
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 or anatomical parameters. The treatment interval may be adjusted to every 8 weeks (2 months) (see "Properties/Actions").
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	25 February 2019
Formal control completed	27 February.2019
List of Questions (LoQ)	06 June 2019
Answers to LoQ	12 August 2019
Predecision	30 October 2019
Answers to Predecision	26 November 2019
Final Decision	16 January 2020
Decision	approval

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2.4 Medical Context

Brolucizumab is a humanised monoclonal single-chain antibody fragment that was developed for the treatment of wet age-related macular degeneration (AMD). The current standard treatments for AMD include the injection of inhibitors of vascular growth factor known as anti-VEGFs (Anti-Vascular Endothelial Growth Factor) into the vitreous body (intravitreal surgical drug administration).

Preparations authorised in Switzerland for AMD:
57664 Lucentis, solution for injection (ranibizumab) in a vial
63277 Lucentis, solution for injection (ranibizumab) in a prefilled syringe
Indications:
• exudative age-related macular degeneration
• loss of vision due to diabetic macular oedema, or due to macular oedema secondary to retinal vein occlusion or due to choroidal neovascularisation as a result of pathological myopia
• visual impairment due to active choroidal neovascularisation

62393 Eylea, solution for injection (aflibercept) in a prefilled syringe
62397 Eylea, solution for injection (aflibercept) in a vial
Indications:
• Exudative (wet) age-related macular degeneration (AMD)
• Macular oedema secondary to central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO), diabetic macular oedema (DME)
• Treatment of subfoveal and juxtafoveal choroidal neovascularisation secondary to pathological myopia (mCNV).

55269, Visudyne, powder for solution for infusion (verteporfin)
Indication:
• Subfoveal choroidal neovascularisation in the eye

3 Quality Aspects

3.1 Drug Substance

Brolucizumab is a humanised single-chain Fv (scFv) antibody fragment with a molecular weight of ~26 kDa which binds to vascular endothelial growth factor A (VEGF-A). Brolucizumab prevents binding of VEGF-A to its receptors, VEGFR1 and VEGFR2, which are expressed on the surface of endothelial cells. The drug substance brolucizumab is produced in *E.coli* using recombinant DNA technology. Brolucizumab is produced by fermentation in a bioreactor. The fermentation broth is harvested as a single batch and is subsequently purified by several chromatographic steps. The drug substance is finally stored frozen.

Several changes were implemented during the development of the brolucizumab drug substance process, including changes to production site, production scale, and drug substance composition. The analytical comparability studies, which included in-process data, batch release data, extended characterisation, and stability data, demonstrate comparability between process changes.

The characterisation of the physicochemical and biological properties of the drug substance and its impurities were performed using state of the art methods.

The specifications include relevant tests and limits, e.g. for appearance, identity, pH, purity /impurity tests (e.g., SE-HPLC), assay of protein, and a cell-based potency assay. Specifications are also based upon regulatory requirements, e.g. Ph. Eur. ‘Monoclonal antibodies for human use’ and ‘USP <771> Ophthalmic products - quality tests’.

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Batch analysis data of non-clinical batches, clinical batches, process validation batches, and commercial scale batches were provided. All the analytical methods are described and the non-compendial methods were validated in accordance with ICH guidelines.

During storage, no significant changes were observed under the proposed storage conditions. A shelf-life of 24 months has been accepted.

3.2 Drug Product

Brolucizumab is formulated as drug product for intravitreal administration as solution for injection in a dosage strength of 6 mg/0.05 mL and is available in two presentations:

- solution for injection in vial (referred to as drug product in vial)
- solution for injection in prefilled syringe (PFS).

Both presentations contain a drug product solution of identical composition. All excipients comply with the European Pharmacopoeia.

The finished product manufacturing process for vials consists of thawing of drug substance, compounding, sterile filtration, filling/stoppering, crimping and visual inspection. The manufacturing process for drug product in PFS versus drug product in vial is similar and encompasses the following steps: thawing of drug substance, compounding, sterile filtration, filling, plunger stoppering, and visual inspection. The PFS are then finally assembled, and blistered into a blister tray.

Brolucizumab solution for injection (for vials and PFS) was validated by manufacturing consecutive full-scale production batches using the same process and the same equipment as the batches intended for commercial supply.

The release and stability specifications include relevant tests and limits, e.g. for appearance, identity, pH, extractable volume, purity/impurity tests (e.g., SE-HPLC), assay of protein, a cell-based potency assay, particulate matter, sterility, and bacterial endotoxins. In addition, for PFS syringe-specific tests are performed. All non-compendial methods are validated in accordance with ICH guidelines.

Batch analysis data of several batches (for vials and PFS) were provided. All batch release data comply with the drug product specifications which were valid at the time of batch release.

The primary packaging container for brolucizumab solution for injection consists of a 2 mL type I glass vial closed with a coated chlorobutyl rubber stopper and sealed with an aluminium cap with a flip-off component. The container for brolucizumab PFS is a sterile single-use 0.5 mL pre-fillable syringe, a standard container for pharmaceutical use.

The drug product (vial and PFS) is stored at 2 – 8°C. Purity decreases only slightly under the proposed storage conditions; the stability studies are ongoing. A shelf-life of 24 months for vials and PFS has been accepted. The proposed in-use shelf-life (24 h at ambient temperature, not above 30°C) and protected from light is justified.

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Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf-life of drug substance and drug product is supported by data from recommended storage conditions, as well as accelerated and stress studies.

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4 Nonclinical Aspects

Introduction
Brolucizumab is a humanised single-chain Fv (scFv) antibody fragment with a molecular weight of ~26 kDa. The applicant performed a tailored toxicology programme considering the nature of the drug substance (scope of ICH S6) as well as the low systemic exposure and rapid elimination. The programme was discussed with multiple health authorities.

Pharmacodynamics
The applicant provided *in vitro* and *in vivo* data to demonstrate the binding of brolucizumab to the vascular endothelial growth factor A (VEGF A) and consequently, inhibit the binding of VEGF-A to its receptors, VEGFR-1 and VEGFR-2. The binding affinity of brolucizumab to human $VEGF_{165}$ was 28.4 pM; comparable values were recorded for other splicing forms. Based on results from intrinsic fluorescence spectroscopy, a complex stoichiometry between brolucizumab and hVEGF of 2:1 is assumed. Experimental data indicate that brolucizumab also binds to VEGF of various other species (mice, rats, cats, dogs and pigs), except in rabbits. The binding of brolucizumab to human and monkey $VEGF_{165}$ is expected to be the same, since the amino acid sequences of human and cynomolgus monkey $VEGF_{165}$ are identical.
Brolucizumab inhibited the binding of VEGF-A to VEGFR-1 and VEGFR-2 with EC_{50} values of 4.03 nM and 0.86 nM, respectively. The consequence of the interaction between VEGF-A and VEGFR-2 was confirmed indirectly by demonstrating inhibition of cell proliferation and migration. Brolucizumab was compared in vitro to other approved VEGF inhibitors and produced similar results under testing conditions.
No animal model is available for wet AMD. Since rodents do not have a macula, surrogate rodent models for oedema and neovascularisation were employed to evaluate the *in vivo* effects of brolucizumab. Overall, the different models showed that brolucizumab has the potential to interfere with aspects relevant in the AMD pathogenesis.
No studies regarding secondary pharmacology and safety pharmacology were provided. The applicant justified this with the low systemic exposure due to the local administration and rapid clearance of the drug substance. Furthermore, the safety profile of systemic VEGF inhibitors is well-established. This is supported by the lack of findings in the toxicity studies with intravitreal (IVT) injections in cynomolgus monkeys. No nonclinical pharmacodynamic drug interactions were conducted.

Pharmacokinetics
For the detection of free brolucizumab and anti-brolucizumab antibodies in ocular tissues and in serum of rabbits and monkeys, ELISA methods were developed and qualified or validated.
The distribution after single IVT application was investigated in rabbits and cynomolgus monkeys. The analyses of blood and ocular tissues samples collected after the IVT application showed that brolucizumab was taken up from the vitreous humour in the retina and RPE choroid, and cleared via the aqueous humour to the systemic circulation. Hence, the vitreous humour acted as a depot from where brolucizumab distributed to the adjacent ocular tissues and serum.
No pharmacokinetic studies were conducted with brolucizumab in pregnant or lactating animals. Brolucizumab is expected to be degraded to small peptides and individual amino acids. In contrast to the high molecular weight immunoglobulins, the scFv is eliminated by kidney filtration. Since antibody fragments are not expected to interfere with the cytokine profile and the expression of hepatic metabolising enzymes, the potential for pharmacokinetic drug interactions was not investigated.

Toxicology
The toxicological studies were conducted in rabbits and cynomolgus monkeys with monthly IVT injections over up to six months. The dosing interval was either identical to or more frequent than the one proposed for clinical use. As described earlier, the amino acid sequences of human and cynomolgus monkey $VEGF_{165}$ are identical, identifying the monkey as a pharmacologically relevant

species. As for the rabbit, pharmacological activity was not shown, but this species qualifies as an adequate model for pharmacokinetic profiling according to the literature.
Single-dose toxicity studies (non GLP) in rabbits and cynomolgus monkeys with IVT administration were conducted with various batches of brolucizumab and also included an excipient tolerability study and a study to evaluate the potential effects of endotoxin in the drug product. The GLP repeated-dose studies in cynomolgus monkeys included, in addition to the conventional parameters, indirect ophthalmoscopic examinations, intraocular pressure measurements, electroretinogram analysis, toxicokinetic analysis of the serum and vitreous or anti-drug antibody analysis of the serum and vitreous. The treatment was well tolerated; there were no relevant ocular findings or findings attributed to systemic drug exposure. The procedure of IVT injection caused minimal inflammation in some animals.
The safety margins were calculated based on the plasma exposure determined at the NOAEL (highest dose tested) in the 6-month study and were between 12 (based on systemic C_{max}) or 6 (based on systemic AUC). Considering the high standard deviations identified in the toxicokinetic analysis, the margins are probably lower (approx. 3). The scaffold generally has a low immunogenic potential, which was also confirmed in an *ex vivo* T-cell proliferation assay. In the repeated-dose studies, 16.6% to 42.6% of the animals had pre-existing Anti-drug antibodies (ADAs) or developed them at a later stage without any impact on safety.

Aspects regarding genotoxicity, carcinogenicity and reproductive toxicity were not investigated experimentally due to the nature of the drug (antibody fragment, scope of ICH S6), the low systemic exposure, and/or the target patient population (typically > 50 years). The repeated-dose studies did not show any signs of adverse effects in the reproductive organs, which is probably due to the low systemic exposure. Considering the structure, a transfer of brolucizumab to the foetus via the placenta is also unlikely (lack of Fc domain). Furthermore, this mode of action and hence the consequences thereof are well known and the label considers this adequately. Overall, the conduct of studies on reproductive toxicity would not be of any added value.
An ERA and the nonclinical safety specifications in the RMP were provided and found to be adequate. A class waiver for the PIP was granted by the EMA since the onset of this disease is after 50 years of age.

Nonclinical Conclusions
Overall, the submitted nonclinical documentation is considered to be sufficient to support the approval of Beovu with the new active substance brolucizumab in the proposed indication. The pharmacological activity spectrum and the toxicological profile of this antibody fragment were sufficiently characterised. All nonclinical data that are relevant for safety are adequately described in the information for healthcare professionals.

5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

Pharmacokinetics
ADME
The PK of unbound Brolucizumab in serum following administration via intravitreal injection has been characterised following single administrations at doses from 0.5 to 6 mg and following three subsequent injections separated by 4 weeks at doses of 3 and 6 mg (sparse sampling only) (Study RTH258-E003).
Brolucizumab was present at low, but detectable, levels in serum in all dose groups. Following the first dose, maximum brolucizumab serum concentrations were observed within the first day postdose. Brolucizumab concentration declined in a mono-exponential fashion with a median terminal half-life of ~120 h (~5 days).
Following administration of three doses (separated by 4 weeks), the serum concentrations 24 h postdose were comparable to those after the first dose, indicating no obvious accumulation of brolucizumab in serum.

Following a single intravitreal injection, C_{max} and AUC increased in a more than dose proportional manner: the median C_{max} increased by 7-fold while the median $AUC_{0\text{-}inf}$ increased by 4-fold with a 2-fold increase in dose from 3 mg to 6 mg.

Brolucizumab is thought to be degraded by proteolysis or excreted by renal clearance. However, these claimed elimination pathways of brolucizumab have not been studied specifically.

The PK of brolucizumab-VEGF complexes in serum has not been investigated.

Special Populations / Intrinsic Factors
There were no obvious differences in the PK of brolucizumab between Japanese and Caucasians.

A potential effect of impaired hepatic function on the PK of brolucizumab was not studied. This is adequately communicated in the information for healthcare professionals.

The effect of renal impairment on the PK of brolucizumab was not studied in a dedicated PK study but a limited number of subjects with impaired renal function was included in study RTH258-E003.
The comparative statistics in the 3 mg and 6 mg dose groups indicate that, in subjects with mild renal impairment (GFR 60 - <90 mL/min (n=22)), C_{max} was elevated to 1.4-fold and 3.0-fold, and $AUC_{0\text{-}inf}$ to 1.4- fold and 2.4-fold compared to subjects with normal renal function (GFR ≥90 mL/min (n=21)). There were only 7 patients with moderate renal impairment (GFR 30 - <60 mL/min). In this limited subject group C_{max} was elevated to 1.7-fold and 4.1-fold, and $AUC_{0\text{-}inf}$ to 1.0- fold and 2.1-fold. There were no patients with severe renal impairment (GFR <30 mL/min) in the study population. The study results suggest that renal function may influence the systemic exposure of brolucizumab. No dose adjustment is considered necessary for subjects with mild renal impairment, while no recommendation is possible for subjects with moderate and severe renal impairment due to limited data.

Interactions
No clinical DDI studies were performed. This is acceptable, since CYP- or drug transporter-based interactions are considered unlikely.

Mechanism of Action and primary Pharmacology
Brolucizumab is claimed to bind to human VEGF-A, which prevents VEGF-A from binding to the VEGF receptors VEGFR1 and VEGFR2. No clinical studies that directly assessed this claimed mechanism of action were submitted.

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Secondary Pharmacology (Safety)
Immunogenicity
Immunogenicity was assessed in phase 3 studies. Across all studies and dose groups 43.7% of the subjects were positive for pre-existing anti-brolucizumab antibodies (ADAs).
In studies RTH258-E003, RTH258-C001 and RTH258-C002, 15.6% of subjects receiving brolucizumab were positive for pre-existing neutralising antibodies (nAb).
Overall, in Study RTH258-C001 and Study RTH258-C002, treatment-induced or treatment-boosted ADAs were observed for 21.6% of subjects at Week 48, and for 26.0% of subjects at the end of study, Week 88.

Effects of ADAs or nAbs on safety
A higher incidence of treatment-emergent intraocular inflammation adverse events was observed in subjects with a treatment-induced or treatment-boosted ADA status versus patients with negative or positive ADA status with no boost:
Pre-existing ADAs and pre-existing neutralising antibodies (nAbs) had no clear impact on the incidence of treatment-emergent intraocular inflammation adverse events.
The presence of ADAs or nAbs seemed not to affect the incidence of treatment emergent systemic hypersensitivity.

Effects of ADAs or nAbs on efficacy
Pre-existing ADAs and nAbs and the presence of boosted or induced ADAs and nAbs did not have a consistent impact on the best-corrected visual acuity (BCVA) response.

Pharmacodynamic Interactions with other medicinal Products or Substances
No studies were submitted, and no defined theoretical risks were identified.

Relationship between Plasma Concentration and Effect
Brolucizumab`s site of action is the eye. Thus, the serum levels of brolucizumab are not considered to be relevant for its efficacy, and an exposure-efficacy analysis would not be meaningful. Nor were any exposure-safety analyses submitted.

5.2 Dose Finding and Dose Recommendation

In a phase 1 dose-finding study (C-10-083), brolucizumab 0.5 mg, 3.0 mg, 4.5 mg and 6.0 mg were compared with the active control ranibizumab (Lucentis) 0.5 mg as a single dose (194 subjects, parallel group design). The primary endpoint was the central subfield thickness (CSFT) after a month, with an extension to 6 months. Brolucizumab 0.5 mg was minimally active, the three higher dosages were all within the range of the active control over time, and slightly more effective numerically after 1°month, but without any clear dose-response relationship. A further phase 2 study (C-12-006) compared brolucizumab 6 mg only with aflibercept (Eylea) 2 mg at monthly intervals for 1 year (90 subjects, parallel group design). The primary endpoint was the best-corrected visual acuity (BCVA) after 3 months. Brolucizumab was slightly less effective numerically, but statistically non-inferior according to the predefined threshold. The benefit/risk profile for 3 mg and 6 mg was further investigated in a phase 3 study (RTH258-C001)

5.3 Efficacy

Two pivotal studies (RTH258-C001/-C002), both randomised, double-blind, multicentre and active-controlled, investigated the efficacy and safety of brolucizumab 6 mg versus aflibercept 2 mg in patients with choroidal neovascularisation secondary to age-related macular degeneration who had not previously been treated with anti-VEGF preparations. Study RTH258-C001 also included a group with brolucizumab 3 mg. Both studies investigated the disease activity with a view to switching from 12- to 8-weekly dosage intervals, while study RTH258-C002 included six additional assessments of

disease activity in the long-term phase. After a start phase with intravitreal injections every three months, aflibercept was administered at 8-weekly intervals and brolucizumab at 8- and 12-weekly intervals respectively for 96 weeks. The primary efficacy endpoint was defined as "Change from Baseline in BCVA to Week 48". The non-inferiority margin was -4 letters, there were around 360 subjects per group and the baseline BCVA was around 60 letters. In study RTH258-C001, the average improvements in BCVA after 48 weeks were 7.0 letters for aflibercept 2 mg, 6.4 letters for brolucizumab 6 mg and 5.9 letters for brolucizumab 3 mg. The lower limits for the 95% Confidence Interval (CI) were -2.1 and -2.5 respectively and demonstrated non-inferiority for both dosages. In study RTH258-C002, the average improvements in BCVA after 48 weeks were 7.6 letters for aflibercept 2 mg and 6.9 letters for brolucizumab 6 mg. The lower limit for the 95% CI was -2.4. These improvements were obtained after around 12 weeks and were maintained up to the 96-week point. The results for the various secondary endpoints were consistent with the primary endpoint and confirmed non-inferiority according to the protocol. In both studies, after the loading dose over 50% of patients followed the 12-weekly treatment intervals without any change in disease activity.

5.4 Safety

In the pivotal clinical trials, the discontinuation rates were low overall, irrespective of the active substance or dose. In the monthly loading dose population, of those organs investigated most of the adverse events were recorded – as expected – for the eye, including conjunctival haemorrhages, vitreous detachments and floaters, pain and visual impairment. In the long-term population with 8- and 12-weekly intervals, the results were qualitatively comparable, although the incidences of ocular adverse events were higher than in the loading dose population. The differences between the groups were relatively small. In the pooled safety data, the incidences of intraocular inflammation, endophthalmitis and arterial occlusions occurred more frequently with brolucizumab than with aflibercept, while all other symptoms were comparable between the groups. The safety of the proposed 6 mg dosage and the lower 3 mg dosage of brolucizumab was slightly worse numerically than that of the reference preparation aflibercept 2 mg. The clinical relevance of these differences is difficult to assess at this time.

5.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Brolucizumab is a humanised monoclonal single-chain antibody fragment that was developed for the treatment of wet age-related macular degeneration (AMD). The current standard treatments for AMD include the injection of inhibitors of vascular growth factor known as anti-VEGFs into the vitreous body (intravitreal surgical drug administration).
Two pivotal studies investigated brolucizumab 6 mg versus aflibercept 2 mg (Non-inferiority Design) in patients with choroidal neovascularisation secondary to age-related macular degeneration, who had not previously been treated with anti-VEGF preparations. Study RTH258-C001 also included a group with brolucizumab 3 mg, while study RTH258-C002 quantified the disease activity in order to investigate the ideal duration of the dosage intervals. The primary efficacy endpoint was defined as "Change from Baseline in BCVA to Week 48", the non-inferiority margin was -4 letters. The lower limits for the 95% CI were -2.1 and -2.5 respectively, and demonstrated non-inferiority for both dosages according to the protocol.
In study RTH258-C002, the average improvements in BCVA after 48 weeks were 7.6 letters for aflibercept 2 mg and 6.9 letters for brolucizumab 6 mg. The lower limit for the 95% CI was -2.4 letters. These improvements were obtained after around 12 weeks and were maintained up to the 96-week point. The results for the various secondary endpoints were qualitatively consistent with the primary endpoint. In both studies, after the loading dose over 50% of patients observed the 12-weekly treatment intervals without any change in disease activity.
Uncertainty exists concerning the selected dosage. The dose/response relationship is flat and, in study RTH258-C001, since both 3 mg and 6 mg were non-inferior to the active control, the selected 6 mg dose is not supported by solid evidence.
In the long-term population the incidences of ocular adverse events were low overall - these included conjunctival haemorrhages, vitreous detachments with floaters, pain and visual impairment - and, although overall comparable between the groups, were numerically elevated for inflammation,

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endophthalmitis and arterial occlusions. According to the investigators' narratives, most adverse events tended to be caused by the intervention rather than the active substances. The absolute differences between the three groups (brolucizumab 3 mg, brolucizumab 6 mg and aflibercept 2 mg) were relatively small. The rest of the safety data for the proposed 6 mg dosage of brolucizumab was slightly worse numerically than that of the reference preparation aflibercept 2 mg.
The formation of new anti-brolucizumab antibodies and the boostering of existing ones occurred during treatment with brolucizumab. An increased incidence of intraocular inflammation was observed in patients who formed these antibodies.
The overall benefit/risk profile for brolucizumab is positive.

5.6 Approved Indication and Dosage

See Information for healthcare professionals in the Appendix.

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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.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the Information for healthcare professionals relating to Beovu, solution for injection 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 documents, which are valid and relevant for the effective and safe use of medicinal products in Switzerland, are the information for healthcare professionals approved and 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.

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▼ 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, 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).

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

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 treatment interval may be adjusted to up to every 8 weeks (2 months) (see "Properties/Actions").The physician may individually define treatment intervals based on disease activity as measured by visual acuity and/or anatomical parameters.
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
Intravitreal injections, including those with Beovu, have been associated with endophthalmitis, intraocular inflammation and retinal detachment (see "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.
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. Both intraocular pressure and perfusion of the point of exit of the optic nerve must be monitored and managed as necessary.

Arterial thromboembolic events
There is a potential risk for arterial thromboembolic events associated with intravitreal administration of VEGF inhibitors. In patients with known risk of stroke or myocardial infarction, the risk may be increased.

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. No animal reproduction studies have been conducted. The potential risk of use of Beovu in pregnancy is unknown. 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

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.

Adverse drug reactions from 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.

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.
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.
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. The clinical significance of anti-brolucizumab antibodies on safety is unclear at this time.

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 EIViS (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 VEGFA, brolucizumab suppresses endothelial cell proliferation, thereby reducing pathological neovascularisation and decreasing vascular permeability.

Pharmacodynamics

Neovascular (wet) age-related macular degeneration (AMD) is characterised by pathological choroidal neovascularisation (CNV). Leakage of blood and fluid due to CNV may cause retinal thickening or oedema or sub-/intraretinal haemorrhage, resulting in loss of visual acuity.
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.

Clinical efficacy

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

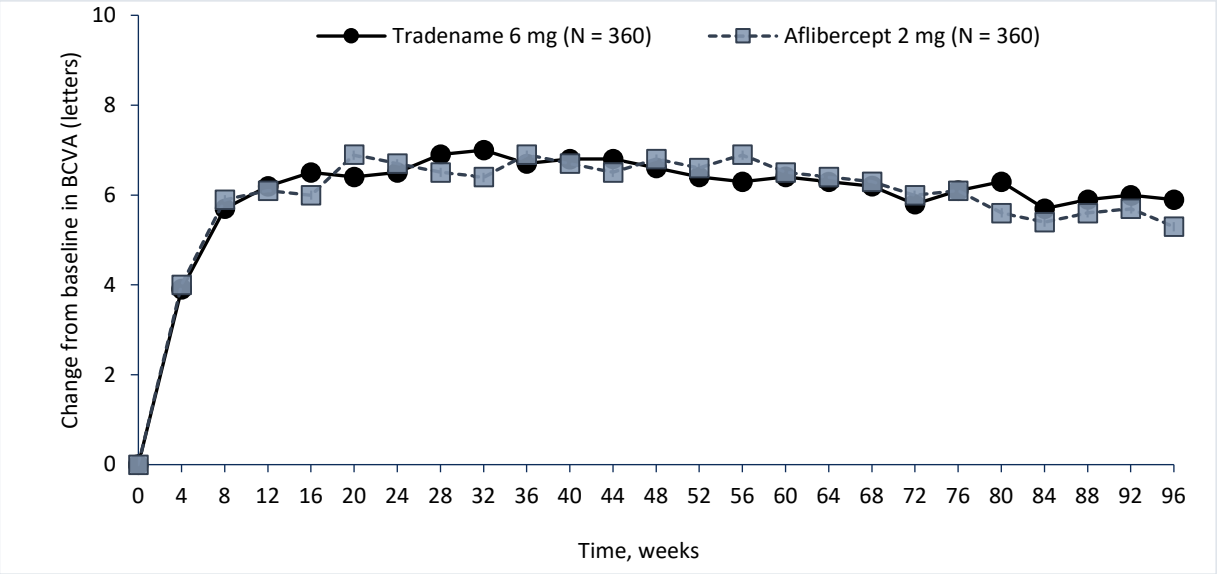
In the HAWK study, at week 48 patients achieved a mean change from baseline of +6.6 letters and +6.8 letters ($p<0.0001$) in the 6 mg Beovu and aflibercept groups, respectively. The mean change from baseline in the 3 mg Beovu group was +6.1 letters ($p=0.0003$). The proportion of patients who achieved 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.

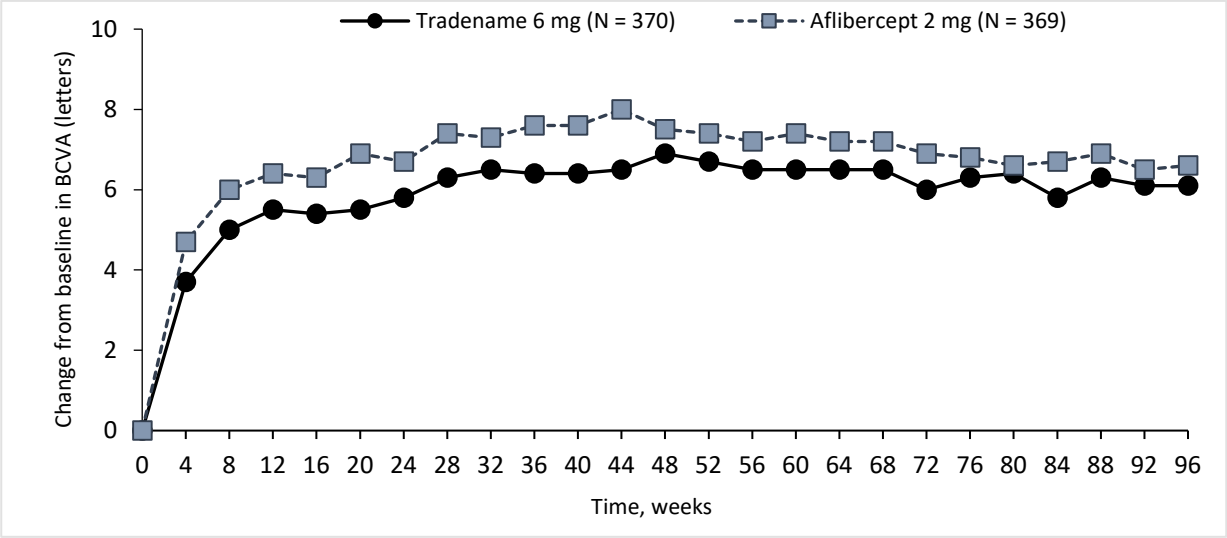
The visual acuity gains observed in the first year were maintained in the second year.

Figure 0-1 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 6 mg 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 12week 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/or 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 6 mg 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 0-1).

Table 0-1 Disease activity evaluation in HAWK and HARRIER studies up to week 96

		HAWK			HARRIER		
Efficacy outcome (pre-specified secondary endpoints)	**At week**	**6 mg Beovu (N=360)**	**Aflibercept 2 mg (N=360)**	**Difference (95% CI) brolucizum**	**6 mg Beovu (N=360)**	**Afliberce pt 2 mg (N=369)**	**Difference (95% CI) brolucizuma**

				ab and aflib ercept			**b and afliber cept**
Mean change in CST from baseline (µm)	16 [d)]	-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

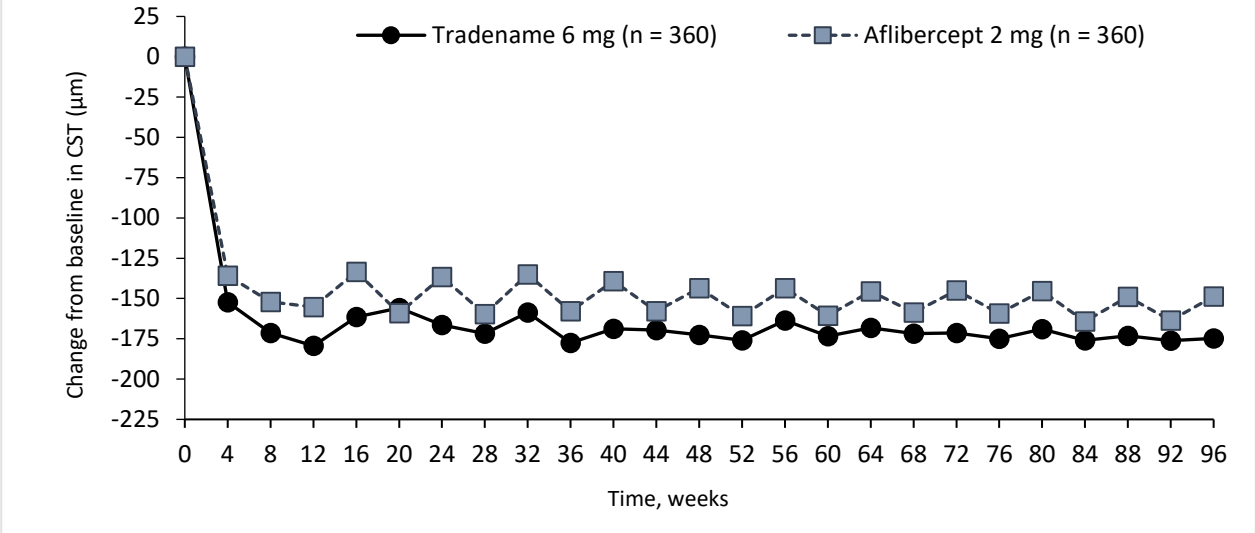
[a)] Secondary endpoint in HARRIER, confirmatory analysis in HAWK. 1-sided p-values for superiority of brolucizumab

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

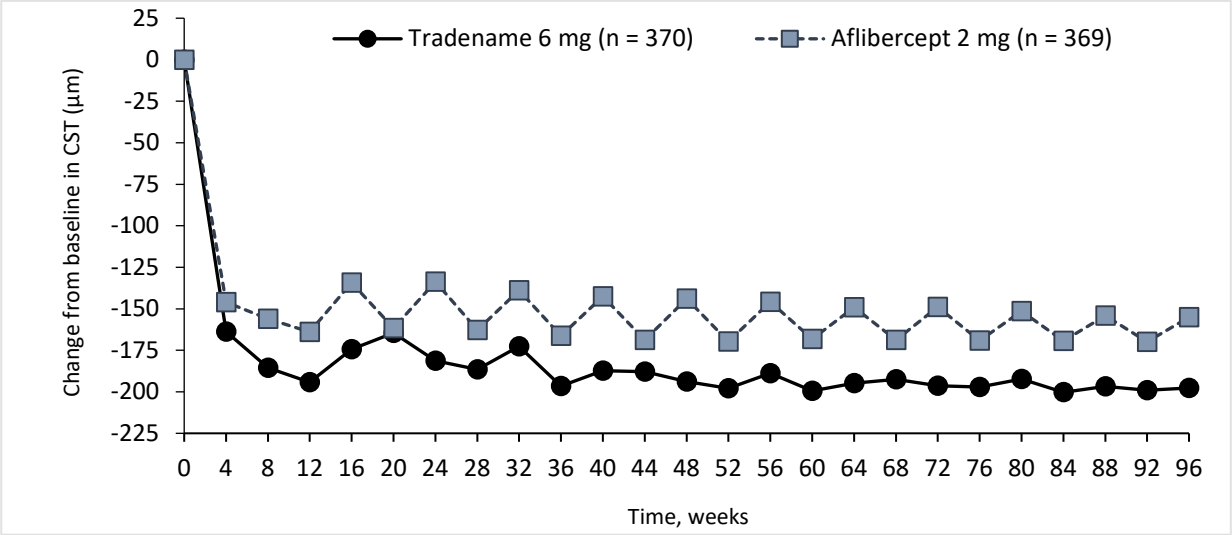
[c)] Up to week 16 treatment exposure was identical, allowing a matched comparison of Beovu and aflibercept.

Figure 0-2 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 the Visual Function Questionnaire of the US National Eye Institute (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).

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

The 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 aging 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

No reproductive or fertility studies have been conducted. 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 for female reproduction, and to embryofetal 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

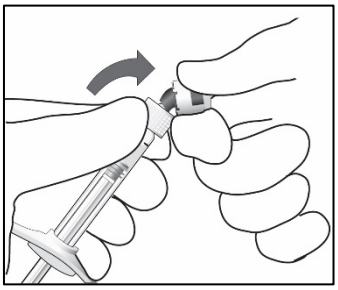
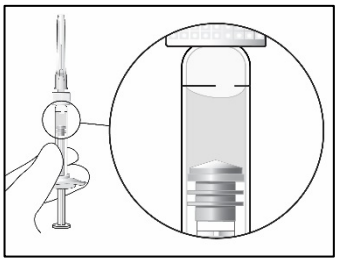
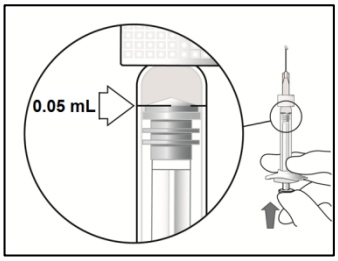
Novartis Pharma Schweiz AG, Risch, Switzerland; domicile: 6343 Rotkreuz, Switzerland

Information last revised

January 2020

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 **0.5 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.